Volume 6 / Number 4 / 2012

HealthMED

Journal of Society for development in new net environment in B&H

Address of the Editorial Board: Sarajevo, Bolnicka BB
phone/fax 00387 33 956 080
healthmedjournal@gmail.com
http://www.healthmedjournal.com
Published by: DRUNPP, Sarajevo
Volume 6 Number 4, 2012
ISSN 1840-2291

HealthMED journal with impact factor indexed in:

- Thomson Reuters ISI web of Science,
- Science Citation Index-Expanded,
- Scopus,
- EBSCO Academic Search Premier,
- Index Copernicus,
- getCITED, and etc.

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Body fat measurement in African-American students at a historically black college and university and its correlation with estimations based on body mass index, waist circumference, and bioelectrical impedance analysis, compared to air displacement plethysmography

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Abstract

It is essential to determine the body composition of individuals undergoing physical training because a low fat-muscle ratio might indicate better physical performance in many types of sports and recreational activities. This study was conducted to determine whether the percent body fat (%BF) estimations made from body mass index (BMI), waist circumference (WC), and bioelectrical impedance analysis (BIA) correlate with the estimations made by air-displacement plethysmography (BOD POD) in African Americans. The subjects recruited for our study were 119 African-American college students (59 male and 60 female) who visited an exercise physiology laboratory in North Carolina A&T State University, Greensboro, NC, USA. The body composition of the subjects was assessed by BMI, WC, BIA, and BOD POD. BMI, WC, and BIA showed highly positive correlation (r = 0.650–0.915) with the estimated %BF compared to BOD POD. The best-fit multiple regression equation included age, BMI, and WC, and R^2 was determined to be 56.0% in male and 73.0% in female subjects for variation in %BF determined by BOD POD. Although compared to BOD POD, the BIA showed a high correlation with the estimated %BF than did the BMI and WC, we suggest that on the field, multivariate regression equation including age, BMI, and WC should be used for the assessment of body composition in African-American college students.

Key words: Body mass index, Waist circumference, Bioelectrical impedance analysis, Air-displacement plethysmography

Introduction

It is essential to determine the body composition of individuals undergoing physical training because a low fat-muscle ratio might indicate better physical performance in many types of sports and recreational activities. Previous studies have used various parameters to calculate percent body fat (%BF), such as body mass index (BMI), waist circumference (WC), waist-hip ratio (WHR), and skin-fold thickness (1-3), whereas recent studies report the measurement of %BF by underwater weighing (densitometry), dual energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), magnetic resonance imaging (MRI), and air-displacement plethysmography (BOD POD) (4). However, densitometry, DEXA, and MRI are expensive, inconvenient for the participant, and not feasible in the field because they involve the use of large, specialized equipment. Hence, the use of these techniques in many studies was limited.

On the other hand, BOD POD and BIA are relatively simple, quick (take only a few minutes), and non-invasive techniques, which give reliable measurements of body composition. Especially, BOD POD studies using regression analyses showed that the %BF estimated by BOD POD had a good correlation with the %BF estimated by DEXA (5-7).

Many studies have compared the values of body composition determined by BOD POD, DEXA, MRI, and densitometry in a laboratory setting. However, since training or recreational activity is often conducted on the field, it was important to determine whether simple on-field measurements

made to assess body composition correlate with the measurements taken in the laboratory.

Most studies also focused on the obese, the elderly, the disabled, and children but not on college students (8). Furthermore, very few studies have been conducted on the African-American ethnic minorities. Hence, there was a need for a study focused on assessing body composition on the field for African-American students. Therefore, this study aimed to determine whether body composition assessed from BMI, WC, and BIA correlates with that assessed by BOD POD and whether these are relatively simple and quick techniques for on-field assessment of body composition, among African-American college students. We further estimated the %BF from the best-fit multiple-regression equation using age, BMI, and WC for on-field assessment.

Methods

Subjects

The subjects recruited for our study were 119 African-American college students (59 male and 60 female). They visited an exercise physiology laboratory at North Carolina A&T State University, a historically black college and university (HBCU) in Greensboro, NC, USA, and BMI, WC, BIA, and BOD POD measurements were taken between March 1, 2010 and February 28, 2011. All subjects signed a written consent form to participate in this study. Moreover, all the study procedures were approved by the Institutional Review Board at North Carolina A&T State University. The characteristics of the subjects are shown in Table 1.

Table 1. Characteristics of subjects (N = 119)

Variable	Male (N = 59)	Female (N = 60)
Age, years	21.00 ± 2.08	21.03 ± 2.44
Height, cm	177.30 ± 8.42	161.95 ± 6.54
Weight, kg	84.43± 15.16	69.40 ± 15.79
BMI, kg/m^2	26.86 ± 4.41	26.39 ± 5.42
WC, cm	79.39 ± 10.28	75.15 ± 11.04
BOD POD, %BF	18.72 ± 7.07	30.40 ± 9.23
BIA, %BF	19.02 ± 7.13	31.05 ± 8.85

BMI, Body mass index; WC, Waist circumference; BIA, Bioelectrical impedance analysis

Experimental procedures

The BMI (kg/m^2) of each subject was calculated on the basis of his/her weight and height.

The WC of each subject was measured at the region of the trunk that is midway between the lower costal margin (bottom of the lower rib) and the iliac crest (top of the pelvic bone), while the subject stood with his/her feet about 25–30 cm apart. The measurer stood beside the subject and fit the tape carefully around the subject's trunk, without compressing any underlying soft tissues. The circumference was measured at the end of a normal expiration, to the nearest 0.5 cm (9).

The %BF was evaluated with a BIA body-fat analyzer (BF-350, TANITA, Japan). This instrument measures the resistance of the fat tissues of the legs to an electric current passed at various frequencies such as 5, 50, 250, and 500 kHz, and it makes use of 4 tactile electrodes: 2 electrodes at the anterior and posterior aspects of the sole of each foot.

The %BF was also evaluated with BOD POD version 1.69 (Life Measurement Inc., Concord, California, USA). Chamber pressure amplitudes were calibrated before each test with a 50-L calibration cylinder. The subject wore a tight-fitted swimsuit or body suit, and the %BF was determined in the chamber. The thoracic gas volume was measured in a separate step. To measure this, the subject was required to sit quietly in the BOD POD chamber and breathe through a disposal tube and filter connected to the reference chamber at the rear of the BOD POD apparatus. After 4 or 5 breaths, the airway was occluded midway during exhalation, and the subject was instructed to blow 3 quick, light, panting breaths into the tube.

All the subjects were prohibited from performing any exercise for 12 h, consuming anything for 4 h, and urinating just before the impedance measurement. The subjects were recommended to wear light clothes and remove any metallic objects that could interrupt the electric current during the impedance measurement. All methods employed for assessing body composition followed the recommendations of the book Applied Body Composition Assessment (10).

Statistical analysis

All results obtained from this study were represented as mean ± standard deviation. Pearson correlations were calculated to examine the relationship between other variables (BIA, BMI, and WC) and BOD POD. Multivariate regression anal-

ysis was performed to determine the %BF regression equation by age, BMI, and WC. Statistical significance was set at $p < 0.05$, and all analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL, USA).

Results

The results of the correlation analysis between BMI, WC, and BIA, and BOD POD are shown in Table 2. For all subjects, BOD POD showed a significant positive correlation with BMI (male: $r = 0.650$, $p < 0.001$; female: $r = 0.847$, $p < 0.001$), WC (male: $r = 0.696$, $p < 0.001$; female: $r = 0.831$, $p < 0.001$), and BIA (male: $r = 0.880$, $p < 0.001$; female: $r = 0.915$, $p < 0.001$).

The results of multivariate regression analyses of age, BMI, and WC are shown in Table 3. The best-fit multiple-regression equation included age, BMI, and WC, and the coefficient of variation for %BF determined by BOD POD. R^2 was 56.0% ($p < 0.001$) in male and 73.0% ($p < 0.001$) in female subjects. The regression equation is given below:

$$\%BF = -33.650 + (0.686 \times age) + (0.498 \times BMI) + (0.310 \times WC)$$ in male subjects (R^2=56.0%)

$$\%BF = -13.003 - (0.077 \times age) + (0.934 \times BMI) + (0.271 \times WC)$$ in female subjects (R^2=73.0%)

Age, years; BMI, kg/m^2; WC, cm

Discussion

The purpose of this study was to determine whether the %BF estimated using BMI, WC, and BIA correlates with that estimated using BOD POD and then, to estimate the %BF from the best-fit multiple-regression equation using age, BMI, and WC as variables, in African-American college students. The results of this study suggest that in both male and female subjects, %BF estimated using BMI, WC, and BIA highly correlated with that estimated using BOD POD. The results also suggested that BMI, WC, and BIA can all be used for the assessment of body composition.

Table 2. Correlation of BMI, WC, and BIA compared to BOD POD in African American college student (N = 119)

Category	BOD POD / Male (N = 59)		BOD POD / Female (N = 60)	
	r	p	r	p
BMI (kg/m^2)	0.650	<0.001***	0.847	<0.001***
WC (cm)	0.696	<0.001***	0.831	<0.001***
BIA (%BF)	0.880	<0.001***	0.915	<0.001***

****p<0.001 by Pearson correlation analysis*
BMI, Body mass index; WC, Waist circumference; BIA, Bioelectrical impedance analysis

Table 3. The multivariate regression analysis by age, BMI, and WC in African American college student (N = 119)

Category	Male (N = 59)						Female (N = 60)					
	B	S.E.	Beta	t (p)	F (p)	R^2	B	S.E.	Beta	t (p)	F (p)	R^2
Constant	-33.650	7.914		-4.252 (***)	23.289 (***)	0.560	-13.003	6.406		-2.030 (*)	50.379 (***)	0.730
Age (years)	0.686	0.305	0.202	2.251 (*)			-0.077	0.288	-0.020	-0.268		
BMI (kg/m^2)	0.498	0.221	0.311	2.254 (*)			0.934	0.348	0.548	2.685 (**)		
WC (cm)	0.310	0.095	0.450	3.264 (**)			0.271	0.176	0.325	1.538		
$\%BF = -33.650 + (0.686 \times age) + (0.498 \times BMI) + (0.310 \times WC)$							$\%BF = -13.003 - (0.077 \times age) + (0.934 \times BMI) + (0.271 \times WC)$					

**p<0.05 **p<0.01 ***p<0.001 by multivariate regression analysis*
S.E, Standard Error; BMI, Body mass index; WC, Waist circumference

The most commonly used indicator of %BF was BMI, although it was well known that it was not perfectly associated with %BF (11-12). Individuals of the same height show considerable variations in the %BF depending on their age, gender, and ethnic group. Interestingly, the association between BMI and %BF was not strong (curvilinear association) among 23,627 UK adults (13); however, another study in the USA found that this association was very strong (linear association) (14). Although it is known that the correlation between BMI and adiposity does differ according to ethnicity, our results showed that the %BF estimated highly correlated with BMI among male and female subjects in the African-American college-student population considered in our study.

The study by Gallagher et al. (1996) did not clearly explain the linear association (14), observed in their results, and our study also did not clearly explain in African Americans ethnic minorities. Therefore, a well-designed investigation is needed to confirm this correlation by epidemiological studies.

Measurement of WC has been widely used to predict risk of cardiovascular disease and metabolic syndrome, and the WC is safe for measuring central adiposity. Daniels et al. (2000) evaluated the correlation between %BF estimated from WC and that measured by DEXA, and they found the correlation coefficient r = 0.79–0.81 (15). Also, Sant'Anna Mde et al. (2009) found a correlation coefficient of r = 0.50–0.62 between %BF determined from WC and that measured by BIA (16). The %BF estimations made in our study are shown to be highly correlated with the WC among male (r = 0.696) and female (r = 0.831) subjects.

The BIA method has been widely used in clinics, sports medicine, and weight reduction programs (17-18). Several studies have compared the estimations of %BF by BIA with those made by reference methods such as DEXA (19-23); however, the results were still controversial. Our study compared the estimations of %BF by BIA and that by BOD POD; we obtained slope values of approximately 1.00 compared to %BF estimation by DEXA (5-7). The %BF estimations made in our study by BOD POD are shown to be highly correlated with the BIA values measured in male (r = 0.880) and female (r = 0.915) subjects, compared with the estimations from BMI and WC. Therefore, we think that BIA is a better indicator of %BF than BMI and WC.

Our results showed that the %BF estimated using BMI, WC, and BIA was highly correlated with that using BOD POD. Therefore, we calculated the regression equation using age, BMI, and WC, which involved simple on-field measurements. The results showed that R^2 was 56.0% in male and 73.0% in female subjects. This model gave the best-fit regression equation on the field. We recommend using this model for African-American college students.

This research has limitations; since it was based on subjects from North Carolina, it cannot represent the total African-American college student population in the USA. Moreover, the number of subjects that participated in this research (N = 119) did not constitute a large sample. However, we believe the greatest merit of this research is that it was conducted on subjects from African-American ethnic minorities.

Conclusion

The %BF estimated using BMI, WC, and BIA have been shown to be highly correlated with that estimated using BOD POD. Although compared to BOD POD, BIA showed a high correlation with the estimated %BF than did BMI and WC, we suggest that on the field, a multivariate regression equation including age, BMI, and WC can be used for the assessment of body composition among African-American college students.

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Cognitive deficiency induced by cerebral hypoperfusion/ischemia improves by exercise and grape seed extract

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Abstract

Background: Permanent bilateral common carotid arteries occlusion (2CCAO) in the rat has been established as a valid experimental model to investigate the effects of chronic cerebral hypoperfusion/ischemia on cognitive function and neurodegenerative processes. The present study was aimed to investigate the effects of chronic administration of grape seed extract (GSE) and forced exercise and together on memory retrieval following hypoperfusion/ischemia.

Methods: Carotid arteries in male rats were ligatured and then cut bilaterally with a 1-week interval between artery occlusions. Passive avoidance task was done after 28 days running on treadmill and oral administration of GSE as alone and both of them in sham operated and ischemic groups.

Results: Chronic forced exercise although increased memory slightly but did not significant. In addition to treatment with GSE improved memory significantly ($P<0.01$). When GSE was associated with forced exercise could improve memory higher than exercise alone in ischemic rats significantly ($P<0.01$).

Conclusion: Our results showed that free radicals elevated significantly in brain tissues after permanent 2CCAO and chronic forced exercise caused raise of free radicals in brain as a stressor and caused neuronal injury too. The possibility that GSE with strong anti-oxidative potential could scavenge oxidants from brain tissues after ischemia and exercise, therefore improve memory. Our study showed that exercise couldn't affect memory of ischemia/hypoperfusion. So, administration of a natural antioxidant such as GSE associate with exercise is beneficial for ischemic patients.

Key words: Cerebral ischemia; cognition; forced exercise; Grape seed extract; rat

Introduction

Disorders of the cerebral circulation are associated with neurological and psychiatric illnesses. Clinical evidence supports the hypothesis that chronic cerebral hypoperfusion is associated with cognitive decline, both in aging and in neurodegenerative disorders (1, 2). Cerebral ischemia, most commonly occurs in patients with stroke, produces extensive damages to neurons, leading to loss of neuronal cells in brain regions such as the hippocampus and cerebral cortex (3). It also impairs cognition in humans (4) and behavioral performance associated with cognitive and motor disorders in rodents (5). The hippocampus is highly vulnerable to ischemic insults (6, 7). Ischemia-induced neuronal degeneration is also observed in other structures, such as the striatum, cerebral cortex and thalamus (6-8). Some studies have found a direct correlation between cerebral hypoperfusion-induced memory deficit and hippocampus CA1 cell damage (9). Permanent bilateral occlusion of both common carotid arteries in rats has been used to model chronic cerebral hypoperfusion (10); the main findings include histopathological damage and impaired spatial learning function (6, 7, 10). This cognitive impairment may be related to progressive loss of hippocampal

pyramidal neurons, an association often observed in human aging and dementia states (10). The neuronal morphologic outcomes in hippocampus after 2CCAO ischemia will be lower than control (11). It was reported that oxidative stress involved in the pathogenesis of some chronic inflammatory disease (12). And believed that Oxygen free radicals or oxidants play an important role in acute central nervous system injury that is produced by cerebral ischemia and reperfusion (13). The free radicals are neutralized by an elaborate antioxidant defense system consisting of enzymes and numerous non-enzymatic antioxidants, including vitamins A, E and C, glutathione, ubiquinone, and flavonoids (14). Grape seed extract contains a number of polyphenols including procianidine and proantocianidine and scavenges free radicals strongly (15). Proanthocyanidins are potent natural antioxidants which belong to a class of polyphenols. (16). Grape seed proanthocyanidins extract (GSPE), a flavonoid, has a beneficial effect on physical health (17). Grape seed extract (GSE) possess cardioprotective abilities by functioning as in vivo antioxidants and by virtue of their ability to directly scavenge ROS including hydroxyl and peroxyl radicals. It was suggested that GSE can protect ischemic neuronal injury by inhibiting DNA damage after transient forebrain ischemia (18). Grape seed hydroalcholic extract has a preventive effect on dementia type of Alzheimer's disease in aged male rats (19).

Several studies showed that learning and memory can be affected by exercise (20). Exercise can cause an imbalance between reactive oxygen species (ROS) and antioxidants, which is referred to as oxidative stress (14). Forced exercises such as swimming (21) and treadmill (22) are main physical activity models. Treadmill training may be beneficial for ischemic brain recovery (23). Running exercise enhances neurogenesis in the normal adult and aged hippocampus (24). However, the effect of exercise on neurogenesis in the ischemic hippocampus is unclearThe positive correlation between running and neurogenesis has raised the hypothesis that the new hippocampal neurons may mediate, in part, improved learning associated with exercise (25). Our knowledge about the effects of physical exercise on brain is accumulating although the mechanisms through which exercise exerts these actions remain largely unknown. Running is a potent stimulator of cell proliferation in the adult dentate gyrus and these newly generated hippocampal neurons seem to be implicated in memory functions (26). Enhanced physical activity is associated with improvements in cognitive function in rodents as well as in humans (27). Treadmill exercise after ischemia reduced stroke volume and raises cognitive function (28). Unlike other researchers that reported, early training after stroke increases degradation rate and reduces improvement (29). Studies have shown that use of exercise and vitamin E (an antioxidant) simultaneously has a protective effect on the age-related reduction of antioxidant enzymes and increases antioxidants in the rat brain (30).

With consideration of the current knowledge and on base of our previous findings the present work was aimed to investigate the effects of 28 days administration of forced exercise and grape seed extract (GSE) as alone and association on passive avoidance learning and memory following cerebral hypoperfusion ischemia in rat model of permanent 2CCAO.

Materials and Methods

Animals and Experimental Procedure: Seventy adult male Wistar rats aged 3 months (220±30g) were obtained from the central animal house of the Jundishapur University of Medical Sciences, Ahvaz-Iran. They were housed individually in standard cages and maintained in a temperature-controlled room (21 ± 2°C) on a 12/12-h light/dark cycle, humidity (50-55%) with food and water available *ad libitum*. All procedures were in accordance with the Guide for the Care and Use of Laboratory Animals adopted by the National Institute of Health (USA) and with the Iranian Local Ethics Committee for the Purpose of Control and Supervision of Experiments on Laboratory Animals. Rats were divided randomly into eight equal numbers groups of 8 in each:

1) Ischemic group submitted to occlusion of both common carotids arteries (Isch);
2) sham-operated control (Sham) with manipulation of both common carotids arteries without occlusion;
3) sham operated animals received 28 days GSE (100 mg/kg,orally)(32,33) (Sham-GSE);

4) ischemic rats received 28 days GSE (Isch-GSE);
5) sham operated animals with 28 days forced running on treadmill (Sham-Exe);
6) sham operated animals that were placed on treadmill without switching on the treadmill motor but electric shock was switching on (Sham-Sh.Exe);
7) ischemic animals with 28 days forced running on treadmill (Isch-Exe);
8) ischemic animals that were placed on treadmill without forced running but the electric shock part was switched on(Isch-Sh.Exe);
9) sham operated that received 28 days exercise associated with GSE (Sham-Exe-GSE);
10) Ischemic rats that received 28 days exercise associated with GSE (Isch-Exe-GSE).

CCAO procedure: Cechetti's method (2010) with little modification was used. In summary, rats were anesthetized with ketamine/xylazine (50/5mg/kg, i.p). a neck ventral midline incision was made and the common carotid arteries were then exposed and gently separated from the vagus nerve. Carotids were occluded with a 1-week interval between interventions, the right common carotid being the first to be assessed and the left one being occluded 1 week later. Sham-operated controls received the same surgical procedures without carotid artery ligation. Animals were randomly assigned to sham or 2CCAO groups so as to avoid any litter effect (11).

GSE preparation: Grape fruits (*vitis vinifera L*) as large clusters with red barriers were

purchased from Qazvin grape gardens- Iran. Seeds removed from the grapes, air dried in shade for one week and milled to fine powder (electric mill, Panasonic Co. Japan). The seeds powder was macerated in 75% ethanol for 72 hours at room temperature. The ethanol extract evaporated (Rotary Ovaporator, Heidolph Co. Germany) to remove ethanol and GSE was obtained as a lyophilized powder (yield 25-30%) (31-33).

Forced exercise: We used exercise protocol that was described earlier (34). Rats were trotted on five tunnels treadmill; Speed and duration of exercise for groups with exercise were kept constant at 17-18 m/min, 60 min daily for 28 days. Inclination was varied during 60 min forced exercise, 0°at first 10 min, 5° at second 10 min, and during next two 20 min periods it was adjusted to 10° and 15°, respectively. Sham.exercise (Sh.Exe) groups were always placed on treadmill without switching on the treadmill motor for the exact duration as the runners but were not forced to run. Electrical part of treadmill delivered light electric shocks when the rats entered the rear of the test chamber. Both runners and non-runners could avoid the shocks by remaining on the treadmill.

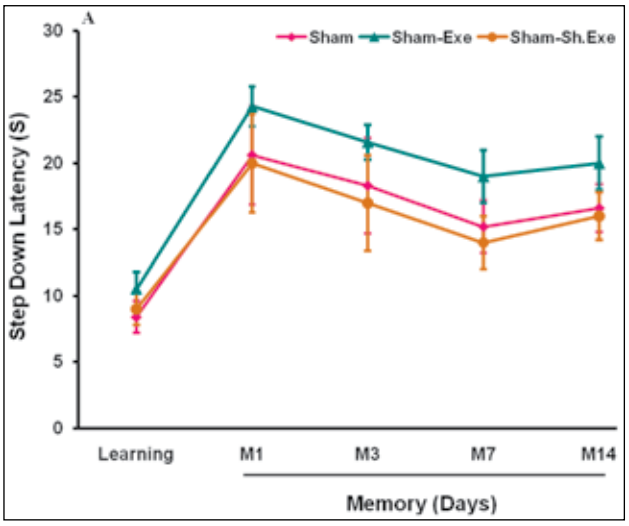
Passive avoidance task: This method was described earlier (34). Briefly, at the first day of experiment, rats were acclimated to the acquisition chamber. At the second day, the rats were gently placed on the wooden platform, and latency of step-down was recorded as learning phase. When all four paws touched the grid, a low level electric shock (0.3 mA, 3 sec.) was delivered. On days 1, 3, 7 and 14 aftershock delivery to their foot paws, step-down latencies (SDL) were measured (maximum 300 sec.) while no shock was applied.

Statistical Analysis: Data were expressed as mean±S.E.M. Step-down latencies at learning and 1st, 3rd, 7th and 14th day of retention trials phases were analyzed by repeated measures two-way ANOVA, that followed by LSD post hoc test. The statistical significance was considered with $p<0.05$.

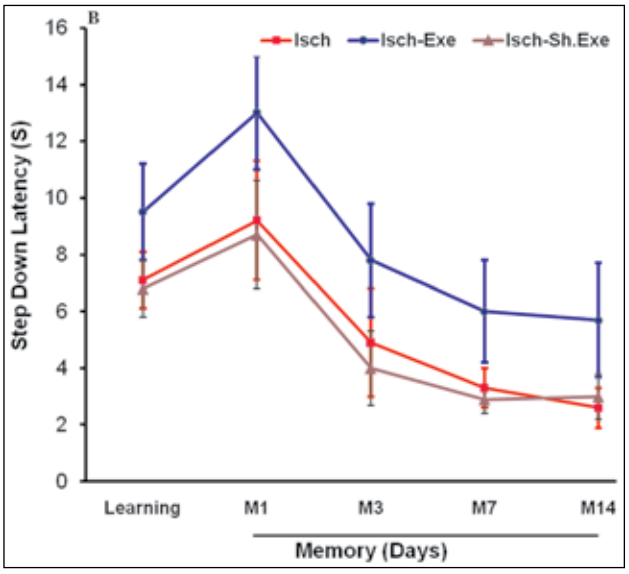
Results

Effects of chronic forced exercise on sham operated and 2CCAO rats (Isch) have shown in figure 1. As shown in panels A&B of figure, exercise increased step down latency as memory retrieval slightly in both groups but not significant. Learning phase didn't affect by exercise neither in sham or ischemic groups (Figure 1 A, B).

Effects of grape seed extract (GSE) as a selected natural antioxidant on sham operated and 2CCAO rats have shown in figure 2. As shown in panels A&B of figure, GSE increased step down latency as memory retrieval significantly in both groups but in contrast of ischemic rats memory retrieval during M14 (14th day of memory trial) reversed to base in sham group while in ischemic rats was persisted. Learning phase didn't affect by GSE in sham operated animals (Figure 2A) while increased significantly in ischemic group (Figure 2B).

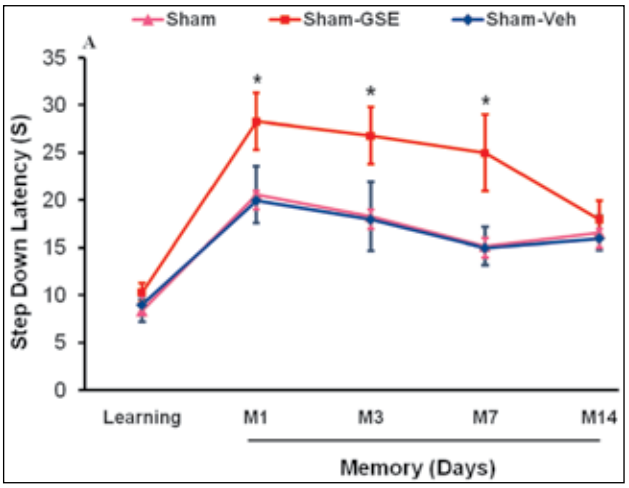


a)

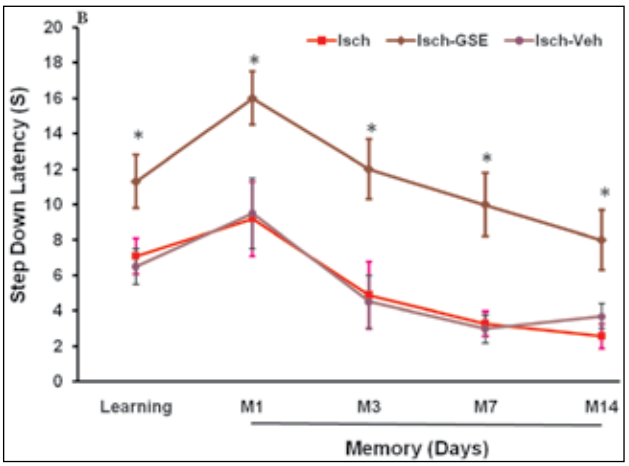


b)

Figure 1. Mean ± SD of step-down latencies (SDL) during different days for sham operated (panel A), 2CCAO ischemic (panel B) received chronic forced exercise alone (Sham-Exe and Isch-Exe) with compare to Sham, Isch, Sham-Sh. Exe and Isch-Sh.Exe groups. Exercise increased memory retrieval slightly in both sham and ischemic groups but was insignificant.



a)

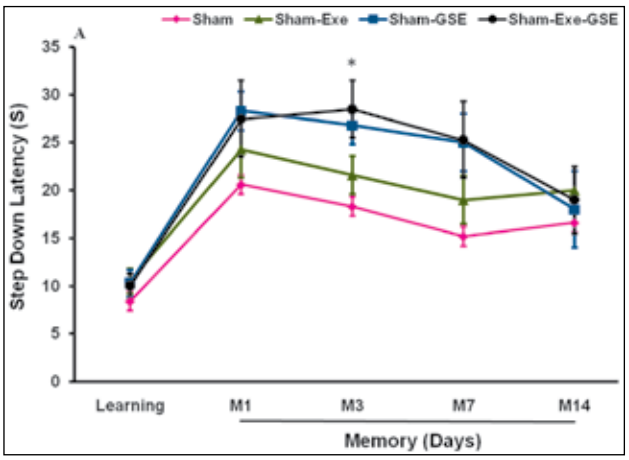


b)

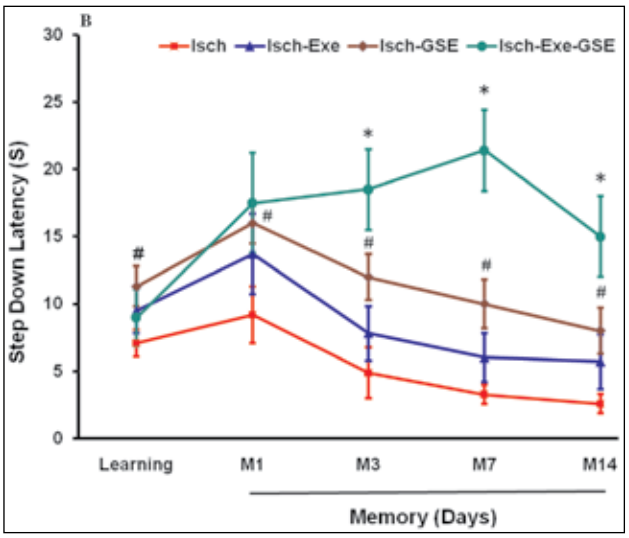
*Figure 2. Mean ± SD of step-down latencies (SDL) during different days for sham operated (panel A), 2CCAO ischemic (panel B) received chronic GSE alone (Sham-GSE and Isch-GSE) with compare to Sham, Isch, Sham-Veh and Isch-Veh groups. GSE increased significantly learning and memory retrieval in ischemic group (*P<0.05), but didn't affect learning and long-term memory retrieval during 14th day after shock delivery (M14) in sham operated group (two-way ANOVA, LSD Post hoc test, n=8, *P<0.05).*

Effects of either of chronic exercise and GSE alone or exercise associated with GSE on sham operated and 2CCAO ischemic animals have shown in figure 3 (panels A&B). Effect of exercise associated with GSE on memory retrieval in sham operated group (Sham-Exe-GSE) was not significant when compared with sham group received exercise or GSE alone (Figure 3A) while in 2CCAO ischemic rats effect of exercise associated with GSE on

memory retrieval during M3, M7 and M14 phases was significant higher (*P<0.05) than ischemic rats received exercise or GSE alone (Figure 3B).



a)



b)

*Figure 3. Mean ± SD of step-down latencies (SDL) during different days for Sham-Exe, Sham-GSE and Sham-Exe-GSE groups (panel A), and for Iche-Exe, Isch-GSE and Isch-Exe-GSE groups (panel B). Exercise associated with GSE increased significantly learning and memory retrieval as persistently in 2CCAO ischemic group, but its effect was decayed during long-term memory (M7 and M14) in sham operated rats. (*P<0.05 for Isch-Exe-GSE vs. other groups and #P<0.05 for Isch-GSE vs. Isch group, two-way ANOVA, LSD Post hoc test, n=8).*

In figure 4 we have compared sham operated and 2CCAO ischemic groups received chronic forced exercise associated with GSE on learning and memory retrieval. Its effect on learning was same in both groups, but memory retrieval during shot-term (M1) and mid-term (M3) memories in sham group was significant higher than ischemic rats (P<0.05), but not in long-term memory (M7 and M14).

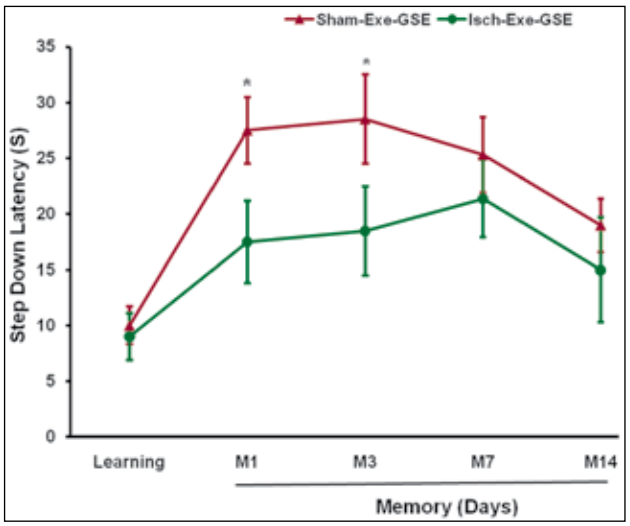


*Figure 4. Mean ± SD of step-down latencies (SDL) during different days for Sham-Exe-GSE, Isch-Exe-GSE groups. Exercise associated with GSE increased significantly learning and memory retrieval as persistently in 2CCAO ischemic group, but its effect was higher in sham operated rats (two-way ANOVA, LSD Post hoc test, n=8, *P<0.05 for Sham-Exe-GSE vs. Isch-Exe-GSE).*

Discussion

According to our findings memory was impaired in hypoperfusion/ischemia and just prolonged strenuous exercise alone didn't effect on memory retrieval significantly in permanent 2CCAO rats, while GSE and also exercise with GSE could improve memory considerably. We have found when GSE administered associated with forced exercise chronically can remove free radicals caused by chronic ischemia and possibly be prevented the creation of free radicals during exercise, it increases the effect of exercise and has a beneficial synergic effect on memory deficiency induced by cerebral ischemia. Different study have shown that cerebral ischemia, most commonly occurs in patients with stroke. (35). During the period of ischemia large quantities of stimulatory amino acids are released and calcium overload, lead to increase in free radicals that is

the signs of point that is called exittoxicity phase (36). Both a great production of free radicals and the deficiency or depletion of many antioxidant systems may reveal exacerbation of the oxidative cellular injury, while the supplementation of many antioxidants generates diverse outcomes (37, 38). A few studies reported physical activity causes a neuroprotective effect on amnesia due to hippocampus damage (20, 39). On the other hand conversely some investigators also didn't observe any useful results of exercise on learning and memory. They hadn't seen positive effects of exercise on spatial learning (40).

Balue and colleagues in 2005 showed that memory impairment in old rats, improved with use of grape seed extract and were attributed to antioxidant properties polyphenols in grape seed extract. These antioxidative substances in brain tissues are factors in prevention and treatment of disorders that induced by oxidative damages (41).

The dietary consumption of grape and its products is associated with a lower incidence of degenerative diseases such as cardiovascular disease and certain types of cancers. Most recent interest has focused on the bioactive phenolic compounds in grape (42). Anthocyanins, flavanols, flavonols and resveratrol are the most important grape polyphenols because they possess many biological activities, such as antioxidant, cardioprotective, anticancer, anti-inflammation, antiaging and antimicrobial properties (42).

Also our previous studies showed that forced exercise influences learning and memory of intact rats (34). On the other hand several investigators in animal studies on rats and mice reported better cognitive performance as a result of increased physical activities (43-45). In human subjects, it was reported that physically fit individuals have better cognitive and memory performance when compared to their sedentary peers (46, 47). In support of better cognitive performance, it appears that exercise could enhance neurogenesis (48) and up-regulate the expression of trophic factors (49).

Although regular physical exercise is beneficial to the body, it is well known that exhaustive exercise causes oxidative stress in muscle. However, there is a little information regarding whether or not exhaustive exercise could generate oxidative stress in brain and the findings are conflicting (50). Since many studies have been shown that exercise influences learning and memory, they were performed with a voluntary running paradigm (e.g. running wheel) in mice. However, such effects of exercise on learning and memory are less well demonstrated using a forced running paradigm (e.g. treadmill) (51).

Treadmill training is used for promoting rhythmical vigorous walking and for task-related training in patients with stroke. Treadmill training after focal cerebral ischemia significantly improves neurological outcome in middle cerebral artery occlusion rats (MCAO). Treadmill training may be beneficial for ischemic brain recovery (28). Our results have proved some previous findings (24) that confirmed exercise has no beneficial effects on memory deficiency due to brain ischemia. These findings suggest that running exercise may have a negative effect on neurogenesis in the ischemic hippocampus.

Conclusion

Our results suggest that in the experimental model of permanent cerebral hypoperfusion ischemia, forced exercise (running on treadmill) doesn't affect cognition efficiently, while it will be influenced by association administration of GSE with exercise as a most potent natural antioxidant. This may be important with respect to assessment of therapeutic approaches for recovery dementia after stroke.

Acknowledgment

This study was financially supported by Ahvaz Physiology Research Center (PRC-36) and Iranian Neuroscience Research Network (INRN).

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Electrocardiogram patterns in intermedius coronary artery occlusion

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Abstract

Background: Despite the very high knowledge about the electrocardiogram (ECG) changes in other coronary vessel oclussions, there are a few researches demonstrating ECG changes seen during the total/subtotal occlusion of intermedius coronary artery (IM). The aim of this research was the ECG review of 66 patients who had a primary percutaneous coronary intervention (PCI) and a total/subtotal occluded IM with ST segment elevation myocardial infarction (STEMI).

Methods: At first, 98 patients out of 6954 primary PCI patients, with IM as the responsible artery for myocardial infarction (MI) were chosen. Due to exclusion criterias 32 patients were eliminated and a total of 66 patients with the electrocardiographic derivations indicating the anatomic characteristics of the supplied region were included in the study.

Results: The most common characteristic finding on ECG was posterolateral MI, observed at 50 (75.7%) patients. Ten patients (15.1%) had high lateral MI, 6 patients (9%) had isolated posterior MI. The other ECG characteristics in the detailed analysis were V1-V3 ST segment depression (90.9%), ST segment elevation in leads DI, AVL (78.7%), ST segment elevation in leads V5-V6 (66.6%), ST depression in leads DII, DIII, AVF (54.5%), totally positive T waves in DII,DIII,AVF (57%) and totally positive precordial T waves (87%).

Conclusion: A statistical analysis is not possible, because the presentation of the ECG finds related to IM artery occlusions is not a comparative study. For the determination of the specific and sensitive values of the ECG particularities of IM, we need more research which allows a comparison with the ECG particularities of the obtuse marginal (OM) and diagonal branches.

Key Words: Myocardial Infarction, Coronary Vessels, Electrocardiogram

Introduction

For patients with suspected acute coronary syndrome, the most easy and cheap diagnostic tool is electrocardiogram (ECG). The ECG gives the physician very important information about the localization of the myocardium affected by total occlusion in patients with ST segment elevation myocardial infarction (STEMI), the blood vessel which is the responsible for the infarction, the starting time of the occlusion and its intensity. The ECG findings are based on repolarization (ST and T wave changes) and depolarization (QRS complex) changes.

Intermedius (IM) artery arises early from the left main coronary artery (LMCA) and trifurcates with the left anterior descending artery (LAD) and the left circumflex artery (LCX), if it is optimally shown in the postero-anterior position. It supplies the high anterolateral region of basal left ventricle. Besides the IM, the blood supply of the same regions can be made by first diagonal and first optus margin (OM) artery as well (1). Concerning the ECG changes caused by IM total occlusions; the diagnosis can be difficult because of the supplied area. In the literature, the ECG changes in STEMI LAD, right coronary artery (RCA) and LCX total occlusions have been studied many times, but the researches investigating the ECG characteristics of STEMI caused by IM artery total occlusions are

very few (K1, K2,..). Here we present the ECG findings of 66 patients with total/subtotal coronary occlusion of IM artery.

Methods

Study population: Ninety eight patients with total/subtotal occlusion of IM artery were selected out of 6954 urgently percutaneous coronary intervention (PCI) performed patients with the diagnosis of acute STEMI between January 2005 and March 2011. In the detailed angiographic evaluation, those who had total or/and critic narrowing in the LCX, RCA and LAD, patients who had previous myocardial infarction and those who had right bundle branch block, left bundle branch block, left ventricular hypertrophy in the ECG were excluded. From the rest, 66 patients who had first 12-hour ECG were included. Clinical findings, ECG and angiographic particularities of the patients were reviewed at their initial admission.

Clinical diagnosis: The study group consists of those patients, who came to the emergency unit with chest pain that lasted for more than 20 minutes, who were diagnosed STEMI after the ECG and whose responsible blood vessel was IM artery. The IM artery is defined as directly arising from the LMCA and as having a diametric thickness of more than 2 mm. The fact that all of the patients had STEMI at their initial admission prevented that the cases of MI related to LCX which developed without ST-T change to be included to this study. Infarct related artery (IRA) is characterized as total or subtotal narrowing and with a thrombotic appearance. Acute myocardial infarction is defined by the presence of 20 minutes' duration or longer chest pain, elevation of creatine kinase over the reference levels by 200% or more (creatine kinase-MB activity ≥7% if the etiology of the total creatine kinase was not exactly known), or elevation of creatine kinase less than 200% of reference levels with serial ECG changes consistent with new myocardial infarction.

Standard 12-lead surface ECG: The standard 12-lead ECG findings of the patients, whose chest pain did not last more than 12 hours after their initial admission to the emergency unit, were analyzed. ST segment deviation at 0.08 second from J point, relative to TP segment, performed with magnifying lenses, calculated by two researchers who did not know the angiography results.

Electrocardiogram findings: Electrocardiogram findings, which can be diagnostic for IM artery in STEMI, in which IRA artery is IM artery, were investigated. The ECG findings which are studied because of that are the ECG changes of the leads relating to the IM supplied regions and their awaited vectored changes. The ECG changes seen are as follows:

- ST depression in V1-V3 leads
- ST segment elevation in DI and AVL
- ST segment elevation in V5-V6
- ST depression in DII,DIII and AVF leads
- T wave polarities in inferior and precordial leads.

Results

The clinical characteristics of the patients during their first admission are summarized in Table 1 below. In these IM involved patients, dominant artery was RCA in 58 (87%), LCX in 6 (9%) and in the case of the last two, patient had balanced coronary circulation. At their admission, 50 of the patients (75.7%) had postero-lateral MI in their ECG (Figure1), 10 of them (15.1%) had high lateral MI, and 6 of them (9%) had isolated posterior MI findings.

Table 1. Clinical Characteristics of Patients (n=33)

Age	**52.9±7.8**
Male/Female	42/24
Atrioventricular Block (%)	0
Time from symptom onset to first ECG (minute)	190 ±67
Active smoker	22 (33%)
Dyslipidemia	16 (24.2%)
Previous angina	18 (27.2%)
Arterial hypertension	28 (42.4%)
Diabetes	4 (6%)

Correlation between ST-T changes and IM related MI is shown at Table 2.

In the V1-V3 leads, ST segment of 60 patients (90.9%) were depressed and the lead with the lowest depression was V3. In 6 patients, isoelectric line was seen in leads V1-V3.

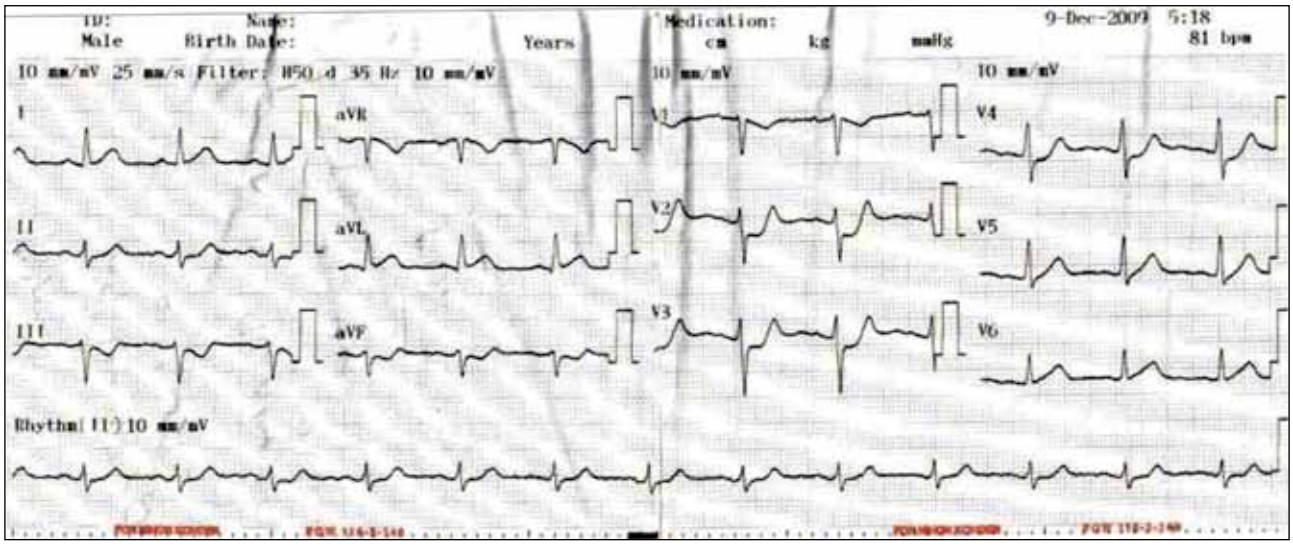

Figure 1. A sample of most commonly seen posterolateral MI in IM total occlusions

Table 2. Correlation Between ST-T Changes and IM Related MI

Criteria	IM Artery (n=66)
V1-V3 ST DEPRESSION	60 (90.9%)
• ST isoelectric	6(9%)
• Most V2	28(42%)
• Most V3	32(48%)
DI aVL ST ELEVATION	52(78.7%)
• DI ST > aVL ST	4 (6%)
• DI ST < aVL ST	48 (72%)
• DI aVL ST isoelectric	14 (21%)
V5 V6 ST ELEVATION	44 (66.6%)
• V5 ST >V6 ST	2 (3%)
• V5 ST <V6 ST	42 (63%)
• V5-V6 ST isoelectric	22 (33%)
INFERIOR ST DEPRESSION	36 (54.5%)
• DII ST depression>other inferiors	10 (27%)
• DIII ST depression>other inferiors	26 (72%)
INFERIOR T WAVE	
• All inferiors lead positive	38 (57%)
• One positive others negative	24 (36%)
• All inferiors lead negative	4 (6%)
PRECORDIAL T WAVE	
• All precordial lead positive	58 (87%)
• All precordial lead negative	0
• V1-V3 positive V4-V6 negative	8 (12%)

In IM occlusions, 78.7% of the patients had ST elevation of DI, aVL and 72% of them had a higher elevation in aVL than in DI.

V5, V6, as the other leads of the lateral area, an elevation was seen in 66.6% of the patients, and 63% of them had a higher ST elevation in V6 than in V5. 33% of the patients had isoelectric line in V5 and V6.

When the inferior leads were investigated, ST segment elevations were not seen, and 54.5% of the patients had ST depression. ST depression in DIII was significantly more (72%) in comparison with the other inferior leads.

In 6% of the IM occlusions, the T waves were negative in all the inferior leads meanwhile T waves in 57% of the patients were positive in all inferior leads.

T wave polarities in precordial leads were completely positive in 87% of the patients. No patients had complete negative precordial T waves.

Discussion

The beginning evaluation of acute coronary syndrome, pre- and post-term risk scoring and the choice of the suitable treatment can be made using ECG. With the coronary angiography, it can be difficult to localize the infarct area and to estimate the wideness in the side branch occlusions. This is caused by the reason that many patients have more than one obstructive lesion and sometimes it is not possible to see the thrombotic lesion. Even if it is not seen very often, a side branch total occlusion at the bifurcation could be skipped by mistake. Because of all that mentioned reasons, the ECG has still an important role in the acute coronary syndrome. While coronary angiography is a reference for the detection of IRA, the ECG is a stan-

dard reference for the presence of ischemia/injury, its localization and its importance.

Most of ECG studies were based on the assumption that each lead represents the same amount of myocardium and that a similar size of ischemic area in different locations of the left ventricle will result in similar magnitude of ST deviation in the same number of leads. But all the regions cannot be shown by the 12 lead ECG. Even if the inferior and anterior walls of the left ventricle are shown very well, the lateral, posterior, septal, and apical regions are relatively ECG silent (2,3). Moreover, ischemia in opposed regions may attenuate or augment ST deviation.

The IM coronary artery arises from the LMCA directly as trifurcation and it supplies the high anterolateral region of basal left ventricle. The intensity of the ischemia and its exact localization, which might occur if there is an IM, can be seen in the ECG. The circumflex artery gives OM branches up to three and these branches supply the left ventricle anterosuperior wall from superior to inferior(4). Left circumflex artery occlusion distal to its first marginal branch causes ischemia/infarction primarily in the basal segment of the posterolateral wall. This expression should replace "posterior" or "posterolateral" to coincide with the expression typically used when the myocardium is visualized directly by clinical imaging techniques (5.6). Occlusion proximal to the first marginal branch produces involvement extending into the middle segment of the posterolateral wall and also the basal and middle segments of the anteriosuperior wall similar to those described for the diagonal branch of the LAD.

Blanke et al (7) analyzed patients with acute STEMI caused by LCX occlusion, no instances of ST elevation in leads V1 to V4 in the patients who had acute myocardial infarction caused by LCX occlusion were found. But, in our IM group, 90.9% had ST depression in the V1-V3 leads; in which 9% of them the ST segment is isoelectric.

Often, posterolateral myocardial infarction findings are seen in the ECG (75.7% of the patients) when IM occlusions are present. Similar ECG findings are also seen at LCX and diagonal branch occlusions. While high lateral and isolated posterior involvement are rarely seen in IM total occlusion, posterior involvements are definitely seen in the LCX (8).

Lateral wall involvement is characterized with ST segment elevations in leads V5-V6 and can be seen in IM, diagonal and LCX occlusions but they are seen more often in LCX occlusions. Lateral wall involvement means larger ischemic areas (9). In 66.6% of the patients of our study group, ST segment elevations in these leads were seen and in most of them (63%) the ST elevation in V6 was more than in V5.

The lead, which shows the anterosuperior region directly in the ECG, is aVL (1, 10). If there is an occlusion in diagonal branch, there is ST elevation in leads I, aVL, and V2 with ST segments in leads V3 and V4 either isoelectric or depressed (11, 1). When ST elevation in leads I and aVL are caused by occlusion of the LCX, reciprocal ST depression is normally seen in lead V2 because the vascular bed supplied by the LCX extends more than posteriorly (12). In our study group, we saw ST elevation in leads I and aVL in 78.7% of the patients and remaining 21% had isoelectric line ST segments.

Posterior wall ischemia is manifested only with ST segment depression and usually considered as unstable angina pectoris rather than myocardial infarction. In such a situation, if the maximum ST depression is inV2 or V3, it is predictive for LCX occlusion (13-15). In 48% of the IM group, maximum ST depression is seen in lead V3 meanwhile 42% of the patients had maximum ST depression in lead V2. In the IM group, the T wave polarities in the inferior leads were seen as completely positive in 57% of the patients and completely positive T waves in the precordial leads were seen in 87% of the patients.

During our research, we observed the ECG findings related to IM occlusions. The ECG changes of the near localizations can be compared with the IM occlusions, after evaluating the diagonal branch and OM branch occlusions separately. With this comparison, the specificity and sensitivity values of the ECG changes in the leads of the near anatomic areas to diagonal branch, the OM branch or the IM, can be calculated. Comprehensive research which will allow us to calculate and to compare those values are necessary.

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The effects on the vascular endothelium function by dialysis and interval hemodiafiltration therapy in the end stage renal diseases

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Abstract

Vascular endothelial lesion is the initial symptom of cardiovascular complications, the leading cause of mortality of end-stage renal disease (ESRD) patients. Dialysis and hemodiafiltration therapy are major clinical treatment for ESRD. However, it is still not clear whether different therapeutic strategies, dialysis alone or dialysis plus hemodiafiltration, could influence vascular endothelium function differently.

Methods: 60 ESRD patients were selected into this retrospective study and separated into two groups. 30 patients received 3 times of dialysis per week. Another 30 patients received twice dialysis and once hemodiafiltration treatment per week. The brachial artery endothelium dependent dilation (EDD) and independent dilation (EID) were measured every half a year. Serum levels of C-reactive protein (CRP), tumor necrosis factor α (TNF-α) and soluble intercellular adhesion molecule-1 (sICAM-l) were also determined.

Results: Within the dialysis group, the EDD and EID values went down significantly, and the CRP, TNF-α, sICAM-1 expression levels went up significantly($p<0.05$). However, within the dialysis plus hemodiafiltration group, significant change of these factors were not observed in same period($p>0.05$).

Conclusion: Combination of hemodiafiltration with dialysis therapy can slow down the damage process of brachial artery endothelium function, and also reduce the accumulation of toxic factors (CRP, TNF-α, and sICAM-1).

Key words: brachial artery, endothelium dependent dilation, tumor necrosis factor α.

Introduction

End-stage renal disease (ESRD) occurs when the kidneys are no longer able to function for daily life. Chronic kidney diseases could worsen up to 90% of normal kidney function [1]. The most common causes of ESRD are diabetes and high blood pressure. Cardiovascular complications are the most common outcomes and leading cause of mortality in the ESRD patients [2]. It has been proved that vascular endothelial lesion is the key early event of the cardiovascular complications [3, 4]. Dialysis is the major clinical treatment for the ESRD patients to get rid of small toxic molecules before kidney transplantation. Hemodiafiltration can eliminate small and big toxic molecules efficiently [5]. Due to the economical reasons, it is not affordable for most ESRD patients to receive regular hemodiafiltration treatment in China. Regular dialysis plus interval hemodiafiltration therapy strategy is often performed in the ESRD patients. However, it is unclear whether this "convenient" therapeutic strategy could influence the ESRD patient vascular endothelial function.

Noninvasive assessment of vascular dysfunction has taken advantage of the high-resolution ultrasound techniques. The most frequently used methods of noninvasive assessment of vascular dysfunction are the flow-mediated endothelium-dependent dilation (EDD) and endothelium-independent dilation (EID) of the brachial artery [6]. These two methods had been proven to be safe and reliable to reflect the vascular function in children and in chronic renal failure [7, 8]. Large-volume infusion of substitution fluid may expose patients to inflammatory contaminants [9]. Inflammatory parameters, such as C-reactive protein (CRP), tu-

mor necrosis factor α (TNF-α) and vacular cell adhesion molecules sICAM-1 were elevated in the ESRD patients [10].

In this study, we tried to compare the different effects on the vascular endothelial function by dialysis alone or dialysis plus hemodiafiltration combinational therapy. The purpose of this study is to find out which therapeutic strategy should be preferred in the clinic.

Methods

Patient Recruitment

In this study, we selected 60 ESRD patients, who had no medical history with stroke, angina pectoris, myocardial infarction, cardiomyopathy, severe infection, chronic infectious diseases, active autoimmune diseases, severe malnutrition, severe liver diseases and tumor. 30 patients had received three times of dialysis per week. Another 30 patients had received twice dialysis and once hemodiafiltration treatment per week.

These patient medical conditions were closely observed for 2 years. The endothelium dependent dilation (EDD) and the endothelium independent dilation (EID) of brachial artery were determined with non-invasive high resolution color doppler ultrasonography. Serum levels of C-reactive protein (CRP), tumor necrosis factor α (TNF-α) and soluble intercellular adhesion molecule-1 (sICAM-l) were also determined. The underlying diseases causing the ESRD status of these patients were listed in table 1.

Dialysis and hemodiafiltration treatment

4008S hemodialysis machine was made in the Fresenius Company in Germany. F60 blood flow devices was used with ultra-filtration coefficient 5.5ml/(mmHg.h). F60 blood filtration devices was performed with ultra-filtration coefficient 40ml/(mmHg.h). In dialysis process, the volume of blood flow was 200~250ml/min, bicarbonate solution flow volume was 500ml/min. In hemodiafiltration process, the volume of blood flow was 200~250ml/min, the replacement liquid volume was 6.0-8.0L/h. It usually took 4 hours to perform dialysis or hemodiafiltration therapy.

Measurement of endothelium dependent/ independent dilation of brachial artery

The endothelium dependent dilation (EDD) and independent dilation (EID) of brachial artery was measured every half a year. The detailed procedure was performed according to other group publications [6, 7].

Measurement of serum levels of CRP, TNF-α and sICAM-l

The serum level of CRP, TNF-α and sICAM-1 was measured before dialysis or hemodiafiltration therapy. The ELISA kits were bought from Jingmei Biotechnology Incorporation, Shenzhen, P.R.China.

Statistical analysis

The statistical analysis between groups was used T test or ANOVA. Kaplan-Meier method was used to perform survival rate test. Comparison of the survival rate was performed by the log-rank test. All the statistical analysis was performed on SPSS16.0 software, $p<0.05$ was regarded as significance.

Results

General medical status indexes comparison data

The general medical status indexes include blood pressure, blood glucose, hemoglobin, albumin, creatinine, urea nitrogen, calcium, potassium, cholesterol, triglyceride, and intact parathyroid hormone (iPTH). The general medical status between the dialysis and dialysis plus hemodiafiltration groups were no significant difference ($p>0.05$). The blood sugar and cholesterol level showed no significant difference between these two groups and the normal control group ($p>0.05$). The blood

Table 1

Diseases / Cases	Chronic glomerular kidney inflammation	Diabetic nephropathy	Hypertensive kidney disease	Obstructive nephropathy	Polycystic kidney
In dialysis group	18	3	4	2	3
In hemo-diafiltration group	16	4	5	3	2

pressure and iPTH levels were significant higher in the ESRD patients than in the normal control group ($p<0.05$). However, the hemoglobin, albumin and calcium levels were significantly lower in the ESRD patients than in the normal control group ($p<0.05$) (Table 2).

Endothelium dilation capability comparison

Brachial artery basic blood flow volume (BBF), reactive hyperemia blood flow (RHB) and nitroglycerin blood flow (NBF) measured together with EDD and EID. Before dialysis treatment, the EDD, EID, RHB and NBF were significantly lower in the ESRD patients than in the normal control group ($p<0.05$). However, the BBF value was similar between these three groups. Within the dialysis group, the EDD, EID, BBF, RHB, and NBF went down significantly after 6 months and one year of treatment ($p<0.05$). However, within the dialysis plus hemodiafiltration group, the EDD, EID, BBF, RHB, NBF went down insignificantly after 6 month and one year of treatment ($p>0.05$) (Table 3).

Measurement of CRP, TNF-α and sICAM-1

The CRP, TNF-α, and sICAM-1 expression levels did not show significant difference between the dialysis and dialysis plus hemodiafiltration group before the therapy. The CRP, TNF-α, and sICAM-1 expression levels went up significantly after 6 months and one year of treatment ($p<0.05$). However, in the dialysis plus hemodiafiltration group, these factors expression levels went up insignificantly after 6 months and one year of treatment ($p>0.05$). At the similar sICAm-1 initial expression level, patients in the dialysis plus hemodiafiltration group had significant lower expression level than patients from the dialysis group after treatment ($p<0.05$) (Table 4).

Discussion

Vascular endothelium cells perform gate-keeping role by the presence of membrane-bound receptors for numerous molecules including growth factors, metabolites and hormones [11]. The endot-

Table 2

Indexes / Groups	Blood pressure (mmHg)	Hemoglobin (g/L)	Albumin (g/L)	Calcium (mmol/L)	iPTH (pg/ml)
Dialysis group	**144**/86*	**82**±15*	**38**±6*	**1.7±0.2***	50±21*
Dialysis plus hemodiafiltration group	**149**/84*	**81**±21*	**37**±8*	**1.5±0.2***	56±26*
Normal control group	110/70	130±8	49±5	2.5±0.4	7±2

**P<0.05*

Table 3

Groups	Subjects	Indexes	Before therapy	6 months after therapy	1 year after therapy
Dialysis group	30	EDD (%)	9±2	7±2*	5±2*
		EID (%)	9±2	7±1*	5±1*
		BBF (ml/min)	81±11	75±8*	68±6*
		RHB (ml/min)	163±19	139±22*	115±14*
		NBF (ml/min)	88±12	75±6*	70±8*
Dialysis plus hemodiafiltration group	30	EDD	9±2	8.5±1	8±1
		EID	9±1	8.5±3	8±3
		BBF (ml/min)	80±10	79±8	79±6
		RHB (ml/min)	158±16	144±24	139±17
		NBF (ml/min)	89±10	88±9	84±8
Normal control group	10	EDD	12±2	-	-
		EID	16±3	-	-
		BBF (ml/min)	79±11	-	-
		RHB (ml/min)	201±13	-	-
		NBF (ml/min)	103±7	-	-

**P<0.05*

Table 4

Groups	Subjects	Indexes	Before therapy	6 months after therapy	1 year after therapy
Dialysis group	30	CRP(mg/L)	5±3	7±3*	9±4*
		TNFa(mg/L)	2±1	3±0.6*	4±0.7*
		sICAM-1	42±10	52±9*	60±12*
Dialysis plus hemodiafiltration group	30	CRP(mg/L)	5±3	6±3	6±3
		TNFa(mg/L)	3±0.6	3±0.7	4±0.5
		sICAM-1	44±11	45±13	48±12
Normal control group	10	CRP(mg/L)	1.5±1.2	-	-
		TNFa(mg/L)	0.2	-	-
		sICAM-1	29±10	-	-

*$P<0.05$

helium cells also play a pivotal role in regulating blood flow, which is regulated, in part, by the secretion of cardio-vascular active substances by the endothelium cells [12]. It has been proved that vascular endothelial lesion is the initial symptom of the cardiovascular complications in ESRD [3, 4].

This study showed that although the basic blood flow of ESRD patient was similar with the normal control subjects, the endothelium dependent dilation, endothelium independent dilation, reactive hyperemia blood flow and nitroglycerin blood flow were significantly lower, and the inflammatory factors like sICAM-1, TNF-α and CRP were significantly higher than the normal control group. Our study proved that ESRD patients exhibited vascular endothelium dysfunction. Therefore, protection of the vascular endothelium function is the major method to prevent cardio-vascular complications.

This study demonstrated that combinational therapy can protect the cardio-vascular endothelium function efficiently. The combination of dialysis and hemodiafiltration could attenuate the vascular endothelial damage. sICAM-1 is the signal factor of endothelium reactivation [13, 14]. After the combinational therapy, the sICAM-1 expression level (48±12) was much lower than patients receiving dialysis alone (60±12) ($P<0.05$). Certainly this discovery needs to be proved by other research groups. These 60 patients was followed-up for further 5 years. It turned out that patients who accepted dialysis plus hemodiafiltration therapy survived better and less chance to have cardio-vascular complications comparing with dialysis alone (data not shown).

Overall, we proved that dialysis plus hemodiafiltration therapeutic strategy could attenuate cardio-vascular endothelium damage. The combinational therapy shall be preferred in the dialysis clinic.

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Computer detection of duplicate prescriptions for hypnotic-sedatives: An experience in Taiwan

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Abstract

Background: Duplicate use of drugs is an important issue for pharmacists and providers in delivering quality care and ensuring patient safety. The extent of drug duplication is rarely reported in healthcare, especially for insomnia patients. With the advent of fast and cheap computing, computer monitoring is expected to help health providers detect duplicate prescriptions and reduce their occurrence, which will increase patient safety and reduce unnecessary drug waste.

Methods: A total of 1,083 patients in 3 medical centers and 2 regional hospitals in Taiwan participated in this study and completed a questionnaire regarding duplicate use of hypnotic-sedatives to treat a sleep disorder. Additionally, patients were required to receive assistance from a pharmacist over the telephone to evaluate their knowledge regarding the appropriate use of hypnotic-sedatives, their adverse effects, and the source of duplicate prescriptions of hypnotic-sedatives provided by physicians. Two strategies were launched 1) to educate patients about preventing duplication of prescriptions and 2) to develop a computer system to a) alert physicians to duplicate prescriptions online, b) remind pharmacists of duplication prescriptions when dispensing medicine to the patient, and c) periodically monitor the number of duplicate drug prescriptions and their description.

Results: We found that 1) 60.2% of patients did not know the long-term side effects of taking hypnotic-sedatives; 2) more than 84% of patients were repeatedly prescribed hypnotic-sedatives by doctors at the same hospital; 3) education by pharmacists had a slightly significant effect, 29.5% of patients decreased the quantity of hypnotic-sedatives used after three months; 4) computer programs are an effective way to prevent physicians and pharmacists from prescribing or filling duplicate prescriptions for patients and to significantly decrease the number of duplicate prescriptions of hypnotic-sedatives (t=35.21, p< .0001).

Conclusions: Individual patient drug profiles should be well established and stored in a single hospital. These drug files can then be monitored and effectively prevent duplication of prescriptions. It is necessary to educate patients and remind physicians to appropriately reduce the dose and quantity of hypnotic-sedatives when the quality-of-sleep has improved.

Key words: hypnotic-sedatives, insomnia, sleep disorder, duplicate prescriptions

Introduction

Duplicate use of drugs is a vital issue for pharmacists in providing quality care and ensuring patient safety. With the advent of fast and cheap computing in the healthcare industry, computers are becoming a feasible option to monitor for duplicate prescriptions. When pharmacists are burdened with detecting and preventing duplicate prescriptions, it requires a considerable amount of their time, is a threat to patient safety and contributes to the escalation of healthcare costs. Therefore, a tool for detecting and reducing duplicate prescriptions is required for patient safety.

Duplication of prescriptions: an example in quality-of-sleep

Insomnia is a subjective complaint of dissatisfaction with the quantity or quality of sleep. [1,2] This disorder is estimated to occur in approximately 12% to 25% of the general population, although this is probably an underestimate as there is evidence that many adults do not report sleep problems to healthcare professionals [3,4]. According to the latest survey in Taiwan, the prevalence of insomnia in people aged 15 years or older is 28%, which is the highest of all the countries in Asia. Treatment of insomnia in the institutional setting is generally aimed at correcting the underlying medical disorders, reducing environmental sleep disruptions, and lowering anxiety with psychological interventions and relaxation training or pharmacotherapy. [5] Benzodiazepines (BZD for short) are the most common drugs used for the pharmacological management of acute insomnia in both institutionalized and ambulatory patients. [6-9] While these agents have proven to be efficacious and relatively safe, benzodiazepines are associated with a multitude of adverse effects, which are most commonly observed with higher doses and prolonged use. [8] Common side effects include residual daytime sedation ("hangover"), anterograde amnesia, and respiratory depression. [9] Rebound insomnia has also been associated with benzodiazepines. Tolerance of the hypnotic effects of the short and intermediate-acting agents can be developed within one to two weeks of use. In addition, abrupt discontinuation can result in withdrawal symptoms such as anxiety, confusion, disorientation, insomnia, and perceptual changes. [9] Benzodiazepines have been frequently implicated in drug-associated hospital admissions. [10] Non-benzodiazepine hypnotics, such as zopiclone, zolpidem, and zaleplon, are now receiving attention as alternatives to the traditional armamentarium for the treatment of insomnia. [11]

Purpose of this study

The inappropriate use of hypnotic-sedatives can result in drug abuse, which is a threat to patient safety. It is known that patients frequently visit the same hospital (or even different hospitals) multiple times to obtain duplicate prescriptions of hypnotic-sedatives. The purpose of this study was to investigate the factors that cause duplicate use of hypnotic-sedatives and to explore strategies to prevent patients from trying to obtain duplicate prescriptions and for hospitals to reduce the occurrence of inappropriate duplicate prescriptions using computer sciences.

Methods

Subjects

This was a retrospective cohort study. Adult patients were recruited to the study when they were prescribed two or more sedative-hypnotics with the same pharmacological mechanism in one week by different physicians in 2008. Data were retrieved from the patients' medical records from 3 medical centers and 2 regional hospitals in Taiwan. One thousand and forty three patients participated in this study and completed a questionnaire regarding their knowledge about prescription duplications by physicians over the past year. All participants consented to participate in this study, which received approval from the ethics committee and the research committee of the Chi-Mei medical center, who also monitored it prior to initiation. The study was conducted from July 1st to December 30th, 2008.

Definition of duplicate prescriptions and the questionnaire

The definition of sedative-hypnotics BZD is in accordance with the WHO ATC code N05BA (anxiolytic BZD) and N05CD (hypnotic BZD). The patients in the study were required to complete a questionnaire during the first visit to the outpatient clinic and received assistance from a pharmacist over the telephone to evaluate patients' knowledge regarding the following advanced topics: the appropriate use of hypnotic-sedatives, the adverse effects associated with the use of hypnotic-sedatives, information about the correct dose and duration of administration of hypnotic-sedatives provided by the physician, the possibility of withdrawal, the occurrence of withdrawal syndrome and reasons the patients may request duplicate prescriptions of hypnotic-sedatives.

Strategies launched to educate patients and prevent duplication of prescriptions

Strategy A: to educate patients about preventing duplication of prescriptions

The studied worksite was in 3 medical centers and 2 regional hospitals in Taiwan. The study period ran continuously from July 1st, 2009 to September 31th, 2010 and was used by pharmacists to follow up on the patients by telephone and to evaluate whether they had reduced the dose or duration of the hypnotic-sedatives that they were taking. Pharmacists then reviewed each individual patient's chart and recorded improvements in sleeping quality and the degree to which education prevented duplication of prescriptions.

Strategy B: to develop a computer system detecting duplicate prescriptions for BZD

Computer programs were devised to detect duplicate prescriptions by physicians and by pharmacists when the drugs were dispensed to the patients. Additionally, control charts[12] were set up to monitor trends and outliers of duplicate prescriptions in the hospital. The three steps at which the computer checked for duplicate drug prescriptions are shown in Figure 1.

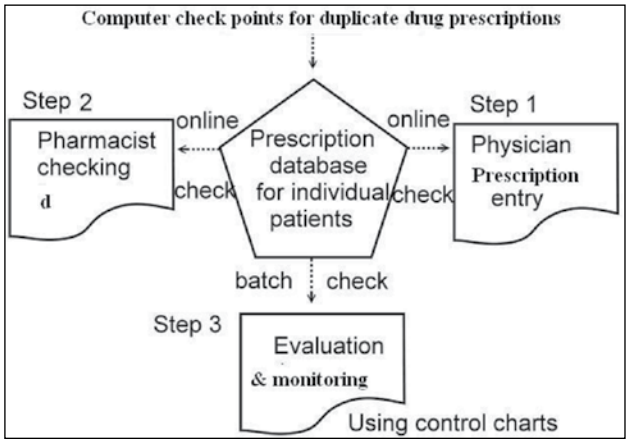

Figure 1. The three computer check-points to monitor duplicate prescription of drugs by physicians

A computer program that checked the patients' previous drug records was developed to alert physicians when drugs with the same components were prescribed (step 1). Pharmacists could check the duplicate notices sent by the computer if the duplicate use of prescriptions was in existence at step 2. Regular evaluation and monitoring (step 3) were conducted each week by a computer that checked the control charts and the number of duplicate drug prescriptions that were prescribed during the last 12 months. A contingency table was drawn with the drug name (in the row) and the outliers that extended beyond the standard deviations (in columns).

Statistical analysis

A 95% confidence interval was calculated and provided for the survey counts. Confidence intervals for the proportions,π, were calculated using the following formula 3:

$$p \pm z\,\sigma_p\,, \quad \text{..... (1)}$$

where p is the proportion in the sample, z depends on the level of confidence desired, and σ_p, the standard error of a proportion, is equal to:

$$\sigma_p = \sqrt{\frac{\pi(1-\pi)}{N}}\,, \quad \text{..... (2)}$$

where π is the proportion in the population and N is the sample size. Since π is not known, p is used to estimate it. Therefore the estimated value of σ_p is:

$$\hat{\sigma}_p = \sqrt{\frac{p(1-p)}{N}}\,, \quad \text{..... (3)}$$

The control chart used to detect abnormality of BZD duplication for patients was designed using the transformation function of $p^* = 2 \times \arcsin\sqrt{p}$ (=2*ASIN(SQRT(p)) in Microsoft Excel) for the proportion p of duplicate prescription due to non-normal distribution of the study proportion values.

Results

Patient demographics

A total of 1,043 patients completed the questionnaire. The characteristics of patients are shown in Table 1, in which 62.8% were female and 37.2% were male; 76.13% of the patients were older than 50 years of age (table 1). The education level was grouped by elementary school (27.04%), junior high school (13.04%), and senior high school (22.91%) (Table 1). A total of 51.2% of the study participants were unemployed.

In total, 82.36% of the patients used hypnotic-sedatives for longer than 6 months (Table 1). The primary reason for duplication of a prescription was insomnia and/or anxiety that was not relieved by taking only one hypnotic-sedative (51.2%) (Table 1).

Patient knowledge about hypnotic-sedatives

Regarding the information about the prescription of hypnotic-sedatives, 93.5% of patients knew that they had been prescribed hypnotic-sedatives and had been informed of the reasons for the prescription by a doctor (Table 2). A total of 60.2% of the patients didn't know the long-term side effects of taking hypnotic-sedatives (Table 2). It is worth noting that 84.9% of the patients were repeatedly prescribed hypnotic-sedatives by doctors at the same hospital (Figure 2), indicating the necessity of preventing duplicate prescriptions using computers (Figure 1).

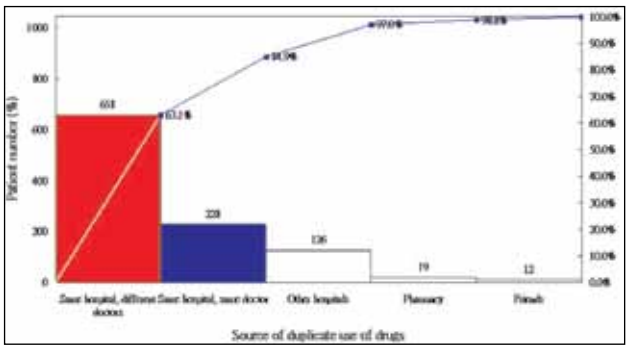

Figure 2. Pareto chart of the source of duplicate drug prescriptions

Table 1. Patient demographics reported in the questionnaire (n=1,043)

Characteristics	Number of patients (%)	95% CI (%)	
		Lower	Upper
Gender			
Male	388 (37.2%)	34.27	40.13
Female	655 (62.8%)	59.87	65.73
Age			
<20 years	1 (0.1)	0	0.29
20~29 years	77 (7.38)	5.79	8.97
30~39 years	171 (16.4)	14.15	18.65
50~59 years	279 (26.75)	24.06	29.44
60~69 years	235 (22.53)	19.99	25.07
>70	280 (26.85)	24.16	29.54
Education			
Uneducated	249 (23.87)	21.28	26.46
Elementary school	282 (27.04)	24.34	29.74
Junior high school	136 (13.04)	11.00	15.08
Senior high school	239 (22.91)	20.36	25.46
Collage	126 (12.08)	10.10	14.06
Graduate school and above	11 (1.05)	0.43	1.67
Duration hypnotic-sedative use			
< 1 month	64 (6.14)	4.68	7.60
1-3 months	85 (8.15)	6.49	9.81
4-6 months	35 (3.36)	2.27	4.45
>6 months	859 (82.36)	80.05	84.67
Reasons for duplicate use of hypnotic-sedatives			
Without improvement[1]	538 (51.2)	48.55	54.61
Prescribed by doctors	106 (10.2)	8.33	11.99
Afraid of drug shortage	51 (4.9)	3.58	6.20
Return to OPD unscheduled[2]	207 (19.8)	17.43	22.27
Others	141 (13.5)	11.44	15.6

Note.[1] For insomnia /anxiety; [2] OPD=outpatient department

Table 2. Patients' knowledge about hypnotic-sedatives (n=1,043)

Questions	Number of patients (%)	95% CI (%)	
		Lower	Upper
About hypnotic-sedatives:			
Ever used			
Known	975 (93.5)	91.98	94.98
Unknown	68 (6.5)	5.02	8.02
Reason for use			
Known	975 (93.5)	91.98	94.98
Unknown	44 (4.2)	3.00	5.44
Missed	24 (2.3)	1.39	3.21
Side effects associate with long-term use			
Known	415 (39.8)	36.82	42.76
Unknown*	628 (60.2)	57.24	63.18
Information provided by the physicians :			
Reasons for prescribing the hypnotic-sedative			
No	113(10.8)	8.94	12.72
Yes	883(84.7)	82.47	86.85
Unknown	47(4.5)	3.25	5.77
Duration of hypnotic-sedative use			
No	630(60.4)	57.43	63.37
Yes	255(24.4)	21.84	27.06
Unknown	158(15.1)	12.97	17.33
Side effects of hypnotic-sedatives			
No*	647(62.0)	59.08	64.98
Yes	291(27.9)	25.18	30.62
Unknown	105(10.1)	8.24	11.90

*Note. * A significant majority were unaware of the side effects of hypnotic-sedatives*

Education effect

The most common drugs that were prescribed in duplicate were zolpidem (44.3%), Fludiazepam (26.6%), Alprazolam (18.9%), Estazolam (9.0%) and Flunitrazepam (7.6%). Eighty percent of patients failed to withdraw from the hypnotic-sedatives and 54.7% of patients complained of rebound insomnia after withdrawal from hypnotic-sedatives. Three months after education by a pharmacist, 63.7% of patients did not change the quantity of hypnotic-sedatives prescribed; however, 29.5% of patients did decrease the amount of hypnotic-sedatives. The patient's quality of sleep was improved accounting for 24.35%, although 69.2% of patients' reported no improvement in their sleep quality.

Computer periodical summary report card

The computer monitoring of duplicate drug use at three steps was strictly implemented from January 2009. A summary report including the occurrence of duplicate drug prescriptions is displayed in a contingency table (not included in this study due to space limitation) by the drug name, and the outliers that extended beyond the standard deviation were periodically evaluated. Additionally, the alerts sent to physicians and pharmacists at step 1 and 2, respectively, are shown in Figure 1. Figure 3 shows that the number of hypnotic-sedatives prescribed in duplicate has dramatically decreased (t=35.21, p< .0001).

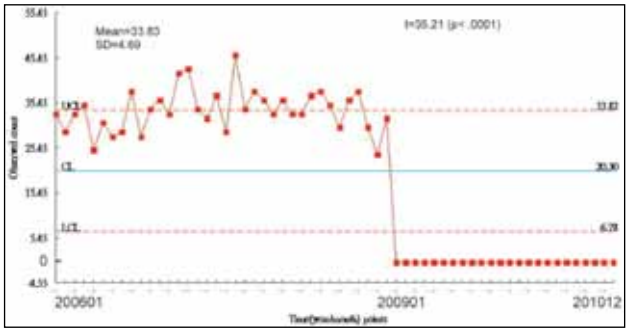

Figure 3. Control chart used for checking trends of Benzodiazepine use

Discussion

Findings

(1) Key findings

The effect of intervention by a pharmacist was slightly significant; 29.5% of the patients decreased the quantity of hypnotic-sedatives used after three months. Of these, 24.35% of the patients reported an improvement in their quality of sleep in the self-response telephone interview. Computer programs provide an effective way to prevent physicians and pharmacists from prescribing duplicate drugs to patients. To implement cost containment and patient safety in the healthcare industry, it is worthwhile to develop a process or system to help providers cut down on drug expenditure, to assist patients in recording their sleep quality and to aggressively urge physicians to adjust the quantity of hypnotic-sedatives used and the dose prescribed.

(2) What this study contributes to current knowledge

Two strategies, patient education and computer monitoring, successfully reduced the number of duplicate prescriptions in the study hospital. These strategies can be applied to other drugs that are frequently prescribed to patients in duplicate and to those that have adverse interactions with other drugs. With the advent of quick and inexpensive computing in the healthcare industry, checking the patient's drug history while prescribing can help reduce duplicate prescriptions by up to 84.9% in a single hospital (Figure 3), such as applying statistical process control (SPC) chart techniques to examine patient-centered performance indicators [12] and drug utilization evaluation of Piperacillin/Tazobactam in a hospital [13]..

(3) Implications of the results and suggested actions

We created a monitoring system that focuses on three steps that are routinely and repeatedly examined by a computer. This system will help hospital pharmacies make large improvements in their daily operations and services that they and their hospitals provide to patients. A tool for detecting duplicate prescriptions and reducing their occurrence is necessary for patient safety.

About patient quality of sleep

This study demonstrates that we should pay more attention to patients who are female, unemployed, older than 50 years of age that use hypnotic-sedatives to control insomnia and/or anxiety. Education by the pharmacist can help patients use hypnotic-sedatives appropriately and improve the quality of sleep. Because most patients are prescribed hypnotic-sedatives by the same hospital, hospitals should establish guidelines or routine computer monitoring to prevent duplicate prescriptions of hypnotic-sedatives. Healthcare units should provide patients with education regarding the appropriate use of hypnotic-sedatives and develop effective strategies to improve the patient's quality of sleep.

Conclusions

Individual patient drug profiles should be well established and stored in a single hospital. If possible, it would be best to construct a national health information database to share information about the drug history of patients and effectively monitor duplication of hypnotic-sedative prescriptions (or other drugs).

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The histopathological evaluation of mediastinal lymph node stations in sarcoidosis

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Abstract

Background: Even if the clinical and radiological findings indicate sarcoidosis, diagnosis can be established by showing histopathologically the sarcoid granulomas in the tissue. Mediastinoscopy is a surgical procedure that is commonly used to obtain histological specimens to examine for mediastinal lymph node involvement in sarcoidosis.

Objective: To demonstrate which of the mediastinal lymph node stations that the biopsies were taken had the highest diagnostic value for histopathological examination in sarcoidosis.

Methods: Operative and histopathology reports of 14 patients who underwent mediastinoscopy and diagnosed with sarcoidosis in the Thoracic Surgery Clinic of Duzce University School of Medicine, between January 2009 and January 2011 were reviewed retrospectively.

Results: On thorax tomography images of the patients with sarcoidosis, lymph nodes of the bilateral lower paratracheal and hilar mediastinal lymph node stations were frequently enlarged to pathological dimensions. In the majority of the cases, biopsies were taken by mediastinoscopy from the bilateral lower paratracheal lymph node stations. Histopathological examination of the biopsy material showed severe noncaseating granulomatous inflammation, most commonly in the right lower paratracheal, followed by left lower paratracheal and at least common highest mediastinal lymph node stations.

Conclusions: During mediastinoscopy to be performed on patients with suspected sarcoidosis, we recommend that priority be given to taking biopsies from the lower paratracheal lymph nodes and sent for frozen examination for definitive diagnosis to prevent unnecessary mediastinal dissection that might result in serious complications.

Key words: Lymph Nodes; Mediastinum; Sarcoidosis, Pulmonary; Mediastinoscopy; Pathology, Surgical

Introduction

Sarcoidosis is a multisystemic disease of unknown etiology that is characterized by noncaseating granulomatous inflammation of affected structures, mainly mediastinal lymph nodes and the lungs [1]. Diagnosis of sarcoidosis is made on the basis of compatible clinicoradiographic findings, histological confirmation of noncaseating granulomas, evidence of disease in at least two organs, and exclusion of other granulomatous diseases [2]. To date, standard cervical mediastinoscopy, a valuable surgical procedure with high diagnostic reliability, low morbidity and mortality is employed frequently in many clinics by Thoracic Surgery specialists for the tissue diagnosis of sarcoidosis [3]. The lymph nodes that can be accessed via standard cervical mediastinoscopy are the highest mediastinal (Station 1), the upper paratracheal (Stations 2R and 2L), the prevascular and retrotracheal (Station 3), the lower paratracheal (Stations 4R and 4L), and the subcarinal (Station 7) and sufficient amount of biopsy materials can be taken from these lymph nodes [4]. However, in a number of cases adequate histopathological evidence for sarcoidosis cannot be obtained after examination of the lymphoid tissue biopsies. In the literature, mainly affected right paratracheal lymphadenopathy accompanying bilateral hilar lymphadenopathy in sarcoidosis and presence of left paratracheal, paraaortic and subcarinal lymphadenopathies have been well documented while there is no information on which lymph node station the noncaseating granulomatous inflammation is more common and dense [5, 6].

In the present study, we aimed to determine the biopsies taken from which mediastinal lymph node stations had the highest diagnostic value in terms of histopathological examination for sarcoidosis and discuss how the results can be implemented in mediastinoscopy.

Material and methods

Population

Among 40 patients who underwent diagnostic mediastinoscopy between January 2009 and January 2011 in the Thoracic Surgery Clinic of Duzce University School of Medicine, 14 patients were diagnosed with sarcoidosis and operative and histopathology reports of these patients were reviewed retrospectively.

Study design

In addition to their demographic characteristics such as sex and age, the patients were analyzed in terms of symptoms, physical examination findings, the lymph node stations with a diameter of 10 mm or more measured in any axis on the thorax tomography, the lymph node stations accessed by mediastinoscopy to get sample, and the lymph node stations with severe noncaseating granulomatous inflammation identified with histopathological examination.

Surgical procedure

Following the cervical mediastinoscopy incision and exploration, the highest mediastinal region, including the deep jugular and brachiocephalic areas were examined first and determined lymph nodes were excised, being recorded as Station 1. Then, the mediastinoscope was inserted and at least four large samples were obtained from each of the lymph node stations that were accessible with a diameter of 10 mm or more measured on the thorax tomography images. There were no complications during or after operation. All mediastinoscopy procedures were carried out by two experienced thoracic surgeons and, in line with the routine practice, the number of samples was kept around the ideal number, sufficient to yield a result.

Histopathological examination

The specimens were promptly fixed in 10% formalin, processed for paraffin embedding, and the sections at 5 μm. were performed. Hematoxylin-Eosin stained sections were used to evaluate histopathological findings by light microscopy. All of the samples were assessed by a single pathologist.

Statistical analysis

The results were recorded by the principal investigator and analyzed statistically upon completion of the study. The statistical analysis was performed using SPSS software, version 11.5 (SPSS, Inc., Chicago, IL). Clinical data were expressed as the median ± the standard error of mean (minimum-maximum). The nonparametric Chi-square test was used for categorical comparisons, and a *P* value less than 0.05 was considered statistically significant.

Results

Patients comprised eight female (57.1%) and six male patients (42.9%). The mean age was 38.5 ± 9.0 (32–65) years.

The most frequent symptoms were coughing (n=11, 78.6%), chest and/or back pain (n=9, 64.3%), fatigue (n=7, 50%), fever (n=7, 50%) and weight loss (n=4, 28.6%). With the exception of weight loss, there were statistically significant differences for all other symptoms (P=0.044). Physical examination revealed erythema nodosum (n=8, 57.1%), hepatomegaly (n=4, 28.6%), rhonchus/rale (n=3, 21.4%), uveitis (n=2, 14.3%) and arthritis (n=2, 14.3%). A statistically significant difference was only found in erythema nodosum (P=0.049).

On thorax tomography images, when the mediastinal lymph node stations larger than 10 mm or more in diameter were examined, lymph nodes of this pathological size were noted in Station 1 in five cases (35.7%), in Station 2R in five cases (35.7%), in Station 2L in seven cases (50%), in Station 3 in six cases (42.8%), in Station 4R in 14 cases (100%), in Station 4L in 11 cases (78.6%), in Station 5 in six cases (42.8%), in Station 6 in six cases (42.8%), in Station 7 in seven cases (50%), in Station 8 in one case (7.1%), in Station 9 in three cases (21.4%), in Station 10R in 13 cases (92.8%), in Station 10L in 13 cases (92.8%), in Station 11R in four cases (28.5%), in Station 11L in two cases (14.2%), in Station 12R in two cases (14.2%) and in Station 12L in one case (7.1%) (Table 1). All of the results were statistically analyzed for si-

gnificance, and statistically significant differences were determined in 4R, 4L, 10R and 10L lymph node stations (P=0.005).

The mean number of lymph node stations sampled was 3.4 (range 2–6) and the mean number of samples taken from each lymph node station was 6 (range 4–7). Mediastinoscopic biopsies were taken from Station 1 in five (35.7%), from Station 2R in five (35.7%), from Station 2L in six (42.8%), from Station 3 in five (35.7%), from Station 4R in 12 (85.7%), from Station 4L in eight (57.1%) and from Station 7 in six cases (42.8%) (Table 1). Statistical analysis revealed a significant difference in 4R and 4L lymph node stations (P=0.026).

Histopathological diagnosis of sarcoidosis was established in all patients. Visualization of dense, noncaseating epitheloid cell granulomas, which is the typical histopathological lesion of sarcoidosis, was the absolute criterion for the diagnosis. When the specimens from the lymph node stations were examined, some depicted hyalinized tissues and occasional mild noncaseating granulomas in a background of fibrosis whereas others showed diffuse, severe noncaseating granulomas, occupying almost all of the lymphoid tissue. Severe noncaseating granulomatous inflammation was noted in one (7.1%), two (14.2%), two (14.2%), three (21.4%), 10 (71.4%), six (42.8%) and three (21.4%) cases in Stations 1, 2R, 2L, 3, 4R, 4L and 7, respectively (Table 1). All of the histopathological results were statistically analyzed for significance, among these data, significant differences were observed only for Stations 4R and 4L. (P=0.029).

Discussion

This study underlines six points: (a) Showing no significant sex difference, sarcoidosis is more frequent in the 3rd and 4th decades of life. (b) Patients commonly presented with coughing, chest and/or back pain, fatigue and fever and the most frequent finding in physical examination was erythema nodosum. (c) The most frequent pathological enlargements of the lymph nodes determined in bilateral lower paratracheal and hilar mediastinal lymph node stations on thorax tomography of the patients. (d) Thorax tomography also showed enlargement of the lymph nodes in the paraesophageal, pulmonary ligament, bilateral interlobar and lobar lymph node stations in a few cases. (e) In the majority of the cases, biopsy was taken from the lymph nodes in the bilateral lower paratracheal

Table 1. Stations of mediastinal lymph nodes with a diameter of 10 mm or more on thorax tomography, the lymph node stations where mediastinoscopic biopsy was taken, and the lymph node stations where severe noncaseating granulomatous inflammation was observed histopathologically

Patients	Station of mediastinal lymph nodes with a diameter of 10 mm or more on thorax tomography	Mediastinal lymph node stations where mediastinoscopic biopsy was taken	Severe noncaseating granulomatous inflammation
1	2L, 3, 4R, 4L, 10R, 10L, 11R	2L, 3, 4R, 4L	4R, 4L
2	2R, 2L, 4R, 5, 6, 7	2R, 4R, 7	2R, 4R
3	1, 2R, 2L, 3, 4R, 4L, 5, 7, 8, 10R, 10L	1, 2R, 2L, 3, 4L, 7	1, 3
4	3, 4R, 5, 6, 10R,10L	3, 4R	4R
5	2L, 4R, 4L, 10R, 10L	2L, 4R	2L, 4R
6	1, 2R, 2L, 4R, 4L, 5, 7, 9, 10R, 10L, 11R, 11L, 12R	1, 2R, 2L, 4L, 7	4L, 7
7	4R, 4L, 6, 10R, 10L	4R, 4L	4R, 4L
8	1, 2R, 2L, 4R, 10R, 10L	1, 2R, 2L, 4R	2R, 4R
9	3, 4R, 4L, 7, 9, 10R, 10L	4R, 7	4R, 7
10	1, 4R, 4L, 7, 10R, 10L	1, 4R, 4L, 7	4L, 7
11	1, 2R, 2L, 4R, 4L, 6, 7, 10R, 10L	1, 2R, 2L, 4R, 7	2L, 4R
12	1, 3, 4R, 4L, 5, 6, 7, 9, 10R, 10L, 11R, 11L, 12R, 12L	3, 4R, 4L	3, 4L
13	3, 4R, 4L, 10R, 10L	3, 4R, 4L	3, 4R
14	4R, 4L, 5, 6, 10R, 10L, 11R	4R, 4L	4R, 4L

lymph node stations during mediastinoscopy. (f) Histopathological examination demonstrated that severe noncaseating granulomatous inflammation was most common in the right lower paratracheal, followed by left lower paratracheal lymph node stations while it was least common in the highest mediastinal lymph node station.

Sarcoidosis, which is common worldwide, can occur in both sexes, all races and at every age. Even though the frequency of sarcoidosis and course of the disease vary among populations, females are generally more commonly affected and the disease starts between the ages of 20-40 [7]. In the present study, despite the fact that number of female patients was higher than that of the males, the difference was not statistically significant. Review of the studies carried out in Turkey showed that sarcoidosis is more common in females though acquisition of epidemiological data is still a big challenge in our country and our data is in agreement with this finding [7, 8]. On the other hand, patients in this study were most commonly between the ages of 30-40. This can be attributed to the fact that socio-cultural and economic status of the people, especially in the Western Black Sea region where this study was carried out is relatively low and insufficient regional healthcare system. This, in turn, translates into few people seeking medical help and/or delay in diagnosis.

Considering that the most common site of involvement in sarcoidosis is the lungs, it is not surprising to find that the coughing and chest and/or back pain were the most frequent symptoms in these patients. Meanwhile, presence of fatigue and fever at a significant rate suggest that sarcoidosis is in fact a systemic disease that might affect all bodily functions. Generally patients with sarcoidosis exhibit very few, if any, pulmonary signs during physical examination [5]. Frequent identification of erythema nodosum among our patients and pathological auscultation findings only in 21.4% of the cases are also consistent with the literature.

In almost all of the cases in the present study, there was lymph node enlargement, as shown by thorax tomography, in the lower paratracheal and hilar mediastinal lymph node stations bilaterally, which is a classical finding of sarcoidosis. When the lymphatic system of the lungs was examined, the hilar lymph nodes were located along lower aspects of the principal bronchi or the pulmonary arteries and veins while the paratracheal lymph nodes were localized to the right and left sides of the trachea, extending superiorly, superficial to the superior tracheobronchial nodes. These lymph node stations are important junctions for the lymphatic drainage in such a way that the lymphatics of the right lung generally drain to the right superior tracheobronchial nodes via the hilar nodes and then to the ipsilateral upper or lower paratracheal and right scalene nodes. Lymphatic drainage of the left lung follows four different routes. The first route is via the subaortic nodes. The second route follows the left phrenic nerve along the paraaortic nodes and reaches the anterior mediastinal and left scalene nodes. The third route travels along the left principal bronchus and reach the left superior tracheobronchial and paratracheal nodes. The final route travels along the lower aspect of the left principal bronchus and reaches the subcarinal nodes. Once through the subcarinal nodes, it either drains into the right superior tracheobronchial nodes or the right upper paratracheal nodes. Even though these routes show anatomical variations, it is known that the lymphatic drainage of the right lung is predominantly ipsilateral and that drainage to the contralateral mediastinal lymph nodes is very rare. In contrast to this, lymph drainage from the left lung to the contralateral side is more common and is usually via the subcarinal nodes [9]. The inflammatory processes which implicated in the etiology of sarcoidosis that are initiated by environmental antigens such as insecticides, talc, aluminum, zirconium and various infectious agents include a stage during which many inflammatory cells, including mainly T-lymphocytes, numerous cytokines and chemokines play roles and the lymphoid tissue becomes hyperactive. We believe that the anatomical features and physiological operation of the pulmonary lymphatic system can explain why hilar mediastinal and paratracheal lymph node stations, which play important roles in the drainage of both lungs, are more commonly involved in sarcoidosis. Furthermore, compared to the left side, the right lower paratracheal lymph nodes reached pathological dimensions in more cases in the present study and this was attributed to the lymphatic drainage of the left lung to the contralateral mediastinal nodes which,

in turn, results in left paratracheal lymph nodes receiving less lymph, becoming smaller in size and fewer in number.

On thorax tomography, lymph nodes in the paraesophageal, pulmonary ligament, bilateral interlobar and lobar lymph node stations were found enlarged in small number of cases. This is an expected finding in sarcoidosis cases. Lymph nodes in the interlobar and lobar lymph node stations, which are classified under the bronchopulmonary lymph nodes, complete their development towards the end of the first decade of life. They start regression afterwards and disappear in adulthood. These stations enlarge only in the presence of a malignancy or serious infection. Sarcoidosis is a chronic disease with hypothetical genetic predisposition in which immunological reactions play roles. Therefore, one might think that sarcoidosis cannot exert the anticipated effects on such atrophied lymph node stations and that lymph node enlargement does not occur. Paraesophageal and pulmonary ligament nodes lie within the posterior mediastinal lymph node group and are connected with the paraaortic lymph nodes beneath the diaphragm as well as with the hilar region. This variability in the distribution of the lymphatic fluid and the presence of very few direct connections between the environmental antigens that precipitate the disease and posterior mediastinal lymph nodes led us to believe that lymph nodes in these stations do not enlarge to a pathological size in sarcoidosis.

During the course of this study, we were able to take biopsy from the lymph nodes in the lower paratracheal lymph node stations bilaterally by mediastinoscopy in the majority of cases. Although mediastinoscopy is used routinely for assessing mediastinal lymph nodes in the staging of non-small cell lung cancer, it is also used for diagnostic purposes in patients with enlarged mediastinal lymph nodes. During mediastinoscopy, the pretracheal fascia over the anterior surface of the trachea is incised and elevated, and the mediastinoscope was inserted after blunt dissection by finger was made on the subfascial plane [10]. With this technique, the tip of the mediastinoscope is generally lies adjacent to the stations 4R and 4L. The lower paratracheal lymph nodes are freed from the surrounding tissues and become accessible as a result of the blunt dissection and elevation until the level of carina of the pretracheal fascia on both sides. In such case, sufficient amount of biopsy can be taken from stations 4R and 4L without further dissection. Since the lymph nodes in the lower paratracheal lymph node stations were enlarged to a pathological size bilaterally and we carried out the dissections as explained earlier, we were able get access to these stations and easily take biopsies by mediastinoscopy in the majority of our patients with sarcoidosis.

Histopathological examination of the specimens showed that severe noncaseating granulomatous inflammation was most frequent in the right lower paratracheal, followed by left lower paratracheal stations. It was least common in the highest mediastinal lymph node station. In sarcoidosis, lymphoid involvement may not always show homogenous distribution in terms of lymph node stations or its location within the lymphoid tissue. Sarcoid granulomas are dense masses with mono-nucleated phagocytes, epitheloid and multi-nucleated cells in the center, surrounded predominantly by CD4+ T-lymphocytes and occasional CD8+ T-lymphocytes and B-lymphocytes. These noncaseating granulomas sometimes occupy the whole lymphoid tissue and appear as massive granuloma. In some lymph nodes, on the other hand, many areas of the lymphoid tissue remain benign and the granuloma appears only in a few subcortical areas. In more than half of the sarcoidosis cases, the disease is self-limiting and granulomas can show spontaneous resolution either by disappearing or ending in fibrosis and/or hyalinization. It is evident that these reactions can be determined by immunological characteristics of the patients and personal physio-pathological responses that apoptosis actively takes place. Due to this and the differences between lymph node stations with regard to the density and size of the lymph node granulomas, sarcoid granulomas may not always be detected in lymph node biopsies. In fact, in addition to the difference in the density and size of the granuloma, the experience of the physician who performs the procedure and the number of biopsies per lymph node affect the possibility of detection of the granuloma. Furthermore, stage of the disease can also influence the histopathological results. In a study on this matter, Trisolini et al suggested that chest lymph node granulomas are less dense in patients with stage II disease [11]. As a matter of fact, presence of diffuse noncaseating

granulomas in the lower paratracheal lymph nodes is expected since this lymph node station is one of the most commonly involved stations in sarcoidosis. Moreover, lower paratracheal lymph node station, especially on the right side, is a key structure in the lymphatic drainage of both lungs and the neck and there are enough soft tissues and vascular structures around this station that allow enlargement of the nodes. These also contribute to this outcome. We believe that the lymph nodes in the highest mediastinal lymph node station are less-affected from the inflammatory processes in the pathologic physiology of sarcoidosis, which results in granuloma, due to the facts that they are generally limited in number and small in size and that they have restricted connections with the lymphatic network of the thorax and the lungs in comparison with the central mediastinal lymph node stations.

What is the impact of these results on clinical practice? Though mediastinoscopy in experienced hands carries low morbidity and mortality, serious complications such as hemorrhage, pneumothorax, recurrent nerve paralysis, tracheobronchial laceration, esophageal perforation, phrenic nerve paralysis, thoracic duct injury, mediastinitis and venous air embolism can be encountered, which warrants additional surgical interventions [10, 12]. These complications tend to occur during the dissection of the multiple lymph nodes from the neighboring tissues to increase diagnostic yield. The finding of the present study that severe noncaseating granulomatous inflammation was most common in biopsies taken from the lower paratracheal lymph node stations signifies the importance of taking biopsies primarily from this station in clinical practice, which is easily accessible during mediastinoscopy, to avoid unnecessary mediastinal dissections that might result in complications. However, it is imperative to have frozen section examination of these lymph node specimens be performed intraoperatively and terminate the procedure once the definitive diagnosis of sarcoidosis is established. In that manner, the likelihood of not establishing the histopathological diagnosis is eliminated and patients are prevented from having repeat mediastinoscopy that carries higher risk of complication.

The present study has clear limitations. Limited number of cases stands at the forefront of these constraints. Moreover, it was a single-center study and we were unable to use a more objective scale in the assessment of the histopathology. The results of the present study would be more meaningful if backed up by conducting multicenter studies with larger sample size, using a specific scale for histopathological assessment. Furthermore; on patients with sarcoidosis, comparison of the histopathological results obtained by mediastinoscopic lymph node biopsy with those obtained by lesser invasive methods such as needle aspiration under the guidance of endoesophageal or endobronchial ultrasound could yield useful information in choosing the most appropriate technique [13, 14].

In conclusion, histopathological examination of the biopsies taken during mediastinoscopy performed on patients with sarcoidosis revealed that severe noncaseating granulomatous inflammation was most common in the lymph nodes of the lower paratracheal lymph node stations bilaterally. Therefore, during mediastinoscopy in patients with a tentative diagnosis of sarcoidosis, physicians should attempt to get biopsy from the lower paratracheal lymph nodes, send the specimens for intraoperative frozen section examination to establish definitive diagnosis in order to prevent unnecessary mediastinal dissection that might result in serious complications.

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Hallucination Experiences in Crystal meth Abusers: a Qualitative Study

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Abstract

Objectives: This study aimed to determine the experience of hallucination in crystal meth users in Ahwaz, Iran.

Materials and Methods: This study is part of a qualitative study conducted as a content analysis approach. Data were collected by selective sampling, by holding a 38 semi- constructed in-depth interviews in Drop in Center (DICs) in Ahwaz, Iran. The participants signed testimonials free of will, then the first round of interviews were over the data were analyzed by applying Constant comparative analysis .After data entry , the new interview process was repeated until the data reached saturation.

Results: Overall, 35 participants used both crack and Crystal meth , one participant was addict to crack, Crystal meth and marijuana and 2 participants were Crystal meth addicted only. 65.5 % of participants were single, 65% of participants had at least one addict person in their family and 85% had a prison record. Six major categories emerged from the data analyses, including: Visual hallucination, Audile hallucination, Cognitive hallucination, Increase empathy, phobic and murder guilt hallucination, Concentration on something and abnormal behavior.

Conclusion: Due to negative effects of hallucination on physical and mental health of participants and their family, and given that Crystal is produced in extensive quantities by illegal laboratories and introduced to the market, it seems necessary to give widespread education especially through mass media to all social groups , increasing public awareness would be particularly helpful for youths and teenagers .

Key words: Hallucination, Crystal meth, Qualitative research, DIC

Introduction and goals

According to the World Health Organization (WHO) report, methamphetamine (METH) abuse is one of the major public health concerns worldwide [1]. Marijuana, used 190 tons annually is the most used drug. Followed by amphetamine drugs [2].More than 35 million people in the world and 10.4 million people in the USA are using amphetamines illegally [3]Ice or crystal is nowadays a widely used amphetamine; this drug in some forms has an appearance like powdered Crystal, i.e. the reason for its nomination. In Iran, amphetamines are mostly used in form of powdered Crystal. It is used by means of special Crystal pipes. The charge is less than one US dollar per person, and it can be used everywhere .In addition, cheapness, wide access, ease of use, having no scent or smoke are considered as the reasons for the increased use of Crystal meth in Iran.

Although there is no valid statistic about using Chrystal meth in Iran but United Nations Office on Drugs and Crime (NIODC) reports show that the use of Amphetamine has been increasing from 2001 to 2009. [4]In Iran between 2008 and 2009 the number of laboratories producing amphetamine has been increasing by 20 percent. In India between 1994 and 2004 the number of these laboratories has increased by 3500 percent. [5]

Crystal meth has both long- and short- term side effects on the body.[6, 7] Examples are increased concern of attention, reduction in weariness, insomnia, increased activity, loss of appetite, fanaticism, nausea, panic, bradycardia, and swoon for the former and addiction, bad temperament, Infarction, weight loss, severe hepatic disorders, and harmful effects on sexual organs [1], dental problems [3] and increased risk of suicide and AIDS[8-10] for the latter.Crystal abuse causes severe side

effects on physical and mental health of the users; and causes social problem as well. [11, 12]One of the long term effects of crystal meth abuse is hallucination. That can be a source of family and social problems. [13]Hallucination after crystal meth abuse has been reported by other studies. [14, 15] Crystal meth is classified in to destructive and hallucinogens family of drugs, it affects the central neurotic system and it causes hallucination. [16] Slade & Bentall (1988) defined hallucination as" a sensory experience which occurs in the absence of external stimulation of the relevant sensory organ, but has the compelling sense of reality of a true perception, is not amenable to direct and voluntary control by the experience, and occurs in an awake state". [17]

Various quantitative studies have been conducted on the hallucinogenic effects of crystal meth [1, 3, 6] ,but for understanding the hallucination phenomenon, we need to access real and firsthand experience , so this study aimed to determine the experience of the hallucination among crystal meth abusers.

Materials and method

This qualitative study was conducted in 2011 in Ahwaz, Iran, by using content analysis approach. In this method, the researcher is looking for participants' real experiences and is trying to classify information obtained from participants' interviews. [18]In this study sampling was done selectively. Thus, after approving proposal in the Ethical Research Committee of Tehran University of Medical Sciences, Tehran, Iran, and getting official permission from Organization of Charity in Ahwaz city, drug addicts to Chrystal were identified and the researcher went to the Drop in Center (DIC s).

Participants were selected among those persons who had experiences in crystal meth use, and agreed to share their experience with the researcher. Having introduced the research, the participants were assured that the data of this study would be kept anonymous, and gathered only through recording voices and published in scientific circles anonymously. To keep ethical observations all participants signed testimonials free of will. Including criteria to enter in to the study was using Crystal meth for at least one week ago. Participants were free to leave the study at what stage they wanted.

Gathering data was done through single considerable semi-constructed interviewing and observing. Pilot believes that the major source of data in qualitative studies is considerable interview of the participants by the interviewer. [19]Interview duration was not determined beforehand, and it varied between 30 to 70 minutes due to the situation, interview procedure and eagerness of participants. The interviews were done from February 2010 to June 2011.They were hold on DICs, participants began the interview by introducing themselves; then the researcher began the interview with asking open – end questions about their Crystal meth abuse .Participants explained their experiences after abusing Crystal meth.

Constant comparative analysis was applied to analyze the data.At first, the recorded voice was inscribed being typed and read and re-read in order to get an overall impression. Then, the data were put on Open Code software to be analyzed and coded. Next, the original codes were classified in larger categories based on similarities and differences. These categories were re-coded based on their content in to secondary codes. Data classification through this procedure was continued to get third-level coding. Thereafter, the new interview process was repeated until the data reached saturation. [18]Data saturation was gained when data were analyzed continuously and comparatively, [19]in data saturation all the key codes were completed and there was no need for new key codes. In total, 38 semi-constructed interviews were done with the addicts.

Results

Of the 38 participants who completed interviews, 35 used both crack and Crystal meth, one participant was addict to crack, Crystal meth and marijuana and 2 participants were only Chrystal meth addicted. Demographic data of participants are summarized in Table 1. Ethnically, 50 percent (20 participants) were Bakhtiary Lors, 35 percent were Arabs and the rest were from other ethnicities. Regarding marital status, 26 participants (65.5 %) were single, 10% were married, and the rest were separated. 50% of the participants lived in households of at least 6 members, and 10%

lived in households with more than 10 members, 65% of participants had at least one addict person in their family. Overall, 85% of participants had a prison record. Moreover, 3 participants were suffering from hepatitis C, 11 were HIV positive, and two participants suffered from both. Some participants had different experiences about hallucination. After analyzing these experiences, they were classified in 6 different groups: types of hallucination are summarized in Table 2.

1. Visual hallucination
2. Audile hallucination
3. Cognitive hallucination
4. Increase empathy
5. Phobic and murder guilt hallucination
6. Concentration on something and abnormal behavior

1-Visual hallucination

This category includes four sub- categories :A- Seeing men and things in smaller size than the real (microscope vision) B- bigger than the real size (macro scope vision) C- seeing things as humans D- seeing movements in inanimate objects

Participant no. 23, for example, expressed that "for about one week I used Crystal every days, I used injecting then I notice midgets like those in Gulliver cartoon talked to me (32- year–old man), participant No. 42 said "I saw the person around as small midgets". Some participants saw objects bigger than real size, for example, participant No. 35, who was a 30- year- old man, and had started using drug from the age of 13 and was suffering from HIV and hepatitis C expressed that" I saw a dog as big as building or if somebody was talking

Table 1. Demographic variables of the study participants

	mean	max	min	mod	Standard deviation
Age	31.5	50	21	26	6.63
The onset of drug use	17.35	25	11	16	4.32
Number of family members	6.03	13	3	7	3.01
Having addicts in the family	1.03	6	0	1	1.35
Education level		Diploma (12.5%)	Illiterate (4.9%)	Primary (22%)	1.35

Table 2. Categories of hallucinations in the study participants

	Category	Subcategory
1	Visual hallucination	Seeing things in smaller size than the real (microscope vision)
		Bigger than the real size (macroscopic vision)
		Seeing thing as humans
		Seeing movement in inanimate objects
2	Audile hallucination	Talk to themselves for a long time
		They heard voices that they didn't hear before
		Felt that something was coming out of their ears
3	Cognitive hallucination	Fall down of the roof
		Disability in proper time justification
		Disability in proper distance justification
		Seeing horrible animals
		Showing abnormal behavior
4	Increase empathy	Hallucination of self-hypnosis
		Hallucination of success
		Hallucination living dead
5	Phobic and murder guilt hallucination	Feeling of risk
		Family umbrage hallucination
		Murder guilt hallucination to others
6	Concentration on something and abnormal behavior	Concentrating on something
		Concentrating on body
		Showing abnormal behavior

to me I thought he was a wolf" or participant No. 12 who was separated said" When I used Crystal, I lost my appetite and I got talkative. I went out for picnic with my husband then we saw stones and I thought this are humans, my husband said they were moving" participant No.39 expressed that "for a couple of nights, I didn't sleep, I was awake all the time ,everything I wanna see, I will see, I can see the beautiful beach, I saw all this."

2- Audile hallucination

This category includes three sub- categories: A- Some participants talk to themselves for a long time, B- they heard voices that they didn't hear before, and C- they felt that something was coming out of their ears. Applicant No.40 expressed that "sometime I thought something near is coming out of my ear, you don't hear anything but you thing you're hearin something, or I was talking to myself for a good couple of hours I thought I was philosopher, I had spoken some word, when I think of them sometimes, I wonder how I fount these words? But it was not under my control I spoke to myself for a good couple of hours" (man-32 years) participant No.35 expressed that "I was sensing somebody that talking to me."

3- Cognitive hallucination

This category includes four sub-categories: A-fall down of the roof, B- disability in time justification, C- disability in proper distance justification, and D- seeing horrible animals. Participant No.16, aged 35 years, expressed that "I was too excited, something was horrible, as if the roof was falling down over my head or under the blanket, I thought it was set to fire I got up and put the fire off. I jumped out of bed, it was real." Applicant No.10 who was wrestler before becoming addict, expressed that "I was walking in the alley, as I opened my eyes there was a trailer, it was parked in the alley but it was far away I told myself I close my eyes it is still away, I was half-slept all the way home, suddenly I knocked the trailer with my forehead, the sore is still keeping "

4- Increase empathy

There are three sub-categories here including subcategories related to the following: A- hallucination of self-hypnosis, B- hallucination of success, and C – hallucination of living dead.

Some participants didn't believe in hallucination, believing that it was sub-product of mind of the person; that its basis is on empathy. Participant No. 21 expressed that" I smoked one gram Crystal meth and didn't go in to hallucination when you're telling yourself it is, empathy that because, when gazing at something telling it has got feet you'll proving yourself it has got feet, I smoked, for 3 successive days I didn't sleep, hallucination is because of insomnia". Some applicants did something in their dream worlds that they might be wishful to fulfill in the real such as dreaming to play in action movies, hallucination about reincarnation of the dead mother. Applicant No.37 expressed that "you're doing something you're not understanding it. I used Crystal meth twice on the roof of the house, I thought I could jump down from there, I did it twice, I broke my hands and leg, I saw some scenes from action movies."Another applicant who lived alone after his mother died expressed that "one night at 2 Am., I telling myself my mother's coming I dressed up and went to the graveyard, the guard come asking what I did there? I told, my mom is coming out of the grave, he told me to leave, I didn't go and telling him my mom's coming out, he called the police they com and arrested me."

5- Phobic and murder guilt hallucination

This category includes three sub-categories: A-Phobic feeling, B- Family umbrage hallucination, and C-Murder hallucination to others

Some participants felt that they are threatened by others or somebody is controlling them. Participant No.37 expressed that "I thought they are after me and some people want to kill me, I woke up my mother, I told her some people are at the door who gonna kill me." Participant No.39 expressed that "when I used Crystal meth, in my hallucination I saw a person sitting on a chair and is spying on me and sees me, this is hallucination controlling me, you know telling about hallucination is very less than its experience in real". Another participant had run away because of the feeling that there might be some threat. For example, participant No 14 who was fired from university because of addiction expressed that "once I used Crystal, for about 4 hours I ran, I took a taxi from one area to another to run away, I was thinking they are af-

ter me with sticks because they wanna kill me, or I was in a car if the driver say something I told myself he was going to kill me, I took off, broke the car windows and ran away."

Family umbrage hallucination; some participants were optimistic about their family members. In their mind the family members were sinners, and made serious trouble for them by doing physical punishment to them, and restricting their public relations, even that they caused physical damages to the family members. Participant No.43 expressed that "I was twice in serious hallucination, I thought my brother is a cat I had a pneumatic gun I pointed to him and shut to his arm. He was operated to take out the bullet. Once my mother was combing her hair, my cousin was at our house a kid of 14 years to whom my mother is an aunt, I wondered why my mother hadn't worn scarf before her brother's son, there was a glass of ice at my reach, I hit her with the glass her head was injured" .Participant No.9 who was left by his wife expressed that "I fought with my wife physically, I was pessimistic about her."

Murder guilt illusion to others; Crystal addicts consider their friend and relatives as enemies in their mind; addicts think that they cabal against them and they are going to kill them. There were some instances of murder attempts in this study. Participant No.40 whose father was a drug seller and got addicted from 12 and was HIV positive expressed that "I took a piece of break to hit my father." In some cases like this, hallucination caused serious and unrecoverable damage. Participant No.37 expressed that "I hit one of my friend in the back with my knife, he can't breathe normally since that my family paid fine to release me from prison".

6-Concentration on something and abnormal behavior

This category includes three sub-categories: A-concentrating on something, B- concentrating on body, and C- Showing abnormal behavior.

Some participants expressed that after using Crystal meth, they are concentrating on something for several hours. Participant No.27 expressed that "I concentrate on equipments, I have aquarium, for example, I don't sleep for 3 days and I think on filtration system of the fish or on the heater." In some cases, participants concentrated on their body hurts, for example, on the rashes of their face. Participant No.22 expressed that "sometimes, it is mid night; I go in front of the mirror and concentrate on rashes then when I become aware that it is 5am." Participant No.7, who had a lot of sores in his face and body, said "when you over used (Crystal) all night long to morning you scratch your body for example you pinch your hand's skin then it is pierced, you get very insensible". Another respondent remarked: "four months ago, one day I fell down and my hand hit a florescent lamp, it was destroyed in my hand, from that time on always splinter Crystal ooze out; Crystal is mixed with my blood, I concentrate on my hand and legs and injure them then ooze out very tiny Crystal particles, if you darken this room I will show you, its shines." (50- year- old-man].

Showing abnormal behavior;

Some participants showed some abnormal behavior after using Crystal meth. One participant expressed that "for 48 hours I didn't say a word, I hate somebody talk to me" (21- year-old man). Participant No.19 expressed that "I went to hallucination in the morning when I got up I noticed I have walked all night in the mountains bare footed, my feet were bleeding, they were injured by thorns." Participant No.10 expressed that "I did extra activity, unconsciously I raised my hand and did exercising movement, I slept sitting."

Discussion and Conclusion

In our study, most participants were educated under diploma. These results are not corresponding with the result in Pavarin study [20], in which 61 percent of the participants were highly-educated. This may be because of the difference in the environment of the study and even that our study was done in a developing country while as their study was done in Italy. In our study most participants used two or more drugs. Likewise, in Pavarin [20] and Victoria et al. [21]studies, the addicts were inclined to use drugs simultaneously. It seems that because of Hellenistic wishes in addicts, these results are corresponding reality.

In this study, some participants experienced visual hallucination such as microscopic imaging, macroscopic imaging and seeing unanimated objects

as humans. Similarly, some other researchers , as Baghott [22] and Akiyama [14], reported visual hallucination after using amphetamines, .It seems that the expressions of the participants interviewed in this study are valid, because the role of amphetamines like Crystal meth is documented in chemical transmitters [23] causing disordered behaviors.

In our study, some participants interviewed were hearing specific voices or were talking to themselves for long hours. Audile hallucination after using amphetamines was also reported by other studies such as Mohoney et al [24] Baghott [22] and Akiyama [14] studies. All participants sharing in this study had insomnia for 2-3 nights. Insomnia for long hours after using Crystal has been proved in other studies as well. Such studies are Anglin et al. [6] Nakatani [25] Edakubo [26], and Wada [27] studies. Cognitive hallucination of the participants was reported in this study such as fall down of the roof, disability in proper time justification, disorder in proper distance justification. Other studies also reported some cases of cognitive hallucination after using Crystal meth, e.g. Wada [27], Gupta [28], Homer [29], and Simon [30]studies. Some participants in this study had some pessimistic believes such as suspension to wife, mother, father and friend. In some cases they tried to injure their friends and relatives. These results are consistent with the findings of studies showing the influence of amphetamine on users, such as Wada [26] and Brookoff [31] studies that showed sixty (92%) of the 64 assailants reportedly used alcohol or other drugs on the day of the assault.

In some cases, participants of the study injured their bodies because they concentrated on body parts. Once, the interviewer observed that a young man aged 26 years, who had injured his face and parts of his belly several times. When he was asked for the reason he replied: "I couldn't abide doing it intentionally and injured myself". In other cases there were a lot of sores on interviewed participants' arms and forearms; these injuries were done by knife by the participants themselves after using Crystal meth. Our literature review revealed similar cases; for instance, Buxton [7]reported cases of skin lesions of meth users that were caused by irritability and psychosis known as "tweaking," which may result in the user having numerous scabs from picking at imaginary insects crawling on or under his or her skin. Nonetheless in our study, participants did not express the specific cause for their actions and considered it as under control behavior. Once, the interviewer observed that a young man with 26 years of age had injured his face and parts of his belly several times. He replied "I couldn't abide doing it intentionally and injured myself." In other cases, there were a lot of sores on interviewed participants' arms and forearms; these injuries were done by knife by the participants themselves after using Crystal meth. After reviewing similar cases , in such studies like epidemiological evaluation done in Australia by Ross to find patterns for harms related to illegal drug use [32], in which some side effects after using Crystal meth were reported . Likewise, the findings of another study in Australia done by Shane [33]showed that 12% of methamphetamine users had committed a violent crime in the preceding year. A study in Canada, done by Barndon [34]showed that most drug abuser youths injured themselves or the persons around.

According to what is expressed for different cases and that hallucination and other side effects of using Crystal meth destroy physical and mental health of drug users, it also influences the health of surrounding persons especially the household members. In conclusion, while nowadays Crystal is produced in extensive quantities by illegal laboratories, is introduced to the market, the suppliers develop this approach that Crystal meth is energetic and causes no addiction; it is necessary to reduce and control Crystal use, increasing public awareness by giving widespread education especially through mass media to all social groups, it would be of crucial importance and help for youths and teenagers as the most vulnerable age group for addiction.

Study limitations

1 – Lack of a private environment for the interview and being forced to stop the interviews temporarily with the entries to the interview room.

2 - Euphoria or a hangover of some of the participants would have caused the jabber or scattering in some cases.

Acknowledgment

This paper is part of a thesis research project, approved and supported by Tehran University of Medical Sciences [grant number 91-01-27-16609]. The researchers thank and appreciate the Welfare Officials of Drop in Service Centers (DIC) of Ahwaz in implementation and collaboration of the study.

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Turkish mothers' who have preterm infants knowledge about risk factors of sudden infant death syndrome

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Abstract

Objective: The aim of this study was to determine the Turkish mothers' who have a preterm infant knowledge about risk factors for sudden ınfant death syndrome (SIDS).

Methods: This study was conducted by mothers who have a preterm infant. This study was composed of volunteers (n=60) who were present at neonatal care unit, University Hospital at the time of research. Data were collected with a questionnaire. Data were analyzed by percentages.

Results: The majority of the mothers had a lack of knowledge about risk factors for SIDS. The majority of the mothers would use a pillow with their sleeping infants, and would place preterm infants in the side position at daytime, nightime and when left alone in rooms. The majority of the fathers did smoke in their homes.

Conclusion: The findings can be used to develop educational programs directed at increasing knowledge about risk factors of SIDS an effort to decrease its incidence.

Key words: Knowledge, Mother, Preterm Infant, Infant Sleeping Position, Prevention Risk Factors, Sudden Infant Death Syndrome, Turkey

Introduction

Risk of SIDS

Despite declines in prevalence during the past two decades, SIDS continues to be one of the leading causes of infant mortality in the post-neonatal period (1). Globally, the risk of SIDS is increased in prematurely born infants compared to those born at term, particularly if they either sleep prone or on their side. The proportion of SIDS victims who are born prematurely has risen from 12% in 1984-1988 to 34% in 1999-2003 (2). SIDS incidence has been repeated to be higher in the winter and on weekends (3). Weather, potentially, has a more important role in influencing clothing and bedding choices than do immediate conditions, such as the climate of the infant's room (4). Overheating has been associated with increased risk of SIDS based on indicators such as increased room temperature, high body temperature, sweating, and excessive clothing or bedding (5). More recently, the highest SIDS rates (≥ 0.5/1000 live births) are in New Zealand and the United States. The lowest rates (≤0.2/1000) are in Japan and the Netherlands (6). In 2005 in Germany 298 infants died of SIDS, emphasizing the continued importance of this disorder. In Porto Alegre and Passo Fundo, cities in the same state, estimated that the infant mortality rates due to SIDS were 0.45 per 1,000 and 1.75 per 1,000 live births, respectively (7). In a multicenter study performed in 1995-1996 including Turkey, the prevalence of SIDS ranged from 0.1-1.4 per 1000 live births, but in this report Turkish prevalence was not mentioned (8). Unfortunately, SIDS prevalence of Turkish infants is still unknown since autopsy cannot be performed widely. There is not a national data that are available regarding risk factors and incidence of SIDS.

Mother's Knowledge

Although SIDS affects infants from all social strata, lower maternal education level are consistently associated with an increased risk of SIDS (7). Overall mothers' knowledge about infant care plays an important role in decreasing their infant's mortality (9).

An important part of mothers (85%) and babies (90%) in Turkey receive care services from health professionals within the two months after delivery (10). Problems experienced by mothers after delivery related to newborn include yellowness, exce-

ssive crying, breast-feeding problems, abdominal distention, canker, eye and belly infections and inadequate weight gain. According to Pregnancy-End Care Directory published in 2008 by Maternal and Child Health and Directorate of Family Planning in Turkey, mothers should be observed in hospital within the 24 hours after delivery, and at least three times at home on the 2nd - 5th days, 2nd week and 4th – 8th week in healthcare institutes. In addition, at least 17 follow-ups should be made for babies between 0-59 months (11).

The content implemented on newborns for the first 6 months of their lives (11).

In pursuit of delivery	Registration of baby. Physical treatment, height-head circumference and weight measurement Breast-feeding is supported by giving education on breast-feeding. Blood sampling from ankle for screening of hypothyroidism within 24-72 hours. Vaccinating the first dose of hepatitis B vaccine
7th day	Physical treatment, height-head circumference and weight measurement
15th day	Physical treatment, height-head circumference and weight measurement Blood sampling from ankle for screening of phenylketonuria
30th day	Physical treatment, height-head circumference and weight measurement
2nd month	Physical treatment, height-head circumference and weight measurement Making DBT1*, OPV1**, BCG, and the 2nd dose of Hepatit B vaccines Questioning the blood sampling from ankle for screening of phenylketonuria
3rd month	Physical treatment, height-head circumference and weight measurement Making DBT 2* and OPV2** vaccines
4th month	Physical treatment, height-head circumference and weight measurement Making DBT3* and OPV3** vaccines
5th month	Physical treatment, height-head circumference and weight measurement
6th month	Physical treatment, height-head circumference and weight measurement Making necessary examinations in the case of any suspicion for anemia

** Diphtheria, Pertussis and Tetanus vaccines*
*** Oral Poliomyelite vaccines*

At present, home care services are not cited among health services in Turkey, and these services are given by midwives employed in the primary healthcare or family doctors in the areas where family practice is carried into action; however, home care services have not reached the desired level (11)

However, parents often reverted to non-supine sleep positions for infants over time, peaking at 3 months, which coincides with the peak incidence of SIDS (12). Efe at al. (2007) found that the mothers who delivered a term infant have little knowledge about risk of SIDS in Turkey. Efe et al. (2007) were determined that 70.6% of mothers would use a pillow with their sleeping infants, and 44.2% would cover their infants' faces. When infants were alone in a room, 96.5% of mothers would leave them in the supine position (13). Yıkılgan et al. (2011) found that 39% of mothers were aware of SIDS and 46% of the mothers preferred a supine sleeping position for their infant and 16% of the parents were bed-sharing with their infants (14).

The content of the discharge education given to mothers with level II premature baby staying in university hospitals in Turkey before discharge from the hospital includes clothing, hygiene, cord care, conserving preserving body temperature, elimination, vaccines, newborn development, minor disorders, and signs of danger regarding newborn health. In Turkey, however, even in university hospital the supine position for infant sleep is not routinely recommended, either during the hospital stay or at discharge. Unfortunately, government policies and public campaigns are lacking about SIDS.

General risk factors of SIDS

SIDS affects infant from all social strata. Factors arising from the mother are shown in some studies, including low socioeconomic status (15), parental smoking (16), parental drug or alcohol abuse (17), unsafe bedding (18), covering of infants' heads with bedding (19), prone sleeping in soft bedding (20), premature born (21), prone and side sleeping (20), bed sharing with parent (22), overheating (5) and infanticide (23).

Other risk factors of SIDS: soft mattresses, older mattresses, fluffy bedding, such as comforters, pillows, sheepskins, and polystyrene-bean pillows, have been associated with a two- to three-fold increased risk of SIDS (3).

The evidence from many countries supports that increased knowledge results in a decreased incidence of SIDS. The literature from Turkey focuses primarily on knowledge of mothers with full term infants (13, 14), but little is known about mothers who have preterm infants. Thus this study is critical to help emphasize the importance of enhancing education on SIDS for mothers with preterm infants living in Turkey.

The aim of this study was to determine the Turkish mothers' who have a preterm infant knowledge about risk factors for SIDS.

Methods

Setting, including NICU policy on visitation

NICU unit is organized in three levels in Turkey. Only the level-1 units provide services to non-complicated deliveries, normal and healthy newborns, and healthy preterm newborns with high gestation age. Level-II units undertake the responsibility of babies born in risky pregnancies and expected to have problems in newborn period. Newborns diagnosed with mild or medium respiratory distress syndrome, premature babies with over 32 weeks of gestation age, and children of diabetic mothers were followed and treated. Level-III units mostly exist in university hospitals. In this type of units, very little premature babies and newborns diagnosed with severe respiratory distress syndrome and requiring ventilator support, surgical intervention or specific science consultation are hospitalized. The university hospital where the study was performed has level – I, level II and level III newborn units. There are 4 rooms in level II unit. There are 2 incubators and 3 baby beds in each room on average. On the other hand, there are 2 rooms and 14 incubators in level III unit on average. Study was implemented on mothers of premature babies in level II unit. The mean daily number of babies in this unit is 10. There are 3 babies hospitalized in each room. Premature babies with stable condition gain weight and grow up in this unit. After premature newborns are transferred to level II unit, their mothers are taken near them. Mothers are trained by nurses in the unit. The content of this training includes holding baby in the right way, hygiene, feeding with plate or orogastric tube, and change of nappies. Mothers with full-term healthy babies are trained by education nurse in the hospital. The content of this training includes breastfeeding techniques, importance of breastfeeding, umbilical cord care, hygiene, immunization, and frequency of baby controls. Following the education of mothers in level II unit, they become responsible of baby hygiene and feeding. The unit nurse is responsible for controlling the accuracy of baby care and feeding. Mothers could receive the support of unit nurse they face problem in baby care. Mothers are allowed to stay with their babies 24 h in level II unit. Mothers are responsible for helping nurses on baby care until baby is discharged from the hospital. Mothers can enter the room with their daily clothes without wearing overshoes or sterile shirt. Caregiver individuals are only allowed to care baby when baby's mother or father cannot care the baby. These individuals can only visit the baby in daytime by taking the permission of unit nurse.

Sample

A convenience sample is used in the study.

The inclusion criteria were as follows: mothers who have had preterm infants, mothers who can stay in the room 24 hours after infant's condition may remain stable and have agreed to participate in the study.

The exclusion criteria were as follows: what if the NICU stay, the acuity of the preterm infant is severe and warrants more intensive care.

Data collection

The questionnaire consisted of two sections: demographic questions and knowledge questions. The knowledge questions are multiple choices. The mothers completed a demographic questionnaire. The first contained questions regarding socio-demographic characteristics of mothers such as age, weight, educational level, employment status, social security and premature infants gestational age, postnatal age, birth weight, gender and delivery. The second included questions about specific knowledge related to mother's knowledge of how she should care for her preterm infant. According to these data, the investigators were able to determine the mothers' knowledge and practices that were risky, (for example, "Will your baby have a separate room?" "Are you considering sharing your bed with your baby?" "What position will you put your

baby in to sleep during the day, at night?" "How long will you breast feed your baby?").

To determine the reliability and validity of the questionnaire form, it was pre-tested on 10 mothers from another hospital in Antalya. The questions considered unclear were revised. For instance, the question, "What position will you put your baby in to sleep during the day at night?" is asked in the present study to 10 mothers as "How do you put you babies to sleep?". Mothers selected the night choice because the question was asked as sleeping. Therefore, it was concluded that the question was not understood, and it was replaced with position.

The mothers who have preterm infants were informed about the aim of the study. Before infants discharge from hospital, the researcher went to the preterm infants' room. The researcher explained the objectives of the study mothers. One of the researchers made the all interviews for consistency. The interviewer is trained in interview techniques. The interview was conducted in the nurse room. The questions were asked face to face to those mothers willing to participate and the responses were noted during the interview. After obtaining these data, the researchers instructed the mothers about SIDS and prevention measures.

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Permission was obtained from the Directorates of the Mediterranean University Medical Faculty.

The mothers who have preterm infants were informed. Information about anonymity, confidentiality, and consent was included in the explanation. Participation in this study was voluntary.

Statistical analysis

Questions were multiple choices. Collected data were recorded and analysed using the Statistical Package for Social Sciences version 11.5 (SPSS, Inc., Chicago, IL, USA). Percentages were calculated.

Results

During the research period, all mothers who stayed with their preterm infants in the neonatal unit were eligible for the study. A total of 70 preterm ınfants lied in the neonatal unit between March and May 2007. Of these mothers, 60 mothers volunteered to participate in the study. This was 85.7 % of the total mothers who were eligible to participate in the study.

Table 1 shows descriptive characteristics of the mothers. The majority of the mothers (71.7%) were aged 21-35 years. The half of the mothers (56.7%) had completed primary school (Table 1).

Table 1. Characteristics of mothers and preterm infants (n=60)

	n	%
Mothers' age groups		
≤ 20 years	7	11.7
21-35 years	43	71.7
≥ 36 years	10	16.7
Mothers' educational levels		
Primary school	34	56.7
High school	10	16.7
University	16	26.7
Mothers' employment status		
Employed	15	25.0
Housewives	45	75.0
Health insurance		
Yes	3	5.0
No	57	95.0
Prenatal care		
Yes	58	96.7
No	2	3.3

Table 2. Characteristics of preterm infants (n=60)

	n	%
Gender		
Female	35	41.7
Male	25	58.3
Gestational weeks		
31 and ↓	23	38.3
32 – 37	37	61.6
Birth weight		
≤ 2499 kg	46	76.7
2500- 4500 kg	14	23.3
Infant age		
0-10 days	27	11.7
11-20 days	8	3.5
21-30 days	4	1.7
31-40 days	2	0.9
41 and	19	8.2
Delivery		
Vaginal	7	11.7
Cesarean	53	88.3

Table 2 shows descriptive characteristics of the preterm infants. The gender of 58.3% of preterm infants was male and the mean age of infants was 41.02 days. Ages ranged from 0-10 days for 11.7% of the preterm infants (Table 2).

Table 3 shows the risk factors by home environment for SIDS. In winter, 51.7% of the mothers use wood/coal burning heaters. 63.3% of the mothers stated that they had room thermometer. 88.3% of the mothers stated that they did not smoke but 45.3% of the fathers smoked. While 68.3% of the mothers stated that they planned to share the same room as their preterm infant, 88.3% would not share the same bed as their infant, and only 6.7% were considering sleeping in the same bed as their preterm infants for 0-6 months (Table 3).

Table 3. Risk factors by home environment for sudden infant death syndrome

	n	%
Method of heating		
Wood-coal heater	31	51.7
Electric heater/air conditioner	25	41.7
Radiator/central heating	4	6.7
Room thermometer		
Yes	22	36.7
No	38	63.3
Cigarette smoking		
Mother smoker	7	11.7
Mother nonsmoker	53	88.3
Father smoker	28	45.3
Father nonsmoker	32	54.7
Guest smoker	2	3.3
Guest nonsmoker	58	96.7
Number of people in the home		
3	36	60.0
4	16	26.7
≥ 5	8	13.4
Number of rooms in the home		
2	8	13.3
3	18	30.0
≥ 4	34	56.6
Sharing a room		
Yes	41	68.3
No	19	31.7
Bed sharing with adults		
Yes	7	11.7
No	53	88.3
Duration of bed sharing		
0-6 months	4	6.7
7-12 months	1	1.7
Don't know	2	3.3

Table 4 shows the condition of infant sleep patterns and feeding for SIDS. It was also determined that 45.0% of the mothers would orthopedic sleep surface. 48.4% of the mothers would cover their infant with a cotton/wool quilt while the infants were sleeping, 76.7% would use a pillow while the infants were asleep, and 48.3% would use a polyester pillow, and 36.0% would cover their infants' faces in order to keep the infant warm and keep insects away from the infant. 58.3% of the preterm infants were feeding with breast milk (Table 4).

Table 4. The Condition of infant sleep patterns and feeding for sudden infant death syndrome

	n	%
Newborn sleep surface		
Cotton/wool	24	40.1
Orthopedic	27	45.0
Foam rubber	5	8.3
Don't know	4	6.7
Characteristics of infant's cover		
Cotton/ wool quilt	29	48.4
Blanket	27	45.0
Don't know	3	5.0
Pillow use		
Yes	46	76.7
No	14	23.3
Pillow characteristics		
Cotton/wool	17	28.3
Polyester	29	48.3
Covering of the head or face with bedding		
Yes	22	36.0
No	38	64.1
Feeding of preterm infant		
Formula food	11	18.3
Breast milk	35	58.3
Formula food + breast milk	14	23.3
Breastfeeding duration		
As long as infant takes it	20	33.3
0-6 months	6	10.0
0-2 years	24	40.0
Don't know	10	16.7

Table 5 shows the mother planned to place their infant in a position during daytime, night, when left alone in their room and after feeding. After discharge, 43.3% of the mothers planned to place their infants in a side position during the daytime, and 48.3% in a side position at night. When left

alone in their rooms, 51.7% of the mothers planned to leave their infants in a side position. After feeding, 63.3% of the mothers planned to leave their infants in a side position (Table 5).

Table 5. The mother planned to place their infant in a position during daytime, night, when left alone in their room and after feeding

	n	%
Daytime position		
Supine position	20	33.3
Prone position	3	5.0
Side position	26	43.3
Supine- prone- side position	7	18.4
Nighttime position		
Supine position	19	31.7
Prone position	4	6.7
Side position	29	48.3
Supine- side position	4	6.7
Don't know	4	6.7
Infant's position when left alone in room		
Supine position	19	31.7
Prone position	1	1.7
Side position	31	51.7
Supine- prone- side position	3	5.0
Don't know	6	10.0
Infant's position after feeding		
Supine position	12	20.0
Prone position	5	8.3
Side position	38	63.3
Don't know	5	8.3

Discussion

This study was the first in Turkey in which we examined what mothers who have preterm infants know about infant sleep practices and the environments.

In the study, most of the mothers were housewives. Unemployment of mothers indicates their economic dependence on their spouses. Therefore, this brings along economic constraints to mothers and to meeting baby's needs at the same time. For instance, they act according to their economic situation when arranging home atmosphere for baby, preparing baby room and setting the heating. Most of the housewives in Turkey cannot provide many requirements in baby care on account of economic problems.

Nearly all the mothers in the study did not have health insurance. This indicates that mothers and their babies could experience problems in receiving health care after discharge because people with no social security in Turkey have to pay certain amount of money to receive health services in hospitals. This restrains people with economic difficulty to adequately benefit from hospital services. Mothers with economic difficulty less frequently bring their babies to hospitals for control purpose after discharge. In general, they go to hospital for vaccination or when baby has a serious health problem (Table 1).

The American Academy of Pediatrics, the United Kingdom Department of Health, and the German Pediatric Association recommend that infants in the first year should not sleep separate from the parents but in the parental bedroom in their own crib (24, 25). This study tends to support this recommendation. We observed that a majority of the mothers planned to share the same room with their preterm infants, but majority of the mothers did not plan to share same bed as their preterm infants. Their opinion was that preterm infants should not be left alone. It is not clear whether the high rate of room sharing in Turkey is a normal cultural practice or a result of increased awareness of SIDS risk factors in the population. There are a few reasons for sharing the same room. For example, infants are seen as a more dependent by mothers. Mothers keep newborns next to their beds "to make sure that they are still breathing", "to breastfeed easily", and "to check the baby during night", but were generally not comfortable with having them in the same bed. Studies have shown that infants who sleep in the same room as an adult (but not the same bed) have a lower risk of SIDS (22). In our study, half of the mothers had four or more rooms in their homes. In spite of the fact that the mothers have enough room in their house, they did not want to prepare a baby room. In Turkey, mothers generally keep their children in their own bedrooms until they are 1 year old, then after that they are put in the living room to sleep. This is a risk for SIDS because babies sleep in the living room with other family members. Crowdedness of room results in air pollution. It should be given information about mothers arranging separate room for babies. The majority of the mothers had three members of family at home. In this study, the majority of the mothers were having their first baby.

It is also recommended that infants sleep without a pillow in their bed. Vennemann et al. (2009) reported that there was no increased risk of SIDS with a pillow in the adjusted analysis. It has been postulated that if the infant is placed prone on a pillow, the head of the infant will sink into the pillow and the infant will rebreathe expired air (26). In Germany infant pillows are mostly very thin and the potential of rebreathing might be very low (26). In our study, we observed that majority of the mothers planned to use a pillow and 48.3% of mothers planned to use a polyester mattress. In Turkey infant pillow are mostly very big, soft and puffy. If the infant is placed prone on a polyester pillow, the head of the infant will sink into the pillow and the infant will rebreathe expired air. It is a very common practice in Turkey for mothers to use a polyester pillow with their infants. These practices put the infant at risk of the SIDS. Unfortunately, the data provide little information on the reasons why parents choose to use polyester pillows, whether to promote sleep, prevent head flattening, or purely as an unquestioned cultural practice. Turkish mothers place their infants on pillows to correct a flattened head shape (occipital plagiocephaly) from a supine sleep position.

In our study, 64.1% of the mothers did not plan to cover their infants' faces with something. Whereas, Efe et al. (2007) found that almost half of the mothers who have full term infants would cover their infants' faces (13). The practice of mothers not covering their infants' faces may prevent risk of SIDS, because the cover could cause the infant to suffocate while sleeping.

In this study half of the mothers used wood or coal burning heaters for winter heating, which contributes smoke to the infant's environment. Infants, their families (mother, father, siblings and family elders), and guests share the same room for heating. In this region, parents try to keep their baby from getting cold, even if the weather is warm. In the winter in Turkey, wood/coal burning heaters are continually burning, and the room temperature is not known. Turkish mothers are afraid that their infants will get cold so they dress them in heavy clothes. Overheating has been associated with increased risk of SIDS based on indicators such as increased room temperature, high body temperature, sweating, and excessive clothing or bedding (5).

Risk factors for SIDS differ across countries and therefore are likely to contribute to the variability in rates. For example, smoking rates are high among the Maori in New Zealand an American Indians, groups in which the rate of SIDS remains high (1). Another risk factor is smoking in the preterm infant's room. In our study, majority of the mothers did not smoke cigarettes, but 45.3% of the fathers smoked in the house. In Turkey, fathers generally smoke cigarettes in the sitting room, on a balcony, in the kitchen, or in the corridor in their homes, which increases the preterm infants' risk of SIDS. Mothers need to be told that cigarette smoking near their infants increases the risk of SIDS.

Another important finding is that 58.3% of the preterm infants were breastfed, and 40.0% of the mothers planned to breastfeed their preterm infants until they were two years old. This might be explained by the education the mothers were given by the nurse in hospital.

The prone sleeping position is now one of the best established risk factors for SIDS and is causally associated with SIDS (26). Senter et al. (2010) demonstrated that 37% of infants were found in the prone position at the time of death (27). In a study by Issler (2009) found that 33 mothers put their infants in the supine position, and among these infants 31 were actually sleeping in that position. Some infants are placed on their side or back and turn to the prone position (secondary prone) (27). Vennemann et al. (2005) have reported that side position is associated with an increased risk of SIDS (29), confirming the results from other study (30). In our study, we observed that 43.3% of the mothers planned to put their preterm infants in a side position during the daytime, 48.3% at night, 63.3% after feeding, and 51.7% when the infant was left alone in the room. It is possible that mothers are influenced by nurses with regard to their choice of sleeping position and mothers may have received incorrect information about sleeping position for preterm infants. The results of this study are similar to Vernacchio et al.'s (2003) study that has highlighted that parents are strongly influenced by practitioners with regard to their choice of sleeping position (12).

Back to sleep campaign reduced the incidence of SIDS in developed countries during the period of 1985-1999 (24). Some countries have promoted nationwide campaigns to increase the prevalence

of the supine position to sleep, resulting in a drop in the infant mortality rate to SIDS (31, 32). The Foundation for the Study of Infant Deaths, together with Bliss, launched a national campaign "Time to get back to sleep" which was specifically aimed at reducing the risk of SIDS in prematurely born infants (33). The campaign stressed the importance of prematurely born infants sleeping in the supine position following neonatal unit discharge and not prone or side sleeping. It also recommended that supine sleeping should be instituted at least 1-2 weeks before hospital discharge (33). Prone sleeping is associated with superior oxygenation, even at 6 weeks post term (34). Parents need to be advised that their infant may need extra supplementary oxygen when slept in the prone position (33). Dattani at al. (2011) indicated that a national campaign "Time to get back to sleep" had demonstrated the recommendations made by neonatal practitioners regarding the sleeping position for prematurely born babies prior to and after neonatal unit discharged (35). Parents of all newborn infants in Brazil receive the Infant Health Booklet, published and freely distributed by the Ministry of Health since 2006. This booklet recommends putting the baby to sleep "on his back" (36). This is national preventive practice policy to prevent SIDS in Brazil. In May 2006, a national network of neonatal nurses was prepared with training and materials to integrate safe sleep practices into the culture of NICU care in New Zealand. From 2009, Safe Sleep Champions are spreading across the country to provide visible leadership and bring more people to education. An online version of an infant safety education programme, "Baby Essentials" (37), with a summary version in twenty languages, is tracking participation and able to focus promotion where it is most needed. In these ways, the safe sleep vision is pulling large numbers of people from across New Zealand society into conversations about protecting babies' lives (38).

Infant sleep position is a risk factor that is easily modifiable in comparison with other factors, interventions aimed at motivating mothers to put their infants to sleep in a supine position have had a significant effect on decreasing infant mortality rates due to SIDS in New Zealand, Australia, United States, Norway, Sweden, and Great Britain (2,39). In a study with primiparous women in Wyoming, USA, mothers in the maternity ward observed a demonstration of the recommended sleeping position (supine) performed by a nurse with their own infants. After the first week following discharge, mothers who observed the intervention put their infants to sleep in the supine position in a significantly higher proportion than those who did not (40).

The AAP recommends that infants be placed on their back to sleep (24). The AAP reaffirmed the recommendation to place all healthy preterm infants to sleep in the supine position (15). In Turkey, however, even in university hospitals, the supine position for infant sleep is not routinely recommended, either during the hospital stay or at discharge. Unfortunately, government policies and public campaigns for the population about SIDS are not found. Turkey indicated little awareness about the risk factors for SIDS. The lack of adequate training of the health care teams who attend mothers may explain the low prevalence of use of the supine position for infant sleep in different countries, including Turkey, and in our study. These results highlight that further education of neonatal staff regarding appropriate sleeping position for prematurely born babies remains imperative.

Nevertheless, our study has some limitations including that it had consisted of a small, select sample of mother who have preterm infant in one neonatal unit in Antalya, so the results cannot be generalized to all of society. However, the results are valuable because this study was the first conducted in Turkey on the subject of SIDS, which is still developing in Turkey. The data obtained in this can also provide a basis for future studies.

Although our study was conducted in the neonatal unit of a university hospital in Antalya in Turkey, it has determined that mothers know the wrong position to put their preterm infants in while they are sleeping. Neonatal nurses have a powerful opportunity to educate families about the risk for SIDS. Nurses also have a responsibility to model evidence-based strategies to reduce those risks. If nurses model back to sleep practices in the NICU and educate parents about the hazards of non supine sleep before hospital discharge, a reduction in the incidence of SIDS among former NICU patients may be possible.

Limitations

Our study has a limitation including that it had consisted of a small, select of mother in one neo-

natal care unit in Antalya in Turkey, so the results cannot be generalized to all the country.

However, the results are valuable because this study was the first conducted in Turkey on the subject of knowledge of mothers who have preterm infants about risk factors for SIDS, which is still developing in Turkey. The data obtained in this study can also provide a basis for future studies.

Conclusions

In this study, it has been determined that when preterm infants' mothers get back home, they may come face to face with situations that could endanger the health of their infant. Therefore, before discharge, according to the research findings, preterm infants' mothers should be informed, especially by nurses, about SIDS and the necessary measures that will protect their preterm infants from SIDS. Nurses can play an important role in educating the public about the link between SIDS and infant positioning during sleep. Further interventions, such as the education of pediatricians and nurses about the recommended sleep position for preterm infants, in addition to enrollment by media and health agencies in actions related to SIDS prevention, might also increase the number of infants who sleep in the supine position.

Acknowledgements

We are grateful to all the parents who participated in this study. This study received external funding from Akdeniz University Scientific Research Project Unit.

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Prescribing practices for the treatment of malaria among public and private healthcare facilities: A comparative cross sectional study from Pakistan.

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Abstract

Background: Inappropriate prescribing is the major contributing factor towards irrational drug use and anti malarial drug resistance resulting in increased morbidity and mortality rate of malaria in Pakistan. Prescribing practices are not up to the mark in both the public and private healthcare facilities of developing countries including Pakistan.

Objective: The study aimed to assess the current prescribing practices for the treatment of malaria among public and private tertiary healthcare facilities in two cities of Pakistan; Islamabad (national capital) and Rawalpindi (twin city).

Methods: A comparative, cross-sectional study design was used to evaluate the case records of patients treated for malaria in public and private tertiary healthcare facilities in Islamabad and Rawalpindi. The study population constituted of ten public and ten private tertiary health care facilities located in federal capital city Islamabad and its twin city Rawalpindi; Pakistan. WHO prescribing indicator form was used to collect data regarding current prescribing practices for the treatment of malaria. A total of 600 malaria encounters thirty from each health facility was recorded. After the data collection, data was coded and entered in SPSS version 16. Descriptive statistics (frequencies and percentages) were used to describe trends in the current prescribing practices. Chi-Squared test was used to find association among the current prescribing practices and different health sectors in the twin cities.

Results: Out of 600 encounters, dose of anti-malarial drugs were given in 84.5% (n = 507), of the cases while frequency of anti-malarial drugs in 58.1% (n = 351), strength of the drugs in 24.3% (n=146) and duration of drugs in 68.8% (n = 413) of the cases respectively. The most commonly prescribed anti-malarial drug was artemether/lumefantrine 45.1% (n = 271). On the other hand, out of 600 encounters, in 29.1% (n = 175) of the cases antibiotics and in 21.6% (n = 126) of the cases injections were prescribed. Drugs were prescribed by generic names in only 3% (n = 18) of the cases. Of the 600 encounters, diagnosis was written in 37.2% (n = 223), of the cases. The common diagnosis included was: malaria 24.5% (n=147), malaria/fever 7.8% (n = 47), malaria/UTI 3.1% (n=19). Moreover significant difference ($p \leq 0.05$) in prescribing practices for the treatment of malaria among public and private health facilities was observed in both the cities.

Conclusion: The results of the present study highlighted that prescribing practices differ among both public and private sector in the two cities and none of the sector was a true representative of ideal prescribing practices and rational drug use.

Practice implications: The present study contributes in identification of the existing gaps in prescribing practices for the treatment of malaria among public and private tertiary healthcare facilities and will serve as baseline to design future interventions for improvement.

Key words: Healthcare system, Irrational drug use, Malaria, Prescribing practices, Pakistan, Tertiary healthcare facilities

Introduction

Malaria is one of the major cause of morbidity and mortality in Pakistan, and largely affects the poor segments of the population living in hot and

humid areas (1). Worldwide, it kills more than one million people each year and an estimated number of annual malaria episodes in Pakistan are 1.5 million of which 24% constitute of confirmed cases of P. falciparum malaria. Due to the lack of good health care facilities and functioning diseases surveillance system, morbidity and mortality in most of the instances goes unreported (2). Malaria is typically diagnosed in the country through clinical impression, and predominantly all the presenting fever cases are suspected and treated for malaria. Hence, there is a potential prejudice for overestimating the burden of the disease in the country (3).

There are many problems associated with the current treatment practices in the country and require further investigation in order to improve the current situation. Few of the key elements in controlling malaria and reducing associated morbidity and mortality rate are early diagnosis, appropriate treatment and good quality patient care services (4). Prescribing patterns might have a direct influence on the effective control of the disease and in promoting irrational drug use. The impact of this inappropriate use of drugs results in ineffective drug therapy, wastage of resources, high costs of treatment, increased risk of adverse drug reactions, emergence of drug resistance and ultimately the psychosocial impacts on patients (5). Polypharmacy, peer influence, pressure to conform with perceived patient demands, lack of appropriate diagnosis and treatment based on clinical impression and non-adherence of prescribers with the standard treatment guidelines are few of the leading factors towards irrational prescribing practices (6).

Patients seek malaria treatment from a wide range of sources ranging from nomadic drug sellers to healthcare facilities and patients often self-treat and then seek advice from formal healthcare providers (7-8). Many countries have complex health care systems because of the differences in the working of the public and private sectors, working along each other. The private sector is more involved in malaria case management with treating over 50% of malaria cases in many endemic countries as compared to the public sector due to easy accessibility and shorter waiting times. (9). Previous studies have reported many problems associated with the prescribing practices in both public and private health care facilities and both private and public practitioners usually do not comply with the standard treatment guidelines (9-10). Overuse of injections and inappropriate prescribing of chloroquine was more prevalent in the private sector as compared to the public health care facilities (6).

Pakistan is listed among moderately malaria endemic countries and malaria is the second most frequently reported diseases from public sector healthcare facilities (11). It is usually expected that use of anti-malarial drugs would be more rational in healthcare facilities as compared to other providers such as retailers and general practitioners (7). But it is often observed that the prescribing and dispensing practices are not up to the mark in public and private healthcare facilities in developing countries and Pakistan is not an exception to it. Polypharmacy, overuse of antibiotic, misuse and overuse of injections, short consultation time and poor patient compliance are common manifestations of irrational drug use observed in the healthcare facilities (10, 12-14). Pakistan has a federal political system, therefore, health care provision is decentralized and primarily the responsibility of the provincial governments. The Federal Ministry of Health is responsible for national policy, planning, coordination and the implementation of the six national health programs on family planning, immunization, HIV/AIDS, tuberculosis, malaria and nutrition. The public healthcare facilities providing services at provincial and district levels are categorized as: primary level health care facilities (basic health units, rural health centers, mother & child health centers, TB clinics and dispensaries), secondary level health care facilities (tehsil headquarter hospitals and district head quarter hospitals) and tertiary level health care facilities (tertiary hospitals, post graduate medical institutes, teaching hospitals). All the tertiary healthcare facilities have a primary section for treating common diseases including malaria. Cases are referred from lower to higher level depending on severity of problem and available infrastructPublic health sector spending by the government is low (2.4% of GDP in 2003) and there is chronic shortage of trained staff, essential drugs, medical and other supplies in most of the public healthcare facilities. As a result patients frequently have to seek medical attention in the private health-

care facilities, which are usually concentrated in main urban areas (16-17). One of the unfortunate anomalies in our current referral system is that the private healthcare facilities are not appropriately categorized and not much attention has been paid in identifying the current prescribing practices at the private tertiary healthcare facilities. Therefore, the main objective of the present study was to assess the current prescribing practices carried for the treatment of malaria among public and private tertiary healthcare facilities in two cities of Pakistan; Islamabad (national capital) and Rawalpindi (twin city). The study will provide baseline data, which can serve as a basis for potential areas for intervention which will improve rational drug use in the healthcare system.

Methodology

A comparative, cross-sectional study was designed to evaluate the case records of patients including (daily registers, medical records, prescriptions, or patient-held record cards) treated for malaria in public and private tertiary healthcare facilities in the twin cities, namely Islamabad (federal capital) and Rawalpindi. The case records were collected from the male and female medicine wards of the facilities. A pre-validated tool i.e. WHO prescribing indicator form was used to collect data regarding current prescribing practices for the treatment of malaria (18). The prescribing form included core indicators and some additional indices such as demographics of patient, type of drug combinations prescribed i.e. anti-malarials, antibiotics and antipyretic , % of encounters having diagnosis, type of parasite, referral for malarial parasite test and malarial parasite results, calculation of anti-malarials dose on the basis of body weight, average number of drugs per encounter, % and average number of antibiotics and injections prescribed per encounter, % of prescriptions containing dose of anti-malarial drugs, strength of anti-malarial drugs, frequency of anti-malarial drugs and duration of anti-malarial drugs, % of drugs prescribed by generic name and their availability on essential drug list. The availability of standard treatment guidelines and essential drug list in the healthcare facility. Data collection was planned and permission for survey was obtained from relevant district health officers (DHO). The study was also approved by the panel of experts at Malaria Control Program, Ministry of Health, Government of Pakistan.

Sampling of facilities and patient encounters

Keeping in view the federal administrative and regulatory structure of the country and due to location and operation of Malaria control program in the capital city, two main cities of Pakistan namely Islamabad and Rawalpindi were selected for the study. The study population included all the public and private tertiary health care facilities treating malaria in Islamabad and Rawalpindi. A list of all the public and private tertiary healthcare facilities was obtained from respective District Health Offices. All the 20 public and private tertiary healthcare facilities were selected for the study and the sample size was Islamabad (n = 10,5 each public and private healthcare facilities) and Rawalpindi (n = 10,5 each public and private healthcare facilities).

For assessing the prescribing practices in each facility, thirty patient treated for malaria by the prescribers over the last one year were reviewed (18). A total of 600 patient encounters i.e. 300 from each sector (public and private) healthcare facilities situated in both cities were collected from daily registers, medical records, prescriptions, or patient-held record cards. At least two patients encounter per month during the low season and four patients encounter per month during the high season for malaria were selected. Retrospective method and interview of the head of the outpatient department on what the recommended prescribing practices were for each of the prescribed medicines was conducted and his or her recommended prescription pattern was applied to all encounters and medicines where records were missing (19).

Data collection and analysis

Data was collected by the principal investigator along with two teams comprised of five trained data collectors in each team trained by the group of experts including principal investigator (19). The data collectors were students of the final year Doctor of Pharmacy program. After the data collection, data was coded and analyzed using

statistical software SPSS version 16. Descriptive statistics (frequencies and percentages) were used to describe trends in the current prescribing practices. Chi-Squared test was used to find association among prescribing practices and different healthcare sectors in the two cities.

Results

A total of 600 malaria cases were collected and analyzed. Out of 600 encounters, 50 % (n=300) were collected from public and 50 % (n=300) from private tertiary healthcare facilities. The mean age of the malaria patients in the encounters was 35.00 years (± 14.04), ranging from 20 to 60 years while 68.3% (n=410) of the patients were male and remaining 31.7% (n=190) were female. The mean number of drugs per encounter was 2.37 (± 0.557), ranging from 1 to 5 drugs per encounter while mean number of antibiotics and injections per encounter were 0.32 (± 0.513) and 0.23 (± 0.470), ranging from 1 to 2 antibiotics and injections per encounter respectively.

The most commonly prescribed anti-malarial drugs were chloroquine phosphate 13.5% (n=81), artemether/lumefantrine 45.1% (n = 271), artemether 15.3% (n = 92), sulphadoxine/pyremethamine 10.5% (n = 63), amodiaquine HCl 6% (n = 36). Ceftriaxone sodium 5.3% (n = 32), ciprofloxacin 14% (n = 84), levofloxacin 4% (n = 24) were the most commonly prescribed antibiotics. Paracetamol 87.6% (n = 526), brufen 2.3% (n = 14) and mefnamic acid 2.3% (n = 14) were the most commonly prescribed anti-pyretics. A detail description of most commonly prescribed anti-malarial drugs, antibiotics and anti-pyretics in public and private tertiary healthcare facilities in both cities is given (Table 1).

Dose of anti-malarial drugs were mentioned in 84.5% (n = 507), of the cases while frequency of the drugs in 58.1% (n = 351), strength of the drugs in 24.3% (n = 146) and duration of the drug in 68.8% (n = 413) of the cases respectively. Antibiotics were prescribed in 29.1% (n = 175) of the cases whereas injections were part of the prescription in 21.6% (n=126) of the cases . Drugs were prescribed by their generic name in only 3% (n = 18) of the cases. While dose of the anti-malarial drugs was not calculated as per patient body weight in any of the encounters. Standard treatment guidelines for malaria were not available in any of the public or private tertiary healthcare facility in the twin cities. Chi-Squared test was used to find the association among prescribing practices in public and private tertiary healthcare facilities in the twin cities. A significant difference ($p \leq 0.05$) was observed in prescribing practices for the treatment of malaria among both sectors in the twin cities (Table 2).

Diagnosis was written in 37.2% (n = 223), of the encounters. The different types of diagnosis most commonly given were: malaria 24.5% (n = 147), malaria/fever 7.8% (n = 47), malaria/UTI 3.1%

Table 1. Commonly prescribed anti-malarial drugs, antibiotics and anti-pyretic for the treatment of malaria in public and private tertiary healthcare facilities in the twin cities

Indicator		Islamabad (n = 300)		Rawalpindi (n = 300)	
		Public n= 150 F (%)	Private n= 150 F (%)	Public n= 150 F (%)	Private n= 150 F (%)
Anti-malarial drugs	Chloroquine phosphate	24 (16%)	19 (12.7%)	15 (10%)	23 (15.3%)
	Artemether/lumefentraine	61 (40.7%)	66 (44%)	72 (48%)	72 (48%)
	Artemether	37 (24.7%)	0 (0%)	35 (23.3%)	20 (13.3%)
	Sulphadoxine/pyremethamine	10 (6.7%)	23 (15.3%)	6 (4%)	24 (16%)
	Amodiaquine HCl	0 (0%)	27 (18%)	9 (6%)	0 (0%)
Antibiotics	Ceftraixone sodium	26 (17.3%)	4 (2.7%)	0 (0%)	2 (1.3%)
	Ciprofloxacin	36 (24%)	5 (3.3%)	24 (16%)	19 (12.7%)
	Levofloxacin	5 (3.3%)	0 (0%)	0 (0%)	19 (12.7%)
Anti-pyretic	Paracetamol	116 (77.3%)	137 (91.3%)	124 (82.7%)	149 (99.3%)
	Brufen	7 (4.7%)	0 (0%)	7 (4.7%)	0 (0%)
	Mefnamic acid	1 (0.7%)	2 (1.3%)	10 (6.7%)	1 (0.7%)

Table 2. Prescribing practices for the treatment of malaria among public and private tertiary healthcare facilities in the twin cities

Indicator	Islamabad (n = 300)			Rawalpindi (n = 300)		
	Public n= 150 F (%)	Private n= 150 F (%)	P value	Public n= 150 F (%)	Private n= 150 F (%)	P value
Dose of anti-malarials given	74 (49.3%)	135 (90%)	0.000	150 (100%)	148 (98.7%)	0.156
Strength of anti-malarials given	0 (0%)	45 (30%)	0.000	68 (45.3%)	33 (22.7%)	0.000
Frequency of anti-malarials given	57 (38%)	144 (96%)	0.000	115 (76.7%)	71 (47.3%)	0.000
Duration of anti-malarials given	70 (46.7%)	95 (63.3%)	0.004	124 (82.7%)	88 (58.7%)	0.000
Antibiotics given	91 (60.7%)	19 (12.7 %)	0.000	24 (16%)	41 (27.3%)	0.017
Injections given	75 (50%)	7 (4.7%)	0.000	0 (0%)	44 (29.3%)	0.000
Prescribing by generic name	9 (6%)	0 (0%)	0.12	9 (6%)	0 (0%)	0.12

Chi-Squared test $p \leq 0.05$

Table 3. Diagnostic practices for treatment of malaria among public and private tertiary healthcare facilities in the twin cities

Indicator		Islamabad (n = 300)			Rawalpindi (n = 300)		
		Public n= 150 F (%)	Private n= 150 F (%)	P value	Public n= 150 F (%)	Private n= 150 F (%)	P value
Diagnosis given on prescription		33 (22%)	52 (34.7%)	0.015	81 (54%)	60 (38%)	0.005
Diagnosis type given	Malaria	15 (10%)	33 (22%)		69 (46%)	30 (20%)	
	Malaria/fever	8 (5.3%)	4 (2.6%)		5 (3.3%)	30 (20%)	
	Malaria/UTI	5 (3.3%)	7 (4.6%)		7 (4.6%)	0 (0%)	
MP test referred		3 (2%)	30 (20%)	0.000	7 (4.6%)	15 (10%)	0.076
Results of MP test	Positive	2 (1.3%)	9 (6%)		0 (0%)	0 (0%)	
	Negative	1 (0.6%)	21 (14%)		0 (0%)	0 (0%)	
	Not given	147 (98%)	120 (80%)		7 (4.6%)	15 (10%)	

Chi-Squared test $p \leq 0.05$

(n=19). Malarial parasite test was referred in 9.2% (n = 55) of the cases. The different types of result of malarial parasite test given on the encounters were: positive 1.8% (n = 11), negative 3.7% (n = 22), and no result given 94.5% (n = 567). Chi Squared test was used to find the relationship among diagnostic practices and public and private tertiary healthcare facilities in both the cities. A significant difference ($p \leq 0.05$) was observed in the diagnostic practices for the treatment of malaria among both sectors in the twin cities (Table 3).

Discussion

Improving rational drug use at the healthcare facilities has always remained a major challenge. Development of resistance to antibiotics, ineffective treatment, adverse effects, drug dependence and economic burden to the patient and society are the major dilemma of present medical practice in the case of malaria treatment (20). Prescribing practices have shown influence on the emergence of resistance to anti-malarial drugs and artemisinin-based combinations are currently the most valuable drugs available for the management of malaria (21-22). The results of the present study showed that artemether/lumefentrine combination was prescribed more than any other anti-malarial drug as a common practice in both public and private healthcare facilities. The results of this study are in line with another study which showed a significant high use of artemisinin based combination therapy for the treatment of malaria in Nigeria (23). This irrational use of Arteminsin combination treatment could undermine one of the goals of combination therapy, which is to prevent the emergence of resistant malaria parasites. The present study showed that artemether and chloroqui-

ne were the most commonly prescribed antimalarial after artemether/lumefentrine. This might be due to the continuous availability of chloroquine tablets due to an affordable price, in both public and private facilities or an established pattern by which most doctors prefer to treat the patients with monotherapy instead of switching to combination therapy. Same reasons were highlighted for the prescribing of Chloroquine and artemether monotherpy in healthcare facilities in Nigeria (24). Other antimalarials, namely sulfadoxine/pyremethamine, amodiaquine and primaquine phosphate, were rarely prescribed. It was observed that most of the malaria encounters were of male patients as compared to females this might be correlated to more frequent travelling of males compared to females. This fact has also been highlighted by Garnham (25).

Antibiotics and injection use is usually not preferred in the treatment of malaria and also do not conform to the treatment guidelines. This study showed that prescribing of antibiotics and injections in treatment of malaria was more prevalent in the public sector. This might be due to lack of laboratory diagnostic test and patient demand. The results are in line with another study indicating overuse of antibiotics and injections promoting irrational drug use and higher rate of emergence of drug resistance (26). The study also revealed a high rate of prescribing by brand names and almost all the prescribed drugs were present on the essential drug list in both public and private facilities. The reason for prescribing drugs mostly by brand names might be due to the availability of some brand name drugs equivalent to the cost of same drug as generic name and influence of pharmaceutical industry on prescribing practices. The overall low generic prescribing observed was comparable to the results of the other studies conducted in Nigeria and Nepal (23, 27).

Rational prescribing requires that prescribers follow a standard process of prescribing and in accordance with standard treatment guidelines. The results of the study showed that usually the practitioners in both public and private facilities were inclined to mention appropriate dose, strength, frequency and duration of drugs on the encounters but still in most of the cases negligence on the part of the prescribers has been observed which can be prominent predictors of irrational prescribing. The present study confirms the findings of the study conducted in Cambodia which concluded that high rate of inappropriate prescriptions for treating malaria are mostly due to inappropriate doses, frequency, dosages and duration of treatment (28).

Over-diagnosis of malaria is common even when malaria parasite testing is available in the hospital settings. Prescribing antimalarial drugs to patients without evidence of malaria parasitaemia and failure of treatment for alternative causes of disease is a common practice (29). Laboratory diagnosis can improve the treatment of malaria, but the results of the present study showed that only few facilities were offering any laboratory diagnostic services for the confirmation of malaria in the patients. This is the most prominent factor promoting inappropriate prescribing practices leading to irrational drug use in treatment of malaria in healthcare system of Pakistan. Reasons underlying this practice might include shortage of malaria parasite testing equipment and technical laboratory staff, poor laboratory skills, attitude of health personnel's and unaffordability of patient towards the cost of the test. However, it was observed that prescribing of anti-malarial drugs after laboratory confirmation only decreased significantly the total number of prescriptions in Malawi (30).

Private sector receives a larger proportion of the population suffering from malaria as compared to the public sector but still prescribing practices remain unknown in the private sector although government regulation do influence this sector to some extent. A common finding of various studies from developing countries highlighted that the prescribing practices for the treatment of malaria were diverse in both sectors and standard treatment guidelines were not followed by most of the prescriber's (10, 31-32). A similar scenario was observed in this study confirming that the prescribing practices differed dramatically among public and private healthcare facilities in the twin cities. Standard treatment guidelines were either not available, or if available were not followed at all in both public and private healthcare facilities. The public sector in Rawalpindi was relatively better in prescribing practices while that was true

for the private sector in Islamabad. This might be due to more frequent and better monitoring and more experienced doctors working in the public healthcare facilities in Rawalpindi. On the other hand, a large number of population living in Islamabad accounts for higher literacy rates and socioeconomic status and prefer private sector for treatment which in turn is a check itself on the practices carried in the private sector.

Conclusion

The results of the present study concluded that prescribing practices differ among both public and private sector in the twin cities and none of the sector was a true representative of ideal prescribing practices and rational drug use. Public healthcare facilities were comparatively better in prescribing practices in Rawalpindi while on the other hand private sector was more rational in their practice in Islamabad. This indicates that private sector has also got the potential to promote rational drug use but usually public healthcare facilities are the major focus of most of the interventions. Innovative approaches are needed to promote rational prescribing and drug use in both the public and private health care facilities. National policies, national programs and stakeholders have to involve private sector in all the interventional programs and promote collaborative working of both sectors to improve the overall impact on performance and practices in the healthcare system for the control of malaria in Pakistan.

Practice Implications

The present study contributes in identification and comparison of the existing gaps in prescribing practices for the treatment of malaria among public and private tertiary healthcare facilities. The study serves as a baseline to design future interventions and to develop methods of better patient handling through appropriate diagnosis and rational prescribing practices to improve therapeutic outcomes of the patient and control of disease.

Acknowledgements

The authors thank the District Health Offices and MS of all the tertiary hospitals of Islamabad and Rawalpindi for their support during the study. Special gratitude to the data collectors.

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Association between stride length and body composition, physical fitness level, and activity of daily living in the Korean elderly population

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Abstract

The purpose of this study was to examine the association between stride length and body composition, physical fitness level, and activity of daily living (ADL) in the Korean elderly population. This study included 98 Korean elderly subjects aged 65–82 years. These subjects visited the health promotion center at Gyeong-Ju, Gyeongsangbuk-Do, Korea, where stride length, body composition, physical fitness level, and ADL were assessed in August 2011. Subsequently, the association of stride length with body composition, physical fitness level, and ADL were assessed using multivariate logistic regression analysis adjusted for gender, age, and body mass index (BMI). The odds ratio (OR) [95% confidence interval (CI)] of a stride length across the 6 min walk groups was 8.042 (range, 3.132–20.650; $p < 0.001$) for the greater level, compared to the smaller level. The OR (95% CI) of a stride length across the grip strength groups was 3.071 (range, 1.307–7.218; $p = 0.010$) for the greater level, compared to the smaller level. The OR (95% CI) of a stride length across the gait speed groups was 0.429 (range, 0.088–0.566; $p = 0.002$) for the greater level, compared to the smaller level. The OR (95% CI) of a stride length across the ADL groups was 2.571 (range, 1.086–5.834; $p = 0.031$) for the greater level, compared to the smaller level. The differences in the OR (95% CI) of a stride length among the following groups were insignificant: fat free mass (FFM), percent body fat, sit ups, sit and reach, and Standing on 1 foot with open eyes, compared to the greater level ($p > 0.05$). We conclude that body composition is not closely related to a greater stride length. However, the association between physical fitness level such as distance covered in a 6 min walk, grip strength, gait speed, and ADL was evident.

Key words: **A**ctivity of daily living, Body composition, Elderly, Physical fitness level, Stride length

Introduction

Recently, an increase in the elderly population has become a serious social and public health problem in Korea. In 2010, the elderly population accounted for 11.0% of the population in Korea. In addition, the percentage of the elderly population is expected to increase to 14.3% in 2018 and 20.8% in 2026 (1). Furthermore, Korea is predicted to rapidly transform into an aged society, compared to other countries (1).

An increase in the elderly population is tightly correlated with a drastic increase in chronic degenerative diseases and medical costs. In Korea, for example, the elderly population increased from 5.8% in 1996 to 9.1% in 2005, and subsequently, medical costs for the elderly increased from 13% in 1996 to 26% in 2005. Statistical data show that the rate of increase of medical costs for the elderly is much higher than the rate of growth of the elderly population (2).

An approach to control the rapid increase of elderly population-related medical costs is to prevent chronic diseases among the elderly through various exercises or increased physical activity (PA) (3-4). Furthermore, walking exercise is the most commonly recommend exercise to improve overall health and fitness of the elderly (5-7). Interestingly, Kim *et al. (*2005) reported that the greater the stride length, the greater is the energy expenditure, because the lower limb joint and muscles are stimulated to a higher degree at a greater stride length than at a normal stride length. Therefore, we recommend a greater than normal stride length to increase energy expenditure (8).

Many previous studies showed that muscle loss, called "sarcopenia," is associated with aging (9-11). According to an epidemiological study, sarcopenia was prevalent in >25% of subjects aged more than 65 years and in >50% in those aged more than 80 years (10). Sarcopenia is not directly related to a cause of death, but the muscle loss generally causes changes in body composition, including reduction in muscle strength, physical fitness, and activity of daily living (ADL), which can restrict independent lifestyle activities. Moreover, it occurs in conjunction with cardiovascular and chronic degenerative diseases such as obesity, type 2 diabetes, hyperlipidemia, and hypertension (11). Therefore, sarcopenia could be a potential risk factor for death in the elderly.

For the maintenance or improvement of the physical fitness and activity of the elderly, prevention and/or treatment of sarcopenia are critical. Because a greater than normal stride length increases energy expenditure and PA, it may help improve body composition, physical fitness level, and ADL. However, to our knowledge, no study has focused on this research topic in the elderly. Therefore, the purpose of this study was to examine the association between stride length and body composition, physical fitness level, and ADL in the Korean elderly population.

Methods

Subject

This study included 98 Korean elderly subjects aged 65–82 years. These subjects visited the health promotion center at Gyeong-Ju, Gyeongsangbuk-Do, Korea, between August 1, 2011, and August 31, 2011, where stride length, body composition, physical fitness level, and ADL were assessed. All study procedures were approved by the Human Care and Use Committee of the Society of Sport Research Institute of Dongguk University. All subjects submitted a written consent form. The characteristics of the subjects are shown in Table 1.

Experimental procedure

Body composition

The body mass index (BMI, kg/m^2) was calculated from the height and weight of the subjects. Fat free mass (FFM) and percent body fat were assessed using an 8 polar electrode impedance instrument (InBody 3.0, Biospace, Korea). This instrument uses 8 tactile electrodes: 2 in contact with the palm and thumb of each hand, and 2, with the anterior and posterior aspects of the sole of each foot. This instrument measures the resistance of the arms, trunk, and legs at frequencies of 5, 50, 250, and 500 kHz (12).

All the subjects were asked to fast for 4 h, prohibited from performing any exercise for 12 h, and

Table 1. The characteristics of the subjects (N = 98)

Variables	Male (N = 43)		Female (N = 55)	
	Range	Mean ± SD	Range	Mean ± SD
Age (years)	65.00 - 82.00	71.30 ± 4.70	65.00 - 78.00	70.00 ± 3.61
Height (cm)	160.00 - 181.00	167.07 ± 5.12	145.00 - 166.00	155.11 ± 4.59
Weight (kg)	50.00 - 81.20	64.41 ± 7.07	39.70 - 77.20	57.41 ± 7.87
BMI (kg/m^2)	16.71 - 27.82	23.06 ± 2.18	16.96 - 30.92	23.82 ± 2.80
Fat free mass (kg)	38.20 - 57.30	46.38 ± 4.75	28.10 - 44.30	36.24 ± 4.33
Body fat (%)	13.40 - 30.70	22.60 ± 3.98	15.90 - 33.30	31.91 ± 6.12
6-min walk (m/ 6 min)	442.00 - 715.00	590.98 ± 69.37	347.00 - 701.00	555.16 ± 73.21
Sit ups (repetitions/30 s)	00.00 - 21.00	10.65 ± 4.05	00.00 - 16.00	3.05 ± 4.04
Grip strength (kg)	11.05 - 45.70	32.38 ± 7.23	6.65 - 29.80	18.94 ± 5.97
Sit and reach (cm)	1.51 - 6.90	3.50 ± 1.18	2.68 - 6.00	4.13 ± 0.69
Standing on 1 foot with open eyes (s)	1.12 - 120.00	25.84 ± 24.32	3.12 - 120.00	23.83 ± 27.17
Gait speed (s/10 m)	5.93 - 12.53	8.13 ± 1.47	6.00 - 16.02	8.88 ± 1.84
Activity of daily living (point)	13.00 - 36.00	27.60 ± 4.92	15.00 - 34.00	24.04 ± 4.57
Walking stride length (cm)	54.00 - 95.00	72.51 ± 9.80	38.00 - 87.00	63.36 ± 8.40

urinating just before the impedance measurement. The subjects were advised to wear light clothing and remove all metallic items, which could interrupt the electric current during the measurement. All methods employed for assessing body composition followed the recommendations of the book *Applied Body Composition Assessment* (13).

Stride length and physical fitness level

The stride length (cm) was measured against a normal step length on the basis of footprints.

The physical fitness measurements included tests for cardiorespiratory endurance (6 min walk [m/6 min]), muscular endurance (sit ups [repetitions/30 s]), muscular strength (grip strength [kg]), flexibility (sit and reach [cm]), balance (Standing on 1 foot with open eyes [s]), and power (gait speed [s/10 m]).

For the 6 min walk test (cardiorespiratory endurance), the total walking distance (m) on a 400 m track during 6 min was recorded.

For the sit ups test (muscular endurance), the subjects were required to lie on a sit up board, bend their knees to 90°, and raise their upper body and bend forward by using only their abdominal muscles. The measurements were based on the number of sit ups completed in 30 s.

For the grip strength test (muscular strength), the control lever of a grip strength tester (TKK 5401 GRIP D, TAKEI, Japan) that had an inbuilt potentiometer control system was adjusted such that the second knuckles of the fingers were at the bottom of the grip bar. The subjects flexed maximally over 3 trials, and the average value of strength (kg) was recorded.

For the sit and reach test (flexibility), the subjects sat on a flexibility measuring instrument (KJ092, Japan), positioned their heels approximately 5 cm apart, placed their heels on the edge, extended their knees, bent their backs forward, and naturally made the measuring instrument board move forward. The average score from the 3 trials was recorded.

For the test in which the subjects had to standing on 1 foot with their eyes open (balance), the subjects stood on the ground by using only their preferred leg with their eyes open. We measured the time until the elevated leg touched either the other leg or the ground or until both hands holding the waist dropped. The average result after 3 trials was recorded.

For gait speed test (power), we measured the walking time (s) immediately after the subjects started walking, and recorded the total walking time (s) covered during 10 m. The average time from the 3 trials was recorded.

Activity of daily living

ADL survey consisted of 12 items, and each item was scored on a 3 point Likert scale (from 1 = "bad" to 3 = "good"). The best and worst scores for the total number of items were 36 and 12, respectively (14).

Statistical analysis

All the results obtained from this study are expressed as mean ± standard deviation. The stride length level, body composition, physical fitness level, and ALD were divided into 2 categories (greater and smaller levels), and the cutoff points were derived from our data. Subsequently, multivariate logistic regression analysis was conducted to evaluate the association of body composition, physical fitness level, and ADL with the smaller and greater stride lengths, after adjusting for gender, age, and BMI. Statistical significance was set at $p < 0.05$, and all the analyses were performed using SPSS ver. 12.0 (SPSS, Chicago, IL, USA).

Results

The multivariate logistic regression analyses of body composition, physical fitness level, and ADL for the low and high stride length groups of the elderly population in Korea are shown in Table 2.

The odds ratio (OR) [95% confidence interval (CI)] of a stride length across the 6 min walk groups was 8.042 (range, 3.132–20.650; $p < 0.001$) for the greater level, compared to the smaller level. The OR (95% CI) of a stride length across the grip strength groups was 3.071 (range, 1.307–7.218; $p = 0.010$) for the greater level, compared to the smaller level. The OR (95% CI) of a stride length across the gait speed groups was 0.429 (range, 0.088–0.566; $p = 0.002$) for the greater level, compared to the smaller level. The OR (95% CI) of a stride length across the ADL groups was 2.571 (range, 1.086–5.834; $p = 0.031$)

Table 2. The multivariate logistic regression analyses of body composition, physical fitness level, and activity of daily living for the low- and high-walking stride length groups of Korean elderlies

	Category		Elderly (N = 98)				
			High- Vs. low-walking stride length				
		Level	ß	S.E.	OR	95% CI	p-value
Body composition	Fat free mass (kg)	Low (bad)	Ref				
		High (good)	0.699	0.484	2.013	0.780-5.192	0.148
	Body fat (%)	Low (good)	Ref				
		High (bad)	-0.628	0.534	0.534	0.187-1.521	0.240
Physical fitness	6 min walk (m)	Low (bad)	Ref				
		High (good)	2.085	0.481	8.042	3.132-20.650	<0.001***
	Sit ups (repetitions/30 s)	Low (bad)	Ref				
		High (good)	-0.107	0.418	0.898	0.396-2.038	0.798
	Grip strength (kg)	Low (bad)	Ref				
		High (good)	1.112	0.436	3.071	1.307-7.218	0.010*
	Sit and reach (cm)	Low (bad)	Ref				
		High (good)	0.686	0.429	1.986	0.857-4.603	0.110
	Standing on 1 foot with open eyes (s)	Low (bad)	Ref				
		High (good)	0.238	0.423	1.268	0.554-2.904	0.574
	Gait speed (s/10 m)	Low (good)	Ref				
		High (bad)	-1.502	0.476	0.223	0.088-0.566	0.002**
Activity of daily living (point)		Low (bad)	Ref				
		High (good)	0.923	0.429	2.517	1.086-5.834	0.031*

S.E; Standard Error, OR; Odd Ratio, CI; Confidence Interval
**p<0.05 **p<0.01 ***p<0.001, tested by multivariate logistic regression analysis adjusted for gender, age, and body mass index*

for the greater level, compared to the smaller level. The differences in the OR (95% CI) of a stride length among the following groups were insignificant: FFM, percent body fat, sit ups, sit and reach, and Standing on 1 foot with open eyes, compared to the greater level ($p > 0.05$).

Discussion

A greater stride length is closely associated with an increase in energy expenditure (8). Therefore, a positive association between a greater stride length and body composition in Korean elderly people might be expected. This study indicates that a greater stride length is not associated with body composition. However, a greater stride length had a positive relationship with physical fitness level and ADLeven after controlling for covariate variables such as gender, age, and BMI.

Old age is a phase of rapid physical decline, central nervous system degeneration, decreased hormone levels, and psychological negative change (14-18). We believe that no relationship was found between a greater stride length and body composition in the elderly, because a greater stride length is a low intensity PA and not a high intensity PA. Therefore, for changing body composition of the elderly a high intensity PA such as jogging, swimming, and cycling might be needed.

Nevertheless, greater stride length is associated with positive physical fitness level such as 6 min walk, grip strength, gait speed, and ADL. We think that although a greater stride length had no effect on body composition, because it is a stimulated PA, it might be associated with an increase in physical fitness level and ADL. However, to determine the benefits of a greater stride length for elderly population in Korea, well-designed studies should be performed in the future.

This study has several limitations. First, it was a retrospective *cohort study.* Thus, we did not determine the cause and effect relationship, but only an interrelationship. Second, because the study subjects were recruited from a health promotion

center at Gyeong-Ju, Gyeongsangbuk-Do, Korea, they did not represent the entire Korean elderly population. Third, the sample size of this study was small (N = 98).

Conclusion

We concluded that body composition is not closely related to a greater stride length. However, the association between physical fitness level such as the distance covered in a 6 min walk, grip strength, gait speed, and ADL are evident.

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The prevalence of congenital hypothyroidism in north of Iran: First report of screening program

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Abstract

Background and objective: Congenital hypothyroidism is one of the most common causes of preventable mental retardation and it seems that the prevalence in Iran is higher than other countries. So this study was to determine the prevalence of hypothyroidism in North of Iran.

Methods: This cross-sectional study was done on 10,573 newborns that participated in thyroid screening program in Mazandaran province (North of Iran) from 2010 to 2011. The congenital hypothyroidism, sex and the city of residence were recorded.

Findings: The overall prevalence of hypothyroidism in this study was 1.4 in 1000 live births (CI95%: 1-1.8) the highest prevalence in Neka (3 in 1000) and the lowest prevalence was found in Savadkooh. Prevalence in males (2 in 1000) was higher than females (1.1 in 1000).

The overall prevalence after screening was calculated 1 in 714 and 1 in 916 and 1 in 587 in female and male, respectively.

Conclusion: The results showed that the prevalence of hypothyroidism in infants is remarkable and screening program need to continue in our region.

Key words: Congenital hypothyroidism, Neonate, Screening.

Introduction

Congenital hypothyroidism as an endocrine dysfunction is an important event to be studied (1). This disease is one of the most common treatable causes of mental retardation (2). Delays in diagnosis and treatment of congenital hypothyroidism will result in intelligence quotient and neurologic development (3). The frequent symptoms in this disease include: lethargy, hoarse cry, constipation, prolonged jaundice and the most common signs are birth weight greater than the ninetieth percentile, umbilical hernia, macroglossia and myxedematous facies. Congenital hypothyroidism is classified into permanent and transient forms. Hypothyroidism is diagnosed after detection by neonatal screening tests (4). Neonatal thyroid screening is an available monitoring tool for the early detection of hypothyroidism (5). The sample used for neonatal screening tests is blood from a heel-prick collected on special filter paper cards. The sample is routinely collected between two and five days of age; some programs use cord blood for screening (4). The prevalence of congenital hypothyroidism is 1 in 3000 to 4000 newborns and this varies depending on the race, ethnicity and the method of screening (6). Nearly all screening programs report a female prodominance, approaching a 2:1 female to male ratio (7,8). Data obtained from national and local screening programs show that the prevalence of congenital hypothyroidism varies worldwide. So the aim of this study was to determine the prevalence of congenital hypothyroidism in North of Iran.

Methods

This is a cross-sectional study. Congenital hypothyroidism screening program began in Iran in 2006 and is being continued. In this screening study, of all infants were born in different cities of Mazandaran province between 19 March 2010 to 20 March 2011, were evaluated. The congenital hypothyroidism, sex and the city of residence were recorded. This study approved by ethical committee of Mazandaran University of Medical Sciences. The coverage percent in our study was 100%.

Congenital hypothyroidism program in Iran: Four drops of blood were taken from the heel in 3 to 5 days after the birth of all babies and the

level of TSH (mU/L) was determined. TSH less than 5 was considered normal and neonate with higher levels of 5 were recalled. TSH between 5 and 9.9 at 4th week and TSH between 10 and 19.9 in second to third week levels were assessed for TSH and T4 blood sample. At a TSH of more than 20 in initial assessment, immediately the TSH values of venous blood determined and medication beginns and medication will stop if TSH and T4 levels were normal in venous samples. The level of TSH more than 10 mU/L or T4 less than 6.5 Mg/dl in venous samles was considered as hypothyroidism.

Laboratory methods: TSH was measured with Iran Kimiapajoohan Co. kits using Enzyme Linked Immunosorbent assay (ELISA) methods. T4 level testing was performed with gamma counter.

Data analysis: Data analyzed with SPSS and confidence interval 95% calculated for prevalence rate. The number needed to screen (NNS) was calculated for this screening program. NNS is defined as the number of neonates that need to be screened for a given period to prevent one adverse event by a prevention program (9).

Results

In this screening study 37117 neonates were evaluated for congenital hypothyroidism, that 18326 subjects (49.3%) were female and 18791 (51.7%) male.

The prevalence of congenital hypothyroidism (permanent and transient) in the general distribution separation of the sex and city is shown in the Table 1. Totally, congenital hypothyroidism was diagnosed in 52 cases with 20 (38.4%) females and 32 (61.6%) males. The overall prevalence of hypothyroidism in this study was 1.4 in 1000 live births (CI95%: 1-1.8), and the highest prevalence was recorded in Neka (3 in 1000) and the lowest prevalence was found in Savadkooh. Prevalence in males (2 in 1000) was higher than females (1.1 in 1000), (Table 1).

The overall number needed to screen was 1 in 714 and 1 in 916 and 1 in 587 in female and male, respectively. The NNS distribution for different city shown in table 2.

Table 1. The frequency and prevalence of Congenital Hypothyroidism (CH) cases in Mazandaran

	Screened			Number of CH			Prevalence of CH (in 1000)		
	Total	Female	Male	Total	Female	Male	Total Prevalence (CI 95%)	Female	Male
Galoogah	559	279	280	1	0	1	1.8 (1.7-5.3)	0	4
Behshahr	2908	1461	1447	5	1	1	1.7 (0.2-3.2)	0.7	1
Neka	1650	806	844	5	3	3	3 (0.4-5.7)	3.7	4
Sari	7763	3786	3977	12	9	9	1.5 (0.7-2.4)	2.4	2
Joybar	1187	595	592	2	1	1	1.7 (0.7-4)	1.7	2
Ghaemshahr	4215	2119	2096	6	4	4	1.4 (0.3-2.6)	1.9	2
Savadkooh	829	398	431	0	0	0	0	0	0
Babolsar	1806	916	890	1	1	0	0.6 (0.5-1.6)	1.1	0
Feridoonkenar	776	323	453	1	1	1	1.3 (1.2-3.8)	3.1	2
Amol	6164	3025	3139	7	4	4	1.1 (0.3-2)	1.3	1
Mahmoodabad	1012	525	487	2	1	1	2 (0.8-4.7)	1.9	2
Noor	1739	873	866	1	1	1	0.6 (0.6-1.7)	1.1	1
Noshahr	1360	700	660	3	1	2	2.2 (0.3-4.7)	1.4	3
Chaloos	1836	911	925	3	1	2	1.6 (0.2-3.5)	1.1	2
Tonkabon	2381	1146	1235	2	0	2	0.8 (0.3-2)	0	2
Ramsar	932	463	469	2	1	1	2.1 (0.8-5.1)	2.2	2
Total	37117	18326	18791	52	20	32	1.4 (1-1.8)	1.1	2

Table 2. Number needed to screen for congenital hypothyroidism in Mazandarn

City	Total	Female	Male
Galoogah	559	0	280
Behshahr	582	1461	1447
Neka	330	269	281
Sari	647	421	442
Joybar	594	595	592
Ghaemshahr	703	530	524
Savadkooh	0	0	0
Babolsar	1806	916	0
Feridoonkenar	776	323	453
Amol	881	756	785
Mahmoodabad	506	525	487
Noor	1739	873	866
Noshahr	453	700	330
Chaloos	612	911	463
Tonkabon	1191	0	618
Ramsar	466	463	469
Total	714	916	587

Discussion

In this study, we determine the prevalence of congenital hypothyroidism in the Northern region of Iran. The overall prevalence of congenital hypothyroidism (both transient and permanent) was 1.4 in 1000 live births (CI95%: 1-1.8), On the other hand the NNS for CH was 714. The present findings show that the prevalence of congenital hypothyroidism was higher than studies in other countries, as the prevalence of congenital hypothyroidism in the Federation of Bosnia and Herzegovina was 1:3957 (10), Zhejiang Province of China 1:1342 (11), Mexican children 4.3:10000 live births (12), Thailand 1:3314 (13), the Konya region of Turkey 1:2183 (14), India 1:3400 (15), Bahrain 1:2967 (16), and Mato Grosso of Brazil 1:9448 (17). In similar to the present finding, in Isfahan- central province of Iran- an overall incidence of congenital hypothyroidism was 3.1:1000 live births (18). So the overall prevalence of congenital hypothyroidism in Iran was higher than that reports in mentioned countries. This difference may be due to different ethnic, environmental, genetic and autoimmune factors (19-21). Additionally, analysis of US data by Hinton et al, showed a different congenital hypothyroidism rate between California, Massachusetts, New York, and Texas (22), in which was similar to our finding about different prevalence of congenital hypothyroidism in different city of Mazandaran province.

The male to female ratio of congenital hypothyroidism in our study was 2:1.1 and this value was similar to the same study in Isfahan, Iran (6) and differs from other studies in other countries, which have generally reported a female prodominance (4,12,23). So, the reasons of this difference need to be studied in future surveys.

In this study, heel-prick method as a minimally invasive method was adopted for sample collection from newborns in a large area of north of Iran and this study was a preliminary report of screening program of congenital hypothyroidism in this area and differentiation between permanent and transient form of hypothyroidism needs longer fallow up. In conclusion, we found high prevalence of hypothyroidism in this area. Hence, screening program needs to be continued in our region to identify neonates with hypothyroidism and treatment should be monitored and it is necessary to fallow up these children.

Acknowledgment

This project was financially supported by Vice Chancellery for Research, Mazandaran University of Medical Sciences. The authors thank Dr. Reza Alizadeh-Navaei for manuscript preparation and Dr. Ali Omranirad for technical edition.

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Rehabilitation nursing: applications for rehabilitation nursing

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Abstract

Rehabilitation nursing is a specialist form of rehabilitation requiring specialist nursing. Furthermore, as in many areas of nursing, nurses in this field recognize that there is a need to increase the quality of and provide the most up-to-date care for their patients and patients' families. To achieve high levels of competence, neurological rehabilitation nurses need to be aware of the existing body of research in this field. Effective hospital and community rehabilitation services are increasingly recognised as a means of meeting the changing pattern of health and social care requirements. This review aims to validate the existing knowledge base in this area by identifying and critically analysing research conducted in the area of neurological rehabilitation nursing.

Key words: rehabilitation; rehabilitation nurses; neurology; rehabilitation management; neurological disorders; head injury; nurse

Introduction

The number of people requiring rehabilitation is increasing.[1,2] Nurses today will care for more patients with chronic neurological problems, more patients with head injury, and more elderly people in need of care, and because these patients often have a wide range of physical, cognitive and behavioural problems, the rehabilitation needs of these patients are diverse and complex.[3,4]

As rehabilitation nursing requires autonomous professional knowledge, it is increasingly gaining momentum[1]. However, like many areas of nursing, nurses in this field recognize that there is a need to strengthen their knowledge in order to ensure that they provide the best possible care for patients and their families. Rehabilitation nurses can start by reviewing their application fields and competencies in order to upgrade their professional skills.

Principles of rehabilitation:

1. The prevention, diagnosis and treatment of concomitant medical problems (co-morbid illnesses, complications)
2. Training for maximum functional independence,
3. To support psychosocial coping and assist in the adaptation of patients and families,
4. To support the return to community life
5. To improve the quality of life of patient and family members who provide care

Rehabilitation nursing

Nurses are qualified health care professionals that provide nursing services to help patients to develop problem-solving and stress management skills and to improve patients' quality of life by following the physiological and psychological changes of the patients.

A rehabilitation nurse is specialized in the care of dependent or semi-dependent individuals, and provides direct patient care, educates patients and their families, and provides care coordination. A rehabilitation nurse should first start with what the patients and their families want to know and what they need, and should be a good trainer and love their work.

A rehabilitation nurse creates a creative and dynamic process which supports the individual's "functional capacity", namely the dynamic interaction with the environment, and plays a role in helping patients achieve their maximum functional capacity. Thus, a rehabilitation nurse commences rehabilitation in the patient's new life by reorganizing the maintenance process of the individual or providing an immediate protective care in the initial phases of an illness or an accident. The disabled person's existing capacity should be considered holistically. A rehabilitation nurse provides care, training and support for individuals and their families.

In addition, it is essential to regulate the adaptation process to the new role and environment, and this is provided by the rehabilitation nurse**.** According to the definition accepted by 'International Council of Nurses', rehabilitation is a special application that can be regulated as a part of care.[1]

Rehabilitation nursing begins with immediate preventive care in the beginning stages of accident or illness, is continued through the restorative stage of care, and involves adaptation of the whole being to a new life. The rehabilitation nurse provides care, education, and support for the patient and the family. They play an active role in encouraging the patients to develop abilities on their own as much as possible, such as meeting basic needs, activities of daily living (eating, drinking, excretion, dressing and undressing), and taking protective measures.[5]

Three main points constitute the goal of rehabilitation nursing and can be summarized as "lifestyle changes in individuals", namely "**adaptation**", "**configuration of functions**" and "**upgrading autonomy**".[6]

Research on the role of rehabilitation nursing has been determined to have a tendency to focus on elderly care centers and general rehabilitation nursing. The majority of them are related to ongoing interventions prescribed by doctors and physiotherapists, and they have reported a tendency to underestimate the role of rehabilitation nurses.[7]

There is a broad spectrum of neurological diseases in the field of rehabilitation. There may be insufficient information on the frequency of neurological disorders in the community [8]. Today, there is an increasing number of patients with disabilities, chronic diseases, degenerative diseases, and elderly individuals in particular. However, up to 10 million people in England are expected to be affected by a neurological condition. Approximately one-tenth of these people have "head injuries" and a few million have neurodegenerative - progressive disorders, such as "Multiple Sclerosis" and "Parkinson's disease". Neurological emergencies constitute 20% of emergency room admissions. Except for long-term care, 850,000 people need to be employed for individuals in need of neurological rehabilitation and 350,000 people for individuals who lack the ability to perform the activities of daily living due to a neurological condition.[9] The needs of these people, who constitute a large part of population, cannot be met in the present status. Except for stroke, there is no definitive treatment or preventive treatment for neurological conditions. Rehabilitation and support should be focused on protection and improvement of the current situation of affected individuals. Flexible, need-responsive, and individual-based studies are needed.[9,10]

History of Rehabilitation Nursing

In the United States, the field of rehabilitation is linked most closely with, and has received its greatest impetus from, the circumstances surrounding the consequences of wartime combat. Rehabilitation principles were first applied by Florence Nightingale, who planted the seeds of rehabilitation nursing in her seminal 1859 book [11.12]. Subsequently, the 1940s saw significant growth in the field of physical medicine. In 1945, eight individuals with Spinal Cord Injury were reported to have been administered psychosocial treatment and vocational therapy. The specialty of rehabilitation medicine became firmly established, and by 1946, physiatrists were being trained in rehabilitation medicine.[13,14]

Rehabilitation Nursing Interventions

A rehabilitation nurse initially plays an active role in helping the patients to function at their best in meeting basic needs, in the activities of daily living (eating, drinking, excretion, dressing and undressing), and in taking protective measures for themselves.

- provides coordination with the other members of the team after assessing the nutritional status of the patient, e.g. in patients who have difficulty swallowing: nutrition may be given via IV (intravenous) route or naso-gastric probe or gastric tube.
- Toilet habits, which particularly affect the social life of the patient, should be established again.
- Maintenance and training practices for bladder emptying and urinary leakage should be performed
- For skin care and prevention of pressure ulcers, patient and family education should be provided about periods of motion limitation, care for wheelchair-bound patients, and accurate positioning.

- The patient's skin-care and self-care deficiencies should be identified and attempts should be made to eliminate the source of the problem.
- In parallel with the changing needs of the individuals, they should be given the opportunity to acquire self-care skills.
- To prevent the formation of contractures and atrophies, proper positioning and active-passive ROM exercises should take place.
- The patient should be encouraged to become independent.
- To evaluate the patient's ways of coping with stress and to help improve problem-solving skills, to support, and to direct the patient to a relevant unit if necessary.
- To provide a safe environment against infections and accidents, to ensure compliance with nursing care techniques (asepsis, sterilization, isolation, etc.), and to provide necessary treatments for isolated patients.
- For patients and their caregivers, to provide moral support and motivation, to provide consulting and education and to inform about the disease and general health issues, and to direct the relevant health professionals and institutions, if necessary,
- To record each phase of nursing applications completely and in a timely manner.
- To promote patients' social participation.
- Vital signs should be monitored.

The rehabilitation process involves the time spent in hospital and some phases after hospital discharge. The patient ultimately should return home. Although it is very important to ensure the continuity of the rehabilitation process at home, it is certain that other people will have to deal with the patient's care. In view of this process, the time spent in hospital is not too short when compared with the life remaining. Maintaining self care as much as possible, or supportive care, is the cornerstone of care. Here, the important point is the education of patients and caregivers.[15]

The common goals should be clarified to achieve success in harmony with the patient and his/her family. In rehabilitation teamwork, nurses should have a broad perspective and have the ability to foresee**.** The more the nurse realizes the extent of the patient's improvement, and how much more rehabilitation the patient needs to achieve maximum improvement, the more the nurse will contribute to the rehabilitation team.[16]

As a result, new roles and functional areas of rehabilitation nursing are emerging.

To provide effective patient and family education, the rehabilitation nurse should be sensitive, open-minded and sincere.[17,18]

Moreover, a few keywords to be added, may be the potential, talent, quality of life, family-centered care, welfare, cultural components of care, and integration.

A few studies focusing on the role of the rehabilitation nurse have reported that neurological rehabilitation requires more autonomy.[19]

Rehabilitation nursing has been reported to have an independent professional role with a wide range of activities, such as training, consulting, communication, management, and collaboration and care giving. Similar findings were reported with regard to how rehabilitation nurses perceive their roles. In some qualitative studies, nurses reported to perceive themselves and their roles in health improvement as independent. The nurses have considered that they have a central role in all phases of rehabilitation.[20,21]

It has been reported that the role of the neurology nurse is not different from that of a rehabilitation nurse in any area (e.g. caregiving activities, education, and upgrading independence that is not specific to neurology).

In the literature, work-related stress has been reported to be very common among rehabilitation nurses working with patients with traumatic brain injury (TBI).[22]

Specific Problems Concerning Rehabilitation Patients

Skin Care: Rehabilitation patients may be faced with various skin problems. During periods of restricted activity and in patients who remain in bed for long periods of time, there is a risk of developing **pressure ulcers.** Changing the position of the patient in the bed, in other words, alternating between laying the patient on their right side and laying them on their left side at intervals of two to three hours would be highly beneficial for the patient. Some important points are to keep the skin clean, taking care not to load excess weight on certain

areas of the body, and to use a pneumatic bed. The same risk also applies to people sitting in a wheelchair. Therefore, the pressure applied to the patient's thigh will be reduced by placing an appropriate wheelchair cushion. In addition, fungal lesions or erythemas may occur underneath the breast in women, in the inner side of the elbows in both genders, or between the body layers in overweight individuals because of the inactivity. It is very important to keep these areas clean and dry.[23]

Pressure ulcers: are ulcers occurring as a result of skin and subcutaneous tissue injury due to poor circulation in the pressure area that come into contact with the bed. Common locations of pressure ulcers: hips, elbows, heels, shoulder blades, knees, protruding areas of the ankle and head, ears and sacrum. The selection of appropriate clothes, active-passive exercise, personal hygiene, and massage can be applied to protect the patient. [24]

Hygiene: Infection is one of the most common complications, especially after stroke. One of the problems of rehabilitation patients is difficulty in swallowing as well as poor oral hygiene. Difficulty in emptying the bladder following a stroke leads to the accumulation of urine and bacterial infection. Inadequate fluid intake is one of the causes of the accumulation of urine. Therefore, it is important for post-stroke patients to take plenty of fluids and to have their catheters changed within twenty days.[25]

If the patient is using a cloth wipe, it is also very important to replace these cloth wipes at two to three hours intervals. This will both relieve the patient and ventilate the back of the patient. During the replacement of the cloth wipes, the urinary region and the areas that are in contact with the cloth wipes should be cleaned with wet wipes or a cotton cloth moistened with water. The perineum and the back of the patients should be checked at certain intervals if the patients are able to maintain their own hygiene.[23]

Bathing: After returning home, it would be beneficial for the patient to take a bath at frequent intervals (depending on the person's health status). This stimulates blood circulation and allows the opening of skin pores. The patient can spend one to two hours in the bath each day. Bath time should be a relaxing time. The healthy hand can rub and massage the opposite side. Individuals are able to regain some function of the hemiplegic hand with time. It is important to set the temperature of the water to prevent burn injuries. It may be convenient to use an automatic, touchless sensor sink. Showering should be preferred to a bathtub. It is beneficial to apply body massage with baby oil or lanolin cream after bathing.[23]

Bed Bath: Water-repellent products should be placed under the patient to protect the bed. Gloves must be used during the post-toilet cleaning of the patient**.** The cleaning procedure must be performed from top to bottom and from interior to exterior. After controlling the room temperature, up to two thirds of the hand bath should be filled with water up to 43 to 46 degrees. The patient's body should be rinsed with soapy water from top to bottom, and from distal to proximal, and dried. The genital area should be cleaned from front to back. It is important to use a moisturizing lotion for moistening the skin.[26]

Toilet: Toilet grip handles can be used to facilitate the ability to sit and stand. Sometimes, raising the toilet seat height can be of critical value.[26]

Eating: Eating with other family members at the same table at home can improve the morale of the patient. In this regard, caregivers should encourage the patient. Nonfunctional body, sensory problems, difficulty swallowing and relaxed facial muscles can make it hard to eat. To divide the food into the small pieces, to use mixers when necessary, to wipe the patient's mouth with a wet wipe, and to use a smock would be useful. Oral care is an important component of eating and appetite.[26]

Exercise: The aim of exercise is to regulate the distribution of oxygen and metabolic processes, enhance strength and endurance, reduce body fat, and improve muscle-joint movements. All of these benefits are necessary for good health and everyone should undertake a routine exercise program in daily life. There is no distinction between young and old people; however, strenuous exercise might have some risks. Exercising for 20 minutes or more, three times a week is sufficient. Fifteen - 25 minutes of daily exercise five or more days a week provides high level of benefits. The exercise period can be started with light warm-ups and completed with stretching exercises.[27]

PEG (percutaneous gastrostomy) or nasogastric tube: If a PEG or NG has been inserted due to poor feeding, the patient's head should be

elevated at least 45 degrees during and one to two hours after feeding. Before and after each feeding, catheters should be washed with 20cc water. The catheter site must be inspected daily, and checked for swelling and erythema, and be kept clean and dry. The catheter should be rotated around itself once a day and adhesion of the catheter to the skin should be avoided.[28,29]

Traveling: If car travel is planned, it would be useful for the patient to sit in the front seat pulled back, and to place a cushion under the buttocks, a U-shaped pillow on the neck, and a pillow supporting the back of the patient. To give short breaks and to wear comfortable and loose clothing during the journey would make the journey more comfortable. It should be kept in mind that a change in air pressure in aircraft travel can have different effects on metabolism, and a medical examination should be done and necessary recommendations should be followed, e.g. wearing varicose stockings that can support venous circulation.[30]

Stroke Rehabilitation: Recovery after a stroke is associated with many factors. Stroke affects the whole body, as well as causes problems such as perception deficiencies, sensory problems, speech disorders, pain, and difficulty in performing the activities of daily living independently. The goal of rehabilitation is to ensure the return of the patient to daily life and to protect quality of life. Rehabilitation should be performed by a health care staff member experienced in hemiplegia, such as medical physical therapist, occupational therapist, speech therapist, nurse and neuropsychologist. Once the patient's condition has stabilized, it is recommended to initiate post-stroke rehabilitation. In our country, usually patients are included in a rehabilitation program in physical therapy and rehabilitation services of hospitals and in private rehabilitation centers. Rehabilitation is a costly and exhausting process. Nursing care is complex and versatile in equipped hospitals that can provide acute or chronic care, rehabilitation centers, or at home. As the stroke can affect the individual in many ways, more than one nursing diagnosis may be appropriate for the care of an individual with stroke.[31]

Motor rehabilitation should be initiated in ischemic stroke patients in the early period. Patients who receive bed rest within the first 24 hours should be mobilized in the following two to three days. Mobilization is the most important way to prevent pressure ulcers, deep vein thrombosis, atelectasis, bronchopulmonary infectious complications, and constipation. The patients that will be mobilized should be monitored for worsening of neurological signs due to orthostatism, and mobilization should be continued if the neurological status does not change. Mobilization alone should not be allowed because of the high risk of falling. It is important for bed-bound patients to alternate sides at short intervals and to use pneumatic beds for pressure ulcer prophylaxis. In order to prevent contractures and orthopedic complications, active or passive ROM exercises should be used for paretic arms and legs. Most stroke patients have difficulty swallowing in the acute phase, and feeding should not be delayed in these patients. In the early period, nasogastric tube or enteral nutrition via gastrostomy can be considered. Oral feeding should not be initiated in any of the stroke patients without the evaluation of the swallowing function. The prognosis of aspiration pneumonia can be worse in patients with impaired swallowing.[32]

Nursing interventions

It is noteworthy that publications on rehabilitation nursing practices are usually international and related to stroke. Studies generally examine issues of nursing care and patient education. [33] In different studies, different assessments have been made on the impact of stroke support groups, self-care skills and perceptions of the patients. In the studies, specific therapeutic applications, such as bowel management, feeding and laughing are mostly included in individual nursing practices. Moreover, the studies have evaluated the differences between conventional nursing approaches and semi-experimental models.[34,35]

The needs of rehabilitation nurses are not precisely defined. For example, the standardization of a guide including behavioral and cognitive factors will be helpful for rehabilitation nurses in terms of the care needs of patients with neurological disability. Thus, the outcome of care can be measured.

Large-scale prospective studies on different cultures will be more informative. In many rehabilitation units, nurses prepare the patient before the application. In addition, in some units, a taxonomic guide can be used. Especially in studies fo-

cused on stroke, when "the perception of patients" for the nurses working with patients with depression after stroke is evaluated, nurses have been found to listen to and support the patients by encouraging them to speak.[36]

The family of the rehabilitation patient

The patient's family plays an important role in rehabilitation. To have a relevant and resourceful family that can provide care is an important factor affecting the rehabilitation process positively. What kind of problems the patient may experience and how these problems affect the patient should be explained to family members. In this way, it will be easier for the family to find solutions after the discharge.

If you are a relative of someone in need of rehabilitation, you should support and encourage him. You should not leave the patient alone in hospital or the rehabilitation center, and should make him/her feel that you are with them. Watching television, listening to the radio, playing chess or card games with family members may make the patient more comfortable. This is a good way to learn how rehabilitation works and how you can help the patient to do better.

It is of utmost importance in rehabilitation to help and encourage the patient to apply relearned skills. A patient diary can be used to clarify what the patient can do alone and what they can do with support. In this way, the patient's family can refrain from executing actions that the patient can do alone. The patient's self-confidence will increase as he/she performs tasks without help. Long-term care and rehabilitation needs can create pressure and despair in patients and their families. Stroke, spinal cord injury and traumatic brain injuries happen so quickly and everybody may be shocked. At the end of the acute period, the most important partner of the health care team is the family. Early inclusion of family members in care interventions will facilitate the long-term struggle with the disease and create an efficient climate of trust. To take a patient approach to problem solving, to offer alternative solutions, and to provide psychological support for the patient and family in long term disability is an important task of health personnel dealing with stroke. In short, it is obvious that the patient's family need to be informed to adapt to the new condition in the early period. In recent literature, the amount of research concerning the patient and family is increasing. In these studies, the education needs of the family of the rehabilitation patients have been mentioned, and the participation of the family in the rehabilitation process has been reported to be important.[31,37-40]

Informal care-givers have been reported to be willing to participate in patient care. Family support has been emphasized to be important in the publications, despite its limitations. More comprehensive research that can clarify this issue may be proposed.

Conclusion

An efficient information network can be created in the field of rehabilitation nursing.

For stroke, cost-effective models can be compared with community-based rehabilitation practices. For neurological conditions other than stroke, well-designed randomized controlled trials and economic evaluation of the service can be carried out.

Patient records related to the long-term care needs involved in the rehabilitation of patients can be created. The importance of these records should be taken into account for the continuity between phases of rehabilitation and service provision.

Volunteer services and web and telephone services can be used more efficiently. Home care can be an alternative to hospital care for patients and their families.

Community-based rehabilitation and therapeutic interventions can be tried for Parkinson's disease, spinal cord injuries and multiple sclerosis.

Follow-up at home can be recommended for epilepsy.

Qualitative studies can be offered to assess the rehabilitation needs of all groups.

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Conversion of diagnostic autoantibodies from positivity to negativity in a patient with autoimmune hepatitis and primary biliary cirrhosis overlap syndrome

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Abstract

The characteristics of autoimmune hepatitis and primary biliary cirrhosis overlap syndrome vary widely between studies. Here, we report a 53-year-old female patient who presented with AIH-PBC overlap syndrome. At the dignosis, her antinuclear antibody (ANA) and antimitochondrial antibody (AMA)-M2 antibody were both positive, however, after the administration of ursodeoxycholic acid (UDCA), prednisolone and azathiopyrine, both of the autoantibodies convert to negativity with the liver function improving. To our knowledge, the situation is seldom reported.

Key words: autoimmune hepatitis; primary biliary cirrhosis; overlap syndrome; autoantibody

1. Introduction

Some patients present with overlapping features between disorders within the spectrum of autoimmune liver diseases (i.e. autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC)) and are commonly classified as having an "overlap syndrome". The pathophysiological mechanisms underlying AIH-PBC overlap remain unclear [1-3]. Due to the lack of standardization and variations in the populations under study, the characteristics of these entities vary between studies [4-11]. Here, we report a case of woman diagnosed as AIH-PBC overlap syndrome exhibiting conversion of diagnostic autoantibodies from positivity to negativity with liver function improving after the administration of ursodeoxycholic acid (UDCA), prednisolone and azathiopyrine.

2. Case presentation

The 53-year-old female patient started to suffer lethargy, anorexia and pruritus in June 2006. She visited our hospital in February 2007, and laboratory data were as follows: ALT 74 U/L (normal, <40U/L), AST 103 U/L (normal, <40U/L), ALP 381 U/L (normal, 40-150U/L), GGT 413 U/L (normal, 7-32U/L), total bilirubin 28 umol/L (normal, <17.1umol/L), IgG 29 g/L (normal, 7.23-16.6 g/L), IgM 5.7 g/L (normal, 0.63-2.77 g/L), ANA titer 1/1280 (negative, <1/80) and AMA-M2 titer 1/640 (negative, <1/80). Anti-smooth muscle antibodies and viral serologies (hepatitis A, B, C, E, cytomegalovirus, Epstein-Barr virus and HIV) were negative and there was no history of drug or alcohol intake. Liver biopsy demonstrated interface hepatitis, plasma cell infiltration and ductal lesion (Figure 1). Both histological and laboratory findings were compatible with AIH-PBC overlap syndrome. The patient was treated with UDCA 25 mg/kg/day in the initial month, however, her serum liver enzymes were persistently rising. From the second month, prednisolone 60 mg/day was added, but her serum liver enzymes were still rising. So, from the third month, azathiopyrine 50 mg/day was added and prednisolone was reduced to 30 mg/day. After that, her liver function improved, and the titer of ANA and AMA-M2 were respectively down to 1/320 and 1/160 with her condition under control in September 2010. In June 2011, her laboratory data were as follows: ALT 14 U/L, AST 44 U/L, ALP 85 U/L, GGT 94 U/L, total bilirubin 18 umol/L, ANA titer <1/80 (negative) and AMA-M2 titer <1/80 (negative). Figure 2 showed the changing process of her liver function during the treatment.

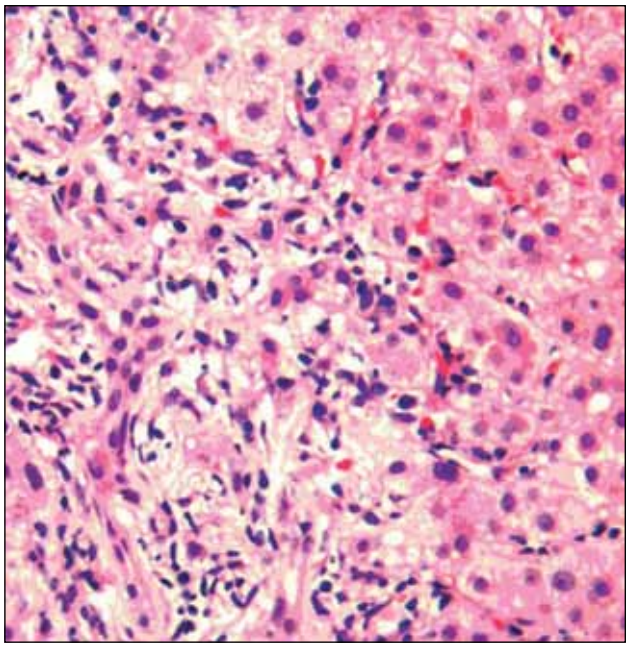

Figure 1. Pathological changes (bile duct lesion, interface hepatitis and plasma cell infiltration) in a female patient diagnosed as autoimmune hepatitis and primary biliary cirrhosis overlap syndrome. (HE, ×200)

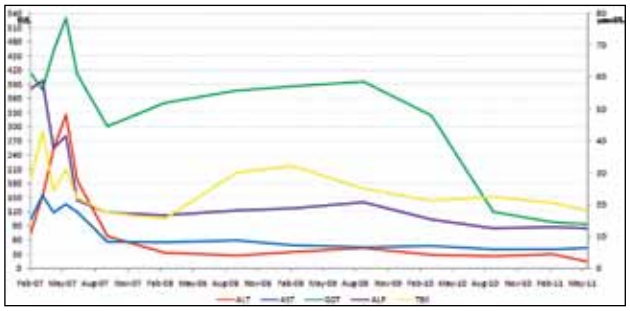

Figure 2. The changing process of liver function during the treatment (ursodeoxycholic acid 25 mg/kg/day administered in the initial month; prednisolone 60 mg/day was added from the second month; azathiopyrine 50 mg/day added and prednisolone reduced to 30 mg/day from the third month)

3. Discussion

As a disease entity, Popper and Schaffner first proposed AIH-PBC overlap syndrome in 1970 [12]. In 1998, Chazouillères O et al [13] proposed the diagnostic criteria for AIH-PBC overlap syndrome which are now widely accepted. The present patient fulfilled the respective criteria for AIH and PBC, and so was diagnosed as AIH-PBC overlap syndrome. In clinic, presentation of autoimmune liver diseases varies widely, ranging from asymptomatic elevations of serum liver enzymes to massive hepatic necrosis resulting in fulminant hepatic failure, and there are no disease-specific clinical features. Günsar F et al [14] reported that, lethargy was the most common symptom in these patients. Similar to the report, the chief complaint of the present patient is lethargy, which is a subsidiary consideration for the diagnosis excluding other forms of liver diseases.

To date, it is generally accepted that patients with PBC and AIH overlap syndrome should continue to receive UDCA, but it is unclear if the degree of AIH overlap of these cases may justify the addition of corticosteroid or immunosuppressive therapy. Some researchers have suggested that UDCA and immunosuppressive combination therapy would be more effective in improving biological indicators for PBC-AIH overlap patients than either UDCA or immunosuppressive therapy administered separately [14,15]. In a study, nine out of twelve patients, nine obtained remission during corticosteroid therapy [16]. In the study by Chazouillères O et al [13], nine patients diagnosed as AIH-PBC overlap syndrome with persistently abnormal liver tests during the treatment with UDCA alone (three) and prednisolone alone (six), showed an overall improvement after they were subsequently given a combination of UDCA and prednisolone for a median of 18 months. The present patient was not respond to UDCA monotherapy or combination of UDCA and prednisolone, but was under control after UDCA, prednisolone and azathiopyrine administered together.

Serum autoantibodies have steadily established themselves as critical biomarkers for the diagnosis of autoimmune diseases [17], nevertheless, with the treatment proceeding, whether the autoantibodies are changing is rarely reported. As for this patient, her two positive autoantibodies definitely converted to negativity when her condition improved. So, we highlight that the titer of the autoantibodies may gradually descend, and even to negativity with the condition under control in aotoimmune liver diseases. To the best of our knowledge, this is the first report on the disappearance of the two diagnostic autoantibodies (ANA and AMA-M2) in a patient with AIH-PBC overlap syndrome during the treatment. It may be important to trace the situation of the autoantibodies with the treatment proceeding for these patients in future.

Abbreviations

AIH, autoimmune hepatitis;
PBC, primary biliary cirrhosis;
PSC, primary sclerosing cholangitis;
UDCA, ursodeoxycholic acid;
ANA, antinuclear antibody;
AMA, antimitochondrial antibody;
ALT, alanine transarninase;
AST, aspartate aminotransferase;
TBil, total bilirubin;
GGT, gamma glutamyl transferase;
ALP, alkaline phosphatase.

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Frequency and predictive factors of non alcoholic fatty liver in patients with metabolic syndrome in Kurdistan province, Iran

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Abstract

Background and Aim: Nonalcoholic fatty liver disease (NAFLD) comprises a disease spectrum which includes variable degrees of simple steatosis (nonalcoholic fatty liver disease, NAFLD), nonalcoholic steatohepatitis (NASH) and cirrhosis. NAFLD is the hepatic manifestation of the metabolic syndrome. Considering the increasing incidence of metabolic syndrome and NAFLD and their complications worldwide, and presence of few data in Iran, we conducted this study in Kurdistan province.

Methods and Materials: In this descriptive-analytic study 65 adults which were diagnosed as having metabolic syndrome in a previous population based study were reevaluated. Finally, 57 patients were assessed for presence of NAFLD by sonography and importance of risk factors in developing NAFLD.

Results: In this study, 29.8 % of patients with metabolic syndrome had NAFLD. In those who had NAFLD; 100% had increased alanine aminotransferase (ALT) levels, while 88.2% had increased waist circumference and triglyceride (TG) levels. Hypertension was seen in 82.4% of patients. Aspartate aminotransferase (Ast), fasting blood sugar (FBS) and high density lipoprotein (HDL) serum levels (52.9%) were not good predictors of fatty liver in patients with metabolic syndrome. BMI [odds ratio, 0.63 (95% CI, 0.39 to 0.99)] and ALT serum level[odds ratio, 0.80 (95% CI, 0.65 to 0.99)] can predict presence of NAFLD in the setting of metabolic syndrome (p= 0.05 and p=0.046, respectively).

Conclusion: NAFLD can be detected in nearly one third of patients with metabolic syndrome. Increased BMI and ALT serum levels have predictive value for NAFLD in metabolic syndrome.

Key words: NAFLD, Metabolic syndrome, liver enzyme

Introduction

The metabolic syndrome (MS) encompasses metabolic and cardiovascular risk factors which predict diabetes and cardiovascular disease (CVD) better than any of its individual components (1). There are different criteria for recognizing metabolic syndrome. The National Cholesterol Education Program (NCEP/ATP III) and International Diabetes Federation (IDF) definitions are the most widely used (2, 3). Nonalcoholic fatty liver disease (NAFLD) comprises a disease spectrum which includes variable degrees of simple steatosis (nonalcoholic fatty liver, NAFL), nonalcoholic steatohepatitis (NASH) and cirrhosis. NAFLD is the hepatic manifestation of the metabolic syndrome, with insulin resistance as the main pathogenetic mechanism.(1,4,5). The histological characteristics of NAFLD are indistinguishable from alcoholic liver disease, but it is nessecerry to exclude patients with a history of excessive alcohol use (more than 20 mg/d) (6, 7). Major risk factors for NAFLD are obesity, type II diabetes, dislipidemia and metabolic syndrome (8). Hepatocellular carcinoma (HCC) is the most rapidly increasing cause of cancer death in the United States. Although many risk factors for HCC are well defined, including hepatitis B virus (HBV), hepatitis C virus (HCV), and alcohol, most series have indicated that 5% to 30% of patients with HCC lack a readily identifiable risk factor for their cancer.

The majority of "cryptogenic" HCCs in the United States is attributed to nonalcoholic fatty liver disease (NAFLD), a hepatic manifestation of the metabolic syndrome (9). The prevalence of metabolic syndrome is rising in different societies. For example in a study in early years of 1990 the prevalence of metabolic syndrome was 26.8% for men and 16.6% for women. Eight years later in 2005 this prevalence rose to 56% for men and 47% for women (10). The prevalence of metabolic syndrome is rising in less developed countries too. It is 23-47% in India (5), 34.6% in Turkey (11) and 34.8-49% in Pakistan (12). In different studies from Iran, this prevalence is estimated to be 23.7 to 31 %(13, 14).

During the past 20 to 30 years, the frequency of patients presenting with nonalcoholic fatty liver diseases (NAFLD) has increased gradually. The prevalence of NAFLD is 8.7% to 23.3 % in developing countries (15-19). Fatty liver can develop with relatively small changes in weight (2-3 kg), often with increasing central adiposity. The metabolic syndrome may precede or follow NAFLD. The prevalence of MS in NAFLD subjects is much higher than that in non-NAFLD subjects. The prevalence of NAFLD in MS subjects is also much higher than that in non-MS subjects (20).

Considering the rising prevalence of metabolic syndrome and its hepatic manifestation (NAFLD) all around the world, and keeping in mind that it can lead to dystrophic conditions like cirrhosis and HCC, we designed this study to determine the frequency of NAFLD in patients with metabolic syndrome in Kurdistan province.

Material and Methods

This descriptive-analytic cross sectional study was conducted on patients with metabolic syndrome who were detected in a national population based study. In the mentioned study 2500 adult (>15yrs) residents of Kurdistan province (northwest of Iran) were randomly selected (by cluster sampling according to national postal code). The sampled population was evaluated for the condition of NCDs (Non-communicable diseases) in the area. They found that 640 of the participants had metabolic syndrome according to ATP III criteria for metabolic syndrome.

For this study we selected three cities (Sanandaj, Divandare and Kamyaran) and invited 65 subjects who previously were diagnosed as having metabolic syndrome. After they signed a consent paper, they were questioned if they took alcohol or certain medications (Amiodarone, nucleoside analoges, valporic acid, tamoxifen, Vit A). Those who had positive alcohol or drug history were excluded from the study. We used ATP III metabolic syndrome criteria to reevaluate our patients. Current ATP III criteria define the metabolic syndrome as the presence of any three of the following five traits:1) Abdominal obesity, defined as a waist circumference in men >102 cm (40 in) and in women >88 cm (35 in), 2) Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides, 3) Serum HDL cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL-C, 4) Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure, 5) Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose(2,3). A trained medical student visited them. He asked them to take off their heavy clothes and shoes and step on a scale while distributing their weight between their feet to take their weight. A stadiometer (Seca 206, Germany) was used to take their height. The BMIs were calculated (weight (kg)/height (m) 2). Waist circumference was measured by an elastic tailoring meter, at the line between iliac crest and the lowest rib, while the participant breathed smoothly. After resting for 15 minutes, the participant's right arm blood pressure was measured by a mercury sphygmomanometer. The medical student took 20cc of their fasting blood to do the necessary lab tests. After centrifuging the blood specimens, obtained serums were stored in the Tohid Hospital's laboratory for further investigations. HBsAg and HCV Ab were checked and those who had positive results for viral markers were excluded. Serum TG, serum Chol, and FBS of the remaining patients were measured. Those who had the criteria for metabolic syndrome were referred to the sonographist for detection of fatty liver. Although liver biopsy is the gold standard for diagnosing fatty liver, it is an invasive procedure and is not used routinely in practice or epidemiologic studies(15,21).That is why noninvasi-

ve routes like imaging(ultrasonography, MRI,CT scan)or lab tests are more acceptable in epidemiologic studies(22-25). Among the imaging methods, ultrasonography is the cheapest and most available method with good sensitivity (60-94%) (26),consequently it is the preferred imaging method in most epidemiologic studies and is accepted by the Asian-Pacific guideline(15-21,23-26).In this study abdominal ultrasound examination was carried out on all patients by one specialist and the same equipment (Sono Site 180), using a convex 3.5 MHz probe. Sagital hepatic sections encompassing longitudinal images of the right lobe of the liver and the ipsilateral kidney were obtained. Fatty infiltration was graded qualitatively into four classes according to subjective assessment of the contrast between the hepatic parenchyma and the renal cortex, in terms of echo intensity: non-observed (grade 0), mild steatosis (grade I), moderate steatosis (grade II) and severe steatosis (grade III) (Figure 1). (25, 26)

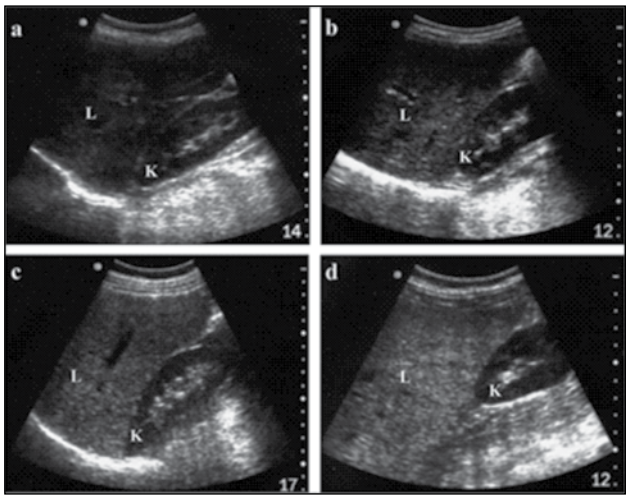

Figure 1. Sagital ultrasound scans showing echo intensities in both liver parenchyma(L) and renal cortex(K).The panels represent cases in which liver steatosis was not observed(a),mild(b),moderate(c) and severe(d).(25)

In our reevaluation, 57 of the subjects had metabolic syndrome. Blood samples of those who had fatty liver in sonography were further examined for serum Iron(SI), total iron binding capacity (TIBC), serum copper(cu), antimitochondrial antibody (AMA), anti-smooth muscle antibodies(ASMA), antinuclear antibodies(ANA), protein electrophoresis and IgA anti tissue transglutaminase. Those who had positive AMA,ASMA,ANA, IgA anti tissue transglutaminase results, or those who had abnormally high levels of gamma globulin in protein electrophoresis (more than 20%), SI/TIBC (more than 50%), and serum cu (more than 20gr/dl) were excluded from the study. In the remaining group, which was recognized as having NAFLD, serum levels of transaminases (AST and ALT) were determined. The results were analyzed via SPSS 13.

Results

Of 57 participants with metabolic syndrome 91.2% were male and 8.8% were female. Also, 36 of these participants (63.2%) were from Sanandaj, while 11 (19.3%) were from Kamyaran and 10(17.5%) were from Divandare. Most of the patients with MS had BMIs less than 19.5 Kg/m2 (68.6%), but 88.2% of those who had MS plus NAFLD, had BMIs more than 25Kg/m2.Increased waist circumference and hypertension were detected in 52.9% and 82.4% of patients with NAFLD. Most of the participants were less than 50 years old (50.9%), while only 17.5% were older than 65 years. Ultrasonography showed that 17 (29.8 %) of participants had fatty liver (7 patients had grade I and the other 10 patients had grade II fatty liver). Total data are shown in table 1.

Logistic regression of metabolic syndrome components (Table 2), demonstrated that BMI [odds ratio, 0.63 (95% CI, 0.39 to 0.99)] and ALT serum level [odds ratio, 0.80 (95% CI, 0.65 to 0.99)] can predict presence of NAFLD in the setting of metabolic syndrome (p= 0.05 and p=0.046, respectively).

Discussion

In our study 29.8 % of patients with metabolic syndrome had NAFLD. NAFLD was first described in 1950 in a group of obese patients who were alcohol abstinences (7). NAFLD is not a problem of just developed countries anymore; developing countries are at increasing risk too. Many epidemiologic studies demonstrate increase in the prevalence of NAFLD in different countries (24, 27-29). In the United States the prevalence of metabolic syndrome and NAFLD is estima-

Table 1. Patients characteristics

Number		Metabolic Syndrome	Metabolic Syndrome + NAFLD	P value
		Number	Number	
Sex	Male	52	13	.19
	Female	5	4	
Age	15-50	29	6	.27
	51-64	18	9	
	≥65	10	2	
BMI	19.5-25	39	2	.001
	>25	18	15	
Waist Circumference	Normal	11	8	.14
	Abnormal	46	9	
BP	Normal	28	3	.02
	Abnormal	29	14	
AST	Normal	7	4	.26
	Abnormal	50	13	
ALT	Normal	3	0	1
	Abnormal	54	17	
TG	Normal	28	2	.01
	Abnormal	29	15	
HDL	Normal	26	8	.91
	Abnormal	31	9	
FBS	Normal	13	3	.75
	Abnormal	44	14	

BMI=Body Mass Index, WC= Waist Circumference, BP=Blood Pressure, AST= Aspartate aminotransferase, ALT= alanine aminotransferase, TG= Triglyceride, HDL= high density lipoprotein, FBS=Fasting Blood Sugar

Table 2. Predictive value of metabolic syndrome components for NAFLD

	Odds Ratio(95% confidence interval)	P-Value
Age	1.04(0.93-1.15)	0.49
Sex	3.49(0.95-12)	0.5
BMI	0.63(0.39-0.99)	0.05
Waist Circumference	1.52 (0.12-19.74)	0.75
BP	0.19(0.23-1.61)	0.75
AST	0.94(0.85-1.04)	0.25
ALT	0.80(0.65-0.99)	0.046
TG	0.99 (0.98-1.01)	0.84
FBS	0.99(0.96-1.01)	0.43
HDL	1.16(0.85-1.61)	0.34

BMI=Body Mass Index, WC= Waist Circumference, BP=Blood Pressure, AST= Aspartate aminotransferase, ALT= alanine aminotransferase, TG= Triglyceride, HDL= high density lipoprotein, FBS=Fasting Blood Sugar

ted to be 25% and 30 % retrospectively in adult population and these rates are increasing (29).In Hamaguchi's population based study on 4401 of Japanese people, those who had metabolic syndrome, had 4 to 11 times increased risk for fatty liver. Men and women who met the criteria for the metabolic syndrome at baseline were more likely to develop the disease during follow-up (adjusted

odds ratio, 4.00 [95% CI, 2.63 to 6.08] and 11.20 [CI, 4.85 to 25.87], respectively).Also nonalcoholic fatty liver disease was less likely to regress in those with metabolic syndrome at baseline (30). Females compared with males have higher prevalence of NAFLD (16.3% versus 10.1%, P = 0.004) and central obesity (33.2% versus 9.9%, P < 0.05) (30). In our study most of the participants were men and consequently we did not find a significant difference between the sexes. It may be due to low cooperation of women in the main national population based study. Liver enzymes have been used as markers for NAFLD from many years ago. It seems that this rise is due to fatty liver infiltrations and inflammatory stimulants. Studies have shown that increased ALT is related to each components of metabolic syndrome (31, 32), and its increase can even predict developing metabolic syndrome (33).Usually liver enzymes rise to 3-4 times normal values and ALT is higher than AST. On the other hand we should keep in mind that many patients with NAFLD have normal ALT levels and the degree of this rise does not correlate with the extend of liver disease and fibrosis (33). In our study 100% and 76.5% of patients with NAFLD had elevated ALT and AST levels, while these values were 94.7% and 50% for those who had just metabolic syndrome. Although there was no significant difference in these two groups, increased serum ALT level predicts the presence of NAFLD [odds ratio, 0.80 (95% CI, 0.65 to 0.99)], (p=0.046).

"Two-hit" theory of Day and James tries to explain the mechanism of developing simple steatosis in liver, and its progression to inflammation (NASH), fibrosis and cirrhosis. Recent researches have shown that different components of metabolic syndrome play roles in different parts of fatty liver pathogenesis in this model. First hit is a consequence of disequilibration between synthesis and circulation of triglycerides. Mitochondria play the main role in this scenario (33). In Kashyap et al study increased levels of serum triglycerides had a strong relation to progressive NAFLD and NASH in obese patients. In this study those who had serum triglyceride levels of more than 150mg/dl, had 3.4 times more risk for NASH in liver biopsies (35). In our study those with NAFLD had significantly higher levels of serum triglycerides (88.2%), but in the Logistic regression analysis hypertriglyceridemia was not a good predictor for presence of NAFLD in the setting of MS. HDL serum level was not significantly increased in NAFLD patients in our study (52.9%).

Obesity is becoming a pandemy, and its rate will still increase in future. It seems that the rate of metabolic syndrome and consequently NAFLD (as hepatic manifestation of metabolic syndrome) are increasing in parallel to obesity(36). Increased BMI and waist circumference are indicators of obesity and central fat distribution and are associated with metabolic syndrome, insulin resistance, hepatic fibrosis and steatohepatitis. Increased fat in the liver and visceral adipose tissue increases the risk of metabolic syndrome (29). In our study 88.2% of patients with MS and NAFLD had BMIs more than 25 while 31.6% of those with just metabolic syndrome were obese (P 0.001). Increased BMI predicts the presence of NAFLD in patients with metabolic syndrome [odds ratio, 0.63 (95% CI, 0.39 to 0.99)]. Increased waist circumference is considered as an independed risk factor for NAFLD (37), but we must keep in mind that there are some differences in ethnicity and morphology of Iranians (Middle East) comparing to Europeans and Americans. Therefore it is logical to reconsider the size of waist circumference in Iranians. In a population based study which has been done in Iran, waist circumferences of 91 and 89 cm were purposed for women and men as criteria for metabolic syndrome (38). In our study just 52.9% patients with NAFLD and MS had abnormal waist circumference according to current ATP III criteria, although it may be underestimated. Increased free fatty acid flux from adipose tissue to nonadipose organs, is a result of abnormal fat metabolism and leads to hepatic triglyceride accumulation and contributes to impaired glucose metabolism and insulin sensitivity in muscle and in the liver (39). Type 2 diabetes, a frequent complication of obesity, has been described in 34 to 75 percent of patients with NASH (40). In our study diabetes was even more frequent in those who had NAFLD (82.4%), comparing to those who had just metabolic syndrome(77.2%) , but it had no significant difference.

Conclusion

NAFLD can be detected in nearly one third of patients with metabolic syndrome. Increased body mass index, TG levels and hypertension are prominent in patients with NAFLD and metabolic syndrome, but increased BMI and ALT serum levels have predictive value for NAFLD in the setting of metabolic syndrome.

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Evaluatıon of pre-procedure anxıety levels for undergoıng mammography women

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Abstract

Purpose: The present study evaluated of pre-procedure anxiety levels for undergoing mammography women.

Methods: This cross-sectional descriptive study was conducted. 15-item questionnaire and the 20-item State Anxiety Inventory, developed by Spielberger et al. were used for data collection. Percentage, arithmetic average, Mann-Whitney U test and Kruskall-Wallis test were used to analyze the data.

Findings: The women , whose average age is 49.78±8.67 ,87.5 % are married; 46.9 % are graduated from primary school;60.9 % are not working; 58.6 % are during the period of menopose; 86.7 % have children and 62.5 % have breast cancer in their family members. The total anxiety score averages of women are 57.17±8.33. The level of anxiety about mammography screening was found to be higher in women with low educational levels and this difference was found to be statistically significant.

Conclusions: From the results of this study it has been determined that women having mammography have a moderate level of anxiety.

Key words: mammography, anxiety, women

Introduction

Breast cancer incidence has been increasing in the general population all over the world,

particularly in areas of low incidence. The worldwide incidence of breast cancer has increased from 720,000 cases per year in 1985 to 1,000,000 new cases in the year 2000(Harrison et al.2010).

In Turkey, according to data of the Ministry of Health, cancer statistics while breast cancer in women was 33.93% in 2003, it has raised 35.47% in 2005 (http://www.saglik.gov.tr./TR,2005). However, breast cancer is a type of cancer whose early diagnosis can provide acure for the disease. Since breast cancer cannot be prevented, the most appropriate way to decrease mortality from breast cancer is to diagnose the disease early (Singh et al.2008). The American Cancer Society (ACS) recommends breast self-examination (BSE), mammography, and clinical breast examination for early diagnosis of breast cancer (Smith et al. 2003). Mammography is the most reliable method to diagnose breast cancer. When used alone, its reliability is 90%; used with clinical examination it is 95%. The American Medical Center recommends that women with no symptoms have their first mammogram at the age of 40 and that they have a mammogram once every one to two years (per physician's recommendation) between the age of 40 and 50, then once a year after age 50(Mandelblatt et al.,2000; O'malley et al. 2001). Studies from Turkey (Koç and Sağlam,2009; Dündar et al.,2006; Seçginli and Nahcivan, 2006) have revealed that most of the women do not have a mammography which is congruent with the studies from other countries (Sadler et al., 2007; Sapir et al., 2003; Ko et al., 2003).

The reason why women were not willing to undergo mammography is the belief that breast tissue is exposed to high doses of radiation (Yücel et al., 2005), pain due to compression of breast tissue between the pressure plates of the mammography apparatus(Lambertz et al, 2008; Davey 2007; Asghari and Nicholas 2004), destruction of privacy, and fear of cancer(Alimoğlu et al.,2004; Consedine et al., 2004; Doyle and Stanton 2002). All these factors cause anxiety in women (Hafslund 2000; Mainiero et al, 2001). For this reason, when patients are prepared for special procedures like mammography, it is important to determine their anxiety level and influential factors.

The present study evaluated of pre-procedure anxiety levels for undergoing mammography women.

Methods

This cross-sectional descriptive study was conducted between February and June 2011 at a university hospital with 128 women who had appointments to have mammography.

15-item questionnaire and the 20-item State Anxiety Inventory, developed by Spielberger et al. were used for data collection. They were completed by the participants using a face to face interview method. On the questionnaire form there are 15 questions about their demographic characteristics and mammography. The State Anxiety Inventory determines individuals' feelings in certain conditions and at that moment. Its translation into Turkish and reliability and validity study was done by Öner and Le Compte in 1989 (Öner and Le Compte 1998). On this inventory there are 40 statements about how the individual feels. The first 20 items measure the situation related anxiety level with 4 choices. These choices are: None (1), Some (2), A lot (3), Always / Completely (4) . In this section there are direct and reversed statements. The results are interpreted as having no anxiety for a score of 0-19, mild anxiety for a score of 20-39, moderate anxiety for 40-59, severe anxiety for 60-79, and in need of professional help for a score 80 or higher. Permission to conduct this study was obtained from the Head of the Radiology Department and informed consent was obtained from each patient. The patients were informed about the aim of the research. The participants were assured of their right to refuse to participate or to withdraw from the study at any stage.

To evaluate the resulting data the Statistical Package for the Social Sciences (SPSS), version 11.5, was used. Percentage, arithmetic average, Mann-Whitney U test and Kruskall-Wallis test were used to analyze the data. All numbers were given as average value ± standard deviation; $p<0.05$ was accepted for level of significance.

Results

The women, whose average age is 49.78±8.67 ,87.5 % are married; 46.9 % are graduated from primary school; 60.9 % are not working ; 58.6 % are during the period of menopause ; 86.7 % have children and 62.5 % have breast cancer in their family members. 38.3 % underwent mammography because of their symptoms ; 78.1 % underwent mammography previously; 88.3 % have knowledge about the process. The total anxiety score averages of women are 57.17±8.33 (Table 1).

In being searced for anxiety score average to women's educational level, it was determined that, anxiety score average on women who graduated secondary school is higher than the other groups and this difference was found statistically significant ($p<0.05$). To having breast cancer in women's relatives, anxiety score average was searced that, anxiety score average was highly determined on women who had breast cancer in their family and this difference was found statistically significant($p<0.05$).

To the reason of screening mammography women in studying group, anxiety score average was considered that, averages in screening mammography group because of breast cancer were determined as the highest. This difference was found statistically significant ($p<0.05$).

When the average were searced according to getting information of women about mammography and having screening mamograpy in their family; Women who got information about mammography and screened mammography in their family had high scores averages . This difference was found statistically significant ($p<0.05$).

There hasn't been found to be statistically significant difference between being the period of menopause, having children, income, working, age, having mammography before and their anxiety score averages.

Discussion

Mammography is a good method for screening programs for early diagnosis of breast cancer. In our study, statistically significant differences were not found in women's anxiety score averages according to their marital status, working, income, having children, being the period of menopause and having mammography before ($p>0.05$). The level of anxiety about mammography screening was found to be lower in women with high educational levels and this difference was found to be statistically significant. Similar results were reported in different studies (Alimoğlu et al, 2004; Ma-

Table 1. Anxiety scores in relation to Sociodemographic Characteristics of the Women (N=128)

Descriptive Characteristics	S	%	Anxiety Level Mean Scores
Total Anxiety Level Mean Scores		57.17±8.33	
Age		49.78±8.67	
Marital status Married Single	 112 16	 87.5 12.5	 57.57±8.17 54.37±9.20 MW-U=755.500 p=.310
Education Level Illiterate Literate Primary school Secondary school High school	 6 33 60 12 17	 4.7 25.8 46.9 9.4 13.3	 58.50±2.73 61.00±6.42 55.96±7.12 62.50± 6.41 49.76± 11.65 KW=23.656 **p=.000**
Work status: Yes No	 50 78	 39.1 60.9	 57.36±10.02 57.05±7.12 t=.204 p=.839
Income Status Income< expenditure Income= expenditure	 68 60	 53.1 46.9	 58.01±6.75 56.21±9.80 t=1.220 p=.225
Having children status Yes No	 111 17	 86.7 13.3	 57.79±7.82 53.11±10.52 MW-U=729.500, p=.132
In menopause Yes No	 75 53	 58.6 41.4	 57.45±9.04 56.77±7.28 t=.453 p=.651
Had close relative with breast cancer Yes No	 80 48	 62.5 37.5	 59.57±6.19 53.16±9.85 t=4.519 **p=.000**
Level of closeness Her/his aunt Her/his mother Oneself Her/his father's sister Other	 61 29 27 5 6	 47.7 22.7 21.1 3.9 4.6	 54.27±9.17 59.79±6.29 61.07±6.89 60.00± 5.47 54.00± 4.38 KW=15.259 **p=.004**
Cause of mammography To scan Doctor's request Breast cancer	 42 49 37	 32.8 38.3 28.9	 52.50±8.81 58.81±7.65 60.29±6.29 F=11.880 **P=.000**
Having mammography before Yes No	 100 28	 78.1 21.9	 56.70±9.19 58.85±3.68 MW-U=1205,500 p=.261
Knowledge about having mammography Yes No	 113 15	 88.3 11. 7	 57.96±8.10 51.20±7.83 MW-U=418.500 **p=.001**
Had a mamography in family Yes No	 107 21	 83.6 16.4	 58.77±5.95 49.00±13.03 MW-U=646.500, **p=.002**

iniero et al., 2001; Brunton et al., 2005; Bölükbaş et al., 2010). Women with a family history of breast cancer in this research were more likely to report higher levels of worry about breast cancer than those women without a family history of breast cancer, and the difference between the two groups was found to be statistically significant. The level of anxiety is higher in the women because of the high risk incidence breast cancer for them. Anxiety score averages of the women who diagnosed with breast cancer with mammography are higher than other groups of women, the difference was found to be statistically significant ($p<0.05$). Alimoğlu and his friends (2004) have made a study to measure pain and anxiety that developing because of screening mammography. In the study they demonstrate that they couldn't find a significant difference between the participants' (had mammography experience and inexperienced) pain and anxiety. This finding is compatible with our study result. Martha et al. (2001) in their study, named 'Mammography-related anxiety effect of preprocedural patient education' They got a group of women watch an educational film about mammography and for the others watch a non-educational funny film. Between the two groups , they have found that there is no significant difference for the levels of anxiety based on processing. These results are similar to our study findings. Thus we think that the factor creates the actual anxiety is not the lack of information about the process or the thought of pain during the process but the fear of getting diagnosed with cancer and uncertainty.

We found significant differences between the anxiety scores of the informed (57.968.10) and uninformed (51.20+7.83) women.

Conclusions

From the results of this study it has been determined that women having mammography have a moderate level of anxiety. Overall, however, contrary to suggestions from other researchers, this study does not demonstrate that screening mammography raises the ongoing level of anxiety in this population of women. The reverse had been shown. The majority of women felt reassured following their mammogram, and levels of anxiety about breast cancer were diminished.

According to different study results (Alimoğlu et al 2004;Bölükbaş et al 2010), it hasn't been found significant differences between the anxiety scores of the informed and uninformed women. But, in our study result we suggest to inform the patients about the process in terms of patient rights and ethics, although it is no use of reducing anxiety.

Nurses can play an important role in breast cancer screening programs. They can evaluate womens' level of anxiety at an early stage and offer appropriate support. Nurses can also ensure the follow up and personalized support required while a patient awaits a diagnosis.

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Behind hirsutism and psychiatric symptoms: ectopic Cushing's syndrome

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Abstract

For a beautiful woman, a pretty face can increase confidence and bring more happiness in her usual life. Hirsutism is often a bothering problem especially expressed on the face; however, it sometimes is suggestive of a serious medical illness. The ectopic Cushing's syndrome is a challenging diagnostic dilemma leading to hirsutism for the difficulty in lesion localization. Clinically, in addition to the problems of the appearance, patients with Cushing's syndrome may also be noted with psychiatric or emotional disturbance especially depression in females. Intact information from the evaluation in physiologic status and mind is the important clue in the diagnosis. The advanced image technology can offer much help in making the exact diagnosis.

Key words: hirsutism, psychosis, ectopic Cushing's syndrome

Introduction

Hirsutism is defined as excess hair growth in the androgen-dependent areas of the body in woman and often a bothering problem for the cosmetic factor. It affects about 5% of woman in the United States[1] that in most women is due to polycystic ovary syndrome or idiopathic.[2] Many etiologies of hirsutism could be classified as ovarian, adrenal, drug-related, idiopathic or genetic; adrenal disorders including Cushing's syndrome. Patients with Cushing's syndrome may present with depression (12%), emotional lability (3%), and psychosis symptoms (8%).[3] The most prevalence of tumors in ectopic Cushing's syndrome is thoracic tumor and surgical resection is the favored policy of treatment.

Case report

A 33-year-old woman without unremarkable medical histories complained about moustache and acne appearing over the face since one month ago (Figure 1); auditory hallucination was also mentioned. She went to the endocrine clinic. Her husband offered the information of his wife profound emotional change from irritability and lability to severe depression. She did not take any medicine except for vitamin C as daily dose 75mg.

Figure 1. A 33-year-old woman complained about acne and moustache over her face

On admission, this patient must stand with assistance due to bilateral leg weakness. She was afebrile and presented relatively stable vital signs except for hypertension (blood pressure: 162/94 mmHg). Physical examination disclosed moon

face, hirsutism (beard over her face) and peripheral edema; neurologic examinations were unremarkable. Laboratory evaluation showed hypernatremia (146 mmol/L, normal: 136-145 mmol/L), hypokalemia (2.3 mmol/L, normal: 3.5-5.1 mmol/L), and alkalosis (pH: 7.512). Chest plain film and abdominal sono showed unremarkable findings. Pregnancy test was negative. Medicine related hirsutism was excluded from her history and drug review. Further hormone studies are arranged.

Initially, the total testosterone and plasma dehydroepiandrosterone-sulfate (DHEAS) was measured which showed elevated testosterone 157 ng/dL (normal: 14-76 ng/dL) and DHEAS 627.7 ug/dL (normal: 98.8-340 ug/dL). Since the testosterone was mainly contributed by ovarian and adrenal gland, further studies for differential diagnosis were ordered. The random plasma cortisol showed 85.51 ug/dL and at 8 a.m. showed 46.46 ug/dl after 1 mg dexamethasone test at midnight. Urine free cortisol 9051ug/day, progesterone 3.58 ng/mL, estadiol 13.38 pg/mL, luteinizing hormone (LH) 4.29 mIU/mL, follicle-stimulating hormone (FSH) 8.45 mIU/mL, prolactin 5.3 ng/mL were also reported. By ultrasound, the polycystic ovaries were denied. Due to positive result of screening test to Cushing's syndrome, low-dose dexamethasone suppression test (0.5 mg every 6 h for 48 h) was arranged with result of cortisol 58.59 ug/dL. Moreover plasma adrenocorticotropic hormone (ACTH) revealed 270 pg/mL; therefore ACTH-depending Cushing's syndrome is highly suspected. Thyroid function study revealed low triiodothyronine (T3) 34.49 ng/dL (normal: 86-187), normal free thyroxine (T4) 0.9 ng/dL (normal: 0.8-2.0), and low thyroid-stimulating hormone (TSH) 0.04 Uiu/mL.

Pituitary tumor is denied after the survey of magnetic remission image (MRI). FDG increased uptake over the pulmonary nodule (1.5cm) in the left lung base (Figure 2, Panel A), bilateral adrenal gland, the nodule over subpleural left lower lung (LLL) (Figure 2, Panel B), and the nodule (1.5cm) in the right lower lung (RLL) base (Figure 2, Panel C) are reported from PET/CT whole body scan. The surgical intervention was performed.

She received the surgical resection and the atypical carcinoid tumor (nodule over RLL) was informed from the pathology report; the diagnosis is ectopic Cushing's syndrome.

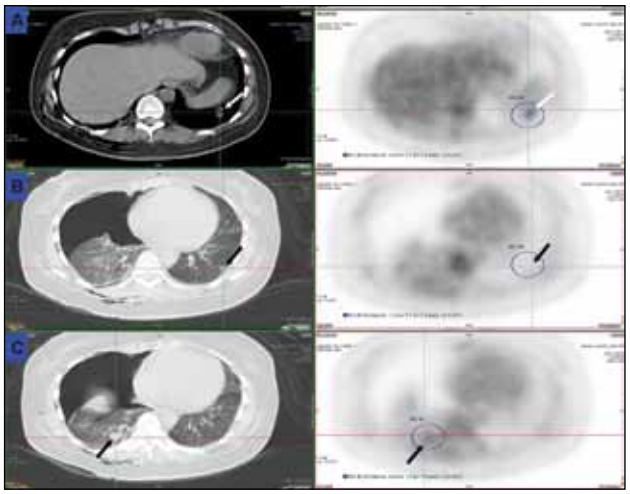

Figure 2. FDG increased uptake over the pulmonary nodule (1.5cm) in the left lung base (Figure 2, Panel A), bilateral adrenal gland, the nodule over subpleural left lower lung (LLL) (Figure 2, Panel B), and the nodule (1.5cm) in the right lower lung (RLL) base (Figure 2, Panel C) are reported from PET/CT whole body scan

Discussion

Due to the suppression of TSH secretion from high cortisol level, this patient also presented with hypothyroidism. In approaching, when patients present the symptoms or signs of cortisol excess the screening of Cushing's syndrome should be considered. In this case, she presented with ACTH-dependent Cushing's syndrome; the adrenal glands were stimulated by ACTH which will result in increased production of androgen and this is the mechanism why she presented with hirsutism. Severe hypokalemia is more prevalent in the patients with ectopic ACTH which may result from adrenal hypersecretion of mineralocorticoids[4,5]; this explained why this patient complained about leg weakness.

Among ACTH-dependent Cushing's syndrome, ectopic Cushing caused by non-pituitary ACTH-secreting tumors accounts for 9-18%.[6]In many instances the responsible tumor is a small-cell carcinoma of the lung; about the true incidence of Cushing's syndrome secondary to lung carcinoid tumor remains not well known and Brown[7] was the first in 1928 to describe its occurrence in a woman. Pulmonary carcinoid tumors are classified as either typical or atypical by the histopathologic report and associated with endocrine disorders inclusive of

Cushing's syndrome.[8] In general, ACTH-secreting carcinoid tumors demonstrate an aggressive entity, lying somewhere on the spectrum of malignancy between hormonally quiescent typical and atypical carcinoids[9,10]; therefore surgical complete resection remains the better treatment of choice.

Ectopic ACTH syndrome is a rare cause of ACTH-dependent Cushing's syndrome and often a diagnostic challenge because the secreting tumor is usually too small and occult to be detected by conventional imaging examinations such as CT or MRI.[11] With significantly high ACTH and negative result of tumor finding from pituitary MRI, the ectopic source was highly suspected in our case. Since the most tumors causing ectopic ACTH syndrome are intrathoracic, the initial image examination should be focused on the chest. However, with the advance of imaging studies, we can perform PET whole body scan to detect the possible tumor site not only limited in the thorax. Although FDG-PET for detection of the ectopic ACTH source has a unsatisfying sensitivity of 64% and positive predictive values of 53 %,[12] combined with other image modality, the diagnostic value could be elevated.[13] In FDG-PET study for pulmonary carcinoid tumor the false-negative results were often noted which is due to hypometabolic characteristic on FDG-PET but with CT image, the limitation could be compensated.[13,14] We arrange the PET/CT scan to identify the location of the lesion; and with good anatomy resolution CT can offer, the tumor lesion was successfully to be demonstrated.

The treatment of Cushing's syndrome depends upon the underlying cause and the management of choice for ectopic ACTH syndrome depends on tumor identification, localization, and classification; this patient's cortisol level finally got back to be between the normal range after surgery treatment.

Conclusion

This case is of clinical educational value for two reasons. Firstly, the clinicians should always keep in mind that the possible etiologies behind hirsutism and psychiatric symptoms inclusive of ectopic Cushing's syndrome. Secondly, PET/CT can be a useful image tool in lesion localization.

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Management of intravenous cannulation: The efficacy of an educational intervention on nurses' knowledge

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Abstract

Background: A number of studies have reported that nurses are not expert peripheral intravenous cannulation managers. Results of these studies emphasize the need for regular education for nurses. The aim of this pre-post test quasi-experimental descriptive study was to assess the effect of an educational intervention on nurses' knowledge and management of intravenous cannulation.

Methods: A convenience sample of nurses who attended an in service interactive lecture-based workshop on intravenous cannulation were invited to participate in the research study. Those who agreed (n=30) completed a test consisting of 18 multiple choice questions (MCQ) to access their knowledge of intravenous cannulation and its management prior to the delivery of the presentation. The MCQ test was repeated after the teaching session in order to determine if there was a change in the participants' knowledge post the intervention.

Results: Consent was given by the participants to use their scores for the purpose of this study. When the points obtained in the test taken before the teaching session were compared with the post-teaching MCQ test results, a substantial and statistically significant development was observed after the teaching Mean = 8.2**,** SD = 1.1 and Mean = 15.5, SD = 1.3 on 18 items, before and after teaching, respectively, $p<0.001$)

Conclusions: Lecture based workshop on administration of intravenous cannulation helps improves nurses' knowledge. The information gained in this study will be valuable baseline for further research and help guide improvements in the implementation of management of intravenous cannulation with the ultimate goal of enhancing safe and quality patient care.

Key words: intravenous cannulation; test, knowledge; nurses; interactive workshop.

1. Introduction

Intravenous cannulation (peripheral or central) is commonly used for vascular access in the hospital environment. Inserting, maintaining, and monitoring of IV sticks required to get a successful vascular access are integral components of patient care. Management of venous access devices is a complex nursing activity with the potential for serious complications (eg, IV infiltrations, infections at sites, pain, difficulty advancing the catheter, damage to vessels, catheter malposition, and bleeding)[1, 2]. Health professionals have a responsibility to be aware of and to ensure that the intravenous cannulation needs of the patient are upheld in order to provide them with the best start possible. Nurses are responsible for the insertion and maintenance of peripheral venous catheters for the prevention of complications[1, 2]. The dangers and consequences of inappropriate administration of venous access devices application have been highlighted previously[3, 4]. A central venous catheterization (CVC) even in experienced hands can be a risky procedure with many complications, some of which can be serious[3, 4]. Therefore the management of intravenous cannulation is one of the most common problems faced by nurses (patients are not faced with management – they experience the lack there of) and health professionals[5-8].

Despite advances in knowledge about venous access devices, preventable complications still occur. A number of studies have reported the problem of intravenous cannulation management[9-14]. Nurses should maintain quality and safety for better patient outcomes related to management of intravenous cannulation complications[6-8]. Awareness of these complications will help the clinician manage these issues appropriately[(3-5)]. Nurses must also improve the dignity and environmental comfort for patients. Better patient outcomes

are achieved when the risks of common catheter-associated complications, such as pain, difficulty advancing the catheter, damage to vessels, catheter malposition, and bleeding are minimized. Post insertion complications such as occlusions, thrombosis, catheter failure, infection, catheter malposition, infiltration, extravasation nerve damage, and tissue necrosis must also be recognized and minimized[15-19]. To avoid complications nurses must master several skills including: selecting and preparing the appropriate equipment, choosing the best vein, preparing the skin, inserting and securing the catheter and initiating/restoring intravenous therapy. In addition, attention must be paid to potential risks in order to resolve them as quickly as possible, thereby avoiding complications[20, 21].

A physician typically orders the insertion of a peripheral intravenous catheter, but a nurse often performs the cannulation and is responsible for its management. The nurse is the key to reducing the associated risks, through her knowledge and skill in cannulation and the intravenous administration of drugs. The nurse must also be able to recognize the early signs and symptoms of complications and act promptly and effectively to limit complications[22]. Nurses are the key to the assessment of appropriateness of continuing indwelling peripheral intravenous catheter use, identifying complications, and implementing care practices to minimize complications[23]. Nurses must be at the forefront of providing comprehensive best practice for indwelling peripheral intravenous catheters[24]. Although common, these practices are not devoid of complications, which may lead to mortality and morbidity, increased duration of hospital stay, and significant costs[25-27]. Therefore, it is widely understood as a cause of morbidity.

Nurses insert and manage catheters, yet studies have shown that most nurses have limited scientific knowledge in the area of catheters and their care. A number of studies have reported that nurses are not expert peripheral intravenous cannulation managers[23, 28, 29]. Results of these studies emphasize the need for regular education for nurses[23, 28, 29]. Basic/regular education on intravenous cannulations are provided in academic nursing programs. Nurses should have the appropriate knowledge and skills in relation to caring for the patient with intravenous cannulation and be aware of the complications and adverse patient outcomes. Nurses should understand how to prevent intravenous cannulation complications, the causes of intravenous cannulation complications, and adverse patient outcomes that results from intravenous cannulation complications. Proper nursing care is key to preventing complications and maintaining the intravenous cannulation until treatment has been completed[30-32].

Educational outreach promotes positive changes in practice behaviors[27-29]. Therefore intravenous cannulation management education programs should be organized for nurses. Nurses must achieve acceptable levels of knowledge to prevent and manage intravenous cannulation; this can be improved with an educational program[28-31]. A multifaceted approach to tackle current deficiencies in knowledge and management of intravenous cannulation should include the provision of evidence-based educational opportunities. Interactive workshops are generally perceived as useful for nurses. Interactivity led to effective learning. If lectures were able to enter into a dialogue with a learner, fellow students gain formative feedback.

Therefore, the aim of this study was to evaluate the efficacy of an interactive workshop on management of intravenous cannulation and its impact on nurses' knowledge.

2. Methods

Study design

This study was conducted by a sample of convenience. This pre-post test quasi-experimental descriptive study was conducted in a Private hospital Istanbul city center in Turkey during the month of May 2010.

Setting and sampling

Nurses working in different departments in the hospital were invited to participate in an interactive lecture-based three hour workshop on management of intravenous cannulation. The workshop was presented by the investigator as part of an in-service training program. Participation was voluntary. A pre-lecture multiple choice question (MCQ) test (Appendix A) was completed voluntarily by nurses (n=30) to test their existing knowledge. The MCQs were derived from topics covered in the presentation. The MCQ items were

obtained by researchers from sources used within this paper. Following the lecture the MCQ test was repeated to assess their knowledge following the interactive lecture. Participants were unaware that they would be tested with an MCQ prior to the lecture or that the MCQ would be repeated at end of the workshop. Participants' provided written permission to use their answers for the purpose of this study. This study was approved by institutional review board of the institution.

Statistical Analysis

Statistical analysis was performed using SPSS_ for Windows _ v 15.0 software (SPSS Inc., Chicago, USA). The Student paired t-test was used to obtain the p of .001 if the differences between the pre-lecture and post-lecture test results were significant.

We performed these tests on just overall score of the test as a whole entity.

3. Results

Thirty nurses participated in the workshop. There was a statistically significant improvement in test scores after the lecture when compared with pre-lecture scores (Table 1,Figure 1).

Table 1. Pre-lecture and post-lecture test scores

	Pre-lecture test (n=30)	Post-lecture test (n=30)
Mean (standard deviation) 95% Confidence interval	8.2 (1.1) 7.8-8.6	15.5 (1.3) 15.0-16.0
Chi Square df Asymp.sig	19.6 5 0.001	19.4 6 0.003

Maximum test score=18.
Paired sample test (2-tailed) p < 0.001.

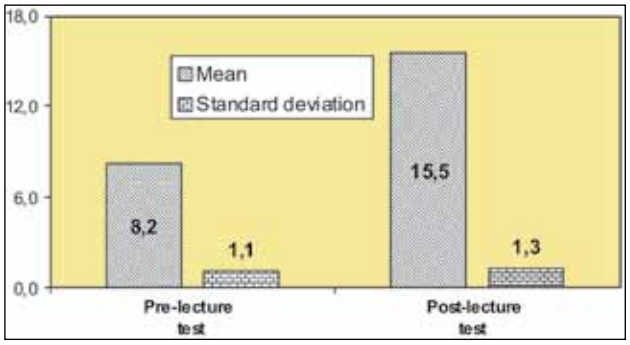

Figure 1. Pre-lecture and post-lecture test scores

4. Discussion

The management of intravenous cannulation is a significant problem in the healthcare service[7,9,10.] Successful management of intravenous cannulation requires that nurses have adequate knowledge of the most common problems. This study was undertaken to determine knowledge and practice for management of intravenous cannulation of nurses and to assess the effect of training given on this subject. Completion of the educational program resulted in improved levels of knowledge. Nurses in this study were at nursing training grades and, having qualified four years earlier would be expected to have a basic understanding of best practice for the management of intravenous cannulation. But the mean pre-lecture test score (Mean =8.2, S.D=1.1) was low.This indicates that ceasing education after completion of a 4-year nursing training degree is not adequate; there is a vast difference between remembering a fact stated in a teaching session and actually understanding its context, being able to put it in practice. A more didactic form of teaching with explanation of the underlying concepts is required to improve knowledge and application of best practice technique for the management of intravenous cannulation, as indicated by the significant improvement in post-lecture test scores (Mean=15.5, S.D=1.3). This has also been indicated in other studies[30,31].

Overall nurses acknowledged the importance and relevance of the subject and felt the workshop was worthwhile. Amongst the limitations of this study was the small number of nurses in this the concenience sampling method study, although the sample represented 40% of the nurses invited to attend this session. Keeping in mind the above-mentioned limitations, this study showed nurses' knowledge in relation to the the management of intravenous cannulation was poor and lecture-based workshop on knowledge and management the management of intravenous cannulation helps improve their knowledge. However, whether this will change the nurses practice remains to be seen.

This study tested immediate recall of knowledge and it remains to be seen whether the knowledge gained as a result of the event will be retained by the trainees and whether their application of best practice to management on intravenous ca-

nnulation habits will be altered as a result. It would be useful to examine nurses' knowledge base and application of best practice for the management of intravenous cannulation sometime after such an event to determine the need for continued and repeated training into this important subject. In addition, the improvement in the MCQ score could be at least partially attributed to an 'order effect'. It is possible that improvement in post-lecture scores could have occurred without the structured workshop, simply because the nurses had the opportunity to think about the questions again and give a more considered answer. This limitation could have been controlled for through the use of randomization to a control group and an intervention group that received the structured learning intervention.

5. Conclusion

Nursing professionals must know the best practice technique for the management of intravenous cannulation and complications caused by intravenous cannulation including ways to prevent and manage these complications. We need not forget that nurses are the ones mainly responsible for improving knowledge and application of best practice technique for the management of intravenous cannulation. As nurses, we are responsible for maintaining our skills and knowledge in relation to all aspects of patient care.

Results of the study showed that at the pre program phase, nurses' knowledge in relation to the management of intravenous cannulation was poor. The referenced study has shown that using interactive sessions with lectures and multiple choice questions improved nurses' knowledge on the topic. The findings of this study suggest that greater emphasis needs to be placed on nurses' education of management of intravenous cannulation. However, this is critical issue in this study and we would argue that the lack of an examination of change to practice are fundamental flaws that need explained further.

Providing nurses with information relating to management of intravenous cannulation essential; it can promote adherence to best practice, self assessment and self reporting of the difficulties relating to the management of intravenous cannulation. The results obtained in this study will be valuable as a base line for further research and aid improvements in the management of intravenous cannulation, with the ultimate goal of enhancing high quality patient centred care.

The literature suggests that to practise safely nurses must have specific knowledge of the actions, benefits and risks associated with administration of intravenous cannulation. Finally, they need to be able to appropriately document assessment findings, decide when signs and symptoms indicate the likelihood of complications, and implement appropriate actions if these complications arise. Thus, the main aim of this research project was to describe nurses' knowledge and practice skill performance regarding the management of intravenous cannulation and to explore relationships between these variables and the education received by the nurses. The study examined nursing knowledge in relation to clinical performance of sensory and motor blockade assessment, the identification of actual or potential complications, and clinical decision-making skills. Education strategies were based on studies that education alone does little to change practice behavior and that interactive and didactic education are more effective when used with other practice-reinforcing strategies. The results of the study would inform educational planning for intravenous cannulation management competencies. These things are being mentioned here for the first time – an indepth explanation of these strategies needs to occur in the methods section as an explanation of the intervention.

It would be reasonable to assume, therefore, that a similar method could be adopted to teach nursing students about intravenous cannulation as well.

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Appendix A

For each given question select the single best answer from the choices provided (A&E)

1. Which one of the following steps to successful insertion of peripheral catheter should be carried out:
   A Selecting the vein, selecting the catheter, cleaning and disinfecting the area, inserting the catheter, fixing the catheter, restoring intravenous therapy, and avoiding complications.
   B Preparing the material, selecting the vein, selecting the catheter, inserting the catheter, fixing the catheter, restoring intravenous therapy, and avoiding complications.
   C Preparing the material, selecting the vein, selecting the catheter, cleaning and disinfecting the area, inserting the catheter, fixing the catheter, restoring intravenous therapy, and avoiding complications.
   D Preparing the material, selecting the vein, selecting the catheter, cleaning and disinfecting the area, inserting the catheter, fixing the catheter, and avoiding complications.
   E Preparing the material, selecting the vein, selecting the catheter, cleaning and disinfecting the area, inserting the catheter, fixing the catheter, and restoring intravenous therapy

2. Suggested to decrease peripheral venous catheters (PVC) associated complications;
   A Good knowledge of complication risks, a good insertion technique and how to care for patients with PVC, a small cannula size, duration of site-use <24 hours, good hygienic handling
   B A good insertion technique and how to care for patients with PVC, a small cannula size, duration of site-use <24 hours, good hygienic handling
   C Good knowledge of complication risks, a small cannula size, duration of site-use <24 hours, good hygienic handling
   D Good knowledge of complication risks, a good insertion technique and how to care for patients with PVC, duration of site-use <24 hours, good hygienic handling
   E Good knowledge of complication risks, a good insertion technique and how to care for patients with PVC, a small cannula size, good hygienic handling

3. Which of the following statements on using alcohol swab, cleanse injection site is true?
   A. Cleanse the site in a circular motion for 15 s and allow to dry for 15 s prior to administration
   B. Cleanse the site in a circular motion for 30 s and allow to dry for 30 s prior to administration
   C. Cleanse the site in a circular motion for 5 s and allow to dry for 5 s prior to administration

D. Cleanse the site in a circular motion for 20 s and allow to dry for 20 s prior to administration
E. Cleanse the site in a circular motion for 10 s and allow to dry for 10 s prior to administration

4. Vascular complications of catheters, including:
   A Hemorrhage, vascular spasm, and arterial puncture, peripheral nerve injury
   B Hemorrhage, vascular spasm, and arterial puncture, brachial nerve plexus
   C Hemorrhage, arterial puncture, peripheral nerve injury and brachial nerve plexus
   D Hemorrhage, vascular spasm, and arterial puncture, peripheral nerve injury and brachial nerve plexus
   E Vascular spasm, and arterial puncture, Peripheral nerve injury and brachial nerve plexus

5. Because of the risk for vein irritation and damage, for therapies that are not appropriate for peripheral administration including:
   A Continuous vesicant drug infusions
   B Parenteral nutrition
   C Infusates with a pH lower than 5 or higher than 9
   D Infusates with an osmolality greater than 600 mOsm/L.
   E All of the above

6. What is the long and large diameter of Subclavian Vein
   A 3–4 cm long and 10–11 mm diameter.
   B 1–2 cm long and 8–9 mm diameter.
   C 3–4 cm long and 8–9 mm diameter.
   D 5–6 cm long and 8–9 mm diameter.
   E 4–5 cm long and 6–7 mm diameter.

7. Whichever is a common complication associated with peripherally inserted central catheters (PICCs)
   A Infection
   B Catheter migration
   C Vessel thrombosis
   D Damaged catheter
   E Skin erosion

8. Indications for central venous catheterization include
   A Emergency venous access and measurement of central venous pressure for optimization of fluid status of the patient,
   B Infusion of vasoactive drugs
   C Parenteral nutrition, and
   D Central venous oxygen saturation (ScvO2) sampling.
   E All of the above

9. Factors that influence Central venous access devices (PICC) functioning may include:
   A The characteristics of the device, product material, medications and solutions infused through the PICC,
   B The characteristics of the device, product material, and the health status of the patient
   C The characteristics of the device, medications and solutions infused through the PICC, and the health status of the patient
   D The characteristics of the device, product material, medications and solutions infused through the PICC, and the health status of the patient
   E Product material, medications and solutions infused through the PICC, and the health status of the patient

10. Central *venous* complications (CVCs) of catheters, including:
   A Cardiac tamponade,
   B Air embolism, pneumothorax,
   C Hemothorax,
   D Hydrothorax, and thoracic duct injury
   E All of the above

11. Routinely, Central venous access devices (PICCs) are used for administration of:
   A Total parenteral nutrition (TPN), hypertonic solutions, chemotherapeutic agents, blood products, fluid administration, antibiotic therapy, and retrieval of blood specimens
   B Total parenteral nutrition (TPN), hypertonic solutions, chemotherapeutic agents, blood products, fluid administration, and retrieval of blood specimens
   C Total parenteral nutrition (TPN), hypertonic solutions, chemotherapeutic agents, fluid

administration, antibiotic therapy, and retrieval of blood specimens

D Total parenteral nutrition (TPN), chemotherapeutic agents, blood products, fluid administration, antibiotic therapy, and retrieval of blood specimens

E Total parenteral nutrition (TPN), hypertonic solutions, blood products, fluid administration, antibiotic therapy, and retrieval of blood specimens

12. Complications associated with indwelling central venous catheters include in the followings are:

A Site infection, catheter occlusion, dislodgment and Twiddler's syndrome, catheter migration, catheter pinch-off syndrome, damaged catheter, superior vena cava syndrome, and skin erosion.

B Site infection, dislodgment and Twiddler's syndrome, catheter migration, catheter pinch-off syndrome, vessel thrombosis, damaged catheter, superior vena cava syndrome, and skin erosion.

C Site infection, catheter occlusion, dislodgment and Twiddler's syndrome, catheter migration, catheter pinch-off syndrome, vessel thrombosis, damaged catheter, and skin erosion.

D Site infection, catheter occlusion, dislodgment and Twiddler's syndrome, catheter migration, catheter pinch-off syndrome, vessel thrombosis, damaged catheter, superior vena cava syndrome, and skin erosion.

E Site infection, catheter occlusion, dislodgment and Twiddler's syndrome, catheter migration, vessel thrombosis, damaged catheter, superior vena cava syndrome, and skin erosion.

13. Which of the following statements about the first symptom of phlebitis may be true?

A Warmth at the insertion site.

B Erythema at the insertion site.

C Discomfort at the insertion site or along the cannulated vein.

D Limb edema

E A palpable cord along the venous pathway, and lowgrade fever.

14. Which of the following statements about among risk factors of phlebitis may be true?

A Material, and length of the catheter; pH and osmolality of the infusate; and rate of flow, administered drugs, and duration of catheterization.

B Material, diameter, and length of the catheter; pH and osmolality of the infusate; and rate of flow, administered drugs, and duration of catheterization.

C Material, diameter, and length of the catheter; and rate of flow, administered drugs, and duration of catheterization.

D Material, diameter, and length of the catheter; pH and osmolality of the infusate; and rate of flow, and duration of catheterization.

E Material, diameter, and length of the catheter; pH and osmolality of the infusate; and rate of flow, administered drugs,

15. Which of the following statements about prevent infiltration and extravasation may be true?

A Selection of an appropriatesize catheter, use of appropriate fluids, stabilization of the catheter, and use of proper administration techniques.

B Selection of an appropriate site for catheter insertion, selection of an appropriatesize catheter, use of appropriate fluids, stabilization of the catheter, and use of proper administration techniques.

C Selection of an appropriate site for catheter insertion, use of appropriate fluids, stabilization of the catheter, and use of proper administration techniques.

D Selection of an appropriate site for catheter insertion, selection of an appropriatesize catheter, stabilization of the catheter, and use of proper administration techniques.

E Selection of an appropriate site for catheter insertion, selection of an appropriatesize catheter, use of appropriate fluids, and stabilization of the catheter

16. Reasons for catheter removal were

A Phlebitis,

B Infiltration,

C Blood flow block,

D Kinking, accidental catheter removal
E All of the above

17. Which of the following statements is incorrect?
A Intravenous catheter sites were evaluated once a day preferably every 24 hours for the development of catheter-related complications.
B The use of an appropriate type of dressings is intended to keep the insertion site clean and dry while also preventing external contamination and trauma
C Teflon and Polyurethane catheters show lower infection complication rates compared to Polyvinylchloride and Polyethylene varieties.
D The catheter was kept patent by either continuous infusion with IV fluid or intermittent flushing with 1.5 mL of normal saline solution at least daily, as well as before and after each drug injection.
E The US Centers for Disease Control and Prevention (CDC) recommended routine replacement of peripheral intravenous catheters every 48–72 hours.

18. Which of the following statements is incorrect?
A The nurse chooses the IV site carefully so as not to decrease the patient's ability
B A tourniquet must be applied, and veins must be assessed.
C Cold, moist compresses are very helpful in dilating veins.
D The cubital fossa veins should be preferred as peripheral venous catheters insertion site.
E The incidence of thrombophlebitis could be reduced by using small size peripheral intravenous catheters.

Answers: 1-C, 2-A, 3-B, 4-D, 5-E, 6-C, 7-A, 8-E, 9-D, 10-E, 11-A, 12-D, 13-C, 14-B, 15-B, 16-E, 17-A, 18-C.

Effect of Salvia reuterana aerial parts on serum parameters in normal and streptozotocin-induced diabetic rats

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Abstract

Background: Herbal medicine has been used for many years by different cultures around the world for the treatment of diabetes. Some species of *Salvia* have been cultivated worldwide for use in folk medicines and for culinary purposes. The main aim of this study was to evaluate the antidiabetic effect of *Salvia reuterana* aerial parts ethanolic extract in normal and streptozotocin-induced diabetic rats.

Methods: Male Wistar streptozotocin-induced diabetic rats administered with *Salvia reuterana* ethanolic extract (0.05, 0.1, 0.25 and 0.5 g/kg body weight) or glibenclamide (600 μg/kg). Normal rats administered with *Salvia reuterana* ethanolic extract (0.05, 0.1, 0.25 and 0.5 g/kg body weight). Control groups treated with distilled water. After 14 days, level of serum glucose, triglycerides, total cholesterol, urea, uric acid, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in normal and diabetic rats were evaluated.

Results: Oral administration of 0.25 and 0.5 g/kg body wt. of the *Salvia reuterana* extract and glibenclamide (= standard antidiabetic drug) for 14 days exhibited a significant reduction in serum glucose, triglycerides, total cholesterol, urea, uric acid, creatinine, AST, ALT and increased plasma insulin in streptozotocin-induced diabetic rats but not in normal rats.

Conclusion: It could be proofed that the traditional use of *Salvia reuterana* as an antidiabetic agent is justified and that extracts from this plant show a dose-dependent activity which is comparable to the standard antidiabetic drug glibenclamide.

Key words: Diabetes; Rat; *Salvia reuterana*; Streptozotocin

Introduction

Diabetes mellitus is a major public health burden worldwide. In year 2000, there were about 171 million diabetes cases worldwide and the number is estimated to rise to 366 million by year 2030 (1). Type 2 diabetes results from the inability of the body to respond properly to the action of insulin produced by the pancreas. It is the most prevalent form of diabetes accounting for around 90% of all diabetes cases. This disorder is basically characterized by high levels of blood glucose caused by defective insulin production and action that are often responsible for severe health problems and early death (2). Pulmonary edema, angina pectoris, myocardial infarction, cerebrovascular insult, hypertension were more common in diabetics than in nondiabetics, and heart failure was more common diagnosis in nondiabetics (3). Ethnopharmacological surveys indicate that more than 1200 plants are used in traditional medicine for their alleged hypoglycemic activity (4-6). The hypoglycemic activity of a large number of these plants/plant products has been evaluated and confirmed in animal models (7-11) as well as in human beings (12-14).

Salvia is an important genus consisting of 900 species in the family Lamiaceae and some species of *Salvia* have been cultivated worldwide for use in folk medicines and for culinary purposes. The name *Salvia* comes from the Latin word Salvare, the healer. Species of *Salvia* have been used as a folk medicine for the treatment of stomach ailments and the common cold. The volatile oils of several species are used as antiseptic, the tannin as a local anti-inflammatory agent, and the bitter taste produces a pleasant sensory feeling in the mouth

and throat (15,16). They also possess antibacterial (17), antitumor (18), antidiabetic (19) antituberculosus (20), carminative, diuretic, hemostatic and spasmolytic activities and as a flavoring agent in perfumery and cosmetics industries (21,22). *Salvia reuterana* Boiss. is a perennial herb which grows in the highlands of center of Iran. The plant popularly referred in Farsi as Mariam Goli Esfahani. It is reported that *Salvia reuterana* has shown antibacterial (23) and anxiolytic effects (24). Due to use of *Salvia reuterana* in folk medicine for treatment of diabetes (25) and the lack of any report on its anti-diabetes activities, this study was initiated. We studied the antidiabetic effect of alcoholic extract of *Salvia reuterana* aerial parts in normal and streptozotocin (STZ)–induced rats and also compared it with glibenclamide as a reference antidiabetic drug.

Materials and Methods

Plant material

Fresh *Salvia reuterana* aerial parts were collected from Ghazvin area and identified in the Department of Botany of Islamic Azad University (Voucher number: 04165, deposited in: I.A.U. Herbarium). The aerial parts were shade dried and finely powdered. The powder was extracted with aqueous 80% ethanol using soxhlet apparatus up to 72 hours. The extract was concentrated on rotavapour under reduced pressure. The extract yield was 12.5%. The obtained alcoholic extract was stored at -20°C until usage.

Animals and Induction of diabetes

Adult male Wistar rats weighing between 200 and 230 g were used in the study. The animals were housed in a well ventilated room maintained at a temperature 23±2 ◦C, relative humidity of 57±2%, on a 12 h light/12 h dark cycle. All the animals received a standard pellet diet (Pars-Dam Food, Iran) and tap water *ad libitum*. Diabetes was induced by a single injection of STZ (70 mg/kg B.W.) freshly dissolved in physiological saline solution into the intraperitoneal. The control rats were only injected with physiological saline solution. Five days after injection, hyperglycemia was confirmed based on a blood glucose level above 300 mg/dl.

Experimental design

The animals were randomly divided into eleven groups of eight animals each and treated as given below. Distilled water was used as a vehicle solution for the oral administration of the extract and glibenclamide. All of groups administrated orally using an intragastric tube. The volume of administration was 1 ml, and the treatments lasted for 14 days. Body weights of rats were recorded initially, and at the end of the experiment.

Group I: normal animals were treated with distilled water; this group of animals served as normal control.

Groups II-V: normal animals were treated with *Salvia reuterana* extract at doses 0.05, 0.1, 0.25 and 0.5 g/kg wt, respectively.

Group VI: diabetic animals were treated with distilled water; this group of animals served as a diabetic control.

Groups VII-X: diabetic animals were treated with *Salvia reuterana* extract at doses 0.05, 0.1, 0.25 and 0.5 g/kg wt, respectively.

Group XI: diabetic animals were treated with 600 μg/kg of glibenclamide.

After 14 days of treatment, the 12 h fasted animals were anaesthetized. Blood samples were drawn from heart.

Biochemical assays

After 14 days of treatments, blood samples were drawn from heart. Serum glucose, insulin, total cholesterol, triglycerides, urea, uric acid, creatinine, aspartate amino transferase (AST) and alanine amino transferase (ALT) levels were determined. Serum glucose was estimated by oxidase method (26). The serum insulin was estimated by using the radioimmunoassay kit (diasorin, Italy), total cholesterol and triglyceride by the method of Rifai, 1999 (27). Serum urea was assayed by the method of Tomas, 1998 (28), while uric acid was measured by the method of Fossati, 1980 (29). Serum creatinine was estimated by the method of Tomas, 1998 (30). Serum AST and ALT were assayed by the method of Moss, 1999 (31).

Statistical analysis

The results were presented as mean ± SEM using one-way analysis of variance test (ANOVA) followed by Tukey post hoc test. The criterion for statistical significance was $p<0.05$.

Results

As shown in Table 1, significant differences were not observed in initial body weights between different groups. After 14 days of experiment, the diabetic control rats gained less body weight than did normal control rats. When compared with untreated diabetic control rats, the body weight gains were significantly increased in *Salvia reuterana* extract-treated diabetic animals in a dose-dependent manner.

Table 1. Effect of Salvia reuterana extract administration on body weight in normal and diabetic rats

Groups	Initial (g)	Final (g)
Normal control	210.2 ± 12	241.7± 18
Normal + extract (0.05 g/kg)	219.4 ± 17	245.5 ± 13
Normal + extract (0.1 g/kg)	215.6 ± 15	249.2 ± 19
Normal + extract (0.25 g/kg)	220.3 ± 12	242.7 ± 16
Normal + extract (0.5 g/kg)	213.8 ± 16	246.8 ± 11
Diabetic control	224.3 ± 11	172.3 ± 21***
Diabetic + extract (0.05 g/kg)	214.7 ± 12	185.6 ± 23
Diabetic + extract (0.1 g/kg)	223.4 ± 15	189.4 ± 17
Diabetic + extract (0.25 g/kg)	219.8 ± 11	203.6 ± 15 +
Diabetic + extract (0.5 g/kg)	212.7 ± 14	210.3 ± 18 ++
Diabetic + glibenclamide	216.8 ± 10	220 ± 19 ++

Values are mean ± S.E.M. for eight rats.
*** *p<0.001, different from normal control rats.*
+ *p<0.05, different from diabetic control rats.*
++ *p<0.01, different from diabetic control rats.*

In the present study, diabetic control rats showed significant increases in blood glucose and decrease in plasma insulin levels after 14 days of experiment compared when compared with normal control rats (Table 2). In extract-treated groups of diabetic animals, we observed a significant dose-dependent decrease in blood glucose level and a significant increase in plasma insulin level, after 14 days of experiment, compared with the diabetic control group, while extract-treated groups of normal rats did not exhibit any significant alterations in these parameters levels duration of the experiment.

Table 3 showed that the effect of the *salvia reuterana* extract on the serum triglycerides and total cholesterol in normal and diabetic rats. The results showed that serum triglycerides and total cholesterol increased, when compared with normal rats. The administration of the *salvia reuterana* extract and glibenclamide significantly decreased serum triglycerides and total cholesterol when compared with control diabetic rats. The administration of the *salvia reuterana* extract (0.05, 0.1, 0.25 and 0.5 g/kg body wt.) did not change serum triglycerides and total cholesterol levels in normal rats.

In normal diabetic rats, a significant increase on the serum urea, uric acid and creatinine was observed when compared to the diabetic control rats. Treatment with *Salvia reuterana* extract and glibenclamide caused a significant decrease on serum urea, uric acid and creatinine when compared with diabetic control rats. The administration of the *salvia reuterana* extract (0.05, 0.1, 0.25 and 0.5 g/kg body wt.) did not change serum urea, uric acid and creatinine levels in normal control rats (Table 4).

Table 2. Effect of Salvia reuterana extract administration on serum glucose and insulin levels in normal and diabetic rats

Groups	Glucose (mg/dl)	Insulin (IU/l)
Normal control	110.7 ± 5.7	13.75 ± 0.61
Normal + extract (0.05 g/kg)	100.4 ± 4.4	12.03 ± 0.50
Normal + extract (0.1 g/kg)	105.2 ± 5	13.2 ± 0.46
Normal + extract (0.25 g/kg)	97.1 ± 4.2	12.5 ± 0.63
Normal + extract (0.5 g/kg)	91.6 ± 6.1	14.5 ± 0.57
Diabetic control	390.6 ± 7.6 ***	2.08 ± 0.14 ***
Diabetic + extract (0.05 g/kg)	352.5 ± 12.5	2.36 ± 0.06
Diabetic + extract (0.1 g/kg)	270.4 ± 15.4 +	2.85 ± 0.09
Diabetic + extract (0.25 g/kg)	232.8 ± 22.7 ++	3.18 ± 0.07 +
Diabetic + extract (0.5 g/kg)	190.7 ± 19.3 +++	3.52 ± 0.11 +
Diabetic + glibenclamide	113.8 ± 20.7 +++	4.01 ± 0.07 ++

Values are mean ± S.E.M. for eight rats.
*** *p<0.001, different from normal control rats.*
+ *p<0.05, different from diabetic control rats.*
++ *p<0.01, different from diabetic control rats.* +++ *p<0.001, different from diabetic control rats.*

Table 3. Effect of Salvia reuterana extract administration on serum triglycerides and total cholesterol levels in normal and diabetic rats

Groups	Triglycerides (mg/dl)	Total cholesterol (mg/dl)
Normal control	89.5 ± 3.2	63.8 ± 7.1
Normal + extract (0.05 g/kg)	93.2 ± 6.3	61.5 ± 5.4
Normal + extract (0.1 g/kg)	98.7 ± 4.6	55.7 ± 2.1
Normal + extract (0.25 g/kg)	83.6 ± 9.8	59.4 ± 8.9
Normal + extract (0.5 g/kg)	86.3 ± 8.5	52.3 ± 6.2
Diabetic control	165.8 ± 12.6 ***	117.1 ± 8.1 ***
Diabetic + extract (0.05 g/kg)	171.1 ± 15.7	110.9 ± 6.5
Diabetic + extract (0.1 g/kg)	140.5 ± 9.1	105.2 ± 7.1
Diabetic + extract (0.25 g/kg)	133.1 ± 8.2 +	85.4 ± 11.3 +
Diabetic + extract (0.5 g/kg)	120.4 ± 11.7 ++	81.3 ± 9.2 ++
Diabetic + glibenclamide	95.6 ± 8.3 +++	70.1 ± 7.8 +++

Values are mean ± S.E.M. for eight rats.
*** *p<0.001, different from normal control rats.*
\+ *p<0.05, different from diabetic control rats.*
++ *p<0.01, different from diabetic control rats.*
+++ *p<0.001, different from diabetic control rats.*

Table 4. Effect of Salvia reuterana extract administration on serum urea, uric acid and creatinine levels in normal and diabetic rats

Groups	Urea (mg/dL)	Uric acid (mg/dL)	Creatinine (mg/dL)
Normal control	30.4 ± 2.3	1.5 ± 0.07	0.61 ± 0.09
Normal + extract (0.05 g/kg)	29.1 ± 1.9	1.4 ± 0.08	0.58 ± 0.13
Normal + extract (0.1 g/kg)	32.6 ± 2.7	1.2 ± 0.16	0.55 ± 0.07
Normal + extract (0.25 g/kg)	28.2 ± 2.4	1.2 ± 0.12	0.54 ± 0.08
Normal + extract (0.5 g/kg)	29.7 ± 3.2	1.1 ± 0.13	0.51 ± 0.11
Diabetic control	59.7 ± 7.5 ***	3.9 ± 0.25 ***	1.8 ± 0.09 ***
Diabetic + extract (0.05 g/kg)	56.1 ± 8.2	2.8 ± 0.18	1.62 ± 0.05
Diabetic + extract (0.1 g/kg)	51.7 ± 4.5	2.6 ± 0.19	1.53 ± 0.06
Diabetic + extract (0.25 g/kg)	48.3 ± 7.6 +	2.4 ± 0.14 +	1.48 ± 0.07 +
Diabetic + extract (0.25 g/kg)	40.7 ± 3.5 ++	2.3 ± 0.16 ++	1.25 ± 0.06 +++
Diabetic + glibenclamide	35.7 ± 6.3 +++	2.1 ± 0.12 +++	0.89 ± 0.08 +++

Values are mean ± S.E.M. for eight rats.
*** *p<0.001, different from normal control rats.*
\+ *p<0.05, different from diabetic control rats.*
++ *p<0.01, different from diabetic control rats.*
+++ *p<0.001, different from diabetic control rats.*

Table 5 showed that the effect of the *salvia reuterana* extract on the serum AST and ALT in normal and diabetic rats. The results showed that serum AST and ALT increased, when compared with normal rats. The administration of the *salvia reuterana* extract and glibenclamide significantly decreased serum AST and ALT when compared with control diabetic rats. The administration of the *salvia reuterana* extract (0.05, 0.1, 0.25 and 0.5 g/kg body wt.) did not change serum AST and ALT levels in normal rats.

Discussion

The present study demonstrated that the *Salvia reuterana* alcoholic extract and glibenclamide (=standard antidiabetic drug) improved insulin secretion, prevented hyperglycemia, hypercholesterolemia, hypertriglyceridemia and reduced serum urea, uric acid, creatinine, AST and ALT in the STZ-induced diabetic rats. Hypoglycemic sulphonylureas such as glibenclamide can increase pancreatic insulin secretion from the existing β-

Table 5. Effect of Salvia reuterana extract administration on serum AST and ALT levels in normal and diabetic rats

Groups	AST (IU/L)	ALT (IU/L)
Normal control	130 ± 11.4	80.5 ± 9.7
Normal + extract (0.05 g/kg)	138 ± 14.5	82.4 ± 7.6
Normal + extract (0.1 g/kg)	128 ± 12.4	78.3 ± 13.4
Normal + extract (0.25 g/kg)	120 ± 10.7	74.6 ± 9.5
Normal + extract (0.5 g/kg)	118 ± 9.6	72.3 ± 10.7
Diabetic control	205 ± 15.2 ***	168.1 ± 14.3 ***
Diabetic + extract (0.05 g/kg)	200 ± 19.3	161.3 ± 12.7
Diabetic + extract (0.1 g/kg)	190 ± 24.7	150.5 ± 9.2
Diabetic + extract (0.25 g/kg)	171 ± 9.8	143.1 ± 21.8
Diabetic + extract (0.5 g/kg)	135 ± 17.4 ++	125.7 ± 15.3 ++
Diabetic + glibenclamide	110 ± 9.6 +++	119.4 ± 14.6 ++

Values are mean ± S.E.M. for eight rats.
*** *p<0.001, different from normal control rats.*
++ *p<0.01, different from diabetic control rats.*
+++ *p<0.001, different from diabetic control rats.*

cells in STZ-induced diabetes by membrane depolarization, and stimulation of Ca^{2+} influx, an initial key step in insulin secretion (32). Moreover, glibenclamide has shown a protection effect against oxidative stress in diabetes (33,34). Glibenclamide is often used as a reference drug in STZ-induced moderate diabetic model. Though sulphonylureas are valuable in treatment of diabetes, their use is restricted by their limited action and side effects (33). Natural plant drugs are frequently considered to be less toxic with lower side effects than synthetic ones (35-37).

Our results showed that the administration of STZ significantly increased serum glucose, triglycerides, cholesterol, urea, uric acid, creatinine, AST and ALT while decreased serum insulin levels in control diabetic rats as compared with control normal rats. It is now well established that STZ selectively destroys the pancreatic cells and produces hyperglycemia (38), which is evidenced by the decreased level of plasma insulin. STZ is commonly used in chemically induced diabetic animal model. The timing of STZ injection is important and will affect the type of diabetes that subsequently develops. If STZ is injected to adult animals (i.e. 3 months or older), type 1 diabetes results. However, if injected during the first week of birth while the capacity of pancreatic β-cell regeneration remains in the animals, type 2 diabetes develops (38,39).

The serum glucose data obtained clearly indicate that the oral administration of alcoholic extract from *Salvia reuterana* produce significant hypoglycemic effects only in STZ-induced diabetic rats and not in normal rats. Many natural resources have been investigated with respect to the suppression of glucose production from carbohydrates in the gut or glucose absorption from the intestine (40). Also, the extract affects insulin releasing from the pancreas of diabetic group. Phytochemical screening of *Salvia reuterana* has revealed the presence of ocimene, gurjunene, germacrened, hexyl acetate (41), germacrene D, caryophyllene, bicyclogermacrene, sesquiterpenes, nonterpenoid compounds (23) and flavonoids (42). It has been demonstrated that some flavonoids exert hypoglycaemic activity in rats (43-46) and are also known for their ability of beta cell regeneration of pancreas (47,48).

Our result also showed that the alcoholic *Salvia reuterana* extract exhibited a significant decrease in the level of serum lipids in diabetic rats. The most common lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia (49,50). Hypertriglyceridemia is also associated in metabolic consequences of hypercoagulability, hyperinsulinemia, insulin resistance and glucose intolerance (51). The observed hypolipidemic effect may be due to decreased cholesterologenesis and fatty acid synthesis (52). Under normal circumstances, insulin activates the enzyme lipoprotein lipase, which

hydrolyses triglycerides (53). However, in diabetic state lipoprotein lipase is not activated due to insulin deficiency resulting in hypertriglyceridemia. Lipoprotein levels can be considered an emerging risk factor for premature atherosclerosis (54). Literature has shown flavonoids, alkaloids to be the active hypoglycemic principle in many medicinal plants with blood glucose and lipids-lowering attributes (55). The presence of alkaloids in the plant extract as reported by Esmaeili et al., 2008, may account for the observed hypoglycemic and hypolipidemic effects of the extract (23).

Urea is the major nitrogen containing metabolic product of protein metabolism; uric acid is the major product of purine nucleotides, adenosine and guanosine; creatinine is endogenously produced and released into body fluids and its clearance measured as an indicator of glomerular filtration rate (56). The diabetic rats had increased levels of serum urea, uric acid and creatinine, which are considered as significant markers of renal function (57), and this is in agreement with the present result. As the duration of diabetes increases, the incidence of nephropathy also increases significantly. Since nephropathy is a forerunner for end stage renal disease, preventive measures can help in preventing renal failure (58). Treatment with the plant extract reversed these parameters to near normal level which could be due to decreased metabolic disturbances of other pathways such as protein and nucleic acid metabolisms as the extract improved glycemic control.

It is reported that liver is necrotized in STZ-induced diabetic rats (59). Therefore, increase in the activities of AST and ALT in plasma may be mainly due to the leakage of these enzymes from the liver cytosol into the blood stream (60), which gives an indication on the hepatotoxic effect of STZ. Administration of the extract lowered the serum AST and ALT activities in diabetic rats. *Salvia reuterana* extract treated with normal rats did not show any significant change in the activity when compared with normal control rats. The increased gluconeogenesis and ketogenesis observed in diabetes may be due to high level in the activities of these transaminases (61).

As a result, it may be concluded that, *Salvia reuterana* aerial parts extract is effective in attenuate of increasing serum parameters resulting from the damage of STZ-induced diabetic rats which is comparable to the standard antidiabetic drug glibenclamide.

Acknowledgment

We would like to thank Iran National Science Foundation, for financial support of the project.

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Air pollution and hospital admissions for chronic obstructive pulmonary disease in Novi Sad

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Abstract

Introduction: The study was aimed at establishing the association between the number of daily hospital admissions for chronic obstructive pulmonary disease and daily concentrations of air pollutants in the city of Novi Sad during 2007 - 2009.

Material and methods: The research data were based on the daily concentrations of sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) measured in 24h air samples and the daily number of hospital admissions of adults (>18 years of age) for chronic obstructive pulmonary disease (ICD10:J44) on the territory of the city of Novi Sad during the observed period. The applied generalized linear model according to the Poisson regression type included the days of week, month of year, season, mean daily temperature and the relative humidity of air as controlled variables in addition to daily hospital admissions (a dependant variable) and sulfur dioxide and nitrogen dioxide concentrations as independent variables. The final statistical model chosen according to the Akaike criteria was also tested with respect to the different lag structure of air pollutants and meteorological parameters.

Results: No statistically significant association was found between the daily number of hospital admissions for chronic obstructive pulmonary disease (n=1001) and daily concentrations of sulfur dioxide and nitrogen dioxide ($p>0.05$). A statistically significant increase in the daily number of hospital admissions for chronic obstructive pulmonary disease was repeatedly observed after weekends, i.e. on Mondays (OR=2.301; 95% CI:1.813-2.920). With respect to monthly variations, it was found that the risk of increased number of daily hospital admissions for chronic obstructive pulmonary disease was statistically significantly higher ($p<0.01$) during February (OR=1.695; 95% CI: 1.282-2.242), March (OR=1.612; 95% CI:1.210-2.149), April (OR=1.703; 95% CI:1.247-2.326) and May (OR=1.809; 95% CI:1.350-2.424) compared to January. According to the applied regression model along with the control of meteorological factors, it was found that each increase in the relative air humidity by 10% on the territory of the city of Novi Sad was statistically significantly associated with the increased number of the hospital admissions for chronic obstructive pulmonary disease by 0.6% (OR=1.006; 95% CI:1.000-1.011) at lag of three days.

Conclusion: The association of the number of hospital admissions of adults for chronic obstructive pulmonary disease was not statistically significant with respect to the determined air quality; however, it was statistically significant with respect to the air humidity, workdays and months of the year.

Key words: Air Pollution; Pulmonary Disease, Chronic Obstructive; Patient Admission

Introduction

Health impact of air quality studies implemented so far have confirmed that the presence of ambient air pollutants adds to the total morbidity and mortality rates [1]. Although studies on mortality are still useful in towns and cities with a bigger urban air pollution problem, the research based on the number of hospital admissions is getting more important for the regions with descending concentrations of air pollutants [2]. Some authors [3] have pointed to the fact that negative health effects of air pollutants can be observed even if the air pollutant concentrations are below the values prescribed by the World Health Organization (WHO) [4-6].

Studies estimating the total human exposure to urban air pollutants have demonstrated the evident association between the air quality and the number of hospital admissions for respiratory diseases [7,8]. The majority of such studies have investiga-

ted various air pollutants with respect to different human health outcomes [9]. Considerable attention has been directed towards sensitive individuals suffering from chronic obstructive pulmonary diseases (COPD) [10]. Anderson et al [11] have confirmed the association of the daily number of hospital admissions for COPD with particulate air pollution [12,13] as well as with the concentrations of gaseous air pollutants (sulfur dioxide and nitrogen dioxide) [14,15].

In the city of Novi Sad, the association between the human health and the air quality has been so far estimated only through individual target studies but not through a systematically organized monitoring [16,17]. The reasons for such a situation lie in the lack of uniform methodology for collecting and processing the data on the population health status and environmental conditions and the absence of indicators defined by law necessary for the evaluation of the effects of air quality on the population health.

This study was aimed at determining the association between daily concentrations of urban air pollutants in Novi Sad and the number of hospital admissions for COPD during the period from 2007 to 2009.

Methods

The research data were based on the daily concentrations of sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) measured in 24h air samples and the daily number of hospital admissions of adults for COPD on the territory of the city of Novi Sad during the period from 2007 to 2009.

The ambient air pollutants were selected according to the continuity of data on their daily concentrations, which were obtained by continuous air quality monitoring in the city of Novi Sad performed by the Centre for Hygiene and Human Ecology of the Institute of Public Health of Vojvodina (IPHV) [18-20]. In the period from January 1st, 2007 to December 31st, 2009, the SO_2 and NO_2 concentrations were determined by the volumetric and spectrophotometric method, respectively, in 1096 24h air samples [21]. The concentration values measured for SO_2 were categorized into SO_2 I category (concentrations of $SO_2<2\mu g/m^3$) and SO_2 II category (concentrations of $SO_2\geq2\mu g/m^3$). The concentration values measured for NO_2 during the observed period were categorized into NO_2 I category (concentrations of $NO_2<4\mu g/m^3$), NO_2 II (concentrations of NO_2 from $4\mu g/m^3$ to $85\mu g/m^3$) and NO_2 III category (concentrations of $NO_2>85\mu g/m^3$).

Data on average daily temperature values and the relative air humidity for the observed period were obtained from the Republic Hydrometeorological Institute of Serbia [22].

Data on the daily number of total hospital admissions of adults for COPD on the territory of the city of Novi Sad were obtained from the Centre for Informatics and Biostatistics in Health Care *of* the IPHV. According to the hospital discharge diagnosis, 1001 patients were found to have diagnosis ICD10:J44 [23] on hospital admission. In addition to data on the daily number of hospitalizations during the observed period, data on the age of the hospitalized individuals were available. However, only the daily number of hospital admissions of individuals older than 18 years of age was taken into consideration.

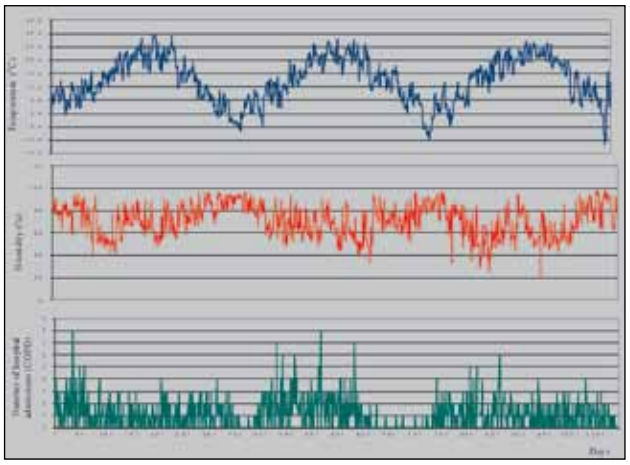
The interrelationship between the selected ambient air pollutants and microclimatic parameters was evaluated using Spearman's rank correlation coefficient. The association between the ambient air pollution and the daily number of hospital admissions for COPD was evaluated by the generalized linear model [24] extending Poisson regression [25]. The daily number of hospital admissions for COPD was analyzed as a dependent variable, whereas days in the week, months in the year and season (each year was divided into the summer season from March 21st to September 22nd and the winter season from September 23rd to March 20th) were analyzed as contrast indicator factors. Meteorological factors (average daily temperature and the relative air humidity) were examined as continuous independent variables. The final statistical model chosen according to the Akaike criteria was also tested with respect to the lag time of the pollutants and meteorological parameters. The values of the approximate relative risk "odd ratio" (OR) and 95% confidence intervals (CI) were calculated for each variable in the final model. The Statistical Package for the Social Sciences (SPSS) (version 17) and R statistical program (version 2.13.0) were applied for all statistical analyses.

Results

The daily concentration values of SO_2 I category were <2μg/m³ during 696 days (63.4%) of the observation period and during 400 days of the observation, the average concentration value of SO_2 II category was 16.33μg/m³, the minimum being 2μg/m³ and the maximum 31μg/m³. The daily concentration values of NO_2 I category were <4μg/m³ during 494 days (44.9%) of the 3-year period and during 591 days of the observation the average daily value of NO_2 II category was 19.93μg/m³, and the maximum value of NO_2 III category during 11 days of the 3-year period was 137μg/m³ (Table 1).

During the observed period, the average daily air temperature was 12.5±8.4°C, the minimum being -12°C and the maximum 29.7°C. The air humidity ranged in this 3-year period from 21% to 99%, and its mean value was 71.1±14.4%. According to the obtained results, one adult patient was admitted to hospital to be treated for COPD on average ($\overline{X}$ =1.13±1.23), and the number of hospital admissions ranged from 0 to maximum 8 during one day (Graph 1).

Spearman's rank correlation coefficients (Table 2) point to a statistically significant, negative correlation (p=0.000) between the temperature and the air humidity, and statistically significant, negative correlation (p_{SO2}=0.028; p_{NO2}=0.019) between the temperature and SO_2 and NO_2 concentrations, i.e. the higher/the lower the temperature, the lower/the higher the air humidity and the average daily SO_2 and NO_2 concentrations.



Graph 1. Micro-climatic indicators and the number of hospital admissions for COPD in the city of Novi Sad during the period 2007-2009

The correlation between the air humidity and the average daily SO_2 concentrations was statistically significantly negative (p=0.026), i.e. the lower/the higher the air humidity, the higher/the lower the SO_2 concentrations in air. No statistically significant correlation between the air humidity and the average daily concentrations of NO_2 was found (p>0.05). The correlation analysis results of air pollutants (SO_2 and NO_2) point to a statistically significant, negative correlation (p=0.017) between them.

The regression analysis results (Table 3) point to the significance of workdays with respect to the increased risk of getting hospitalized for COPD. When compared with weekend days, all workdays were statistically significantly associa-

Table 1. Values of air pollutants in the city of Novi Sad during the period 2007-2009

Pollutant	Total number of days of measure-ing in the period 2007-2009	Number and % of days of measuring		Mean daily values of concentrations	Min values	Max values
		n	%			
SO_2 I category	1096	696	63.5	-	-	-
SO_2 II category		400	36.5	16.33	2	31
NO_2 I category	1096	494	45.1	-	-	-
NO_2 II category		591	53.9	19.93	4	85
NO_2 III category		11	1,0	99.40	86	137

SO_2 – sulfur dioxide (μg/m³), NO_2 – nitrogen dioxide (μg/m³)

Table 2. Spearman's correlation of the examined pollutants and micro-climatic parameters

	Sulfur dioxide		Nitrogen dioxide		Temperature		Air Humidity	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Sulfur dioxide			**-0.063**	**0.017**	**-0.082**	**0.028**	**-0.083**	**0.026**
Nitrogen dioxide					**-0.060**	**0.019**	**-0.048**	**0.170**
Temperature							**-0.573**	**0.000**
Air Humidity								

r - Spearman's coefficient
p – statistical significance

Table 3. Final basic model of the applied regression analysis

Observed parameters	ß	OR (95%CI)	p
(Intercept)*	**-1.554**	**0.211 (0.110-0,406)**	**0.000**
Monday	**0.833**	**2.301 (1,813-2,920)**	**0.000**
Tuesday	**0.597**	**1.816 (1.417-2.327)**	**0.000**
Wednesday	**0.618**	**1.855 (1.449-2.375)**	**0.000**
Thursday	**0.716**	**2.046 (1.605-2.608)**	**0.000**
Friday	**0.617**	**1.853 (1.447-2.373)**	**0.000**
Saturday	**-0.333**	**0.717 (0.527-0.975)**	**0.034**
Air Humidity (lag3)	**0.060**	**1.006 (1.000-1.011)**	**0.036**
February	**0.528**	**1.695 (1.282-2.242)**	**0.000**
March	**0.478**	**1.612 (1.210-2.149)**	**0.001**
April	**0.532**	**1.703 (1.247-2.326)**	**0.000**
May	**0.593**	**1.809 (1.350-2.424)**	**0.000**
June	**0.380**	**1.463 (1.091-1.960)**	**0.011**
July	**0.337**	**1.401 (1.033-1.901)**	**0.030**
August	**0.140**	**1.158 (0.837-1.602)**	**0.377**
September	**-0.269**	**0.764 (0.539-1.084)**	**0.132**
October	**0.313**	**1.367 (0.997-1.875)**	**0.052**
November	**0.061**	**1.063 (0.761-1.484)**	**0.721**
December	**-0.494**	**0.610 (0.411-0.906)**	**0.014**

*ß –coefficient of regression; OR – odd ratio; CI –confidence interval; p – statistical significance; * – the constant of model; lag 3 – the period of delay activity, i.e. the value of air humidity 3 days before hospitalization*

ted (p=0.000) with the number of hospital admissions for COPD, the risk of getting hospitalized for COPD being the highest after weekends, i.e. on Mondays (OR=2.301; 95% CI: 1.813-2.920). If January is regarded as the reference month, the analysis of the monthly variations of the number of daily hospital admissions for COPD yielded the results indicating the statistically significant, positive association (p<0.01) with the number of hospital admissions in February (OR= 1.695; 95% CI: 1.282-2.242), March (OR=1.612; 95% CI:1.210-2.149), April (OR=1.703; 95% CI: 1.247-2.326) and May (OR=1.809; 95% CI: 1.350 - 2.424), whereas the above significance was getting less and less during the summer months till the end of year compared to January as the reference month.

The regression analysis demonstrated that the relative air humidity was statistically, significantly, positively associated (p=0.036) with the number of hospital admissions for COPD (Table 4). Each increase in the relative air humidity by 10% on the territory of the city of Novi Sad was significantly associated with the increase in the number of hospital admissions for COPD by 0.6% (OR=1,006; 95% CI: 1,000-1,011) at lag of three days (lag3).

The applied regression model, in addition to the control of contrast indicator factors and meteorological factors, did not demonstrate any statistically significant association (p>0.05) between the daily number of hospital admissions for COPD and the daily NO_2 and SO_2 concentrations.

Discussion

The air quality in the city of Novi Sad is characterized by the concentrations of air pollutants (SO_2 and NO_2) which are below the daily limit values set by the national standard [26]. Not for once did the daily concentrations of SO_2 exceed the prescribed daily limit values [18-20]. The daily concentrations of NO_2 exceeded the prescribed daily limit values during 11 (1%) days of the observed 3-year period [18-20].

The microclimatic factors included in this study demonstrate that air in the city of Novi Sad is characterized by high relative air humidity (over 70%) and temperature (12.5°C) over 10°C, which is specific for the moderate climate zones [27]. Contrary to other studies [28], which have found the association between the temperature and the number of hospital admissions for COPD, the daily number of hospital admissions for COPD was not found to be in association with the air temperature in this study.

With respect to the monthly variations of the daily number of hospital admissions for COPD, Osborne et al [29] recorded the maximum number of hospital admissions for COPD during February and March, which declined in the following months and this finding is similar to the results of this study. According to the results of a study performed in Hong Kong [30], seasonal oscillations of the number of hospital admissions for acute exacerbation of COPD among people over 65 years of age were due to influenza virus, and this fact underlines the necessity for further research, i.e. inclusion of influenza virus-induced diseases as one of the variables to be controlled. A similar finding was recorded in our study.

In this research, the relative air humidity at lag 3 (third day after exposure) was statistically significantly associated with the increase in the number of hospital admissions for COPD (OR=1.006; 95% CI:1.001-1.012), that being in accordance with the results from other studies [27,31]. Contrary to such results, other authors [32] have not found any association.

Even though numerous studies have pointed to a significant association between the ambient air pollutants with the number of hospital admissions for COPD, the results of this study regarding SO_2 and NO_2 concentrations do not corroborate such an association. With respect to the available literature, it could be supposed that low concentrations of air pollutants in the city of Novi Sad might have affected the obtained result. Although some studies [33] which point to the association between the concentrations of air pollutants and the number of hospital admissions for COPD rarely mention specific concentrations of these pollutants, in study performed in Barcelona, Sunyer et al [34, 35] confirmed the association between the urgent hospital admissions for COPD and SO_2 concentrations ranging from 17μg/m^3 to 160μg/m^3, which were higher than our SO_2 concentrations. The same study showed that this association remained even when all SO_2 concentrations above 72μg/m^3 were removed from the analysis. On the other hand, Biggeri et al [36] found a significant association between lower SO_2 concentrations (from 7μg/m^3 to 20μg/m^3) and the hospital admissions for COPD regarded as respiratory diseases. However, since their data about hospital admissions for COPD were not regarded as an individual health outcome indicator but within a group of respiratory diseases, our results cannot be directly compared with theirs.

In some studies, the mean daily NO_2 concentrations, examined with respect to the number of hospital admissions, were also much higher than our values of NO_2 concentrations. For example, in the cities, such as Amsterdam, Barcelona, London, Milan, Paris and Rotterdam, where the association between the ambient air quality and the increase in the number of hospital admissions for COPD was confirmed, the mean daily NO_2 concentrations ranged from 42μg/m^3 to 46μg/m^3 [11]. Nevertheless, Chen et al [37], point to the fact that the results obtained for one region or country could not be directly compared with other regions because of the exposure to different concentrations of air pollutants and differences regarding individual sensitivity.

On the other hand, the comparison of our results with the results from previous studies is made somewhat more difficult because of the different methodological approaches regarding the studied indicators, defined lag time and applied analytical approaches [11, 38-46].

The inconsistency of research is also evident with respect to the choice of the examined air pollutants. Thus, the study which was performed in

Valencia with the aim to examine the short-term association between the daily variations in soot, sulfur dioxide, nitrogen dioxide, carbon monoxide, ozone concentrations and urgent admissions for COPD, found a significant association only for ozone and CO, but not for other pollutants, that being in accordance with our results regarding NO_2 and SO_2 [46]. Neither did the research performed in China confirm a statistically significant association between SO2 concentration and hospital admissions of adult population for respiratory diseases [43][47]. The results of this study did not deviate significantly from the results of other studies either [38,47] regarded from the aspect of the association between NO_2 concentrations and COPD. A research with methodological approach similar to ours was conducted at the University Hospital in Istanbul in the period from 1997 to 2001. Besides the controlled effects of average daily temperature, air humidity and air pressure, no association was found between the average daily CO, SO_2, PM_{10}, NO and NO_2 concentrations and recorded 1586 hospital admissions for COPD. Neither Morrow confirmed in his study the association between the NO_2 concentrations and the number of hospital admissions for COPD, but he did find that the patients with COPD were more sensitive to the influence of NO_2 than healthy individuals [50].

However, the available literature provides the insight into a great number of studies which, contrary to ours, speak in favour of a statistically significant, positive association between the measured concentrations of SO_2 [51] or NO_2 [11, 52, 53] with the number of hospital admissions for COPD. Some authors believe that such an interpretation of the results may be found in prejudiced publications stating only positive results, whereas those studies which have not demonstrated a significant association between the air pollutants and the health outcomes indicators are doomed to become an example of a "file-drawer effect" [54].

Low average daily concentrations of the observed air pollutants in the city of Novi Sad, as well as low number of total hospital COPD admissions compared with other regions or countries could be the reasons for a much higher probability of differences of our results from others [38]. A study performed in Spain gave results for the controlled climatic factors (air temperature and relative humidity) similar to those obtained in our study, and the average number of daily hospital admissions for COPD, minimum and maximum number were almost identical to ours. Although the NO_2 and SO_2 concentrations were much higher than ours, their association with the number of hospital admissions for COPD was not determined [46].

In addition, a big problem regarding the use of hospital databases for evaluation of air pollution adverse effects is the reliability of diagnosis and other kinds of information. Some studies have concluded that hospital databases provide more reliable information of air pollution adverse effects when broad diagnostic classes are used as health indicators of the air quality [55]. One of the drawbacks of this study may be reflected in the fact that the total number of hospital admissions was analyzed with reference to the air quality, without the possibility to separate urgent admissions for COPD from total COPD admissions.

Guided by empirical data that the elderly people are more sensitive to the influence of the ambient air pollution [56], only the adult population was included in our study; however, Wilson [57] has stated that the level of risk of each individual is defined not only by the age but also by their genetics and biology, nutritional status, the presence of other respiratory or cardiovascular symptoms or the administration of certain medicines, of which none was included by our database. Similarly, the additional factors, such as life-style, i.e. smoking habit, exposure to allergens [58,59] as well as their interactive effect with the air pollutants [60] which may contribute to the exacerbation of COPD symptoms, were not taken into consideration because of the incomplete database.

Due to the fact that the people living in urban regions spend most of their time indoors [61], the measurements of the ambient air pollution cannot reflect the degree of exposure in urban environments. The afore-mentioned could have influenced our results regarding the association between NO_2 and COPD, because the indoor air quality has a far greater role in the evaluation of the association between the determined NO_2 concentrations and COPD.

Conclusion

The air quality in the city of Novi Sad is characterized by concentrations of sulfur dioxide and nitrogen dioxide below the prescribed limit values on the daily level.

The correlation between the number of hospital admissions of adult population for COPD and the determined air quality is not statistically significant. The risk of being hospitalized for COPD is highest after weekends, i.e. on Mondays, and the daily number of hospital admissions for COPD demonstrates dependence on the month of the year and air humidity at lag 3.

Funding

The authors acknowledge the financial support of the Ministry of Education and Science of Serbia, within the project Biosensing Technologies and Global System for Continuous Research and Integrated Management No.43002

Abbreviations

COPD - chronic obstructive pulmonary disease
SO_2 - sulfur dioxide
NO_2 - nitrogen dioxide
WHO -the World Health Organization
IPHV - the Institute of Public Health of Vojvodina
SPSS - Statistical Package for the Social Sciences
OR - odd ratio
CI – confidence interval

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Evaluation of quality of life of nasopharyngeal carcinoma patients treated in a single institution

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Abstract

Aim: To evaluate the Quality of Life (QOL) of patients with nasopharyngeal carcinoma (NPC) treated in the Izmir Oncology Centre (IOC) as part of a retrospective survival analysis study.

Methods: 31 patients with Nasopharyngeal Cancer (NPC) and treated in the Izmir Oncology Centre between April 2001 and January 2008 were included in the study. Basic demographic and clinical data were extracted from the patients` files. Histopathological evaluation was done according to WHO criteria, and clinical staging was done according to the American Joint Commission on Cancer (AJCC 1997). Radiotherapy was given by standard technique with a routine dose of 70Gy to the primary tumour and metastatic lymph nodes, and in most cases this was combined with chemotherapy. All the patients completed the European Organization for Research and Treatment of Cancer Core QOL Questionnaire (EORTC QLQ-C30) and head & neck specific module (QLQ H&N-35). Both had been translated into Turkish and validated in a previous study.

Results: The overall median follow up time was 55 months (range, 12 month- 90 month). The mean global health score for QLQ-C30 (ver. 3.0) was high (63.4), and the functional scale scores were higher. The lowest functional scale score was the physical functioning score (83.9). The highest functional scale scores were for cognitive functioning and social functioning (98.9 and 95.7) respectively. The highest adverse symptom scores were for insomnia (26.9) and fatigue (24.0). None of the patients complained of diarrhoea. No statistical significance from normal was found for physical functioning, role functioning, emotional functioning, cognitive functioning for gender, treatment, histopathology, and staging. These satisfactory scores, in conjunction with a high 5 year survival rate of 55%, support the policy of the Izmir Oncology Centre in the use of radiotherapy combined with chemotherapy in the treatment of NPC.

In conclusion the QOL of cancer patients is an important criterion in evaluating the outcome of the treatment and should be integrated into the programmes of treatment centres.

Key words: Quality of life, Nasopharyngeal carcinoma, Questionnaire

Introduction

Nasopharyngeal Cancer (NPC) is endemic in certain regions, such as Southern China and Southeast Asia with incidence rates varying between 15 to 50 cases per 100,000 persons [1, 2]. However it is a rare disease in Turkey (incidence range from 15 to 20 cases per 100,000 persons) compared to other cancer types such as lung cancer and breast cancer [2, 3]. NPC occurs in a young age group and is not associated with smoking or alcohol abuse [1].

The symptoms of the disease are often not recognised as NPC. It has a tendency to spread widely into adjacent structures; most importantly to the surrounding lymph nodes. Curative surgery is difficult, but NPC is sensitive to radiation. Hence treatment is by radiotherapy or a combination of radiotherapy with chemotherapy.

Different radiotherapy techniques have been used over the course of 15 years in the treatment of NPC with improvement in the outcome. The University of Texas M D Anderson Cancer Centre (MDACC) research group has analyzed these techniques and their complications [4]. These complications included; connective tissue changes (fibrosis, trismus), damage to bone, endocrine

changes (pituitary, thyroid), and nervous system changes (cranial nerve, spinal cord, and hearing loss). It was found that the frequency of later complications was reduced as a result of improvements in treatment techniques.

Cancer treatment reduces the quality of life of patients considerably. The main purpose of quality of life studies is to aim to improve patients` quality of living. University research centres and the Ministry of Health in Turkey have started new programmes to gather such data for research. Izmir is outstanding in Turkey for cancer statistical data collection. Ege University`s "Fight Against Cancer, Practice and Research Centre" has been collecting cancer data since 1991. The Izmir Oncology Centre, one of the oldest private oncology centres in Izmir, has collected a total patient database of around 12000 patients since 1998.

The standardized method for evaluation of a specified cancer treatment is survival analysis. The 5-year overall survival for NPC patients treated in the Izmir Oncology Centre is 55% in patients treated by radiotherapy with or without adjuvant chemotherapy, or by a combination of radiotherapy and chemotherapy [5]. In addition to survival quality of life however is an important measure of the success of the treatment.

In recent years much research has been conducted concerning the quality of life of cancer patients. Various types of questionnaires have been developed and validated, inquiring into a wide range of information. Tschiesner has reviewed quality of life questionnaires for head and neck cancer in order to choose the best type to use for certain objectives [6].

To record different patient characteristics, such as social and cultural level, requires a multidimensional evaluation. Psychosocial functions and physical symptoms need to be included in quality of life evaluations as well as functional well being, and this requires a detailed assessment. Quality of life assessment of an individual`s well being is very subjective. It is a personal assessment and is thought to reveal a balance between reality and the persons' expectations [7]. Such routine collection of such QOL data is beneficial to both clinicians and patients [8].

Particularly in the case of nasopharyngeal cancer treatment it is very important to evaluate surviving patients' quality of life; since basic functions such as breathing, oral communication and swallowing may be affected.

The aim of this study was to measure the quality of life of NPC patients treated in Izmir Oncology Centre in Izmir-Turkey with a validated evaluation method, and to integrate this method into our routine clinical work.

Materials and methods

Questionnaires

The EORTC QOL questionnaires were chosen for this study because they are suitable for long term usage; both the general questionnaire (QLQ-C30) and head and neck specific module (QLQ H&N-35) have been translated into Turkish and validated and have been used by research groups and treatment centres [9, 10, 11].

EORTC QLQ-C30 is a 30 question instrument measuring global health status; with functional scales; physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning; and symptom scales / items include; fatigue, pain, dyspnoea, insomnia, and appetite loss.

Global health status, symptoms, and functioning were calculated for each patient according to the EORTC QLQ-C30 scoring manual [12]. A high score for global health status represents a high QOL. Similarly, healthy functioning means high functional scale scores. On contrary, a high score for a symptom scale/item represents a high level of symptomatic problems.

The EORTC QLQ-H&N35 module is used with the core questionnaire which is specifically designed for head and neck cancer patients. The module inquires into pain, swallowing, sense problems, speech problems, social eating, social contact, sexuality; and also into the mouth and teeth, ill feeling, use of pain killers, weight loss or gain, and nutritional supplements.

The head & neck cancer module (QLQ-H&N35) incorporates seven multi-item scales that assess pain, swallowing, senses (taste and smell), speech, social eating, social contact and sexuality. Also eleven single items are included in the module. The scoring for the QLQ-H&N35 module is identical in principle to that of the QLQ-C30. High scoring indicates more problems.

Staging

The latest edition of International Union Against Cancer (UICC) and the American Joint Commission on Cancer (AJCC), since its improvement both in prognostication and stage distribution, was used [13]. Tumour staging was done according to AJCC 1997.

The most important prognostic factor is the histological type which has a clear impact on the outcome of treatment. According to World Health Organization, nasopharyngeal carcinoma is classified into three histological categories. Type I are the differentiated squamous cell carcinomas with keratin production. Type II includes non-keratinizing carcinomas. Type III are described as undifferentiated carcinomas [14, 15].

Treatment

The standard therapeutic option for early stages of NPC is radiation. Higher response rates were reported when radiation therapy and chemotherapy were combined in the more advanced stages [16-18]. All patients were treated with the conventional radiation therapy for primary carcinomas of the nasopharynx except for the advanced patients who received concurrent chemotherapy with radiotherapy. Conventional fractions were given at a weekly interval with 2 Gy/fraction (50 Gy for subclinical, 66 - 70 Gy for primary tumor and lymph nodes).

Statistical analysis

Statistical analysis was performed using SPSS statistical software, version 15 for Windows for the Kruskal-Wallis test for variables with more than 2 categories and the Mann-Whitney U-test for pairwise comparisons that accounted for the non-parametric distribution of the QOL scores. Statistical significance achieved when $p<0.05$.

Patient follow-up

A total of 31 patients treated for NPC between April 2000 and January 2008 were included in this study. 19 (61.3%) of these patients were male and 12 (38.7%) were female. The mean age was 49 years (Range 20-78). The overall median follow up time was 55 months (range, 12 month- 90 month). 8 patients were followed for 1-3 yrs, 10 patients were followed for 3-5 years, and 13 patients were followed longer than 5 years.

The patients were asked to attend a routine follow-up in the treatment centre. On completion of the Consultant examination; they were informed about the aim of the study. They were asked to fill in the two cancer specific quality of life questionnaires. The Turkish version of EORTC QLQ-C30 version 3.0 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) and its diagnostic specific module EORTC QLQ H&N-35 (European Organization for Research and Treatment of Cancer, Questionnaire Module Head and Neck) were used.

Basic demographic and clinical data obtained from patient files were evaluated. These parameters included age, gender, tumour staging (according to AJCC 1997), histopathology, and treatment

Results

According to the UICC/AJCC 1997 staging system; 3 patients were classified as stage I. 6 patients were classified as stage IIb, 17 patients were classified as stage III, and 5 patients were classified as stage IV (IVa and IVb). Stage III and stage IV patients were grouped as advanced and stage I and stage II as early stage. Two thirds of the patients were classified as advanced patients (22 patients, 70.9%).

Histologically according to World Health Organization criteria; 5 patients (16.1%) were classified as keratinized differentiated squamous cell carcinomas (Type I). 17 patients (54.8%) were classified as non-keratinized carcinomas (Type 2), 8 patients (25.8%) were diagnosed as undifferentiated carcinomas (Type 3) and 1 patient was diagnosed with an adenoid carcinoma [11, 12]. The characteristics are given in Table 1.

A total of 24 patients (77.4%) received concurrent chemotherapy with radiotherapy, 6 patients (19.4%) received neoadjuvant chemotherapy, and 1 patient received only radiotherapy according to the treatment protocol. All patients, except for 2, received 70 Gy radiotherapy.

The mean global health score for QLQ-C30 (ver. 3.0) was found to be high at 63.4, and the functional scale scores were considerably higher (Table 2). The lowest functional scale score was for physical functioning (Score 83.9). The highest functional scale scores were for cognitive functioning and social functioning (98.9 and 95.7) respectively.

Table 1. Evaluation of patient characteristics

Characteristics	Number	%
Sex		
Male	19	61.3
Female	12	38.7
Stage (AJCC 1997)		
I	3	9.7
IIa	0	0.0
IIb	6	19.4
III	17	54.8
IVa	4	12.9
IVb	1	3.2
Histopathology		
WHO I	5	16.1
WHO II	17	54.8
WHO III	8	25.8
Adenocarcinoma	1	3.2
Treatment		
None (only radiotherapy)	1	3.2
Concurrent RT + CT	24	77.4
Neoadjuvant CT	6	19.4
Follow-up		
1-3 years	8	25.8
3-5 years	10	32.3
>5 years	13	41.9
Radiotherapy dose		
<70 Gy	2	6.5
≥70 Gy	29	93.5

The symptom scale scores were markedly low for this group. The highest symptom scale score for EORTC QLQ-C30 were insomnia (26.9) and fatigue (24.0). None of the patients had any complaint of diarrhoea. The lowest symptom scale score was for nausea and vomiting (3.2).

The affect of the financial burden of cancer treatment on the QOL of patients was discussed by researchers using different questionnaires such as SF-36 and Fact-G. However, financial issues are not considered as a problem of our patients, since they are supported by National Social Security System of Turkish government.

Twenty two patients (70.9%) had advanced stage disease before treatment. When the advanced stage patients were compared to non-advanced patients for global health status, the non-advanced patients were found to have a higher global health status than the advanced patients, but statistically there was no significant difference (p=0.123). Similarly non-advanced patients were found to have higher physical functioning (p=0.329), role functioning (p=0.298), emotional functioning (p=0.908), and cognitive functioning (p=0.522) scores, but again there was no significant difference. Surprisingly however advanced patients were found to have higher social functioning scores

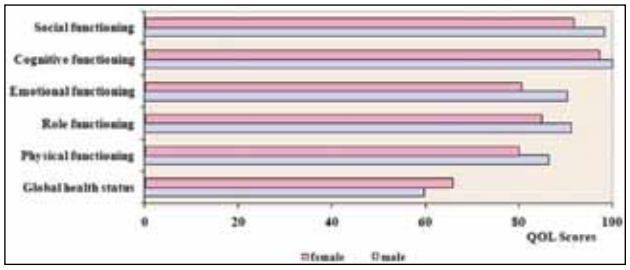
Table 2. Calculated scores for QLQ-C30 version 3.0

Scale name	Mean score	Median score	IQR	Range
Global health status/QOL				
Global health status	63.4	66.7	(50.0-75.0)	(16.7-100.0)
Functional Scales				
Physical functioning	83.9	93.3	(73.3-100.0)	(20.0-100.0)
Role functioning	88.7	100.0	(100.0-100.0)	(16.7-100.0)
Emotional functioning	86.6	91.7	(75.0-100.0)	(50.0-100.0)
Cognitive functioning	98.9	100.0	(100.0-100.0)	(66.7-100.0)
Social functioning	95.7	100.0	(100.0-100.0)	(50.0-100.0)
Symptom scales				
Fatigue	24.0	11.1	(0.0-44.4)	(0.0-88.9)
Nausea and vomiting	3.2	0.0	(0.0-0.0)	(0.0-33.3)
Pain	18.3	16.7	(0.0-33.3)	(0.0-83.3)
Dysponea	18.3	0.0	(0.0-33.3)	(0.0-100.0)
Insomnia	26.9	0.0	(0.0-66.7)	(0.0-100.0)
Appetite loss	10.8	0.0	(0.0-0.0)	(0.0-66.7)
Constipation	9.7	0.0	(0.0-0.0)	(0.0-66.7)
Diarrhea	0.0	0.0	(0.0-0.0)	(0.0-0.0)
Financial difficulties	14.0	0.0	(0.0-66.7)	(0.0-33.3)

IQR = interquartile range, QOL = quality of life, QLQ = quality of life questionnaire

than non-advanced patients, but again the difference was not significant (p=0.262).

Functional health status was found to be higher for male patients compared to females. The highest functional health status was for cognitive functioning; and the lowest functional health status was for physical functioning in both males and females. Global health status was found to be lower in males compared to females. (See Graph 1)



Graph 1. Median global health status and functional scale scores by gender

No relation was found when physical functioning, role functioning, emotional functioning, cognitive functioning were compared for gender, treatment technique, histopathology, and staging AJCC1997 (95% CI). The "p" values according to the Kruskal Wallis Test are shown in Table 3.

The symptom scale scores are given in Table 4. They were favourably low for the group. The highest symptom scale scores were for dry mouth (73.1) and painkillers (64.5). The lowest symptom scale scores were reduced sexuality (4.3), trouble with social eating (9.7), and weight loss (9.7). None of the patients required a feeding tube, so there was no symptom score for this category.

Discussion

Our previous study showed that the 5-year overall survival for NPC patients was 55% and that

Table 3. p values for gender, treatment, and histopathology and staging related to functional scores and global health status (95% CI)

	Gender (p)	Treatment (p)	Histopathology (p)	Staging 1997 (p)
Physical functioning	0.15	0.56	0.82	0.69
Role functioning	0.68	0.61	0.41	0.42
Emotional functioning	0.14	0.59	0.50	0.73
Cognitive functioning	0.21	0.86	0.86	0.15
Social functioning	0.53	0.91	0.17	0.36
Global health status	0.50	0.92	0.72	0.31

Table 4. Calculated scores for symptoms (QLQ H&N35)

Scale name	Mean score	Median score	IQR	Range
Symptom scales				
Pain	16.7	8.3	(0.0-25.0)	(0.0-75.0)
Swallowing	22.3	16.7	(8.3-33.3)	(0.0-58.3)
Sense problems	12.9	0.0	(0.0-16.7)	(0.0-66.7)
Speech problems	10.4	0.0	(0.0-11.1)	(0.0-88.9)
Trouble with social eating	9.7	0.0	(0.0-16.7)	(0.0-83.3)
Trouble with social contact	12.6	8.3	(8.3-16.7)	(8.3-58.3)
Less sexuality	4.3	0.0	(0.0-0.0)	(0.0-33.3)
Teeth	16.1	0.0	(0.0-33.3)	(0.0-100.0)
Opening mouth	16.1	0.0	(0.0-100.0)	(0.0-33.3)
Dry mouth	73.1	100.0	(66.7-100.0)	(0.0-100.0)
Sticky saliva	36.6	33.3	(0.0-100.0)	(0.0-66.7)
Coughing	22.6	0.0	(0.0-33.3)	(0.0-100.0)
Feeling ill	20.4	0.0	(0.0-100.0)	(0.0-33.3)
Pain killers	64.5	100.0	(0.0-100.0)	(0.0-100.0)
Nutritional supplements	16.1	0.0	(0.0-0.0)	(0.0-100.0)
Feeding tube	0.0	0.0	(0.0-0.0)	(0.0-0.0)
Weight loss	9.7	0.0	(0.0-0.0)	(0.0-100.0)
Weight gain	19.4	0.0	(0.0-0.0)	(0.0-100.0)

the disease free survival was 36% [5]. In addition to survival, the quality of life of the surviving cancer patients is an important criterion and should be considered as an important factor in assessing the outcome of the treatment. Various questionnaires have been developed for the evaluation of different aspects of the quality of life. Although the main concern in an oncology treatment centre is the successful treatment of the cancer, the rehabilitation of patients and the quality of life is also important. With this in mind, quality of life questionnaires are being integrated into follow-up clinics in Turkey. The EORTC QLQ-30 questionnaires have been integrated into our follow-up clinics, since they are consistent, validated, and in use by different research groups in Turkey.

The results in our study are very favourable. The mean global health score for QLQ-C30 (Ver. 3.0) was high at 63.4, and the functional scale scores were markedly high for this group, which means a healthy level of functioning. The lowest functional scale score was physical functioning score (83.9). The highest functional scale scores were calculated to be cognitive functioning and social functioning (98.9 and 95.7) respectively. The symptom scale scores were considerably low for this group, which means a low level of symptomatic problems. The highest symptom scale scores for EORTC QLQ-C30 were insomnia (26.9) and fatigue (24.0), and the lowest symptom scale score was found to be nausea and vomiting (3.2). The highest symptom scale scores for QLQ H&N35 were; dry mouth (73.1) and painkillers (64.5), and the lowest symptom scale scores were; reduced sexuality (4.3), trouble with social eating (9.7), and weight loss (9.7).

Although 70.9% of the patients had advanced stage disease, apart from a shorter survival time than non-advanced patients [5], their global health status although lower was not significantly so (p=0.123). Even though non-advanced patients were found to have higher physical functioning (p=0.329), role functioning (p=0.298), emotional functioning (p=0.908), and cognitive functioning (p=0.522), the differences were not statistically significant

Conclusion

Our earlier report confirmed that the addition of chemotherapy to radiotherapy improved survival and reduced the risk of distant metastases in the early-stage NPC patients [5]. Our present study of the quality of life shows that the addition of chemotherapy, whilst improving the prognosis, resulted in no statistical difference in the quality of life for physical functioning, role functioning, emotional functioning, cognitive functioning in relation to gender, treatment, histopathology, and staging.

Early diagnosis is an important factor for successful treatment in NPC. In addition to improved survival, the QOL of the surviving patients is an important factor and should be assessed. Treatment centres in Turkey need to integrate QOL assessment to their treatment programs for improved patient therapy and recovery.

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Waist Circumference Estimated on the Basis of Body Mass Index in Koreans

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Abstract

The purpose of this study was to predict waist circumference (WC) on the basis of body mass index (BMI), gender, and age data and BMI on the basis of WC, gender, and age data in Korean adults. The subjects included 1,465 Korean adults aged 20–85 years old who visited a Promotion of Health Center for inclusive medical test during 2010; gender, age, BMI, and WC measurement data were taken. BMI (kg/m^2) was calculated from height and weight. WC was measured at the part of the trunk located midway between the lower costal margin and the iliac crest while the subject was standing. As a result of predicting WC, the F-value was 1181.686 ($p < 0.001$) and R^2 was 70.8%. The best-fit multiple regression equation is as follows: WC (cm) = 34.302 + (-5.317 × gender) + (0.059 × age) + (1.999 × BMI). As a result of predicting BMI, the F-value was 1118.146 ($p < 0.001$) and R^2 was 69.6%. The best-fit multiple regression equation is as follows: BMI (kg/m^2) = -2.782 + (1.279 × gender) + (0.016 × age) + (0.310 × WC). Because the regression models of WC based on the data of BMI, gender, and age and BMI based on the data of WC, gender, and age have significant predictive value, we conclude that they can be used in clinical practice to identify metabolic syndrome.

Key words: Body mass index, Waist Circumference, Prediction Equations

Introduction

Reaven (1988) suggests the concept of X-syndrome for the cluster of risk factors for cardiovascular disease such as hypertension, impaired glucose tolerance, hypertriglyceridemia, and high-density lipoprotein (HDL) deficiency (1). This cluster of risk factors was recently known as insulin resistance syndrome, metabolic syndrome, and cardiovascular syndrome (2-4).

In 1998, the World Health Organization (WHO) established diagnostic standards in clinical medicine for identifying and preventing type II diabetes, impaired glucose tolerance, insulin resistance, hypertension, dyslipidemia, obesity, and microalbuminuria for patients with the risk factors of cardiovascular disease (5). In addition, WHO suggested a partially modified standard of diagnosis for metabolic syndrome through the Group for the Study of Insulin Resistance (EGIR) in 1999 (6), the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP-ATPIII) in 2001 (7), the American College of Endocrinology (ACE)/American Association of Clinical Endocrinologists (AACE) in 2002 (8-9), the International Diabetes Federation (IDF), and the Heart Association/National Heart Lung and Blood Institute (AHA/NHLBI) in 2005 (10-11).

The diagnostic standard for metabolic syndrome provided by these 6 institutions consists of 4 or 5 categories. All of these institutions define obesity as a category of the prognosis of metabolic syndrome. The standard of obesity is considered on the basis of body mass index (BMI) by WHO and the AACE, and waist circumference (WC) by the EGIR, NCEP-ATPIII, IDF, and AHA/NHLBI. Therefore, a researcher can choose a standard according to the purpose of their study and methods. However, there would be some limitations about the process of a given study if the research is conducted on the basis of measured data such as a retrospective cohort study.

For example, researchers cannot use the standards of the NCEP-ATPIII if they only have BMI data regarding obesity; they cannot measure WC again because of the WC data provided for the classification of obesity since some researchers are required to use the standards of the NCEP-ATPIII

to categorize metabolic syndrome. Therefore, the purpose of this study was to predict WC on the basis of BMI, gender, and age and BMI on the basis of WC, gender, and age. Further studies are needed regarding the prediction of metabolic syndrome using the results of this study.

Methods

Subjects

A group of 1,465 Korean adults (1,053 males and 452 females) over age 20 were chosen as subjects. Subjects visited the Promotion of Health Center at Yang-Cheon Gu, Seoul, in 2010, and gender, age, height, weight, and WC data were obtained. All subjects completed a written consent form before participating in this study. In addition, all study procedures were approved by the Human Care and Use Committee of the Institute of Sports Science of Seoul National University.

Experimental procedures

Height and weight were assessed with the patients wearing a light gown using an Inbody 720 (Biospace, Seoul, Korea), and BMI (kg/m^2) was calculated from height and weight measurements. People with a BMI <23, ≥23 to <25, and ≥25 were classified as normal, overweight, and obese on the basis of WHO's Asia–Pacific standard of obesity (12).

While the subjects were standing with their feet about 25–30 cm apart, the midpoint between the lower costal margin (bottom of the lower rib) and the iliac crest (top of the pelvic bone) in the trunk was measured as WC. When the WC was measured, the tape was fit snugly without compressing soft tissue at the end of expiration (13).

Statistical analysis

All results from this study are expressed as means and standard deviations. Stepwise multiple regression analysis was performed to formulate the prediction equation of WC from the data of gender, age, and BMI as well as the prediction equation of BMI from the data of gender, age, and WC. Statistical significance was set at $p<0.05$, *; $p<0.01$, **; $p<0.001$, *** and all analyses were performed using SPSS ver. 12.0 software(SPSS, Chicago, IL, USA).

Results

The characteristics of the subjects

The characteristics of the subjects are shown in Table 1. The average age of the subjects was 39.85 ± 15.23 years and ranged from 20 to 85 years; the average height was 169.36 ± 9.33 cm and ranged from 142.10 to 196.00 cm; the average weight was 66.03 ± 9.07 kg and ranged from 38.90 to 110.00 kg; the average BMI was 23.02 ± 2.57 kg/m^2 and ranged from 14.62 to 34.48 kg/m^2; and the average WC was 80.44 ± 6.67 cm and ranged from 54.30 to 111.76 cm. According to the subjects' BMIs, 773 subjects (52.8%) were of normal weight, 423 (28.9%) were overweight, and 269 (18.4%) were obese.

Table 1. The characteristics of the subjects (N=1,465)

Variables	Range		Mean ± SD
Age, years	20.00 - 85.00		39.85 ± 15.23
Height, cm	142.10 - 196.00		169.36 ± 9.33
Weight, kg	38.90 - 110.00		66.03 ± 9.07
BMI, kg/m^2	14.62 - 34.48		23.02 ± 2.57
WC, cm	54.30 - 111.76		80.44 ± 6.67
Groups	Normal	Overweight	Obese
Total population (%)	773 (52.8%)	423 (28.9%)	269 (18.4%)

BMI; Body mass index, WC; Waist circumference

The regression equation of WC on the basis of gender, age, and BMI

The regression equation of WC on the basis of gender, age, and BMI is shown in Table 2. As a result of predicting WC, the F-value was 1181.686 ($p < 0.001$) and R^2 was 70.8%. The best-fit multiple regression equation is as follows:

$$WC\ (cm) = 34.302 + (-5.317 \times gender) + (0.059 \times \times age) + (1.999 \times BMI)$$
$$(R^2 = 70.8\%, p < 0.001***)$$

The regression equation of BMI on the basis of gender, age, and WC

The regression equation of BMI on the basis of gender, age, and WC is shown in Table 3. As a result of predicting BMI, the F-value was 1118.146 ($p < 0.001$) and R^2 was 69.6%. The best-fit multiple regression equation is as follows:

Table 2. The regression equation of WC on the basis of gender, age, and BMI (N = 1,465)

Model	Slope (B)	SEE	ß	t (p)	F (p)	R^2
Constant	34.302	0.873		39.300 (***)	1181.686 (***)	0.708
Gender (0, 1)	-5.317	0.253	-0.369	-21.038 (***)		
Age (years)	0.059	0.008	0.135	7.038 (***)		
BMI (kg/m^2)	1.999	0.041	0.772	48.806 (***)		
WC (cm) = 34.302 + (-5.317 × gender) + (0.059 × age) + (1.999 × BMI)						

**** $p < 0.001$ by multiple regression analysis*
SEE, Standard error of estimate; BMI, Body mass index; WC, Waist circumference
Gender, 0=male, 1=female

Table 3. The regression equation of BMI on the basis of gender, age, and WC (N=1,465

Model	Slope (B)	SEE	ß	t (p)	F (p)	R^2
Constant	-2.782	0.488		-5.705 (***)	1118.146 (***)	0.696
Gender (0, 1)	1.279	0.109	0.230	11.784 (***)		
Age (years)	0.016	0.003	0.092	4.643 (***)		
WC (cm)	0.310	0.006	0.803	48.806 (***)		
BMI (kg/m^2) = -2.782 + (1.279 × gender) + (0.016 × age) + (0.310 × WC)						

**** $p < 0.001$ by multiple regression analysis*
SEE, Standard error of estimate; BMI, Body mass index; WC, Waist circumference
Gender, 0=male, 1=female

$$BMI\ (kg/m^2) = -2.782 + (1.279 \times gender) + (0.016 \times age) + (0.310 \times WC)$$
$$(R^2 = 69.6\%,\ p < 0.001^{***})$$

Discussion

Metabolic syndrome is a cluster of cardiovascular risk factors caused by insulin resistance and obesity. In clinical practice, metabolic syndrome has been used to evaluate the risk of type II diabetes and cardiovascular system disease. There are 5 criteria describing metabolic syndrome: triglycerides, HDL-cholesterol, blood pressure, fasting blood sugar, and obesity. Metabolic syndrome is diagnosed when more than 3 metabolic risk factors are present.

All 6 institutions that currently provide guidelines for diagnosing metabolic syndrome suggest obesity as one of the variables. However, WC and BMI are different measures for determining obesity; their application has caused some researchers to be confused.

For example, suppose a researcher applies the NCEP-ATPIII criteria to diagnose metabolic syndrome in a retrospective cohort study. However, the NCEP-ATPIII criteria are not applicable if only BMI data and not WC data are available. Since the AACE criteria use BMI as a tool for determining obesity, it might also be useful for diagnosing metabolic syndrome. However, unlike the NCEP-ATO criteria, the AACE criteria do not include fasting blood sugar as a determining variable of metabolic syndrome. Thus, it is difficult for researchers to choose appropriate criteria for determining metabolic syndrome.

The cause of metabolic syndrome cannot be reduced to a set of absolute clinical criteria. Therefore, an equation for calculating WC from BMI would enable researchers to apply the WC criteria of the NCEP-ATPIII.

WC was predicted on the basis of BMI and vice versa. In addition, the BMI multiple regression equation predicted regression more accurately, because changes in body shape can be produced by the factors of age, gender, and WC (14-15). As a result, R^2 was 70.8% for the WC regression model based on age, gender, and BMI and 69.6% for the BMI regression model based on age, gender, and WC.

Cohen (1988) reports that if R^2 is larger than 35% and 70% in liberal arts and 70% in scientific research, respectively, predicted regressions can be statistically significant and useful in general (16).

The regression equation would be useful in clinical practice because R^2 represents regression on a 70% level. Depending on the purpose of the

study involving metabolic syndrome, researchers can use the regression equation and standards for diagnosis. A limitation of this study is that it was based on subjects from Seoul; therefore, the results cannot represent all adults in Korea or Asia. However, the greatest strength of this study is the large number (n = 1,465) of subjects. In addition, further studies determining regression equations are needed for other populations and races.

Conclusion

We conclude that the WC regression model based on age, gender, and BMI and the BMI regression model based on age, gender, and WC show significant relationships. The results of this study can be used effectively in clinical practice for assessing metabolic syndrome.

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Left ventricular systolic and diastolic functions and mean platelet volume in familial mediterranean fever

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Abstract

Background: Familial Mediterranean Fever (FMF) is an inflammatory autoimmune disease characterized by recurrent attacks of fever and sterile polyserositis. We investigate left ventricular systolic and diastolic functions and platelet activation represented by mean platelet volume (MPV), in addition to the association between MPV and echocardiographic findings in uncomplicated FMF patients without any cardiovascular risk factors.

Methods: Thirty-eight FMF patients and 35 healthy controls were enrolled. Complete blood count including MPV, biochemistry, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, fibrin degradation products were measured. Complete echocardiographic examination was performed.

Results: Median MPVs of the FMF and control groups were not significantly different (8.2[1.57] fL vs 8.1[1.33] fL p:0.733 respectively). Median values of ejection fraction (EF) and early diastolic flow velocity (E) were lower in the FMF group compared to healthy controls (60% vs 63% p:0.030; 0.83 m/s vs 0.92 m/s p:0.034). Median isovolumetric relaxation time (IVRT) was higher in the case group than the controls (78 msec vs 68 msec p<0.001). There were no significant differences between groups in terms of other echocardiographic parameters; late diastolic flow velocity (A), tissue doppler A', E/A ratio , deceleration time (DT). There were no correlations between MPV, ESR, fibrinogen, fibrin dimer and any of the echocardiographic parameters. Only CRP was associated with E/A (r:-0.294 p:0.015).

Conclusion: Left ventricular systolic and diastolic parameters are impaired in FMF. MPV is not elevated in uncomplicated FMF patients on colchicine therapy.

Key words: Familial mediterranean fever, mean platelet volume, echocardiography

Introduction

Familial Mediterranean Fever (FMF) is an autoimmune disease characterized by recurrent attacks of fever and sterile polyserositis affecting mainly peritoneum, pleura and synovium (1). It is particularly common in people from Mediterranean ancestry; the prevalance of the disease in Turkish population was reported as 1:1000 by Turkish FMF study group(2). FMF is inherited autosomal recessively, and the genetic mutations in the Mediterranean Fever gene (MEFV) are mapped on chromosome 16 (3). Subclinical ongoing inflammation have been demonstrated during the attack free periods (4). Relationship between FMF and cardiovascular diseases has been a popular subject of investigation because inflammation accelerates atherogenesis and thrombosis.

Platelet aggregation is an early event in the atherosclerotic process (5). Increase in platelet size has been recently reported to be associated with atherosclerosis and it's risk factors such as hypertension and diabetes mellitus (6,7). There are scarce studies with controversial results about the platelet size in FMF (8,9)

Left ventricular functions in FMF were investigated using different echocardiographic techniques; some studies have revealed impaired diastolic function whereas some have found comparable

results with healthy controls (10,11). We aimed to investigate left ventricular systolic and diastolic echocardiographic indices and platelet activation represented by mean platelet volume (MPV) in addition to the association between MPV and echocardiographic findings, if any, in uncomplicated FMF patients without any cardiovascular risk factors.

Method

Thirty-eight FMF patients who admitted to the Gastroenterology department and 35 controls recruited from the healthy voluntary blood donors admitted to the blood transfusion center of the hospital were enrolled. The study was designed as a case-control and was conducted according to the recommendations of Declaration of Helsinki on Biomedical Research involving human subjects. Local ethics committee has approved the study and all participants gave written informed consent . FMF was diagnosed according to Tel-Hashomer criteria(1). All of the patients were in attack free period. Disclusion criteria consisted of history of coronary artery disease, hypertension, diabetes, hyperlipidemia, renal failure, amyloidosis, presence of moderate or severe cardiac valvular pathology, morbid obesity, any other chronic disease state, rhytm other than sinus.

After a detailed medical history and physical examination; complete blood count including mean platelet volume(MPV), biochemistry, erythrocyte sedimentation rate, C-reactive protein, fibrinogen, fibrin degradation products were measured in the core laboratory of our hospital using standart techniques. For MPV measurement, blood samples were collected in sodium citrate (4:1 blood/citrate) and analysed within 1 hour (12).

Echocardiography

All participants have undergone echocardiographic examination using a System Five (GE Vingmed Ultrasound, Horten, Norway) cardiac ultrasound with a 2.5MHz probe. Two-dimensional, M-mode, color flow and pulsed wave Doppler echocardiographic examinations were performed in addition to Tissue Doppler Echocardiography in left lateral decubis position. For each parameter, five consecutive cycles were averaged. Left ventricular diameters and left ventricular ejection fraction were measured from parasternal long axis view(13) by M-mode examination recorded at the speed of 50mm/s. For the measurement of diastolic function of the left ventricle, pulsed Doppler sample volume was placed at the mitral leaflet tips; Doppler signals were recorded at 100 mm/s. Early diastolic peak flow velocity (E), late diastolic peak flow velocity (A), E/A ratio and E wave deceleration time and isovolumetric relaxation time (IVRT) were measured (14). All echocardiographic examinations were performed by the same blinded cardiologist. Intraobserver variability which was tested by repeating the procedure on 15 patients at two different days was less than 5% .

Statistical Analysis

SPSS for Windows 11.5 program was used for data analysis. Shapiro Wilk test was used to determine if continuous variables were distributed close to normal. Descriptive statistics were given as mean ± standart deviation for continuous variables or median (minimum-maximum); whereas nominal variables were represented as number of cases and percentages. The significance of differences between groups in terms of means were tested by Student's T test. Mann Whitney U test was used to test significance of difference between groups in terms of medians. Nominal variables were analysed using Pearson's Ki Square test. Results were considered significant for $p<0,05$.

Results

Baseline characteristics of the study population are provided in Table 1. The ratio of women and men were similar between FMF and control groups (p:0.062); whereas FMF patients were older than healthy controls (p: 0.049). Median disease duration was 6 years (min: 1 yr – max:35 yr) as well as median duration of drug therapy (min: 1 yr – max: 35 yr). Although erythrocyte sedimentation rates were found to be higher in FMF patients ($p<0.001$); C-reactive protein (CRP), fibrinogen, fibrin dimer levels were not significantly different (Table 1). Median mean platelet volumes of the FMF and control groups were not significantly different (8.2[1.57] fL vs 8.1[1.33] fL p:0.733 respectively).

Echocardiographic measurements are provided in table 2. Median values of EF and E were

Table 1. Hb: Hemoglobin, WBC: White blood cell, PLT: platelet, HDL: high-density lipoprotein, LDL: low-density lipoprotein, CRP: C-reactive protein, ESR:erythrocyte sedimentation rate

	Control (n:35)	FMF (n:38)	p
AGE *[mean±sd]*	28.1±9.1	32.8±11.0	0.049
SEX *Female/Male*	16/19	20/19	0.632
Hb *[mg/dL]*	14.9±1.87	14.7±1.80	0.652
WBC *[×10³]*	7.1	7.7	0.249
PLT *[×10³]*	258.8±84.88	284.4±62.34	0.142
Systolic blood pressure *[mm Hg]*	121.4±12.2	117.6±13.3	0.125
Diastolic blood pressure *[mm Hg]*	80.1±5.4	79.5±6.0	0.119
HDL cholesterol *[mg/dL]*	48.4±11.2	47.3±12.8	0.550
LDL cholesterol *[mg/dL]*	110.43±25.5	105.7±28.4	0.346
Trigyceride *[mg/dL]*	132.6±19.9	129.9±23.3	0.130
Fasting glucose	78.7±10.4	80.1±12.3	0.244
Smoker *[%]*	34.5%	37.4%	0.080
Fibrinogen *[mg/dL]*	312.4	314.7	0.800
Fibrin dimer *[µg/L]*	160.8	118.5	0.306
ESR *[mm/hr]*	5.5	17.0	<0.001
CRP *[mg/dL]*	3.0	2.6	0.912

lower in the FMF group compared to healthy controls (60% vs 63% p:0.030; 0.83 m/s vs 0.92 m/s p:0.034). Median IVRT was higher in the FMF group than the controls (78 msec vs 68 msec p<0,001). There were no significant differences between groups in terms of other echocardiographic parameters; A, A', E/A, DT.

Table 2. EF: ejection fraction, E: Early diastolic peak flow velocity, A: Late diastolic peak flow velocity, DT: deceleration time, IVRT: isovolumetric relaxation time

	FMF	Control	p
EF *[%]*	60.0	63.0	0.030
E *[m/s]*	0.83	0.92	0.034
A *[m/s]*	0.61	0.65	0.488
E/A	1.22	1.39	0.079
DT *[msec]*	165.0	160.0	0.680
IVRT *[msec]*	75.0	68.0	<0.001

There were no correlations between MPV, ESR, fibrinogen, fibrin dimer and any of the echocardiographic parameters. Only CRP was associated with E/A (r:-0.294 p:0.015).

Discussion

We evaluated systolic and diastolic functions in FMF patients and found that median ejection fraction was lower than the control group although it was within the normal range. In addition to that, median early diastolic filling wave of the patient group was lower than the control; and IVRT, which is a marker of diastolic dysfunction was elongated in the FMF group.

Cardiac functions were evaluated in chronic inflammatory disorders which potentially have the capacity to impair cardiovascular system due to their systemic inflammatory activity. Most of these studies report impairment especially in echocardiographic indices of diastolic function (15,16).

Results of the studies about echocardiographic evaluation of Familial Mediterranean Fever are rather contradictory. Calıskan et al. have reported impairment in left ventricular diastolic parameters and the severity of impairment was correlated with hs-CRP (17). Another group investigated systolic and diastolic left and right ventricular functions by tissue Doppler Echocardiography (TDE) in a young patient group, with a mean age of 22±2 during attacks and attack free period; and found out that ventricular functions were preserved (11). Tavil et al. have reported impaired diastolic function and comparable systolic function using TDE in an older patient group of 35±7 years of age(18). Most recenty, Kalkan et al. have reported comparable conventional and tissue doppler systolic and diastolic functions with the healthy controls but lower strain and strain rate values (19)

We think different results are because of different ages of study populations, disease duration, time delay until diagnosis which was reported to be approximately 6.9 years in our country (2), homogeneity of genetic mutation, use of Colchicine treatment and environmental factors. Although subclinical inflammation, cytokine activation ,endothelial dysfunction (20) are mostly blamed for cardiovascular manifestations; we could only demonstrate an association between CRP and E/A.

Mean platelet volume which is increased in thrombocyte activation has been investigated in two studies to our knowledge; one of which reported higher MPV in FMF patients and negative association between MPV and duration of Colchicine treatment (8) whereas the other reported no difference from healthy controls in patients on Colchicine treatment (9). We have also failed to demonstrate any increase in mean platelet volume or any correlation with echocardiographic parameters. Our's was the first study to investigate if there was any association between MPV and echocardiographic findings. It remains unanswered if we could detect an increase in MPV during the attack period.

In conclusion, we have detected diastolic impairment in a study population all of which were on Colchicine treatment. Our results are concordant with the studies reporting diastolic dysfunction in FMF patients; but we don't think that the difference detected in systolic ejection fraction between groups have any clinical relevance; because both groups have normal range systolic functions.

Case control design of the study doesn't allow us to extrapolate the mechanism of cardiac findings. Prospective long term studies which also compare the patients who are on Colchicine treatment and not are needed to light up the etiopathogenesis of the impairment in diastolic indices.

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Correlation between intracranial hemorrhage in preterm infants and serum levels of Insulin-like growth factor

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Abstract

Introduction/Aim: Peri-intraventricular hemorrhage (PVH-IVH), the most common form of intracranial hemorrhage in preterm infants, is significant because of the far-reaching consequences for the health and quality of life for this population at risk. Most PVHs occur in the first week of life. Most common in infants <32 weeks gestation. Studies from recent years indicate a similarity to pathophysiology of the disease of prematurity and a significant share of Insulin-like growth factor (IGF) system, especially IGF-type1 (IGF-1) to pathophysiological mechanism. The aim of this study was to examine the relationship between one of the angiogenic factors, Insulin-like growth factor type 1 and intracranial hemorrhage in premature infants.

Material and methods: This prospective, cohort study included 74 preterm infants of gestational age up to 33 weeks, who were hospitalized from April 2008 to July 2009. The diagnosis of intracranial hemorrhage was made in ultrasonic examination, while hemorrhage was graded into four levels. The primary cohort, after receiving the information about the existence of signs of PVH-IVH, was divided into two secondary cohorts, the cohort of infants with PVH-IVH and the cohort of infants without PVH-IVH. The cohort of infants with PVH-IVH was stratified by the degree of hemorrhage. Levels of Insulin-like growth factor type 1 (IGF-1) was determined by "Enzyme Linked Immuno Sorbent Assay" method in the 33 rd postmenstrual week.

Results: In 22 (29.7%) preterm infants in our study ultrasound finding was normal, while PVH-IVH appeared in 52 (70.3%) infants. The average birth weight (BW) of primary cohort was 1698.24±403.79g. Secondary cohorts with intracranial hemorrhage (1641.92±377.69) and without (1831.36±440.39) intracranial hemorrhage, did not differ significantly in the average BW ($F=2.24$ $p>0.05$). Average gestational age (GA) was 31.22±1.87 weeks. The difference in GA among the cohort with (30.87 ±1.91) and without (31.90±1.57) intracranial hemorrhage was significant ($F=2.88$ $p<0.05$). The incidence of intracranial hemorrhage in preterm infants from single pregnancies was significantly higher ($X^2=13,74$ $p<0,01$) than in preterm infants from multiple pregnancies. Average level of IGF-1 in the primary cohort was 23.73±5,79. The difference was insignificant in the levels of IGF-1 among cohorts with (23.46±5.27) and without (24.39 ±6.98) intracranial hemorrhage ($F=1.25$ $p>0.05$)

Conclusion: There was no relationship between serum levels of insulin like growth factor type 1 in the 33rd postmenstrual week and intracranial hemorrhage in preterm infants. Incidence of intracranial hemorrhage was significantly higher in preterm infants of shorter gestation age and in preterm infants from single pregnancies.

Key words: peri-intraventricular hemorrhage, Insulin-like growth factor, preterm infant, diseases of prematurity.

Introduction

Preterm infant (infant born before 37 weeks of gestation age -WHO definition from 1961.) belongs to the population of 'endangered newborns' because of difficulty adjusting to exstrauterine life, the need for special care, as well as for specific diseases. Later, these children from premature birth are children with "risk for developing" (1).

The incidence of premature birth of infants varies according to the region and ranges between 5 to 10% of newborns. For Montenegro, the percentage in the last few years ranges between 4.5 and 6%, with a tendency to increase (1,2).

Mortality of preterm infants has a large share in the total perinatal mortality. Two-thirds of neonatal mortality, which serves as a measure for comparing health systems, makes preterm infant mortality. Specific morbidity, i.e. diseases of prematurity, including: peri-intraventricular hemorrhage (PVH-IVH), retinopathy of prematurity (ROP) and chronic lung disease (CLD) of the newborns is connected to the category of preterm infants (3).

Peri-intraventricular haemorrhage (PVH-IVH) occurs in the germinal matrix in 90% of cases and in 10% of the cases in the plexus and extends in the ventricle. The germinal matrix is only transiently present as a region of thin-walled vessels, migrating neuronal components and vessel precursors. It has matured by 34 weeks gestation, such that hemorrhage becomes very unlikely after this age. The germinal matrix disappears at about the 35th week of gestation.

Most PVHs occur in the first week of life (most often in the first 72 hours of life). Most common in infants <32 weeks gestation. The incidence of PVH-IVH is negatively correlated with the gestational age. In premature infants of gestation age shorter than 28 weeks the incidence of PVH-IVH is up to 60%, while in term newborns, only 4%. The predisposing factors for the development of PVH-IVH are transport of a newborn to perinatological Centre, hypercapnia and acidosis, use of mechanical ventilation, changes in systemic pressure. There is no significant relationship between low Apgar scores and increased risk of PVH (4,5).

PVH-IVH complicates the clinical course and prolongs hospitalization of preterm infants and is also significant because of the far-reaching consequences for their health and quality of life. The consequences of PVH-IVH include: cerebral palsy and other neurological sequelae (motor disorder, disorder of sensory functions - vision and hearing, disorder of mental function, behavioral problems or complex phenomena that are referred to as "minimal cerebral dysfunction") that lead to different degrees of disability and frequent rehospitalization to pediatric intensive units. Therefore efforts to prevent premature childbirth are understandable and as for already preterm born infants it is important to ensure optimal conditions which will reduce the effect of risk factors responsible for diseases of prematurity. Efforts are focused on the timely treatment of diseases in prematurity. Better understanding of pathogenesis of diseases of prematurity, would facilitate the prediction, prevention and treatment of diseases of preterm infants (3,6,7).

Studies from recent years indicate a similarity in the pathogenesis of the diseases of prematurity. The association between retinopathy of prematurity and intraventricular hemorrhage in very low birth weight infants may be an important consideration in the pathogenesis of both vascular diseases. Studies highlight a significant share of insulin-like growth factor (IGF) system, especially IGF type 1 (IGF-1) to pathophysiological mechanism (8,9).

IGF-1 is a polypeptide that is in the serum in a large percentage related to the binding protein of which IGFBP 3 is the most significant. In the adults it is synthesized by the liver while fetal IGF-1 is mostly synthesized by the placenta. It is important to physiology and pathophysiology of the human body. In preterm infants, after the birth, there is a noticeable decrease of IGF-1 and IGFBP3. This decline was dramatic in terms of inflammation and is associated with an increase in the value of proinflamatory cytokines in umbilical cord blood . (10). Low values of IGF-1 are associated with a slower postnatal growth and development. Besides its role in the pathophysiology of the disease of prematurity, IGF-1 is also important in diabetes, atherosclerosis, osteoporosis, cancer (11, 12, 13).

The first interpretation of the role of IGF-1 in the pathogenesis of the diseases of prematurity, was published in 2002 on the case of retinopathy of prematurity. It is proved that IGF-1 affects the vascularization of human retina indirectly through locally produced Vascular endothelial growth factor (VEGF). Later studies confirmed that low levels of IGF-1 (below 33 mcg/l) in the 33rd postmenstrual week are predictive for the development of diseases in prematurity, and values below 25 mcg/l predict heavier forms of diseases in prematurity (14, 7, 6).

Comparative study in which the serum levels of IGF-1 were repeatedly measured during the first 4-6 postnatal weeks, then morbidity factors were determined (the degree of PVH-IVH and ROP), also reported an association of low levels of IGF-1 and more advanced forms of diseases of prematurity (15).

The aim of our study was to examine the correlation between intracranial hemorrhage in preterm

infants and serum levels of IGF- 1. We took postmenstrual age of 33 weeks as a term blood sampling because most PVHs occur in the first week of life and most common in infants <32 weeks gestation. For preterm infants with ROP postmenstrual age of 33 weeks is the time when the phase 2 of ROP begins.

Material and Methods

This study was designed by the type of cohort, prospective, longitudinal study, based on other similar studies (16). The study included all preterm infants (n=74), gestational age of 33 weeks or less (≤ 33 weeks) who were hospitalized in the Center of Neonatology, Clinical Centre of Montenegro, from April 2008 up to July 2009. This study did not include infants with conspicuous congenital anomalies.

The data base was formed, with demographic data, data from the medical history of pregnancy and delivery (the mode of the delivery, the evaluation of vitality at birth, anthropometric measures at birth), and data from clinical monitoring of the newborn.

In every newborn included in the study, venous blood sample (0.5 ml), was taken in the 33rd postmenstrual week. Extracted serum was frozen and stored in a freezer (at -20 up to -80 º C), until the completion of a series of samples. A quantitative value of the requested biomarkers (IGF-1), in all samples was performed simultaneously, under the same conditions, by using immunochemical ELISA (Enzyme Linked Immuno Sorbent Assay) a method widely used for the measuring of this hormone (17).

The diagnosis of peri-intraventricular hemorrhage (PVH-IVH.), in the participants of the study was made by ultrasonic examination of endocranium. Check ups were done by Aloka ultrasound device, in the first week of life. Mechanical, sectorial sonda of 7.5 MHz which was used, had a small touch area (1x1cm), with good resolution and slight penetration, corresponding to the small size of the preterm infant's head. All the findings were stored on the printer, as images of 10 x 7.5 cm in size. The pictures also contain information about the date of the check up and the name of the patient. Findings of intracranial hemorrhage were graded by the system of gradation Papilla et al., according to which grade I is isolated subependymal hemorrhage, grade II - subependymal hemorrhage with extension into lateral ventricles without ventricular enlargment, grade III - subependymal hemorrhage with extension into lateral ventricles and grade IV - intraparenchymal hemorrhage. Specificity and sensitivity of this method in the diagnosis of PVH-IVH range from 96 -100 % (5).

The primary cohort, after receiving the information about the existence of signs of PVH-IVH, was divided into two secondary cohorts, the cohort of infants with PVH-IVH and the cohort of infants without PVH-IVH. The cohort of infants with PVH-IVH was stratified by the degree of hemorrhage.

Ethics Committee of the Clinical Centre of Montenegro in Podgorica approved the development of this study (The consent number 03/01-3813/4), in the accordance with standard operating procedures of the Ethics Committee of the Clinical Center of Montenegro and international guidelines for the performance of biomedical research on humans.

Statistical data processing began by determining the measure of central tendency (minimum, maximum and average), a measure of variability (standard deviation) using the methods of descriptive statistics. Statistical significance was determined at $p < 0.05$, using the software package SPSS (SPSS Softwarw GmbH, version 15).

Pearson's X^2 test was used to calculate the statistical significance of differences in the incidence of PVH-IVH in newborns with different concentrations of IGF-1. Estimation of differences in the frequency of PVH-IVH among male and female newborns, between the newborns from multiple and single pregnancies, the newborns from natural childbirth and cesarean section as well as between ventilated and unventilated newborns also was determined by Pearson's X^2 test. Analysis of Variance (ANOVA) was applied to compare birth weight (PTM) and gestational age (GA) of newborns with varying degrees of PVH-IVH and newborns without PVH-IVH. ANOVA was applied to compare the significance of difference in the mean values of IGF-1 in newborns with various degrees of PVH-IVH and with no PVH-IVH. To investigate the relationship between ratings of vitality - Apgar score (AS) and PVH-IVH. We used a nonparametric Kruskal-Wallis's test for comparison of ranks.

Results

The study included 74 preterm infants (42 male and 32 female). Table 1 shows the distribution of male and female newborns according to the presence and the degree of PVH-IVH. To compare the significance of difference in the frequency of PVH-IVH between male and female newborns Pearson Chi-Square test was used. There was no statistically significant difference (X^2 =7.54 p>0.05) in the frequency of PVH-IVH between male and female preterm infants.

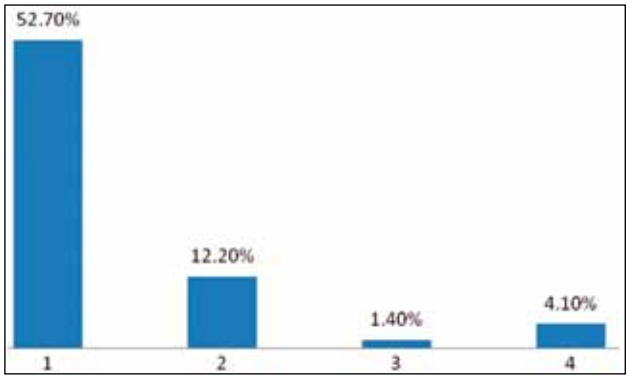

Figure 1. Distribution of infants according to the degree of PVH- IVH

Of 74 newborns from the primary cohort, 32 (43.2%) were born by caesarean section, 42 (56.8%) by normal labor. Table 1 shows the distribution of the newborns from cesarean section and normal labor according to the degree of PVH-IVH. The statistical significance of differences in the incidence of PVH-IVH between the two secondary cohorts was assessed by using Pearson Chi-Square test. The type of delivery had no significant effect on the incidence of PVH-IVH (X^2 =5.73 p>0.05).

The average birth weight (BW) of the newborns from the primary cohort was 1698.24 ± 403.8 g (range 990-2860g). Table 2 shows the average BW in cohorts based on the information obtained on the presence of hemorrhage, or the degree of hemorrhage. By using ANOVA we compared BW among the secondary cohorts, formed on the basis of data about the presence and the degree of PVH-IVH. There were no statistically significant differences in the secondary cohorts, that is BW variability between groups was not significantly greater than the variability within a group (F=2.24 p> 0.05).

Average gestational age (GA) of the newborns from the primary cohort was 31.18 ± 1.87 weeks (range 26-33 weeks). Table 2 shows the average GA (in weeks) in the cohorts, based on the information obtained on the presence of hemorrhage, or on degree of hemorrhage. The difference in the variability of GS between the groups (F=2.88

Table 1. Distribution of infants according to clinical and epidemiological data in relation to the presence and degree of PVH-IVH

Features	Without hemorrhage		With hemorrhage								Significance
			1st level		2nd level		3rd level		4th level		
Sex	n	%	n	%	n	%	n	%	n	%	
male	9	40.9.	23	59.0	8	88.9	1	100	1	33.3	X^2=7.54 p>0,05
female	13	59.1	16	41.0	1	11.1			2	66.7	
Total	22	100	39	100	9	100	1	100	3	100	
Mode of delivery											
normal labor	9	40.9	23	59	6	66.7	1	100	3	100	X^2=5.73 p>0,05
caesarian	13	59.1	16	41	3	33.3					
Total	22	100	39	100	9	100		100		100	
Pregnancy											
single	9	40.9	30	76.9	9	60	1	100	2	66.7	X^2=13.74 p<0,01
multiple	13	59.1	9	23.1	0		0		1	33.3	
Total	22	100	39	100	9	100	1	100	3	100	
Mechanical ventilation											
No	12	54.5	24	61.5	5	55.6					X^2= 0,009 p>0,05
Yes	10	45.5	15	38.5	4	44.4	1	100	3	100	
Total	22	100	39	100	9	100	1	100	3	100	

p<0.05) was examined by using ANOVA. There was a statistically significant difference in gestational age among the newborns from different cohorts in relation to the presence and degree of PVH-IVH.

Table 1 shows distribution of newborns according to a history of pregnancy (single and multiple pregnancies). Using Pearson Chi-Square test for comparing the incidence of PVH-IVH among the cohorts of newborns from multiple and single pregnancies, statistically significant difference (X^2=3.74 p<0.01) was obtained. The incidence of PVH-IVH in newborns who come from single pregnancies is significantly higher.

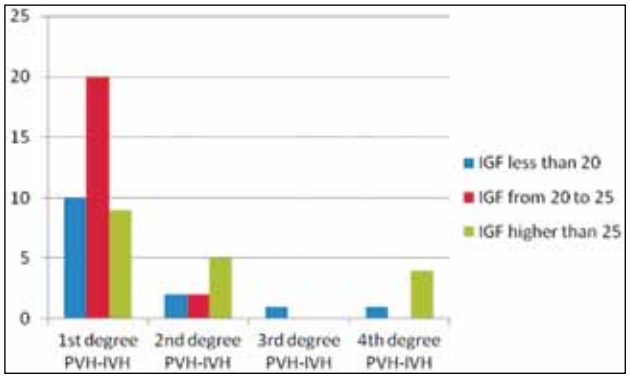

Figure 2. Distribution of infants according to the categories of values of IGF-1and the degree of PVH-IVH

Of 33 (44.6%) infants who during hospitalization were receiving mechanical ventilation, 23 (69.7%) infants were diagnosed with PVH-IVH. Of 41 (55.4%) infants who were not ventilated during hospitalization, 29 (70.7%) were diagnosed with PVH-IVH. Table 1 shows the distribution of ventilated and unventilated newborns according to the presence and degree of PVH-IVH. Statistical importance of the differences in the incidence of PVH-IVH in ventilated and unventilated newborns was determined by Pearson Chi-Square test (X^2=0.009 p> 0.05). There was no statistically significant correlation between mechanical ventilation and the incidence of PVH-IVH.

Distribution of newborns from the primary cohort according to the level of IGF-1: in 19 newborns (25.7%) level was less than 20 mcg/l in 33 (44.6%) from 20-25 mcg/l and 21 (28.4 %) newborns had IGF-1 above 25 mcg/l. Average level of serum IGF-1 in the primary cohort was 23.73 mcg/l ± 5.79, in newborns without PVH-IVH 24.39 ± 6.98, while in those with PVH-IVH 23.46 ± 5.27 (max 46.33, min 15.44).

The distribution of newborns according to ultrasound findings of endocranium is shown in Figure 1. In 22 (29.7%) newborns the findings were normal, 52 (70.3%) had PVH-IVH.

Distribution of newborns according to the values of categories of IGF-1 and the degree of PVH-IVH is shown in Figure 2. Of the 19 newborns from the primary cohort whose level of IGF-I was less than 20 mcg/l, 14 newborns (73.7%) were diagnosed with PVH-IVH. Of the 33 newborns with IGF-1 values from 20-25 mcg/l 22 (66.7%) were diagnosed with PVH-IVH. In the cohort of newborns (22 newborns) with the values of IGF above 25 mcg/l, 16 (72.7%) newborns had signs of PVH-IVH. The statistical significance of the differences in the frequency of PVH-IVH in newborns with different levels of IGF-type 1 (X^2=0.37 p>0.05) was noticed by using Pearson Chi-Square test. There were no statistically significant differences in the frequency of peri-intraventricular hemorrhage among newborns with different levels of serum IGF-1.

The average values of IGF-1 in cohorts with different degree of PVH IVH and those without PVH-IVH are shown in Table 2. We compared the differences in the values of IGF-1 in newborns with various degrees of PVH-IVH and without PVH-IVH by using ANOVA and got that F=1.25 p>0.05. The difference in the IGF-1 levels between newborns with different degrees of PVH-IVH and without PVH-IVH was not statistically significant.

Discussion

Intracranial hemorrhage is a significant problem of preterm infants, particularly immature as well as preterm infants with very low body weight at birth and with intrauterine growth restriction (IUGR). The most common form of intracranial hemorrhage in preterm infants is peri-intraventricular hemorrhage (PVH-IVH) (5).

During the last few years attitudes on the pathogenesis of the disease of prematurity have significantly changed. It is believed that PVH-IVH, ROP and CLD have a similar pathogenesis in which the

role of the angiogenic factors is important, particularly IGF1 which achieves its function of modulation of angiogenesis through VEGF (8).

Latest studies have linked preterm birth itself both with low values of angiogenic factors and with the breaking of angiogenesis in all fetal organs. Another thing shows the connection between prematurity and IGF-1. It is the discovery that the gene (locus 15q26.3) in the fetal genome which is responsible for susceptibility to preterm birth lies in a region which contains the IGF1R gene which encodes the synthesis of receptors for IGF-1 (18, 19).

Occurrence of the disease of prematurity is associated with rapid decline in IGF-1 in serum, after preterm delivery when the maternal sources of IGF-1 are lost. Low values of IGF-1 are predictive for more severe forms of the diseases of prematurity (8, 3).

The results of the research have been published in which the association between low levels of IGF-1 and more severe forms of the disease of prematurity was found, based on the repeated measurements of the level of IGF-1 in the first 4-6 postnatal weeks and the determination of the degree of PVH-IVH (15, 9).

Better knowledge of the pathogenesis of the disease of prematurity, particularly the role of angiogenic factors has resulted in pharmacotherapeutical approach in the therapy of the retinopathy of prematurity.

Incidence of PVH-IVH in primary cohort in our study was 70.3%. This high incidence of PVH-IVH stems from the fact that the participants of our study are 'endangered' preterm infants who, after their birth, had to be transferred to the Center for neonatology. Center for neonatology is the only institution for the care for 'endangered' preterm infants in Montenegro. This fact implies higher presence of the 'risk factors for development of PVH-IVH (transport of a newborn, oxygen therapy, mechanic ventilation, exchange transfusion, specific metabolic derangements).

Our results showed a statistically significant difference in the gestational age among the newborns with and without PVH-IVH. Infants with PVH-IVH were, on average, of significantly shorter gestation age in comparison to the infants without PVH-IVH.

Newborns from single pregnancies had significantly higher incidence of PVH-IVH than babies from multiple pregnancies.

No statistically significant differences appeared in the average BW among infants with PVH-IVH and without PVH-IVH. Using our results we couldn't confirm the fact that the preterm infants with lower body weight at birth are in the greater risk of developing PVH-IVH.

The fact that there was no statistically significant difference in the BW with newborns from the secondary cohort, while at the same time there is a statistically significant difference in GA, talks about a possible role of the IUGR in the etiology of PVH-IVH, which should be examined in future studies.

No statistically significant differences appeared in the incidence of PVH-IVH among male and female newborns.

The mode of delivery does not affect the incidence of PVH-IVH, according to our results. There is no statistically significant correlation between ratings of vitality at birth and PVH-IVH.

In addition, we didn't get a significantly higher frequency of PVH-IVH in newborns who were receiving mechanical ventilation in comparison to those who were not ventilated during hospitalization.

Average level of serum IGF-1 in primary cohort is 23.7mcg/L, which-at the same time- is average level of IGF-1 in postmenstrual age of 33 weeks in endangered preterm infants in Montenegro.

The results of our study did not confirm the correlation between IGF-1 values in the 33rd postmenstrual week and the incidence of PVH-IVH. We neither got the anticipated lower average level of serum IGF-1 in the cohort of infants with PVH-IVH, nor the difference in the values of the average IGF-1 levels between cohorts stratified by the degree of PVH-IVH. Also there is no significant difference in the frequency of PVH-IVH in newborns within different categories of values of IGF-1.

In premature retinopathy, which is the most researched disease of prematurity, the two phases in the pathogenesis and the different roles of IGF-1 in these phases are described. In the ROP phase 1 (which begins after premature birth) low levels of IGF-1 are predictive of more severe form of ROP, while in the ROP phase 2 (which starts in the 33rd postmenstrual week) elevated levels of IGF talk about the progression of ROP (3, 7). The latest understanding of similar pathogenesis of ROP and PVH-IVH, could explained the lack of significant differences in the level of IGF-1 between the

newborns, with and without PVH-IVH in the 33rd postmenstrual week.

Conclusion

Through presented results we can conclude that there is no connection between the level of IGF- 1 in the 33rd postmenstrual week and the appearance of PVH-IVH in the preterm infants. There is also no correlation between IGF - 1 values and the degree of PVH-IVH. Our results showed that the incidence of PVH-IVH was significantly higher in infants of shorter gestation age and in newborns from single pregnancies.

We think that the investigation of the relationship between angiogenic factors and the diseases of prematurity should be continued, but the values of angiogenic factors should be determined repeatedly during the neonatal period. Obtained results could be used in a better understanding of the mechanisms underlying their pathogenesis.

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Atherosclerotic risk factors among diabetic and non diabetic patients on chronic hemodialysis

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Abstract

Aim: The aim of this study was comparison of CRP levels between diabetic and non-diabetic patients and determination if difference in inflammatory activity could explain the worsened lipid profile in diabetic patients on chronic hemodialysis.

Method: In this study were included 170 patients undergoing the program of chronic hemodialysis. 69 patients with C-reactive protein (CRP) levels over than 10 mg/L and 100 patients with CRP levels in the normal range, Lp(a), total cholesterol, triglycerides, LDL-C, HDL-C and serum albumin were determined in relation to CRP, as a sensitive marker of an activated acute phase response. Patients with elevated CRP levels were divided into two groups: 48 non-diabetic and 21 diabetic.

Results: Show that serum concentration of CRP and triglycerides, in 21 diabetic patients, was significantly higher than in non diabetic patients (58.11mg/L vs. 39.12mg/L, $p<0.01$ and 3.35 mmol/L vs. 2.61 mmol/L, $p<0.01$). Diabetic patients had significantly lower serum levels of HDL-C and albumin than non diabetic (0.72 mmol/L vs. 1.0 mmol/L, $p<0.01$ and 29.12 g/L vs. 35.37 g/L, $p<0.01$). No significant differences were detected in Lp(a), total cholesterol and LDL-C. In patients with elevated CRP level correlation was positive with Lp(a) and negative with HDL-C and serum albumin,but not in healthy controls.

Conclusion: According to results diabetics have greater risk for atherosclerotic cardiovascular disease than do non diabetics. During the follow-up period of three years, of 69 patients 18 died from cardiovascular events, 11 were diabetic and 7 nondiabetic patients.

Key words: C-reactive protein, chronic hemodialysis, lipoprotein(a), lipids, lipoproteins, serum albumin, cardiovascular disease

Introduction

The morbidity and mortality of cardiovascular disease are substantially higher among dialysis patients, than in the general population[1]. The annual mortality rate is 20% per year with over 50% of deaths due to cardiovascular disease[2]. This has led to the formulation of an «accelerated atherogenesis» hypothesis in uremic patients and has been commonly linked with the metabolic alterations associated with uremia. Inflammation is considered one of the key factors in accelerating atherosclerosis and endothelial dysfunction and advancement in the understanding of the pathogenesis of atherosclerotic vascular disease in end stage renal disease (ESRD)[3]. Recent epidemiological data have documented associations between C-reactive protein (CRP), the prototypical acute phase response protein, and cardiovascular disease in general population[4]. The uremic state is associated with an altered immune response, which is associated with elevated proinflammatory cytokine levels[5]. Intermittent stimulation by endotoxins originating from the dialysis water supply and artificial vein grafts or bioincompatibility caused increased circulating inflammatory proteins, such as plasma CRP[6]. Stenvinkel, outlined studies showing an inverse relationship between glomerular filtration rate and inflammatory biomarkers, such as CRP[7]. Measured by a simple blood test, high serum levels of CRP could be identified as a prominent risk factor for cardiovascular events in apparently healthy people[8]. Pati-

ents with impaired renal function exhibit significant alterations in lipoprotein metabolism, which in their most advanced form may result in the development of severe dyslipidemia[9]. Chronic renal failure results in profound lipid disorders, which stem largely from deregulation of high density lipoprotein (HDL) and triglyceride-rich lipoproteins metabolism. The down regulation of the expression of several genes along with the changes in the composition of lipoprotein particles and the direct inhibitory effect of various uremic 'toxins' on the enzymes involved in lipid metabolism, represents the most important pathophysiological mechanisms underlying the development of hypertriglyceridemia[10]. In hemodialysis patients low density lipoprotein (LDL) levels are usually not elevated[11], because the reduced catabolism of LDL is masked by the decreased production. Several mechanisms, working in concert, may underlie the reduction in HDL levels, which is usually indicative of impaired reverse cholesterol transport. Specifically, maturation of HDL is impaired and its composition is altered[12]. Interest on inflammatory biomarkers predicting the risk of clinical events increases[13]. Main function of acute phase proteins is expressed by remodeling of HDL creating dysfunction and reduced serum concentration of HDL-C as a result[14].

The contribution of cardiovascular events to the extraordinary high mortality in end-stage-renal disease (ESRD) has generated some interest in non traditional atherosclerotic cardiovascular disease risk factors that are prevalent in ESRD, such as lipoprotein(a)[15].

Serum levels of lipoprotein(a)[Lp(a)] are determined largely by genetic variation in the gene encoding for apo(a). Apo(a) is very homologous to plasminogen[16] and exhibits an extreme size polymorphism with the apo(a) isoproteins. High plasma concentrations of Lp(a) are considered a major risk factor for atherosclerosis and cardiovascular disease[17] .

Lp(a) levels are frequently elevated in patients receiving chronic hemodialysis[18]. Elevated plasma Lp(a) levels in chronic hemodialysis patients have been associated with a frequency distribution of apolipoprotein(a)–Lp(a) isoforms, similar to those found in general population. This indicates that elevated Lp(a) levels in these patients are not due genetic origin[19]. Elevated plasma Lp(a) levels in chronic hemodialysis patients have been associated with a frequency distribution of apolipoprotein (a) – Lp(a) isoforms, similar to those found in general population. This indicates that elevated Lp(a) levels in these patients are not due genetic origin[19] It has been suggested that kidneys have an important role in Lp(a) metabolism. There is decrease in Lp(a) catabolism or increase in Lp(a) production by liver.[20] Although it has not been fully explained, high Lp(a) levels in hemodialysis patients may also be due to activated acute phase reactants.[21]

Patients with diabetes mellitus undergoing chronic hemodialysis treatment have the worst outcome on dialysis due to an increased rate of cardiovascular complications and demonstrated much worse survival rates than do nondiabetic patients[22] Atherosclerosis is responsible for 80% of all deaths in diabetic patients[23]. Compared with non-diabetic, diabetic patients have a two- to four-fold increased risk of coronary disease[24]. Inflammatory activity is increased in individuals with type 1 and type 2 diabetes and strongly associated with risk of atherothrombosis[25].

The principal features of the impaired lipid metabolism in nondiabetic uremic subjects include the increase in the very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) fractions, which are mainly due to a defect in the catabolism of triglyceride-rich lipoproteins and the decrease in the HDL fraction. In contrast, diabetic lipid abnormalities in the absence of renal insufficiency are reported as hypertriglycemia, with a decreased concentration of HDL and an elevated level of VLDL, which is mainly due to an increase in VLDL-triglyceride synthesis[26]

In hemodialysis patients, hypoalbuminemia is also known to be associated with cardiovascular disease. Since albumin is a negative acute-phase reactant, non-nutritional factors like inflammation depress albumin synthesis. [27]. Some studies have demonstrated a significant inverse relationship between serum Lp(a) and albumin concentration in hemodialysis patients[28,29].

AIM

The aim of this study was comparison of CRP levels between diabetic and non-diabetic patients and determination if difference in inflammatory

activity could explain the worsened lipid profile in diabetic patients on chronic hemodialysis.

Material and methods

This study was performed on 170 patients, undergoing hemodialysis treatment in the Clinic of Internal Diseases from the Clinical Centre in Prishtina. Here are included patients who were treated with hemodialysis more than 6 months, which is considered as chronic hemodialysis. The blood samples were collected between February and April 2007. We initially determined CRP and sedimentation rate by three measurements, in a period of 1-3 month, to be sure that CRP levels were not occasionally elevated, but remain elevated over time, as a chronic inflammation. Than the patients were divided in two groups: group of 69 patients (32 female and 37 male) with elevated CRP levels over than 10 mg/L and sedimentation rate of over 50mm/h, in all blood samples and group of 101 patients with CRP levels in the normal range. For the first group, based in patients history, angina, possible myocardial infraction, cerebrovascular events were excluded and the concentrations of the last measurement of CRP, were taken in consider. Patients with elevated CRP levels were classified into two groups: 21diabetic and 48 non-diabetic subjects. According to age, patients were divided in a group of 20-40 years old patients and a group of 41-60^{+} years old patients. A part of CRP, among all the patients, serum levels of Lp (a), triglicerides total cholesterol, LDL-C, HDL-C and albumin were determined. 50 healthy people(20 females and 30 males), were included as a control group. Measurements of serum CRP, Lp(a) and albumin were performed on fresh samples. The serum concentration of CRP was measured by the turbidimetric method based in combines of CRP with specific antibody to form insoluble antigen antibody complexes. Diazyme's Lipoprotein (a) assay is based on a latex enhanced immune-turbidimetric method. The normal range for CRP is less than 10 mg/L, and the range for Lp(a) is less than 30mg/dl. Total cholesterol and triglycerides were measured by enzymatic methods (cholesterol by CHOD-PAP and triglycerides by GPO). HDL-C was measured directly with detergent which solubilizes the HDL lipoprotein particles, releasing HDL-cholesterol. LDL-C was determinated with precipitation method.

Measurement of serum albumin was carried out by a timed endpoint method, using the bromocresol purple.

Statistical analysis

The data were analyzed using the descriptive statistics for each biochemical parameter that was followed. Statistically significant differences were analyzed using the student's t-test, with the acceptance of statistical significance at the level $p<0,01$. Relationships and correlations between biochemical parameters were analyzed using Pearson Chi-square ($\chi 2$) test.

Results

In this study were included 170 patients undergoing chronic hemodialysis. Serum CRP was found to be elevated more than 10 mg/L in 69, patients, respectively in 40,6% of them. Mean serum CRP concentration in patients was significantly higher than in control group (mean ± SD, 44.62 ±18.47 mg/L versus 8.75 ± 4.82 mg/L, respectively $p<0.01$-tab.1). Among the 69 hemodialysis patients, mean CRP values were higher in older group (41-60 years or older), who were no longer in hemodialysis treatment, compared to those between 20 and 40 years (51.84 ± 15.34 mg/L vs. 22.55 ± 3.6 mg/L, $p <0.01$-tab.4). These results indicated that high CRP values are linked not only with age, but also with duration of hemodialysis. Among hemodialysis patients 43 of them or 25,3% had an Lp(a) level higher than 30 mg/dl, compared to 16% in the control group, with the difference being statistically significant. Mean Lp (a) values were significantly higher in hemodialysis patients than in healthy controls (31.37mg/dl versus 19.69mg/dl, respectively $p<0.01$-tab.2) Result showed that mean value of Lp(a) was significantly higher in patients exhibiting elevated CRP than to those patients with CRP in normal range.(35.39mg/L versus 28.6 mg/L, respectively $p<0.01$- tab.3)

Triglycerides serum concentration was significantly higher in hemodialysis patients than in the controls, (2.76mmol/L versus 1.32 mmol/L, respectively $p<0.01$-tab.2), but no difference was found between group of patients with elevated CRP and

group of patients with CRP in normal range. (tab. 3) No significant difference was detected in total cholesterol and low density lipoprotein cholesterol (LDL-C) serum concentration, between hemodialysis patients and control group(tab.2) and between group of patients with elevated CRP and group of patients with CRP in normal range.(tab. 3). High density lipoprotein cholesterol(HDL-C) and serum albumin, were significantly lower in hemodialysis patients than in the control group (1.14mmol/L versus 1.35mmol/L, respectively p< 0.01 and 34.92g/L versus 39.67g/L respectively p<0.01 – tab.2). Patients with elevated CRP had significantly lower serum levels of HDL-C and serum albumin, than patients with values in normal range. (0.91mmol/L versus 1.29mmol/L, p<0.01 and 33.56g/L versus 35.86g/L,p< 0.01 - tab. 3)

Patients in older group exhibited higher levels of CRP, Lp(a) and lower levels of total cholesterol, HDL-C and serum albumin.(tab. 4). Mean serum concentration of CRP and triglycerides were found to be significantly higher (58.11mg/L vs.39.11mg/L,p<0.01 and 3.35mmol/L vs.2.61mmol/L, p<0.01-tab. 5) whereas HDL-C and serum albumin were significantly lower (0.72mmol/L vs 0.99 mmol/L, p<0.01 and 29.12g/L vs 35.37g/L, p< 0.01 - tab. 5) in diabetic than in nondiabetic hemodialysis patients. No differences were found in total cholesterol and LDL-cholesterol concentration. Lp(a) mean value was higher in diabetic patients compare with non diabetic(37.4 mg/dl vs 32.3 mg/dl - tab.5), but no significant difference was find.

CRP levels correlated positively with Lp(a) (r=+0.58, p<0.01, fig.1) and negatively with total cholesterol (r=-64, p< 0.01, fig. 3), HDL-C (r=-0.88, p<0.01, fig.2) and serum albumin(r=- 087 p<0.01, fig.4), in group of patients with elevated CRP, but not in the controls. In group of patients with elevated CRP, Lp(a) levels correlated negatively with HDL-C (R=-0,53; p< 0,01,fig. 5) and serum albumin (R=-0,57; p< 0,01, fig.6). Correlation coefficient was not significant in healthy controls. During the follow-up period of three years, 18 out of 69 patients (26%) had died, from cardiovascular events. Diabetic patients demonstrated a higher mortality rate, compared with nondiabetic patients, because 11 patients were diabetic and 7 nondiabetic. Fifteen patients who died, were in older group (age 41-60+) with higher CRP values and only three patients were in younger group (age 20–40) with significantly lower CRP values.

Table 1. CRP values in hemodialysis patients with activated acute phase response and in healthy controls

	CRP > 10 mg/L (N = 69)	**Healthy controls (N = 50)**
X ± SD	44.62 ± 18.47	8.75 ± 4.82
p <	0.01	

Table 2. Lipids lipoproteins and albumin in hemodialysis patients and healthy controls

	All patients (N = 170)	**Healthy controls (N = 50)**	**P <**
Lp(a)	31.37 ± 11.25	19.6 ± 7.87	0.01
Tg	2.76 ± 0.89	1.32 ± 0.56	0.01
Chol	4.46 ± 0.9	4.37 ± 0.64	NS
HDL	1.14 ± 0.38	1.35 ± 0.35	0.01
LDL	2.44 ± 0.63	2.25 ± 0.65	NS
Alb	34.92 ± 3.9	39.67 ± 4.98	0.01

Data are given as mean ± SD. Lp(a) - lipoprotein (a), alb-albumin, HDL-C - high density lipoprotein cholesterol

Table 3. Lipids lipoproteins and albumin in hemodialysis patients with low and elevated serum

	Levels of CRP		
	CRP > 10 mg/L (N = 69)	**CRP < 10 mg/L (N = 101)**	**P <**
Lp(a)	35.39 ± 13.7	28.6 ± 8.21	0.01
Tg	2.83 ± 0.99	2.71 ± 0.82	NS
Chol	4.4 ± 1.04	4.49 ± 0.81	NS
HDL	0.91 ± 0.27	1.29 ± 0.37	0.01
LDL	2.32 ± 0.55	2.15 ± 0.78	NS
Alb	33.56 ± 4.58	35.86 ± 3.14	0.01

Data are given as mean ± SD. Lp(a) - lipoprotein (a), alb-albumin, HDL-C - high density lipoprotein cholesterol

Table 4. Biochemical parameters in hemodialysis patients with elevated CRP based on age

	Age 20 - 40 (N = 17)	**Age 41 - 60+ (N = 52)**	**P <**
CRP	22.55 ± 3.6	51.84 ± 15.34	0.01
Lp(a)	29.19 ± 8.25	37.42 ± 14.56	0.01
Tg	3.29 ± 1.10.	2.67 ± 0.90	0.05
Chol.	4.81 ± 0.82	4.21 ± 1.07	0.05
HDL	1.25 ± 0.23	0.80 ± 0.18	0.01
LDL	2.03 ± 0.71	2.19 ± 0.80	NS
Alb	37.76 ± 3.53	32.18 ± 4.05	0.01

Data are given as mean ± SD. CRP- C reactive protein, Lp(a) - lipoprotein (a), alb-albumin, HDL-C - high density lipoprotein cholesterol

Table 5. Biochemical parameters in nondiabetic and diabetic hemodialysis patients

	Non diabetic (N = 48)	Diabetic (N = 21)	P <
CRP	39.12± 14.82	58.11 ± 19.92	0.01
Lp(a)	32.3 ± 11.6	36.4 ± 11.8	NS
Chol	4.47 ± 0.88	4.08 ± 1.34	NS
Tg	2.61 ± 0.64	3.35 ± 1.43	0.01
LDL	2.25 ± 0.78	2.03 ± 0.73	NS
HDL	0.99 ± 0.26	0.72 ± 0.21	0.01
Alb	35.37 ± 3.70	29.12 ± 3.42	0.01

Data are given as mean ± SD. CRP- C reactive protein, Lp(a) - lipoprotein (a), alb-albumin, HDL-C – density lipoprotein cholesterol

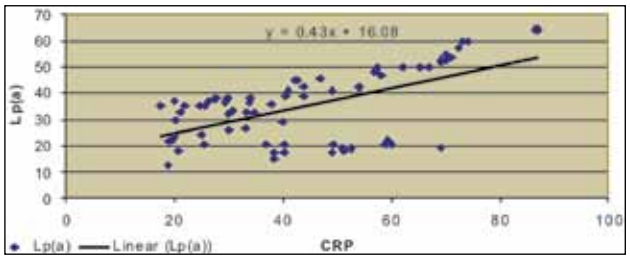

Figure1. Positive correlation between CRP and Lp(a)

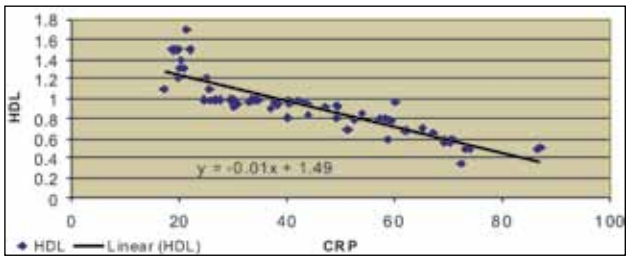

Figure 2. Negative correlation between CRP and HDL-C

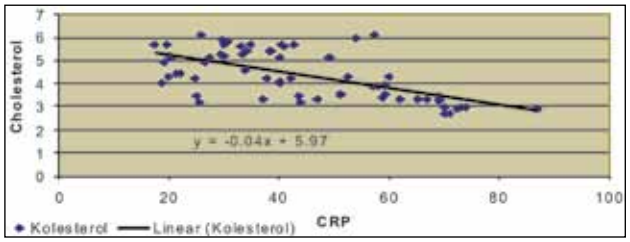

Figure 3. Negative correlation between CRP and Cholesterol

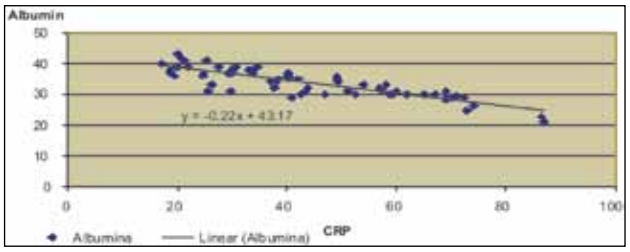

Figure 4. Negative correlation between CRP and albumin

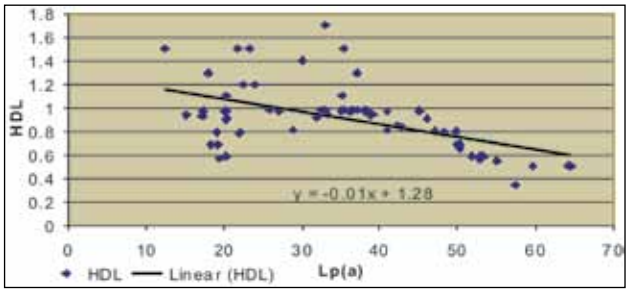

Figure 5. Negative correlation between Lp(a) and HDL-C

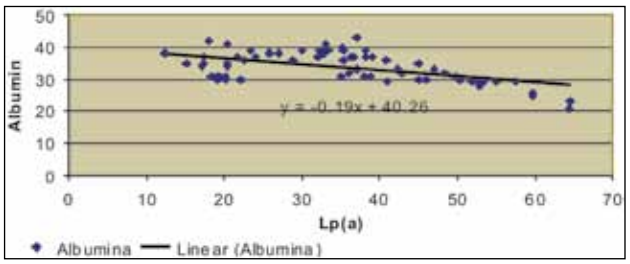

Figure 6. Negative correlation between Lp(a) and albumin

Discusion

Approximately 50% of patients on hemodialysis, have evidence of chronic inflammation which is linked to atherosclerotic cardiovascular disease by a number of mechanisms and contributes to the high mortality seen in this patient group.

The inflammatory response to a given stimulus can be evidenced by a number of acute phase proteins; the most established is CRP, as a prominent product of the inflammatory response and a marker of overall and cardiovascular death in the general population as well as in hemodialysis patients.

CRP is elevated 8–10-fold in hemodialysis patients as compared with healthy controls[30] and appears to be a common feature in dialysis patients.A single determination of CRP is a powerful indicator of all cause and cardiovascular death even after a follow-up period of 4 years, in hemodialysis patients.

In our study, a considerable proportion of patients (40.6%) exhibited an activated acute phase response (APR), characterized by an increase of CRP concentration. Mean CRP values in patients were significantly higher than those in the control group (tab.1). Patients in older group, who were on hemodialysis treatment for a longer duration of time, exhibited higher concentration of CRP, in compare with younger group (tab.4). According to the results high CRP values are linked with age and with duration of hemodialysis. We have found significant correlation between the CRP and lipoproteins which have been proven as having an atherogenic effect in blood vessels. Moreno et al.[31] found that, in diabetic patients, coronary tissue exhibits a larger content of lipid-rich atheroma, macrophage infiltration, and subsequent thrombosis than tissue from patients without diabetes, suggesting that there is an increased vulnerability for plaque disruption and thrombosis in diabetic patients. The same author reviewed the pathogenesis of diabetes atherosclerosis[32] and supported the idea that those patients have more inflammatory activity than the general population with atherosclerosis. We also found a higher CRP levels in diabetic in compared with nondiabetic patients (tab. 5).The accumulation of advanced glycation end products is greatly accelerated among diabetic patients and might further promote chronic inflammation.[33] In ESRD some lipid disturbances are observed even in early stage of the disease. Their intensification is raising with the progress of the disease. Dialysis can moderately attenuate dyslipidemia, but its character remains unchanged. Lipid abnormalities captured by routine measurements are not impressive in patients with kidney disease, HDL-C concentrations tend to be low and triglycerides levels tend to be elevated[34]. Hypertriglyceridemia is a typical finding in hemodialysis and represents an early feature of renal failure. Previous studies have shown that patients with impaired renal function exhibit increased concentration of triglycerides even hough serum creatinine levels are within normal limits. According to our results there was significant difference in triglycerides concentration, between hemodialysis patients and control group (tab. 2), but no difference between group of the patients with elevated CRP and those patients with values in normal range(tab. 3). We also did not find any difference in LDL-C concentration in hemodialysis patients and control group (tab. 2), which confirmed that most hemodialysis patients do not have elevated LDL-C.[34,35] Of particular interest was the levels of HDL-C We find the significant difference in HDL-cholesterol levels between hemodialysis patients and the control group(tab. 2). In ESRD, HDL-C is now emerging as a key entity in both determining risk and providing protection, although none as yet specifies HDL as a target for treatment[12]. Inflammation is one of the powerful factors also contribute to its decreased levels[14] Our study results showed significantly lower levels of HDL-C in the group of patients with elevated CRP, in compare with the patients with CRP in the normal range (tab.3) and negative correlation of HDL and CRP (fig.2) These results indicate that the inflammatory condition may be responsible for low HDL-C. Hypercholesterolemia has been reported to be a predictor of high mortality in hemodialysis patients.[36] According to our results, the negative correlation between the CRP levels and total cholesterol shows that in hemodialysis patients low cholesterol concentration can be caused not just because of malnutrition but also because of inflammation (fig.3) This correlation corresponds with study results, where the significant negative correlation was found, between the levels of IL-6, the major cytokine stimulus for CRP production and cholesterolemia.[36] Lp(a) is another important risk factor for cardiovascular disease in the general population, as well as in dialysis patients. Though the concentration of serum Lp(a) is mostly determined by genetic factors, secondary factors such as APR and end ESRD also contributes to its increase. Lp (a) levels are frequently elevated in hemodialysis patients[18]. In this study 23.3% of patients had an Lp(a) level higher than 30 mg/dl, compared to 16% in the control group. The mean serum Lp (a) value in hemodialysis patients was significantly higher than in controls. (Table 2.), which confirm that kidney have an important role in Lp(a) metabolism.[20] Some studies have demonstrated a close relationship between high Lp(a) levels and the APR, as shown by correlations with CRP and IL-6.[37] Because seven IL-6–responsive element sequence motifs can be identified in the 5' flanking regulatory region of the apo(a) gene on chromosome 6, it is likely that apo(a) responds as

an acute phase reactant [38.] Uremia can be considered to be a state of activated APR and in the micro-inflammatory milieu, a number of atherogenic proteins like Lp(a) are elevated and a number of anti-atherogenic factors like HDL-C and serum albumin are diminished. In this study Lp(a) mean value was significantly higher in patients with elevated CRP than to those patients with CRP levels in the normal range (Table 3.). Based on results, APR exhibited higher serum levels of Lp(a), respectively Lp(a) reacts as an acute phase protein in patients with high CRP levels[37] . For this reason Lp(a) levels correlated in the positive way with CRP (Figure 1.) While serum Lp(a) levels showed a positive correlation with CRP, with HDL-C correlated negatively (Figure 5). Because of the characteristics of an acute phase reactant, it is meaningful that Lp(a) levels correlated negatively with HDL-C.[39] . Although the cause of atherosclerosis and cardiovascular disturbance in patients with diabetic uremia, is probably multifactorial, the dyslipidemia associated with diabetic renal insufficiency appears to be a major risk factor for atherosclerosis. In diabetic uremic patients, lipid abnormalities, in the absence of renal insufficiency, are reported as hypertriglycemia, with a decreased concentration of HDL. In this stady there was significant difference in triglicerid and HDL cholesterol levels between diabetic and non diabetic patients and no significance in total cholesterol and LDL cholesterol levels (tab.5). Lp(a) concentration was higher in diabetic patients compare with non diabetic, but no significant difference was find. Our results provide the evidence that hemodialysis diabetic patients were more affected to accelerated atherosclerosis and ischemic heart disease than non diabetics.

Hypoalbuminemia is known to be strongly associated with ischemic heart disease in dialysis patients and it is thought to be one of the cardiovascular risk factors. According to the results there was the significant difference in albumin levels between a group of the patients with elevated CRP and those patients with CRP in the normal range(tab.3). The same significant difference exist between diabetic and non diabetic patients (tab.3).Albumin levels correlated in the negative way with CRP (fig 4.), which proved that hypoalbuminemia in hemodialysis patients is partially a consequence of inflammation. Different studies have reported, that by increasing serum albumin, in renal failure, serum Lp(a) levels were decreased[40]. Based in our results a significant inverse relationship existed between serum albumin and Lp(a) in hemodialysis patients with elevated CRP(fig 6). It is a significant indicator for cardiovascular death of hemodialysis patients[41].Diabetic patients undergoing hemodialysis, demonstrate worse survival rates than do non diabetic. During follow-up period of three years, 18 out of 69 patients respectively 26%, had died, from cardiovascular events. Patients who died as a result of cardiovascular disease more commonly had diabetes mellitus in compared with survivors. The strategy to reduce mortality rates should consider the differences in risk factor profiles for diabetic and nondiabetic patients on chronic hemodialysis[44,45,46].

Conclusion

Changes of the atherogenic risk profile, in hemodialysis patients, namely elevated Lp(a), as well as decreased HDL-C and serum albumin, are partly the consequence of an activated APR. We found significant correlations of CRP with Lp(a), HDL-C, and serum albumin, which have been proven as a predictors of cardiovascular mortality in hemodialysis patients. The results further show that diabetic patients exhibited higher levels of CRP, Lp(a) and triglicerides and lower levels of HDL-C and serum albumin. Our findings indicate that in diabetic hemodialysis patients same atherogenic risc factors are more enhanced and mortality rate was higher in compare with nondiabetic patients.

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Acute Effects of the Cellular Immune System on Aerobic and Anaerobic Exercises

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Abstract

Objective: 18 university students, who have been kept sedentary and whose ages are 21,6 years averagely, have participated, voluntarily, in this study in order to inspect for the acute responses of the immune system to the aerobic and anaerobic exercises.

Method: The Max VO2 values of the volunteers were determined using the Astrand Bicycle Ergometer testing method. The volunteers were subjected to aerobic exercises using 50% of Max VO2 for a time period of 45 minutes, and then to anaerobic exercises using 120% of Max VO2 until they exhausted. In the study, venous blood samples of the volunteers were taken before exercises, immediately after the exercises and 24 hours after exercises respectively; and therefore, the levels of cellular immune, T-lymphocyte and B-lymphocyte were examined accordingly. The statistical analyses were performed using One-Way ANOVA testing method.

Result: Meanwhile, whereas the differences in the levels of T-lymphocyte, B-lymphocyte and components of the cellular immune measured immediately after exercise and 24 hours after exercise were found meaningless when compared to the levels obtained prior to exercises for the aerobic exercises ($p>0,05$), increased levels (leukocytosis, lymphocytosis, neutrophilia, monocytosis, and B-lymphocyte) obtained immediately after the exercises, and especially the decrease in the level of T-lymphocyte were meaningful for the anaerobic type of exercises ($p<0.05$). Therefore, decreased levels obtained 24 hours after the anaerobic exercise (for leukopoenia, lymphopenia, neutropenia, B-lymphocyte), and increased levels for T-lymphocyte were considered statistically meaningful. When both type of exercises were compared to each other, whereas significant differences were found in the levels of leukocyte, monocyte, neutrophilia, basophil, T-lymphocyte, and B-lymphocyte immediately after the exercises ($p<0,05$), no meaniningful difference was observed for eosinophilia ($p>0,05$).

Conclusions: As a result, it has been assumed that intensive and exhausting type of exercises have been placing much more effect, immediately after exercise, on the elements of the cellular immune system than the moderate type of exercises, and meanwhile it might be resulted from the leukocytes those entering the circulation system from the marginating pool through demargination, and also from the damages occurring in the organism. It has been thought, on the other hand, that the decrease observed 24 hours after the exercises was caused possibly by the intensive and exhausting type of exercises those applying suppression on the components of the immune system.

Key words: Acute effect, immune system, aerobic, anaerobic, exercises

Introduction

It has been known for a long time length that making exercises is beneficial in physical aspects, and they affect the condition of health positively and use their role effectively for defending oneself against some diseases[1,2]. The exercises are also considered among the physiological and psychological factors those influencing our health such as sleep, diet, stress, etc.[3,4].

Therefore, the exercises causing some changes on the parameters of the immune system have made the researchers to turn their heads towards this subject[5,6], and a great many studies have been published recently about the effects of the exercises on the physical fitness and immune response[7,8,9,10,11,13]. When it was taken into consideration that a stress condition exists during the intense

exercises, it is certain that the immunological responses against exercises shall not to be different from the reactions those to be observed during injuries of thermal or traumatic type; operations; and acute myocardium infarcts[12,14].

During the exercises, different amounts of stress hormones are secreted into blood depending on the intensity of the exercises[15.16.17]. Aforesaid hormones become rather effective on the sub-groups leukocyte and lymphocyte in blood. Whereas such an effect cannot be observed in moderate density (in a level of 50% of Max.VO2) after an exercise application, it comes into being in maximal density (as 80 to 90% of Max.VO2) as neutrophilia, lymphocyteos and monocyteos after an exercise[12].

It has been claimed in various studies that the exercises applied regularly in moderate and light intensities strengthen the immune system, decrease the risk of respiratory channel infections, and perform its protective barrier service against the stresses such as depression[18,19]. It has been considered, on the other hand, that the exercises of irregular, intense and long term types have caused deteriorations in the immune system, and increased the risk of having been caught to some infection diseases and also the frequency of allergies[20,21,22].

Although an increase has been observed for the numbers of T and B lymphocyte when the sub-groups of Lymphocyte were examined, no change has been found in the relative levels of percentages[11,12]. Not only is it important to know how the exercises affect various parameters of the immune system, but also it is important to realize in what points the exercises may be beneficial or otherwise harmful to individuals in clinical aspects. This study has been carried out, therefore, in order to reveal what type of exercises would have more beneficial effects on the immune system of the individuals particularly those making exercises only for their health by determining the effects of aerobic and anaerobic exercises on the cellular immune system.

Material and method

Subjects (Volunteers)

18 university students, who have been kept sedentary and whose ages are 21,6 ±1,6 years averagely, with heights of 174,78 ±6,03 cm and weights of 69,39 ±7,15 kg on an average have participated, voluntarily, in this study. The subjects were picked out carefully from the ones who have no background of any kind of infection, and all of them were subjected to through physical inspection.

First of all, the contents of the study were explained in detail to the participants of the study, and their permits, informing their willing participation in the study, were obtained thereby. The study, therefore, has the approval of the Ethics Board of the Seljuk University. We have this study followed the Helsinki Declaration.

Initially, the protocol of aerobic exercise prepared was applied to the subjects. And then, the protocol of anaerobic exercise was applied to the same subjects. After applying both exercise protocols, the leukocyte formulas, and the levels of ANAE positive and negative lymphocyte were examined accordingly.

Determining Maximum Oxygen Consumption (Max VO_2)

The Max VO_2 levels of the subjects involved in the study were measured using the Astrand Bicycle Ergometer testing process[23]. The ergometric bicycle exercise was applied, and a brand Polar pulse tracking instrument was used during exercises for monitoring pulse rates.

Exercise Protocol

Aerobic Exercise (A); The volunteers were subjected to bicycle exercises at a level of 50% of Max $V0_2$ for a period of 45 minutes.

Anaerobic Exercise (AA); The volunteers were subjected to bicycle exercises at a level of 120% of Max $V0_2$, and until they exhausted. They used, during both exercises, brand Monark Ergomedic, model E5 ergometric bicycles.

In the study, the venous blood samples of the subjects were gathered before exercise, immediately after exercise and 24 hours after exercise, and the acute effects of the aerobic and anaerobic exercises were examined thereby.

Blood sampling

For the aerobic and anaerobic exercises, blood samples were gathered, before exercises, in ES1 tubes, then after ES2's in the tubes with EDTA, in normal tubes as 2 cc venous from the fore arm veins for examining full blood parameters (wbc,

rbc, hgb, hct, plt), erythrocite (x10^6/µl), leukocyte (x10^3/µl), hemoglobin (g/dl), hematocrit (%), thrombocyte (x10^3/µl); and in normal tubes as 2 cc for examining the levels of leukocyte sub-groups (lymphocyte, monocyte, neutrophilia, eosinophilia, basophil). A Roche Sismex 2000 XLI kit/device was used for settling full blood parameters.

Alpha Naphthyl Acetate Esterase (ANAE) Enzyme Demonstration

The levels of ANAE positive lymphocyte in the heparinised blood samples of peripheral blood were determined in order to separate the T and B lymphocytes. Therefore, the ANAE demonstration was performed in the frothies prepared from the blood samples gathered for this purpose. Briefly, the frothies were found in the compound of glutaraldehyde-acetone. 2,4 ml of hex sotys pararosaniline prepared from, mixing in equal amounts, the pararosaniline (Sigma) solution of 5% and the sodium nitride (Merck) solution of 4% was added in the phosphate plug of 40 ml (pH 5.0). Following this process, alpha naphthyl acetate esterase (Sigma) soluted in 0,8 ml acetone (Merck) was added in the hex sotys pararosaniline compound. Then, the pH level of the prepared compound was set to 5,8 using 1 N NaOH. This mixture, which was strained through a filtering paper, was used as a incubation compound. The frothies found were subjected to the incubation compound for 2 hours. At the end of this time period, the frothies were washed using distilled water, and left in methyl green compound of 1%, which was prepared using a acetate plug with a pH level of 4,8, for 10 minutes for nucleus painting purpose. The frothies washed using distilled water were subjected to the series of alcohol and xylol, and then covered up using entellan. 200 lymphocytes were counted within each prepared ready-made drug, and so the levels of ANAE positive and negative lymphocyte were determined as % values. The counting process was accomplished by means of immersion objective through Leica DM 2500 microscope[54].

Statistical Analysis

The statistical analysis procedures of this study was performed using SPSS 10.00 (for Windows) package program in personal computers. The Kolmogorov-Simirnow testing of normality trial was applied to the findings. The comparisons were carried out using the parametrical tests since the findings have shown a normal distribution. The comparisons of time intervals of measurements were accomplished by means of Repeated Measure Anova. The Tukey HSD method among Post-Hoc tests was applied, therefore, in order to find out which measuring time has caused the differences. The meaningfulness's relating to the relevant differences were investigated at the levels of $p<0,05$. The independent simple t test, meanwhile, was applied so that similar times of two different exercises could be compared to. The level of meaningfulness was designed as $p<0,05$.

Result and Discussion

Some different results have been obtained in the studies accomplished relating to the effects of the exercises on the immune system. However, these results couldn't be based on single one reason[35.48]. In addition to many factors such as the groups being different, exercise program, and the type, time interval and intensity level of the exercises applied, also some other factors those haven't been yet known could affect the results thereby[24].

In this study, when all of aforementioned factors have been taken into consideration, the groups consisting of sedentary individuals were accepted to the study in order to minimize, as more as possible, the effects of the factors those might be resulted from individual differences and those might influence the results. The average ages of the subjects were determined as 21,6 ±1,6 years, heights as 174,78 ±6,03 cm and weights as 69,39 ±7,15 kg, and $MaxVO_2$ level as 2,91±0,20 L/minutes in this study.

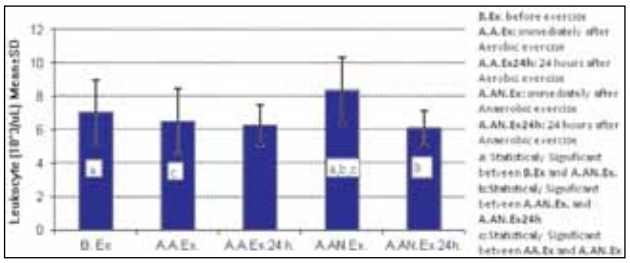

Figure 1. Comparison of Leukocyte Levels

When the leukocyte levels of the subjects participated in the study were observed (see Figure 1), it was determined for the aerobic exercises that there

was no meaningful difference in the levels measured before exercise, immediately after exercise, and 24 hours after exercise ($p>0,05$). For the anaerobic exercise, on the other hand, some meaningful increases were observed when the levels measured before exercise and immediately after exercise were compared to ($p<0,01$). Therefore, when soon after the anaerobic exercise and 24 hours after exercise were compared to, some meaningful differences were found out ($p<0,01$). Whereas meaningful differences were found for the levels taken soon after exercise when similar time periods of two different exercises were compared to ($p<0,01$), it was observed that there was no meaningful difference between the levels of 24 hours after exercise for both type of aforesaid exercises ($p>0,05$).

In the study performed, it has been claimed that after an sub-maximal exercise, there was an increase in the level of leukocyte following the exercise period, and subject levels returned to their normal values 24 hours after the exercise[25]. Another study, therefore, revealed that the number of leukocytes soon after an intensive exercise period of 30 minutes increased from 5390 to 9070, but the number decreased as 70% one hour after the exercise period[26]. It has been claimed meanwhile that in a study accomplished by applying an exercise protocol at an intensity of 75% and above the level of Max VO2, and with moderate time interval the number of leukocytes increased 100%, decreased below 50% of the first level in 30 minutes after the exercise, and also such a situation was resulted from the lymphopenia[27]. In addition, long-term exercises and strength/endurance exercises have also caused considerable changes in the composition and concentration of the leukocyte[28].

This study revealed, therefore, that when the leukocyte levels measured for both type of exercises soon after the exercises were observed, the increase for the exercise of aerobic type was not meaningful, but the increase for the exercise of anaerobic type was meaningful otherwise. It was observed, on the other hand, that the leukocyte levels returned to normal levels 24 hours after the exercises for both type of exercises. As a result of these values obtained by the study, the leukocyte response of the organism to the anaerobic type of exercise soon after the exercises was at very high levels. It has been known well that the exercises those having exhausting/explosion effects and also in high intensities have been causing more much stress when compared to the exercises of strength/endurance and in low intensities, and increased the production of leukocytes depending upon this[29,30]. It has been observed that the increases those occurring after the exercises of anaerobic type have been supported by the forgiven references.

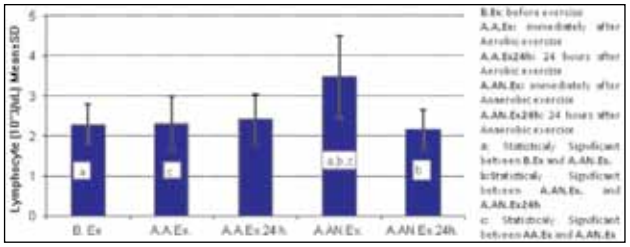

Figure 2. Comparison of Lymphocyte Levels

When the lymphocyte levels of the subjects joined in the study (refer to Figure 2) was observed, no meaningful difference was found when, for the aerobic exercises, the levels of before exercise were compared to both the levels of soon after and 24 hours after the exercises ($p>0,05$). On the other hand, when the levels of before exercises were compared to the levels of soon after the exercises for the anaerobic type of exercises, the increase was considered meaningful ($p<0,01$). When the levels of soon after the anaerobic exercises were compared to the levels of 24 hours after, a meaningful decrease was determined thereby ($p<0,01$). No meaningful difference was found when the levels of before exercise was compared to the levels of 24 hours after anaerobic exercises ($p>0,05$). When similar time intervals of two different exercises were compared to, the increase in the level of lymphocyte measured immediately after the anaerobic exercises was considered meaningful statistically ($p<0,01$).

When the effects of the chronic and acute exercises in the immune system were examined accordingly, the level of increase measured after a long-term exercise such as marathon could be able to rise up even to the levels of 90 to 100%[30]. Therefore, the lymphocyte level fell well below of the level measured before the exercises within 30 minutes after the exercises, and was able to keep this level for about 3 to 6 hours[22,31,32,33,34]. In another study in which the effects of acute exercises on lymphocytes were investigated, the results of measurements ta-

ken after subjecting the strength/endurance sportsmen to some exhausting type of exercises were compared to the levels measured before applying the exercises, and no difference was found in the number of lymphocytes for the exercises [37].

The main duty of the lymphocytes is to perceive the well-being of microorganisms, and also to produce some antibody against them, and then to destroy damaged tissues using the phagocytose method[54]. It has been claimed that the increase of lymphocyte levels has resulted from muscle damages due to exercise and damages has been higher for the exercises with maximal loading[29]. Whereas the lymphocyte levels have shown a meaningful increase statistically after the anaerobic exercises in this study, the increase for the aerobic exercise has been found unmeaningful statistically. Also the lymphocytes have returned, in a way similar to the levels of leukocytes, to their normal levels 24 hours after the exercises. Aforestated results have shown, therefore, that the exercises of the anaerobic types have been causing much more lymphocytes to be produced.

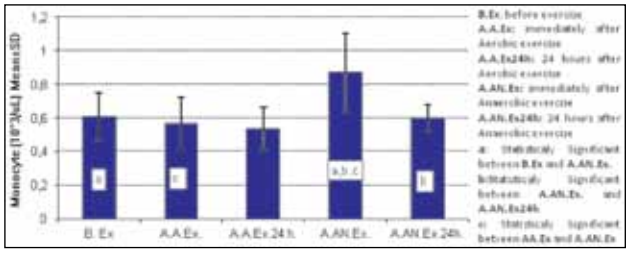

Figure 3. Comparison of Monocyte Levels

When the monocyte levels of the subjects participated in the study were taken into account (refer to Figure 3), no meaningful difference was found for the aerobic exercises when the levels measured before the exercises were compared to the levels obtained soon after the aerobic exercises and also to 24 hours after the aerobic exercises ($p>0,05$). Therefore, some meaningful increase has been observed in the monocyte levels measured soon after the anaerobic exercises when the levels of before the exercises were compared to the levels measured immediately after the anaerobic exercises for the anaerobic type of exercises ($p<0,01$). A meaningful difference was observed when the levels measured soon after the aerobic exercises were compared to the levels obtained after 24 hours ($p<0,05$). No meaningful difference was observed, on the other hand, when the levels of before the exercises were compared to the levels measured 24 hours after the anaerobic exercises ($p>0,05$). When similar time intervals of two different exercises were compared to each other for the levels of soon after the exercises, the increase in the level of monocyte measured for the anaerobic exercises was meaningful statistically ($p<0,01$). Therefore, in another study it was found that the increase in the level of monocyte measured for the continuity of strength endurance exercise increased soon after the exercises, but decreased again 24 hours after the exercises[29]. Another study shown that the level of circulating monocyte measured after the exercises increased continually for a period of several hours, the level of total increase was approximately 30 to 90% generally, and some kind of exercises could be able to increase such an increase up to about 100 to 150 %[31]. Meanwhile, in another study it was found that the level of monocytes measured soon after the exercises with moderate intensity returned to the beginning levels accordingly. For the long-term and high intensity exercises, on the other hand, the numbers of monocytes were in high levels for a time length of 24 hours[36]. The study accomplished has shown that the level of monocytes measured immediately after the anaerobic type of exercises increased at some level, such an increase was much more than the increase obtained for the aerobic type of exercises, and therefore, the level of monocytes returned to normal levels in 24 hours following the exercises. It was observed that the exercises of anaerobic type have much more triggering effects on the production of monocytes.

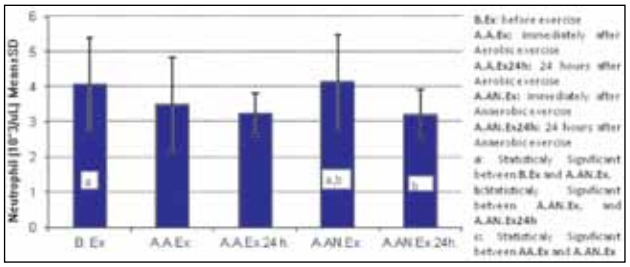

Figure 4. Comparison of Neutrophilia Levels

When the neutrophilia levels of the subjects participated in the study were observed (see Figure 4), a meaningful increase was found in the level of ne-

utrophilias before the exercises and soon after the exercises, and a meaningful decrease 24 hours after the exercises for the anaerobic exercises ($p<0,01$).

Neutrophils usually make up 50-70% of circulating white blood cells and serve as the primary defense against infections[37]. The neutrophilias take their place among the leukocytes those responsing the exercises at high levels[38]. The level of leukocytes has developed rapidly for the sportsmen those applying some activities with short-term intensity. The level, therefore, has returned to normal ranges in 30 minutes after the exercises. The time period has increased up to 24 hours for long-term and low intensity exercises[36]. It has been claimed, on the other hand, that the intensity of exercises has so much great effects on the oxidative stress of blood, and, depending on this condition, the neutrophilias would possibly be exposed to oxidation following the exercises[39]. The killing capability of the neutrophilias after the exercises applied in 1 moderate intensities for one hour has sustained at high periods up to 6 hours[40]. Another study revealed some increases following a sub-maximal exercise in the level of neutrophilias after the exercise, and relevant levels returned to normal ranges in 24 hours following the exercise[41].

It was claimed for another study that the neutrophilia functions have shown, after a running activity of 20 kilometers, some gradual decrease during 3 days[32]. Some evident changes would occur, during the exercises, also for the neutrophilia which is among the parameters of the immune system. The exercises have acute effects on the function of neutrophilia. The chemotaxis, phagocytose and oxidative burning in the neutrophilias have increased somewhat even for the exercises with low intensity. The functions, except for chemotaxis and degranulation, have been suppressed following a high intensity activity[22,27.40.42].

The study carried out revealed that the differences in the level of neutrophilia have been increasing in a way similar to the other leukocyte components after anaerobic type of exercises. Therefore, the increase in the level of neutrophilias could be due to the response of neutrophilia functions depending on the intensity of the anaerobic type of exercises[37], and the decrease after 24 hours could be resulted from suppressing other functions except for chemotaxis and degranulation[22].

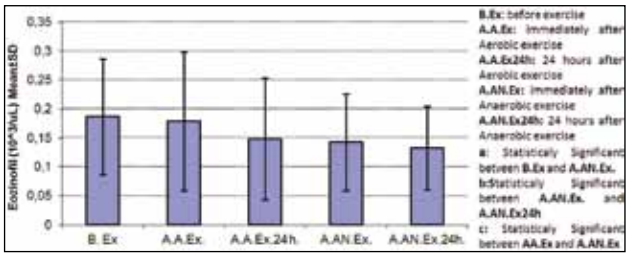

Figure 5. Comparison of Eosinophilia levels

It was found, when the levels of eosinophilia of the subjects joined in the study were examined that (refer to Figure 5), there was no meaningful difference in the levels measured before the exercise, soon after the exercise and 24 hours after the exercise respectively, and also when the similar time periods of two different exercises were compared to each other for aerobic and anaerobic type of exercises ($p>0,05$).

That what kind of a response the eosinophilia has shown for different type of exercises and how they work during the exercises couldn't be identified yet[36]. The study performed revealed that the eosinophilia has shown no considerable difference for both exercise types. It has been assumed, however, that the tendency of decreasing in the levels measured soon after and 24 hours after the anaerobic type of exercises might be due to the intensity degree of the exercises.

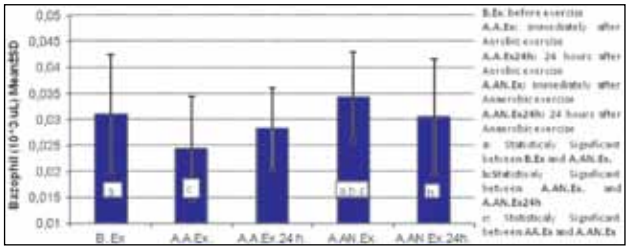

Figure 6. Comparison of Basophil Levels

It was observed, when the levels of basophil of the subjects involved in the study were examined that (refer to Figure 6), there was no meaningful difference in the levels measured before the exercise, soon after the aerobic exercise and 24 hours after the aerobic exercises for the aerobic type of exercises ($p>0,05$). For the anaerobic type of exercises, therefore, when the levels of before exercise and soon after exercise were compared to, a meaningful increase was found in the levels of monocyte measured soon after the exercises ($p<0,01$). A meaningful decrease was identified when the

levels measured soon after and 24 hours after the anaerobic exercise were compared to ($p<0,05$). When the similar time periods of two diffrent type of exercises were compared to, on the other hand, the increase in the level of basophil measured soon after the exercises was considered meaningful for the anaerobic type of exercises ($p<0,01$).

The response of basophil and mast cells to the exercises hasn't been lightened clearly yet[22,33.34.43]. Still the study revealed that the production of basophil was much higher after the exercises of anaerobic type, and the difference was not meaningful for the aerobic exercise. Such a result has shown that the production of basophil was much more high during the anaerobic exercises.

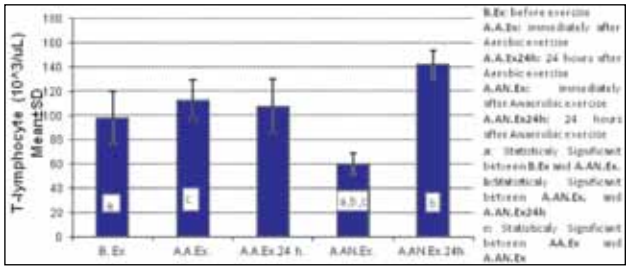

Figure 7. Comparison of T-lymphocyte Levels

When the levels of T-Lymphocyte in the subjects involved in the study were observed (see Figure 7), whereas no meaningful difference was determined for the time periods of the aerobic exercise ($p>0,05$), some meaningful decrease was observed soon after the exercise for the anaerobic exercise in comparison with the levels of before exercise, and some meaningful decrease was found in a way similar to the levels of 24 hours after the anaerobic exercises ($p<0.001$). When similar time periods of both different exercises were compared to, whereas some meaningful increase was observed in the levels measured soon after the exercises for the anaerobic exercises ($p<0.001$), there was no meaningful difference between the levels obtained after 24 hours.

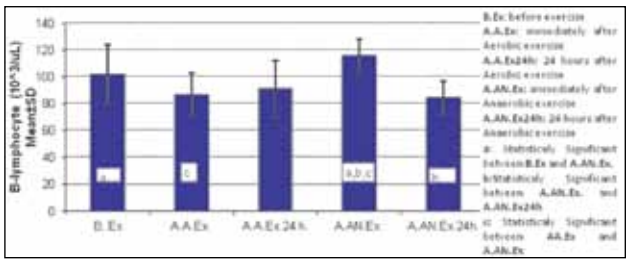

Figure 8. Comparison of B-lymphocyte Levels

Whereas, when the levels of B-Lymphocyte of the subjects involved the study (see Figure 8), we found no meaningful difference between the time intervals of measurement for the aerobic exercises ($p>0,05$), it was determined for the anaerobic exercises, when compared to the levels of before exercise, that there was some meaningful increases soon after the exercise, and decreases 24 hours after the anaerobic exercises ($p<0.01$). When similar time periods of both different exercises were compared to each other, on the other hand, there was meaningful differences in the levels taken soon after the exercise, and it has shown much more high activity for the anaerobic exercises ($p<0.01$).

Although the levels of T-lymphocyte for sub-maximal exercises have shown somewhat increases, the levels of B-lymphocyte couldn't been affected so much[44]. The cell levels of T-lymphocyte were observed after the exercises in maximal intensity those lasted 30 minutes during the studies carried out, and too much increase was observed in the levels of T-lymphocyte[40.,45]. Whereas no difference was identified in the levels of lymphocyte sub-groups for the low-intensity exercises, the researchers found an increase in the level of B-lymphocyte, and reverse of this condition in the levels of T-lymphocyte / B-lymphocyte for intense and hard type of exercises[46]. A study carried out after applying exercises in moderate intensity revealed somewhat increases in the levels of the lymphocyte sub-groups, and relevant increases returned to normal levels 40 minutes after the exercises[47]. Meanwhile, another study claimed a decrease in the level of T-lymphocyte, and increase in the level of B-lymphocyte following the exercises applied in moderate intensity[48]. A study accomplished on sedentary males whose average ages were 20.8 revealed an increase in the level of B-lymphocyte, but a decrease in the level of T-lymphocyte within 1 minute after the exercise when the blood samples those taken before exercise, after 1 minute, 30 minutes, one hour and 2.5 hours respectively were analysed for the exercises carried out in a level of 60% of Max $V0_2$. It was claimed, therefore, that high cortisol level of blood might have caused such a condition[34]. Another study, accomplished after the sub-maximal type of anaerobic exercises, indicated a decrease in the number of the cells of T-lymphocyte both during and after the exercises, and an increase in the num-

ber of the cells of B-lymphocyte both during and after the exercise [49,50,51].

Whereas this study revealed no difference in the number of lymphocytes for aerobic exercises, the study indicated a decrease in T-lymphocyte and an increase in B-lymphocyte for the anaerobic exercises. It was found, on the other hand, that the numbers of both T and B lymphocytes returned to base levels 24 hours after both type of exercises. An aforesaid result has shown a parallelism against the results obtained beforehand.

It has been assumed, therefore, that though the reason for fast changes in the number of the lymphocyte couldn't be explained clearly, it was possibly resulted from the changing numbers of the sensor receptors in these bodies. B-lymphocyte, meanwhile, has much more intensity of β adrenergic receptors than the intensity in T-lymphocyte[52].

As a result, it was determined that the exercises with anaerobic characteristics have been much more intense and exhausting than the exercises with aerobic characteristics, and caused much more stress in the organism, and thereby all of the sub-groups of the cellular immune system responsed in a gradually increasing way to the exercises with anaerobic characteristics. It has been assumed, therefore, that such a variation could be possibly resulted from the damages occurring in the organism following some exhausting type of exercises, and particularly from some changing immune responses due to oxidative stress to be developed depending on the acute exercises, and the free radicals produced by the oxidative stress. Meanwhile, the increases those occurring soon after the exercises could be based on the leukocytes those beginning to circulate in the body from the marginating pool through demargination. It has been claimed, meanwhile, that the decreases observed 24 hours after the exercises have been probably resulted from the intense and exhausting type of exercises those suppressing the components of the immune system. The reason for the considerable response of the cellular immune system to the exercises of aerobic type is due to the aerobic type of exercises which developed stress in much more intensities.

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Effects of Selected Combined Training on Muscle Strength in Multiple Sclerosis Patients

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Abstract

The purpose of this study was to determine the effect of eight weeks combined training on muscle strength in multiple sclerosis patients. Twenty volunteers men were randomized into two groups, experimental group (N =10) and control group (N=10).The experimental group participated in selected combined training program 3 times a week for 60 minutes and the control group did not participate in training protocol and performed routine program. Participants completed pretest (included testing on all muscle strength measures: chest press test, knee extension and paddle test), before begin of the intervention and after 8 weeks, completed posttest. The data were analyzed with SPSS18 software and t- test for paired samples significant with level at (P≤0/05). The result of this study showed that combined training on all muscle strength measures in experimental group were significantly increased (P<0/05). But improvement in all muscle strength measures in control group MS patients did not significantly increased (P>0/05). However, the result suggests that combined training program can increase muscle strength in multiple sclerosis patients.

Key words: combined training, multiple sclerosis, and muscle strength.

Introduction

The Multiple Sclerosis (MS) is the most prevalent disease of the central nerve system. MS is a chronic disease which effects on different aspects of individual life.[1] The prevalent symptoms of MS include reduction of ability in the walking and balance, increase of skeletal muscle weakness and tiredness that leads to reduction of movement, and the reduction of movement in these individuals leads to atrophy of muscular fibers, which the consequence is the muscular fibers reduction of slow twitch fibers [2].

MS can have a negative impact on both physical and psychological well being [3,4], and individuals with this disease often report lower quality of life scores than when compared to healthy individuals [3]. Fatigue and depression levels are higher in MS patients than healthy individuals, and these conditions may negatively impact upon quality of life. However, participation in regular physical activity has been suggested to positively influence feelings of fatigue [5,6] and depression [7], as well as modify quality of life [8,9] in persons with MS. Fatigue is the most common symptom reported by persons with MS [3,10], and has been negatively associated with quality of life scores [11]. In many MS patients show reduced physical activity levels and suffer from inactivity- induced muscle atrophy and loss of muscle strength, reducing daily life physical functioning as indicated by Motl et al.[12] To date, resistance training may also improve contractile characteristics, cellular respiration, quality of life and walking speed and distance, which have been reported to be deficient in MS.[13,14,15,16] Cross-sectional analyses in non-MS populations suggest that individuals who participate in regular exercise are less likely to suffer from depression [17]. If regular physical activity also positively influences depression in persons with MS, then it follows that associated improvements in quality of life may be observed.

As a consequence, MS patients are neither able to fully activate muscles in the lower limbs [18-19] nor to drive active motor units at high firing frequencies (rate coding) [20]. Accordingly, the muscle strength of MS patients is 30-70% lower compared to healthy control subjects, stating that muscle weakness is a common symptom of MS [21-19]. Strength training has been shown to increase the

neuromuscular activity in skeletal muscles through the use of surface electromyography [22].

Chronic mild to moderate stroke patients often have a non-paretic and paretic body side caused by upper motor lesions resulting in asymmetric muscle strength.[23,24] Because in a healthy population resistance training induces greater neuromuscular adaptations in weaker versus stronger muscles,[25] progressive unilateral resistance training has already been applied in stroke patients to optimize training stimulus. As observed by Chung et al., many MS patients also develop asymmetric leg strength.[26] However, given the underlying disease mechanisms such as increased central conduction time[27] and reduced motor unit recruitment and firing rates,[28] it is unclear if unilateral strength training in MS has similar effects.

In a study of the time of walking at short distances (7.62m) 12% and high distances (500m) 16% and 10% showed increase of knee flexor and had no effect on knee extensor, aerobic power, balance, Expanded Disability Status Scale (EDSS) and life quality of these patients [29].

De Souza–Teixeira et al have studied of the effect of an eight-weeks progressive resistance training on different strength manifestations, muscle mass and functionality in multiple sclerosis. The exercise was done during 8 weeks 2 times in a week. Intensity ranged from 40-70% of their maximum voluntary contraction. After 8 weeks strength training period, isometric strength 16%, muscles endurance 84%, and maximum power 51%, muscular hypertrophy from slice 6.27 to slice 11.67 of both things and functionality improved significantly [30].

Widener et al have studied resistance training effect on the balance on functional capacity of 16 of MS patients. They divided the patients to two groups of light and heavy, the light group wore a waistcoat with the weight of 0.23 kg and the heavy group wore a waistcoat with a weight of 1.5% of body weight while training. The results from investigation showed improvement in balance and functional capacity at the both of groups [31].

Dalgas et al have studied effect lower extremity progressive resistance training during 12 and 24 weeks on improvement of muscle strength and functional capacity of 38 MS patients. The exercise group completed a biweekly 12-week lower extremity progressive resistance training program and was afterward encouraged to continue training. After the trial, the control group completed the progressive resistance training intervention. Muscle strength of the knee extensors and functional capacity improved after 12 weeks of progressive resistance training in the exercise group, and the improvements were better than in the control group. The improvements of knee extension and functional capacity in the exercise group persisted at follow-up after 24 weeks [2].

Current research is demonstrating overwhelming benefits when people with Multiple Sclerosis exercise. Aerobic exercises and strengthening program improve maximal aerobic capacity [32] and muscular force production, power, work and endurance [33, 34].

Further benefits of exercise for people with MS include improved fatigue, cognitive ability and energy [35, 36]. Published exercise program have shown the benefits of specific strengthening regimens [37, 34], aquatic [33] and aerobic program [38, 32].

The duration of this program vary from four to fifteen weeks, with most participants attending three times a week. In a single case study of a person with MS Van Sint Annaland & Lord (1999) showed that a combined program of aerobic, strengthening and balance exercises was beneficial but again the participant attended the program three times a week over a five-month period [39].

Combined training is advanced type of exercise which is not specified its effects on the physiological adoptions of body, few researches used the combined training their executive protocol was executed at home and was not under the observation and gathered information was the result of participants feeling in the research, which the results of research should be studied carefully. Also primary results show that the tolerance of MS patients to combined training is better than endurance and resistance training and also this should be studied carefully. So with regard to existence of intensive protocols and the number of different frequencies and alternations in this type of exercise, extensive studies should be done to all of the aspects related to this way of exercise be reviewed. To the authors' knowledge the reported resistance training studies in MS all use 'classical' bilateral training methods.[21,22] Unilateral resistance training applying relative workloads to investigate

strength gains in weaker versus stronger legs has not been applied in this population yet [13].

The present study compared functional capacity, balance and muscle strength in persons with MS who did regularly participate in physical activity. It was hypothesized that persons with MS who participated in regular physical activity would report favorable functional capacity, balance and muscle strength when compared to those with MS who were classified as Non-exercisers.

The purpose of this study was to assess the effects of a 8-week selected combined training on muscle strength in subjects with EDSS. So researcher wants to answer following question: Does the combined training increase muscular strength of MS patients?

Methods and Materials

Twenty of MS male patients, free from any other known disease, were recruited while attending a selected combined training at Mazandaran in Iran. All subjects participated in daily physical activity for six months prior to the study (3 times per week). EDSS score in the participants were ranged from 2 to 3.5, indicating moderate disability and consumed interferon α. Subjects gave informed written consent prior to participation.

The volunteers were randomized into two groups, experimental group (N =10) and control group (N=10).The experimental group participated in selected combined training program and the control group did not participate in training protocol and performed routine program. Before testing, each participant completed a familiarization period (2 sessions), which included testing on all muscle strength measures: chest press test, knee extension and paddle test. After the familiarization period, participants completed pretest before begin of the intervention and after 8 weeks, completed posttest. The scores of pretest and posttest were registered by researcher. All testing sessions were performed at approximately the same time of day.

Procedures

The muscle strength training consisted of eight weeks of selected combined training performed three times per week. Subjects in experimental group performed four different exercises (combined training) after 5 minutes warm up.

A training protocol can be described in terms of sets, repetitions and load. Between set and exercises a rest period of approximately 2-3 minutes was allowed. The program was to increase the absolute level of peak torque of the muscles throughout repeated maximum strength. The principle of the program was to have low-load, relatively long pauses of rest between exercises and at least 1 day of rest between the training sessions. The intention was to perform 3 sets of exercises, with 10 repetitions of each exercise per set (3x 10), and exercised at least 3 days per week for 60 to 90 minutes per session. If the subjects managed to perform the exercises against resistance, the load throughout the training was 40% to 50% of 1 repetition maximum, defining 1 repetition maximum as the maximum load a subject was able to sustain throughout the range of motion.

The resistance training protocol was adopted from American College of Sports Medicine's resistance-training guidelines and recognized criteria for load assignment in older individuals.[40] The training protocol for experimental group were included strength exercises, aerobic fitness (stationary cycling) and balance exercises, and were done three times per week for eight weeks under the supervision of one physiotherapist. The resistance used in the strengthening exercises was progressed by increasing the number of repetitions performed.

Statistical Method

Data were expressed as mean and standard deviation. Data analysis was performed using pretest to posttest changes that assessed by t- test for paired samples. $P \leq 0.05$ was considered statistically significant. SPSS version 18.0 was used for all statistical analyses.

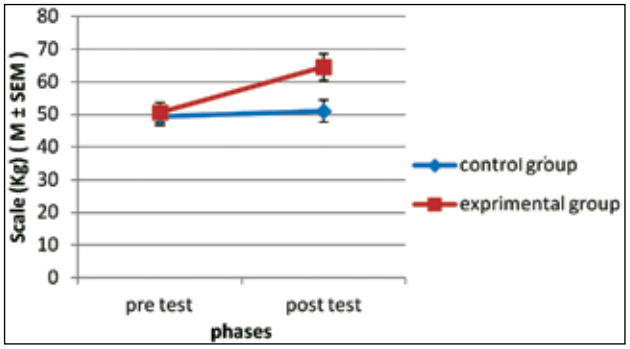

Figure 1. Mean ratings of pretest and posttest during chest press test

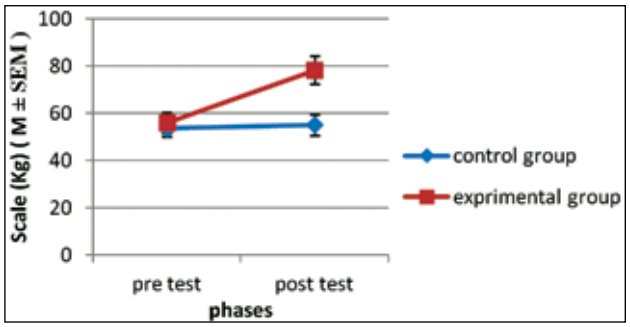

Figure 2. Mean ratings of pretest and posttest during extension knee test

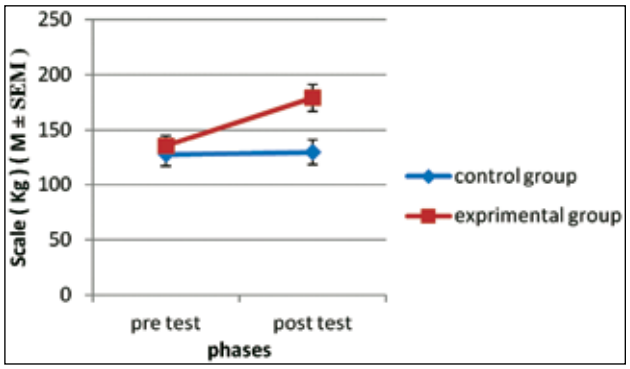

Figure 3. Mean ratings of pretest and posttest during paddle test

Results

There were no differences between the groups in any of the pretest measures. All patients in the experimental group were able to complete 24 sessions during the 8-week period.

The Figure1 showed the relationship between the pretest and posttest scores in chest press. Correlation of the experimental group between pretest (50.60±3.07) and posttest (64.50±4.16) was statistically significant and for the control group did not significant changes between pretest (49.45±2.74) and posttest (50.95±3.40) in chest press test (P≤0.05). The Figure 2 showed the relationship between the pretest and posttest scores in knee extension test. Correlation of experimental between among pretest (55.89±4.36) and posttest (78.23±6.03) was statistically significant and for the control group did not significant changes between pretest (53.48±3.54) and posttest (55.00±4.39) in knee extension test (P≤0.05). The Figure 3 showed the relationship between the pretest and posttest scores in paddle test. Correlation of experimental group between pretest (135.70±8.87) and posttest (179.10±12.21) was statistically significant and for the control group did not observe significant changes between pretest (127.65±10.62) and posttest (129.62±11.31) in paddle test (P≤0.05).

Pretest and posttest results for the measures of muscular strength tests were presented in above Figures. No differences between training modes (resistance-exercise and routine exercise) were found for any of the measures of muscular strength tests in pretests. However, analysis of the data found that all measures of experimental group significantly improved with 8- week combined training protocol.

Discussions

It is obvious that MS patient have deficits in various areas of physiological profile. In theory, optimal rehabilitation aiming at a normalization of the physiological profile would therefore require the application resistance training. Presently, the concept of combined training is however so sparsely investigated in MS patients that solid evidence-based recommendations cannot be provided [13].

In this study, significant increases for experimental group in chest press, extension knee and paddle test were found and no significant differences for control group in chest press, extension knee and paddle test observed. These changes are more indicative of normative tests of subjects without known impairments and thus support our hypothesis. Furthermore, our subjects showed improvements in chest press, extension knee, paddle test and isotonic muscle strength.

Limited research has been conducted on strength training in persons with MS. Kraft et al, found improved function, strength, and psychosocial well-being in 8 MS patients who strength trained for 3 months [41]. Debolt and McCubbin found that a home-based resistance-training program was well tolerated by persons with MS and improved their leg extensor muscle power [42]. McCartney et al. found improvements in arm (19_/34%) and leg (11_/50%) strength after a nine week strength-training program [43]. In addition, Spector

et al. found large increases in muscle strength in post polio patients [44]. For example, increases in knee extension (41_/61%) and elbow extensor (54_/71%) strength were observed following 10 weeks of strength training [44]. All subjects in this study completed the 8-week program with no

appreciable musculoskeletal problems or exacerbation of MS symptoms. In addition, isotonic strength indices improved with training, suggesting that persons with MS can safely participate in a resistance-training program. These results are in agreement with those reported [1, 5, 15, 30, 45].

However, in that they observed improvements in muscle strength as a result of combined training program. In neither study, cartel et al. found that 12 weeks of twice weekly combined training were well tolerated, that muscle strength was improved, and that the level of effect of walking was reduced (46). In addition, Romberg et al. and Surakka et al. found that combined training was well tolerated by MS patients. Surprisingly, none or only small (10%) improvements were seen in knee extensor and knee flexor muscle strength after the training intervention, and no significant differences were noted when compared to the control group [29, 46].

The results of this preliminary study suggest that combined training program cause increase in muscle strength in MS patients. Brief moderate physical exercise improved physical fitness in the study by Bjarnadottir et al. [47].

The physiological reasons for the improvement in strength observed in this program were most likely due to neural changes. In the normal population it has been suggested that short-term training program, similar to that in the current study, have lead to more efficient muscle recruitment, increased neural activation and motor unit synchronization and a decrease in golgi tendon organ inhibition [48]. Harvey et al reported improvements in quadriceps maximum voluntary contraction (MVC) of 28-48%, this was not significant, which is probably a result of a small sample size (n=7) and suggested that people with MS undergo neuromuscular adaptations during strengthening program [37]. A further reason for observed changes in muscle strength in people with MS may be due to increased willingness and confidence of participants to participate in physical activity [34].

In this study, the isotonic strength in chest press, knee extension and paddle test improved significantly after training for experimental group. Although not statistically significant were observed in control group after routine daily training for all muscle strength tests. Also, results suggested that the routine daily training did not effect on muscle strength in MS patients. However, with a small sample size, additional studies are needed to confirm these observations. In addition, the combined training protocol used in this study may not have highlighted the full benefit or dangers of strength in persons with MS. Strength gains observed in this study should be interpreted cautiously because subjects trained isotonically, whereas strength testing were isotonic and performed on major limbs; therefore, the strength gains reported may not represent the entire strength. Despite these limitations, there were significant improvements in all parameters in experimental group that performed combined training protocol for 8- week. More studies that include muscle strength measures, with larger sample size, EDSS with high score, and increased duration and intensity of training, are recommended.

In conclusion, this paper reported on the effects of a combined training program on muscle strength for in MS patients. The results of the present study suggest that an 8-week selected combined training program can increase muscle strength in MS patients.

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Factors associated with preventive practices for cervical cancer in women in Serbia: Data from the National Population Health Survey in Serbia 2006

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Abstract

The aim of this study was to examine factors associated with behavior related to reproductive health and undertaking preventative measures among women in Serbia.

Methods: This study represents a secondary analysis of the National Population Health Survey in Serbia in 2006. Total of 5314 women aged 25 to 64 years completed the interview. Univariate and multivariate logistic regression analysis were performed to assess relationships between possible risk factors as independent and regular checkups at gynaecologist, and the last Pap test as dependent variables. **Results:** Women aged 55 to 64 years are least likely to go for check-ups at gynaecologist compared with younger women (OR= 0.21, 95%CI, 0.17- 0.26). Women with higher education are significantly more likely to use preventive services and undergo Pap test on their own initiative than women with primary and secondary education. Women with the highest standards of living are significantly more likely to use preventive services and more often undergo Pap test on their own initiative than women with lower standard. (OR= 2.43, 95%CI 1.55-3.81). Type of settlement is significant for the preventive activities.

Conclusions: Our study showed that sociodemographic factors were significantly associated with preventive practices for cervical cancer. Younger women, those with higher level of education and women of higher socioeconomic status were more likely to undertake preventive measures.

Key words: cervical cancer, reproductive health, preventive practices, contraception

Introduction

Cervical cancer is increasingly common in younger women, between the 35th and 50 years. Cervical cancer is the second most common malignancy of women in Serbia, after breast cancer, the standardized rate of 27.2 to 100 000 women. Compared with other European countries, the incidence of cervical cancer in Central Serbia is the highest. Regional differences in incidence are significant, with the lowest incidence rate (16.6 per 100,000 women) registered in western and highest rates in eastern Serbia and the region of Belgrade, capitol city (32.5-38.1 per 100,000 women). [1] Mortality rates from cervical cancer are high and place Serbia, with mortality rate of 10.1 per 100 000 women, in the second place in Europe, after Romania (13.0). [2].

According to current knowledge, the most important risk factor for cervical cancer is infection with human papilloma virus (HPV). [3] Numerous researches identified also some other important factors associated with increased risk for cervical cancer such as: the chemical factors (smoking), [4] sexual habits (early entry into sexual relations before 16 years of age, promiscuity), [5] [6] factors related to male partners (promiscuity). [7] living conditions, poor socio-economic conditions, [8] immunosuppression (weakened immune system, HIV, conditions after organ transplants), [9] abortion and childbirth in adolescence. [6]

Women at high risk for getting cervical cancer are: women who do not take Pap smear regularly, women with high parity, [10] women younger than 30 years, [11] women who were exposed to intrauterine diethylstilbestrol (DES). There is an

increased risk among women who take birth control pills. Systematic review of 28 studies, which included 12,531 women with cervical cancer, have shown that the relative risk of cervical cancer increases with increasing length of use of oral contraceptives. [3]

It has been shown that public health measures including primary prevention through control of risk factors and secondary prevention including screening for early detection, have significant potential for controlling cervical cancer in population.

A part from pilot projects in some regions, there was no organized screening for cervical cancer in Serbia, so far, only opportunistic screening was implemented. [12] Organized prevention activities and screening included a small portion of the female population (only 2.0%), and there are also marked geographical variation and the type of settlement (5.2% in eastern Serbia, where the incidence of cervical carcinoma the highest). [13] However, many women do not go to regular gynaecological examinations mostly those who have completed childbearing, older women and postmenopausal women from rural areas. According to National Health Survey 7.9% of women from rural areas and 5.0% of women from urban areas have never visited gynaecologist. [13] In the last 3 years 41.8% of women from urban areas have done Pap test and only 25.6% of women from rural areas. [13] In Poland there are also significant differences, women from rural areas participate less in the screening program compared to urban dwellers (15.2% to 8%). [14] A similar situation is in rural areas of Greece, in Crete, 52.1%; a woman has ever done the screening for cervical cancer. [15] In a study of Swedish authors, women in rural areas and those with lower socio-economic status, less responding to calls for Pap testing and have less knowledge of recommendation for screening intervals. [16] The knowledge that women in rural areas have about risk factors for cervical carcinoma, especially of HPV as the main cause, are insufficient and less than women from urban areas. [17] [18]

Lack of knowledge of women in Serbia on reproductive health, poor attitudes of gynaecologists and personal barriers associated with negative experience in primary health care, cause the low priority of preventive practices, both for women and for gynaecologists. [1] [19]. All these factors have led to the fact that about 500 women each year lose their lives in Serbia due to cervical cancer. In 2003, the Council of the European Union for cancer has recommended that the organized cervical cancer screening to ensure all women in all EU member states, as well as two candidate countries, Croatia and Serbia. [20]

The aim

The aim of this study is to examine the prevalence of risk factors for cervical cancer and behavior related to prevention of cervical cancer reproductive health in women aged 25 to 64 years in Serbia.

Materials and Methods

This study represents a secondary analysis of the National Population Health Survey in Serbia (excluding Kosovo) in 2006. conducted by the Ministry of Health of Serbia with financial and technical assistance from the World Bank, World Health Organization, Regional Office for Europe and the Institute of Public Health of Serbia "Dr Milan Jovanovic Batut". [National Health Survey Republic of Serbia. Key Findings: Ministry of Health Republic of Serbia, 2006].

In this research we used two-stage stratified sample of households, registered in the 2002 census. In order to provide statistically reliable estimates of health indicators at the national level. In the randomly selected 7.673 households, 6.156 of them successfully interviewed in the September-October 2006. The household response rate was 80.2%. All members of the interviewed households older than 7 years were eligible for interviews. total of 5.314 women aged 25 to 64 years completed the interview Information on demographic characteristics, health service use, smoking and sexual behavior of adult women were obtained

Dependent variables related to the use of preventive health care practices for cervical cancer and how decisions are made for Pap examination. In the use of health care, we analyzed three variables:

1. zs28dihotom-number of visits for regular checkups with a gynecologist (once in year, once in 2 years, less frequently, not to go)
2. zs36dihotom-last Pap test (within the previous 12 months ago 1 to 3 years, more than 3 years,

more than 5 years, I do not remember, never, I do not know what kind of test)

3. zs37dihotom-decision for the Pap test (on its own initiative, on the advice of your doctor, on the advice of doctors in the screening).

Independent variables

Socio-demographic variables in this study are: sd5interval-age (in years), dk1-education (primary school, secondary school and higher education), dm6-type of settlements (rural / urban), SD5-region (northern region, Vojvodina, the capital, Belgrade, with the southern region and Central Serbia), se122kc-distance from the nearest Health Center (up to 500 m, from 501m to 1 km, 1.1 km to 2.0 km, 2.1 km to 5 km, more than 5 km), wlthind5-socio-economic status was measured by Wealth index (very bad, bad, average, good and very good), dk3-number of children (zero, one, two, three or more).

Behavior related with reproductive health variables are: sp2interval- years of first sexual intercourse (<16godina, from 17 to 19 years, 20 to 22 years, from 23 to 26 years,> 27godina), sp6_1 sp6_2 sp6_3 sp6_4 sp6_5 sp6_6 sp6_7 sp6_95-the use of contraceptive methods (pills, condoms, IUU, coitus interruptus, method of fertile days, the local means of contraception and other methods) and the number of sexual partners in the last 12 months (one, two, three or more) and pu6-smoking (no, occasional and daily).

Statistical analysis

We analyzed the factors associated with regular gynecologic examinations and Pap test as the last and the decision of the Pap test.

Descriptive statistics was performed for each of potential risk factors, regular checkups with a gynaecologist, and the time of last Pap test. Univariate and multivariate logistic regression analysis were performed to assess relationships between the dependent and independent variables. Preventive measures (number of regular control visits to a gynaecologist, and the last Pap test, and reason for undertaking Pap test) were entered in analysis as dependent (resulting) variable, while independent variables were age, education, socio-economic status (measured by wealth index), type of settlement, region, distance from the nearest health centre, smoking, age of first sexual intercourse, use of contraceptive methods (pills, condoms, IUU, coitus interruptus, method fertile days, the local means of contraception and other means of contraception) and the number of sexual partners in the last 12 months. Independent variables, for which the univariate analysis showed statistical significance, were included in the multivariate logistic regression analysis.

Results are presented as odds ratio (OR), and the corresponding 95% confidence intervals (CI). A p-value< 0.05 (two-tailed) was used to establish statistical significance. Analyses were performed using SPSS software package (version 19).

All respondents were informed about the purpose of the investigation and agreed to participate. The Review Board of the Ministry of Health of Serbia and the Institute of Public Health of Serbia approved the study.

Results

Descriptive analysis of risk factors for cervical cancer and behaviors related to reproductive health of women, along with the results of univariate and multivariate logistic regression are presented in Tables 1.2. 3 and 4.

Table 1 presents descriptive analysis and univariate logistic regression for regular check-ups at gynecologist. The analysis showed that the age of women is significantly associated with their decision to undertake regular check-ups at gynecologist. Younger women (aged 25-34 years) go for regular checkups significantly more often, than women in the oldest group (aged 55-64 years) (OR= 0.18, 95%CI 0.15 – 0.22). Women who have completed high school / college, compared to those with primary education significantly more often go for check-ups. Most women with university education (41.1%) go to regular gynecological examinations at least once a year, which is significantly more often than women with only primary education (OR= 4.40 95%CI 3.64- 5.32).

Wealth index is a factor that significantly affects the decision of women to undertake regular annual visits to gynecologist. If the standard of living is higher, women are more likely to go to regular check-ups. Women with the highest standard of living are significantly more likely to go regularly to gynecologist than do those with the lowest standard, (OR= 4.01, 95%CI 3.24- 4.96).

The population of women from urban areas more often go to regular gynecological examinations at least once a year compare to women who live in rural areas, (OR= 0.60, 95%CI 0.54-0.68). According to the regional division, a woman from Belgrade, the capital, most often undergo regular gynecological examinations at least once a year compared to women from northern province, Vojvodina (OR=1.97, 95%CI 1.65-2.35). The greater the distance from the nearest health center, the likelihood of regular check-ups at gynecologist is lower. If the nearest health center is more than 2km away, women are significantly less likely to go to regular visits to gynecologist. Interestingly, women that live more than 5 km from the nearest health center , are not less likely to go to gynecologist compared to those who live less than 500 meters from the health center. Women who had first sex with 17-19 years, significantly more often undergo regular gynecological examinations at least once a year, compared to women who had first sexual intercourse before 16 years of age (OR=1.39, 95%CI 1.17-1.65). Among all analysed contraceptive methods, only users who occasionally use condom more often go to regular gynecological check-up, compared to those that do not apply the condom as a contraceptive method (OR=2.48, 95%CI 1.83-3.36). Smoking is significantly related to decision for the regular gynecological examinations. Women who smoke occasionally are less likely to go for regular gynecological check-ups (OR= .80, 95%CI 0.65-0.99) and the likelihood of regular checkups is even lower for those who smoke regularly (OR=0.57, 95% CI 0.37-0.88). Descriptive analysis and univariate logistic regression for the time of the last Pap test are shown in Table 2. This study showed that the age of women is significantly associated with their decision to go for Pap test. Women in the oldest age group were less likely to go to Pap test compared to younger women (aged 25-34 years) (OR=0.34, 95%CI 0.27 – 0.42). A half of women with a university education undertake Pap test at least once a year,, and are 4 times more likely to do so compared to women with primary education (OR= 4.01, 95%CI 3.24-4.96). Women in the wealthiest quintile (measured by wealth index) were significantly more likely to undertake Pap test, compared to women from the poorest quintile (OR= 5.08, 95%CI 3.88-6.66). Analysis showed that women from rural areas, were significantly less likely to undertake Pap tests compared to women from urban areas (OR= 0.55, 95%CI 0.48-0.64) Women from the region of Central Serbia are much less likely to undertake Pap test regularly comparing to women from northern province, (OR= 0.70, 95%CI 0.59-0.83), and on the other hand women from Belgrade are more than twice more likely to undertake regular Pap test comparing than women from northern province. According to the initiation of sexual activity, women who began sexual activity between 17 and 19 years, go to Pap test more often than those who began sexual activity before age of 16-year, (OR= 1.41, 95%CI 1.15- 1.73). As for the use of contraception, women who use condoms occasionally are significantly more likely to undertake Pap tests less than women who do not take condoms. Women who smoke occasionally or every day are less likely to undertake Pap tests once a year than women who do not smoke. (OR= 0.74 95%CI 0.59-0.93, and OR=0.60, 95%CI 0.36-0.98, respectively).

Table 3 presents descriptive analysis and univariate logistic regression analysis of undertaking Pap test on woman's own initiative as opposed to organized screening. Out of 2636 women, 769 (29.6%) undertook Pap test on their own initiative. Women older than 45 were significantly less likely to undertake Pap test on their own initiative compared to women in age group 25-34 (OR= 0.67, 95%CI 0.52-0.87), The likelihood of undertaking Pap test on one's own initiative increases with the level of education, i.e. women with secondary education were 2.6 times more likely to initiate Pap test, and women with university degree were 4 time more likely to initiate Pap test compared to women with elementary school. Living standard is also significantly associated with initiating Pap tests. The likelihood of initiating Pap test on their own increases with living standard and women pertaining to the wealthiest quintile were more than 4 times more likely to initiate Pa test than women from the poorest quintile. Women from rural settlements, significantly less, than women from urban areas undertook Pap test on their own initiative (OR= 0.51, 95%CI 0.42- 0.62). Women from Central Serbia are less likely to initiate Pap test compared to women from the northern province (OR= 0.53, 95%CI 0.43-0.66). Regarding contraceptive methods, only women who used condom occasionally were more likely to undertake Pap test on their own (OR= 1.84

95%CI1.28- 2.63). Smoking is not significantly associated with the decision to undertake Pap test.

Table 4 presents results of the multivariate logistic regression analysis. Variables, for which the univariate analysis showed significant association (age, education, Wealth index and type of settlement) with preventive practices were included in the model of multivariate logistic regression analysis, as independent variables. Age of women was significantly associated with their decision to go for regular check-ups at gynaecologist. Oldest categories, women aged 55 to 64 years, are least likely to go for check-ups at the gynaecologist, (OR= 0.21, 95%CI 0.17- 0.26). According to the time when they had the last Pap test, only the oldest category of women are significantly less likely to have it in the last year, (OR= 0.39, 95%CI 0.31- 0.50). As for the initiative to undertake Pap test, women older than 35 were less likely to do it on their own initiative, compared with younger women. As for education, women with higher education are significantly more likely to use preventive services and undertake self/initiated Pap test than women with primary and secondary education. Women with the highest standards of living were significantly more likely to use preventive services than those with lower standard. Women pertaining to fourth and highest quintile of wealth index were more likely to undertake Pap test. (OR=1.71, 95%CI 1.0- 2.66, OR= 2.43, 95%CI 1.55- 3.81). Type of settlement is not statistically significant for the preventive practices of women, or the decision to take Pap test on their own initiative.

Discussion

This study was designed to investigate behaviors related to reproductive health that are relevant for the prevention of cervical cancer and preventative measures for cervical cancer, in a representative sample of women in Serbia.

Out of the examined factors (education, age, number of children, Wealth index, type, distance to nearest health center, age of first sexual intercourse, the use of measures of contraception, number of sexual partners and smoking), only education, age, Wealth index and type of settlement showed highly statistically significant association with preventive practices. Multivariate analysis showed that the type of settlement is not statistically significant for preventive activities of women, except for self initiated Pap test where women in rural areas are less likely to initiate Pap test than women from urban settlements.

All of these factors were analyzed in the contexts of preventive measures, regular gynecological examinations and screening for cervical cancer. Few studies have examined the importance of regular gynecological examination for preventive purposes, [**21, 22]** because almost all countries have organized national screening programs.

Our study, similar to some others, [**21]** confirmed the importance of education as factor associated with preventive practices. Most women with university education go for regular gynecological examinations, as well as women with the highest standard of living. The population of women from urban areas more often goes to regular gynecological examinations, as opposed to women from rural areas. Women who had first sexual intercourse at the age of 17 to 19 years, compared to women who had first sexual intercourse before age of 16, more often undergo regular gynecological examinations. Number of sexual partners in this study was not statistically significant, but only 2.75% of women answered the question.

Regarding contraceptive methods used, only condom proved to be associated with preventive practices of women, even though only 37.4% of women used condom in sexual relationship. The percentage of women using condoms during sexual intercourse is close to results from some other studies [23]. **Pizarro [24]** examined the reliability of reports of Pap testing. They came to the conclusion that women, who had undergone only a gynecological examination, were false reporting Pap test, which was confirmed by comparing the medical records of patients with their report. In this study, the same number of women (4.894) claimed gynecologic examinations and Pap tests, but we were not able to verify their statements. This study showed that the age of women is significantly associated with their decision to go for Pap testing. Most women with university education undertake Pap test, as well as women with the highest standard of living. In our study, univariate logistic regression showed that women in rural areas were significantly less likely to undergo Pap

tests once a year, as opposed to women from urban areas. Multivariate logistic regression, however, showed no statistically significant difference. Numerous studies have investigated barriers to the response to screening. [19,21,22,25,26,27,28,29] Wealth index was significantly associated with women's decision to undergo Pap test, even after controlling for education and age. Some studies have Pap screening and response testing, linked with socio-economic status of women. [**21,27,30]** This study, along with some others, identified higher levels of education as an important factor for deciding to undertake Pap screening [**8,27,30].** In this study, age is a significant factor, women in the oldest age groups were less likely to initiate Pap test compared to those in the youngest group.

The importance of this study is that it has used nationally representative data set and has identified factors associated with preventive practices. This study may provide information for further analysis of potential barriers to implementation of National screening and to identify categories of women that should receive special attention for screening.

Limitations

The study was cross sectional, so no conclusion about cause-effect relationships could be drawn. Secondly, data were based on self-reporting, which is characterized by bias and has not included medical records to validate obtained information.

Conclusion

Our study showed that socio-demographic factors were significantly associated with preventive practices regarding cervical cancer screening. Younger women, those with higher level of education and women of higher socioeconomic status were more likely to undertake preventive measures. Type of settlement was not significantly associated, except for the undertaking Pap test on their own initiative, which was more prevalent among urban women, even after controlling for age and education. Use of contrastive was not significantly associated with regular visits to gynecologist and regular Pap test, except use of condoms. Women occasionally using pills or condoms were more likely to undertake preventive measures.

Acknowledgments

The authors wish to acknowledge the Ministry of Health Republic of Serbia because the study is a part of the "National Health Survey of the Population of Serbia" funded by the Ministry of Health of the Republic of Serbia.

Authors' contributions

Ljiljana Antic was included in planning and designing of the study, data acquisition, analysis of the data and drafting the article

Bosiljka Djikanovic was included in planning and designing of the study, analyzing and interpreting the results and drafting the article

Dejana Vukovic was included in interpreting and presenting the results and drafting the article

Bojana Matejic was included in interpreting and presenting the results and drafting the article

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Table 1. Frequencies and univariant logistic regression analysis for Attending gynaecological visits regularly

	Frequencies			Univariant logistic regression analysis	
	Total	**no (%)**	**P value**	**OR (95%CI)**	**P value**
Education	4894	1642(33.6)	<0.000		
Elementary school	1700	310 (18.2)		1.00 (referent)	
Secondary	2457	967 (39.4)		2.91 (2.51-3.37)	<0.001
University degree	737	365 (49.5)		4.40 (3.64-5.32)	<0.001
Age	4894	1642 (33.6)	<0.000		
25-34	1056	538 (50.9)		1.00 (referent)	
35-44	1209	458 (37.9)		0.59 (0.50-0.70)	<0.001
45-54	1389	452 (32.5)		0.46 (0.39-0.55)	<0.001
55-64	1240	194 (15.6)		0.18 (0.15-0.22)	<0.001
Children	4805	1599 (33.3)	<0.000		
0	464	220 (47.4)		1.00 (referent)	
1	3754	1236 (32.9)		0.54 (0.45-0.66)	<0.001
2	453	120 (26.5)		0.40 (0.30-0.53)	<0.001
>3	134	23 (17.2)		0.23 (0.14-0.37)	<0.001
Wealth index	4894	1642 (33.6)	<0.000		
Poorest	822	159 (19.3)		1.00 (referent)	
Poorer	1009	271 (26.9)		1.53 (1.23-1.91)	<0.001
Middle	1042	315 (30.2)		1.81(1.45-2.27)	<0.001
Richer	1031	412 (40.0)		2.77 (2.24-3.43)	<0.001
Richest	990	485 (49.0)		4.01(3.24-4.96)	<0.001
Type of settlement	4894	1642 (33.6)	<0.000		
urban	2737	1051 (38.4)		1.00 (referent)	
rural	2157	591 (27.4)		0.60 (0.54-0.68)	<0.001
Region	4894	1642 (33.6)	<0.000		
Vojvodina	1259	404 (32.1)		1.00 (referent)	
Belgrade	911	439 (48.2)		1.97 (1.65-2.35)	<0.001
Central Serbia	2724	799 (29.3)		0.88 (0.76-1.01)	0.078
Distance from the nearest Health Centre	4894	1642 (33.6)	<0.000		
<500 m	809	301 (37.2)		1.00 (referent)	
501m-1km	920	364 (39.6)		1.01 (0.83-1.24)	0.88
1.1km do 2 km	844	317 (37.6)		0.83 (0.68-1.02)	0.72
2.1km do 5 km	849	280 (33.0)		0.55 (0.46-0.67)	<0.001
<od 5 km	1375	340 (24.7)		1.18 (0.77-1.81)	0.44
Age of first sexual intersourse	4551	1581 (34.7)	<0.000		
>16	813	252 (31.0)		1.00 (referent)	
17 – 19	1968	756 (38.4)		1.39 (1.17-1.65)	<0.001
20-22	1309	428 (32.7)		1.08 (0.90-1.30)	0.415
23-25	358	112 (31.3)		1.01 (0.77-1.33)	0.922
26 an more	103	33 (32.0)		1.05 (0.68-1.63)	0.830
Partners in the last 12 months	121	57 (47.1)	0.086		
1	86	40 (46.5)		1.00 (referent)	
2	18	12 (66.7)		2.30 (0.79-6.70)	0.126
3 and more	17	5 (29.4)		0.48 (0.15-1.48)	0.200

Contraception method used					
Pills	3534	1347 (38.1)	0.011		
No	2648	1003 (37.9)		1.00 (referent)	
Yes, occasionaly	90	40 (44.4)		2.11 (1.28-3.48)	0.003
Yes, everyday	64	36 (56.3)		0.95 (0.80-1.12)	0.532
IUU	3534	1347 (38.1)	0.062		
No	2573	982 (38.2)		1.00 (referent)	
Yes, occasionaly	38	20 (52.6)		1.28 (0.93-1.78)	0.131
Yes, everyday	156	69 (44.2)		0.91 (0.77-1.08)	0.274
Local contraception	3534	1347 (38.1)	0.039		
No	2683	1028 (38.3)		1.00 (referent)	
Yes, occasionaly	31	18 (58.1)		2.25 (0.71-7.12)	0.166
Yes, everyday	12	7 (58.3)		0.92 (0.78-1.08)	0.322
Condom	3534	1347 (38.1)	<0.000		
No	2221	780 (35.1)		1.00 (referent)	
Yes, occasionaly	428	232 (54.2)		2.48 (1.83-3.36)	<0.001
Yes, everyday	185	106 (57.3)		0.90 (0.75-1.08)	0.243
Diafragma	3534	1347 (38.1)	0.235		
No	2680	1036 (38.7)		1.00 (referent)	
Yes, occasionaly	12	7 (58.3)		1.23 (0.46-3.32)	0.677
Yes, everyday	16	7 (43.8)		0.89 (0.76-1.05)	0.162
Method of fertile days	3534	1347 (38.1)	0.007		
No	2218	826 (37.2)		1.00 (referent)	
Yes, occasionaly	337	155 (46.0)		1.19 (0.91-1.57)	0.206
Yes, everyday	234	97 (41.5)		0.95 (0.80-1.13)	0.579
Coitus interruptus	3534	1347 (38.1)	0.001		
No	1982	734 (37.0)		1.00 (referent)	
Yes, occasionaly	399	185 (46.4)		1.14 (0.92-1.42)	0.224
Yes, everyday	423	170 (40.2)		0.93 (0.78-1.11)	0.418
Other contraception method is used	3534	1347 (38.1)	0.124		
No	1086	402 (37.0)		1.00 (referent)	
Yes, occasionaly	2	2 (100.0)		0.46 (0.13-1.67)	0.241
Yes, everyday	14	3 (21.4)		1.07 (0.92-1.24)	0.357
Tobacco smoking	2229	873 (39.2)	0.025		
No	509	224 (44.0)		1.00 (referent)	
Yes, occasionaly	343	125 (36.4)		0.80 (0.65-0.99)	0.039
Yes, everyday	1264	489 (38.7)		0.57 (0.37-0.88)	0.012

Table 2. Frequencies and univariant logistic regression analysis for Undertaking PAPA test once a year

	Frequencies			Univariant logistic regression analysis	
	Total	**no (%)**	**P value**	**OR (95%CI)**	**P value**
Education	4894	1642 (33.6)	<0.000		
Elementary school	1700	310 (18.2)		1.00 (referent)	
Secondary	2457	967 (39.4)		2.39 (2.00-2.85)	<0.001
University degree	737	365 (49.5)		4.01 (3.24-4.96)	<0.001
Age	4894	1642 (33.6)	<0.000		
25-34	1056	538 (50.9)		1.00 (referent)	
35-44	1209	458 (37.9)		0.92 (0.76-1.12)	0.412
45-54	1389	452 (32.5)		0.82 (0.68-0.99)	0.042
55-64	1240	194 (15.6)		0.34 (0.27-0.42)	<0.001
Children	4805	1599 (33.3)	<0.000		
0	464	220 (47.4)		1.00 (referent)	
1	3754	1236 (32.9)		0.76 (0.45-0.66)	0.013
2	453	120 (26.5)		0.61 (0.45-0.84)	0.002
>3	134	23 (17.2)		0.42 (0.25-0.71)	0.001
Wealth index	4894	1642 (33.6)	<0.000		
Poorest	822	159 (19.3)		1.00 (referent)	
Poorer	1009	271 (26.9)		1.31 (0.62-1.77)	0.085
Middle	1042	315 (30.2)		2.57 (1.94-3.39)	<0.001
Richer	1031	412 (40.0)		3.61 (2.75 -4.75)	<0.001
Richest	990	485 (49.0)		5.08 (3.88-6.66)	<0.001
Type of settlement	4894	1642 (33.6)	<0.000		
urban	2737	1051 (38.4)		1.00 (referent)	
rural	2157	591 (27.4)		0.55 (0.48-0.64)	<0.001
Region	4894	1642 (33.6)	<0.000		
Vojvodina	1259	404 (32.1)		1.00 (referent)	
Belgrade	911	439 (48.2)		2.40 (1.98-2.91)	<0.001
Central Serbia	2724	799 (29.3)		0.70(0.59-0.83)	<0.001
Distance from the nearest Health Centre	4894	1642 (33.6)	<0.000		
<500 m	809	301 (37.2)		1.00 (referent)	
501m-1km	920	364 (39.6)		0.81 (0.65-1.01)	0.68
1.1km do 2 km	844	317 (37.6)		0.68 (0.54-0.86)	0.01
2.1km do 5 km	849	280 (33.0)		0.43 (0.35-0.54)	<0.001
<od 5 km	1375	340 (24.7)		1.30 (0.84-2.02)	0.241
Age of first sexual intersourse	4551	1581 (34.7)	<0.000		
>16	813	252 (31.0)		1.00 (referent)	
17 – 19	1968	756 (38.4)		1.41 (1.15-1.73)	0.001
20-22	1309	428 (32.7)		1.16 (0.93-1.45)	0.177
23-25	358	112 (31.3)		1.03 (0.75-1.41)	0.864
26 an more	103	33 (32.0)		1.18 (0.72-1.95)	0.509
Partners in the last 12 months	121	57 (47.1)	0.086		
1	86	40 (46.5)		1.00 (referent)	
2	18	12 (66.7)		1.29 (0.44-3.75)	0.646
3 and more	17	5 (29.4)		1.25 (0.40-3.95)	0.704

Contraception method used					
Pills	3534	1347 (38.1)	0.011		
No	2648	1003 (37.9)		1.00 (referent)	
Yes, occasionaly	90	40 (44.4)		1.11 (0.63-1.97)	0.722
Yes, everyday	64	36 (56.3)		1.07 (0.89-1.30)	0.460
IUU	3534	1347 (38.1)	0.062		
No	2573	982 (38.2)		1.00 (referent)	
Yes, occasionaly	38	20 (52.6)		1.50 (1.05-2.14)	0.025
Yes, everyday	156	69 (44.2)		1.05 (0.87-1.27)	0.614
Local contraception	3534	1347 (38.1)	0.039		
No	2683	1028 (38.3)		1.00 (referent)	
Yes, occasionaly	31	18 (58.1)		16.79(3.67-76.84)	<0.001
Yes, everyday	12	7 (58.3)		1.04 (0.86-1.24)	0.708
Condom	3534	1347 (38.1)	<0.000		
No	2221	780 (35.1)		1.00 (referent)	
Yes, occasionaly	428	232 (54.2)		2.02 (1.47-2.76)	<0.001
Yes, everyday	185	106 (57.3)		0.96 (0.78-1.18)	0.702
Diafragma	3534	1347 (38.1)	0.235		
No	2680	1036 (38.7)		1.00 (referent)	
Yes, occasionaly	12	7 (58.3)		1.01 (0.33-3.12)	0.982
Yes, everyday	16	7 (43.8)		1.02 (0.85-1.23)	0.816
Method of fertile days	3534	1347 (38.1)	0.007		
No	2218	826 (37.2)		1.00 (referent)	
Yes, occasionaly	337	155 (46.0)		1.44 (1.07-1.94)	0.017
Yes, everyday	234	97 (41.5)		1.08 (0.89-1.32)	0.428
Coitus interruptus	3534	1347 (38.1)	0.001		
No	1982	734 (37.0)		1.00 (referent)	
Yes, occasionaly	399	185 (46.4)		1.14 (0.89-1.45)	0.308
Yes, everyday	423	170 (40.2)		1.07 (0.88-1.31)	0.483
Other contraception method is used	3534	1347 (38.1)	0.124		
No	1086	402 (37.0)		1.00 (referent)	
Yes, occasionaly	2	2 (100.0)		0.56 (0.12-2.51)	0.447
Yes, everyday	14	3 (21.4)		1.04 (0.88-1.23)	0.669
Tobacco smoking	2229	873 (39.2)	0.025		
No	509	224 (44.0)		1.00 (referent)	
Yes, occasionaly	343	125 (36.4)		0.74 (0.59-0.93)	0.010
Yes, everyday	1264	489 (38.7)		0.60 (0.36-0.98)	0.040

Table 3. Frequencies and univariant logistic regression analysis for Trigger for PAPA test (self-initiated vs. organized screening)

	Frequencies			Univariant logistic regression analysis	
	Total	**no (%)**	**P value**	**OR (95%CI)**	**P value**
Education	2594	769 (29.6)	<0.000		
Elementary school	530	78 (14.7)		1.00 (referent)	
Secondary	1505	461(30.6)		2.56 (1.96-3.33)	<0.001
University degree	559	230(41.1)		4.05 (3.02-5.43)	<0.001
Age	2594	769 (29.6)	0.003		
25-34	555	194 (35.0)		1.00 (referent)	
35-44	692	215 (31.1)		0.84 (0.66-1.06)	0.147
45-54	796	214 (26.9)		0.68 (0.54-0.86)	0.002
55-64	551	146 (26.5)		0.67 (0.52-0.87)	0.002
Children	2546	746 (29.3)	0.001		
0	264	103 (39.0)		1.00 (referent)	
1	2046	586 (28.6)		0.63 (0.48-0.82)	0.001
2	196	48 (24.5)		0.51 (0.34-0.76)	0.001
>3	40	9 (22.5)		0.45 (0.21-0.99)	0.048
Wealth index	2594	769 (29.6)	<0.000		
Poorest	216	32 (14.8)		1.00 (referent)	
Poorer	399	85 (21.3)		1.56 (1.00-2.43)	0.052
Middle	552	120 (21.7)		1.60 (1.04-2.45)	0.031
Richer	669	211 (31.5)		2.65 (1.76-3.99)	<0.001
Richest	758	321 (42.3)		4.22 (2.82-6.31)	<0.001
Type of settlement	2594	769 (29.6)	<0.000		
urban	1706	583 (34.2)		1.00 (referent)	
rural	888	186 (20.9)		0.51 (0.42-0.62)	<0.001
Region	2594	769 (29.6)	<0.000		
Vojvodina	698	254 (36.4)		1.00 (referent)	
Belgrade	754	248 (32.9)		0.86 (0.69-1.06)	0.162
Central Serbia	1142	267 23.4)		0.53 (0.43-0.66)	<0.001
Distance from the nearest Health Centre	2594	769(29.6)	<0.000		
<500 m	503	171 (34.0)		1.00 (referent)	
501m-1km	562	192(34.2)		0.89 (0.69-1.16)	0.389
1.1km do 2 km	518	163(31.5)		0.75 (0.57-0.99)	0.046
2.1km do 5 km	430	120(27.9)		0.42 (0.31-0.56)	<0.001
<od 5 km	516	92 (17.8)		1.77 (1.05-2.98)	0.032
Age of first sexual intersourse	2496	748(30.0)	0.006		
>16	401	91 (22.7)		1.00 (referent)	
17 – 19	1123	354 (31.5)		1.57 (1.20-2.04)	0.001
20-22	711	228 (32.1)		1.61 (1.21-2.13)	0.001
23-25	203	62 (30.5)		1.50 (1.02-2.19)	0.037
26 an more	58	13 (22.4)		0.98(0.51-1.90)	0.962
Partners in the last 12 months	71	19 (26.8)	0.594		
1	49	12 (24.5)		1.00 (referent)	
2	10	4 (40.0)		2.06 (0.49-8.53)	0.321
3 and more	12	3 (25.0)		1.03 (0.24-4.42)	0.971

Contraception method used					
Pills	2027	623 (30.7)	0.596		
No	1514	462 (30.5)		1.00 (referent)	
Yes, occasionaly	54	20 (37.0)		0.73 (0.36-1.51)	0.402
Yes, everyday	41	10 (24.4)		1.04 (0.82-1.31)	0.746
IUU	2027	623 (30.7)	0.391		
No	1462	440 (30.1)		1.00 (referent)	
Yes, occasionaly	28	12 (42.9)		1.22 (0.82-1.83)	0.326
Yes, everyday	113	39 (34.5)		1.05 (0.83-1.33)	0.683
Local contraception	2027	623 (30.7)	0.484		
No	1541	469 (30.4)		1.00 (referent)	
Yes, occasionaly	21	9 (42.9)		0.51 (0.11-2.36)	0.387
Yes, everyday	11	2 (18.2)		1.05 (0.84-1.32)	0.666
Condom	2027	623 (30.7)	<0.000		
No	1224	336 (27.5)		1.00 (referent)	
Yes, occasionaly	285	120 (42.1)		1.84 (1.28-2.63)	0.001
Yes, everyday	139	57 (41.0)		1.08 (0.84-1.40)	0.551
Diafragma	2027	623 (30.7)	0.020		
No	1544	466 (30.2)		1.00 (referent)	
Yes, occasionaly	9	7 (77.8)		0.87 (0.23-3.28)	0.834
Yes, everyday	11	3 (27.3)		1.08 (0.86-1.35)	0.521
Method of fertile days	2027	623 (30.7)	0.363		
No	1278	384 (30.0)		1.00 (referent)	
Yes, occasionaly	205	74 (36.1)		0.96 (0.65-1.43)	0.847
Yes, everyday	130	388 (29.2)		1.03 (0.81-1.31)	0.808
Coitus interruptus	2027	623 (30.7)	0.514		
No	1142	357 (31.3)		1.00 (referent)	
Yes, occasionaly	247	81 (32.8)		0.81 (0.59-1.11)	0.190
Yes, everyday	234	63 (26.9)		0.95 (0.74-1.22)	0.691
Other contraception method is used	2027	623 (30.7)	0.075		
No	603	175 (29.0)		1.00 (referent)	
Yes, occasionaly	1	1(100.0)		4.89 (0.89-26.95)	0.068
Yes, everyday	6	4 (66.7)		1.11 (0.90-1.37)	0.317
Tobacco smoking	1353	424 (31.3)	0.680		
No	339	105(31.0)		1.00 (referent)	
Yes, occasionaly	199	58 (29.1)		1.07 (0.81-1.41)	0.628
Yes, everyday	755	245 (32.5)		0.81 (0.44-1.50)	0.504

Table 4. Multivariate logistic regression analysis for women's preventive reproductive health behavior and trigger for PAP test

	Regular gynecological visits n=4894		Regular PAP test n=5036		Trigger for PAP test (self-initiated vs. screening) n=2632	
	OR (95%CI)	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**
Age						
25-34	1.00		1.00		1.00	
35-44	0.59 (0.50-0.70)	<0.000	0.95 (0.78-1.15)	0.589	0.85 (0.67-1.09)	0.204
45-54	0.52 (0.44-0.62)	<0.000	0.92 (0.76-1.11)	0.387	0.75 (0.59-0.95)	0.019
55-64	0.21 (0.17-0.26)	<0.000	0.39 (0.31-0.50)	<0.000	0.75 (0.58-0.99)	0.042
Education						
Elementary school	1.00		1.00		1.00	
Secondary	1.69 (1.43-2.00)	<0.000	1.34 (1.10-1.64)	0.004	1.86 (1.40-2.48)	<0.000
University degree	2.20 (1.76-2.75)	<0.000	1.85 (1.44-2.37)	<0.000	2.35 (1.69-3.26)	<0.000
Wealth index						
Poorest	1.00		1.00		1.00	
Poorer	1.31 (1.04-1.66)	0.023	1.15 (0.84-1.57)	0.375	1.27 (0.80-2.00)	0.305
Middle	1.46 (1.15-1.84)	0.002	2.19 (1.63-2.93)	<0.000	1.22 (0.78-1.90)	0.384
Richer	1.97 (1.54-2.51)	<0.000	2.79 (2.06-3.77)	<0.000	1.71 (1.10-2.66)	0.017
Richest	2.53 (1.95-3.28)	<0.000	3.54 (2.58-4.86)	<0.000	2.43 (1.55-3.81)	<0.000
Settlement						
urban	1.00		1.00		1.00	
rural	0.93 (0.80-1.08)	0.374	0.96 (0.81-1.14)	0.665	0.79 (0.64-0.99)	0.041

Investigation of Demodex SPP. On the perinea in women visiting urology and gynecology policlinics

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Abstract

Aim: It is reported that species of *Demodex* can be found in various locations on human body and transmitted via close contact. Types of Demodex are reported to be located in various places of human body. The aim of this study is to investigate the relationship between age and incidence of *Demodex* spp. among female patients complaining of pruritus in the perinea area.

Method: Samples taken from perinea areas of the women using standardized surface skin biopsy (SSSB). Accordingly, samples were obtained using SSSB method from the faces and perinea areas of 431 women aged 18-55, which were then covered with entellan and sent to the parasitological laboratory. Specimens were covered with entellan and evaluated in Parasitology Laboratory.

Results: Among the 431 specimens, 21.1% revealed *Demodex spp.,* 1.6% revealed mite, 3.05% revealed *Enterobius vermicularis* eggs, 0.2% revealed *Taenia spp.* eggs, and 0.2% revealed *Phthirus pubis.*

Conclusion: It was concluded that it should be taken into consideration that species of *Demodex* can be found in the women perinea region, thus specimens should be taken from patients consulting with pruritus or allergic reactions in order to diagnose the parasite, and treatment protocol should be planned in this direction. In addition, experimental studies may be planned to investigate the relationship between the parasite intensity in perinea region and pathogenity.

Key words: *Demodex spp*., women, parasite, Perinea area.

Introduction

Demoedex folliculorum, which is one of *Demodex* types of permanent ectoparasites commonly found in humans and lives in the spaces between hair follicles alone or in groups. Another species, *D. brevis* is found alone deep in the Sebaceous glands [1-4] . *Demodex* species are reported to be found in various places in human body including nasolabial region, base of eyelashes, chin, forehead, outer ear canal, nipple, back, penis, and hips [1,4,5]. The first case of demodex was detected by Saygı et al.[6] in periana area using cellophane tape method in Turkey.

It has been reported that *Demodex* species are transmitted to other people through close contact and, in turn, plays a pathogenic role in rosacea, acne vulgaris, perioral dermatitis, seborrhoeic dermatitis, micropapillary-pruritic dermatitis, and blepharitis[7]. Methods used for diagnostic purposes include cellophane tape, skin scraping, punch biopsy and standardized surface skin biopsy (SSSB). In order to detect the pathogenesis of the parasite, one should know the mite intensity of the parasite per cm^2 [3]. Especially the SSSB method is effective in the diagnosis of *Demodex* spp., because, the follicular content is collected completely together with the surface part of the stratum corneum where the parasite inhabits, thus making it easier to detect the mite intensity per cm^2 [2 8-10].

In this study it was aimed to investigate the prevalence of *Demodex spp.* in skin biopsy specimens obtained from female patients applied to the clinic suffering from chronic pruritus in the perine area by using standardized surface skin biopsy (SSSB) and relationship with the clinic situation.

Materials and Methods

Prior to the study, health staff working in obstetrics and urology policlinics were given an in-service training by a parasitolog about *Demodex* spp. and their parasitism, the purpose of the study and planned process, obtaining specimens from women's perinea area using SSSB method. The method was explained in detail and shown practically by a parasitolog. The specialized doctors who would obtain the specimens made practices on volunteering subjects. Before the evaluation, the surface part of the stratum corneum together with the hair follicles in the obtained specimens was observed.

The participants comprised a total of 431 women aged 18-55 who visited the obstetrics and urology policlinics of the hospital through January-June 2009. The detailed information about the study was given by specialist. Specimens were taken from the perinea area of the volunteer women by using SSSB method. For SSSB, a microscope slide with cyanoacrylate adhesive on 1cm2 pen-marked area was pressed over the skin, applying the adhesive to the skin and leaving there for one minute. It was then gently removed, then the specimens were covered with entellan and sent to parasitology laboratory. Specimens were examined in parasitological laboratories via light microscope at 100 and 400 times magnification, and even if one *Demodex spp.* was observed it was considered as positive. Diagnosis was made with respect to the *Demodex spp* adult form. Each preparation was examined in terms of other ecto-parasites and Helmint eggs in the anal area. The participating patients with positive *Demodex spp.* were first informed about the results and forwarded to the relevant policlinic.

Statistical analysis

Statistical analyses were done using independent samples *t* test and Pearson chi-square test. The data were presented with mean values, standard deviation, number and percentage. The statistical significance was determined as $p<0.05$ and analyses were done using SPSS 13.0 software.

Results

Differential diagnosis was done microscopical cigar shaped long body with an abdomen forming two thirds of its lenght, short and obtuse legs and cone shaped termination of the body was diagnosed as Demodex spp. (figure 1).

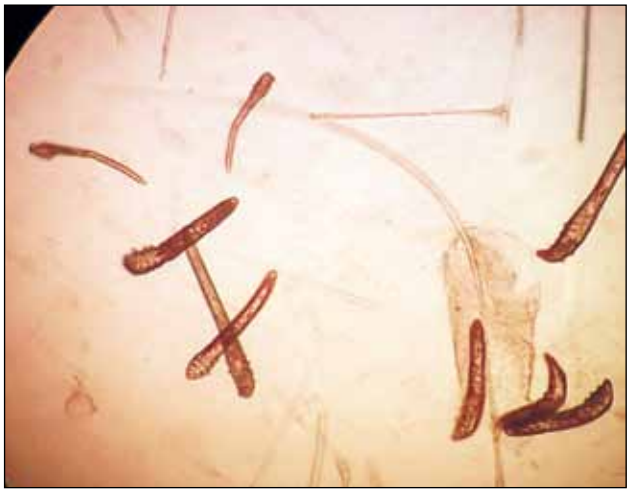

Figure 1. Adult Demodexs (15 minutes after it was detected with entellan) (100 times magnified)

Among the specimens obtained from the 431 women, 21.1 % revealed *Demodex* spp. (Figure 2), 1.6% revealed mite, 3.05% revealed *Enterobius vermicularis* eggs (Figure 3), 0.2% revealed *Taenia spp*. eggs, and 0.2% revealed *Phthirus pubis* (Figure 1, 2)

Table 1. Distribution of the prevalence of parasites according to species (%)

Parasites	Positive		Negative		Total	
	Number	%	Number	%	Numbers	%
Demodex spp.	91	21.1	340	78.9	431	100.0
Mite	7	1.6	424	98.4	431	100.0
Enterobius vermicularis	15	3.5	416	96.5	431	100.0
Phthirus pubis	1	0.2	430	99.8	431	100.0
Taenia spp.	1	0.2	430	99.8	431	100.0

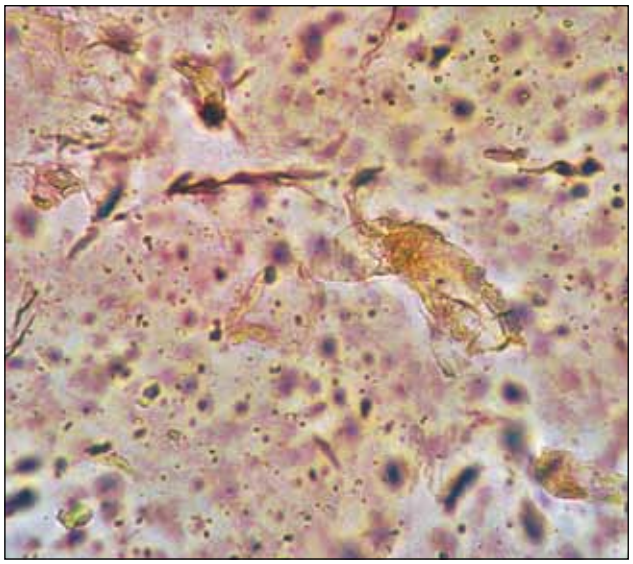

Figure 2. Demodex Adult (3 days after it was detected with entellan) (100 times magnified)

The participants were aged 38.1 ± 11.5, and the distribution of the prevalence of *Demodex* spp. and other parasites are given in Table 1.

A significant difference was observed between the parasites examined in terms of positivity and negativity ($p<0.001$). Average ages according to positivity and negativity of the Demodex and other parasites are given in Table 2. A significant correlation was observed between prevalence of *Demodex spp.* and average age.

Figure 3. Enterobius vermicularis egg (100 times magnified)

Discussion

Especially the SSSB method is effective in the diagnosis of *Demodex* spp., Taking into account the literature SSSB method was used in this study [8-10].

There are various arguments about the pathological and clinical symptoms caused by different types of Demodex[11-14]. While some researchers consider inhabitance of *Demodex spp.* in pilosebase follicles harmless, others reported that *D. folliculorums* can play an etiopathogenic role in

Table 2. Distribution of the prevalence of parasites according to species and different age groups

Parasites	Number	Mean age±SD	p
Demodex spp.			
Positive	91	35.8±10.3	0.03
Negative	340	38.7±11.7	
Mite			
Positive	7	34.1±10.9	0.36
Negative	424	38.2±11.5	
Enterobius vermicularis			
Positive	15	40.5±11.1	0.40
Negative	416	38.0±11.4	

rosacea, acne vulgaris, blepharitis, perioral dermatitis, pustular folliculitis, papular-pustular lesions on hairy skin, and pustular lesions in acquired immune deficiency syndrome[15,16].

The different studies were done about the prevalence of Demodex specimens on human face. It was reported that the prevalence of *Demodex spp.* increases as the patients grow older assessed the relationship between the age groups and *Demodex*, and reported *Demodex* rates: 8.3% in the age group of 11-15 and 12.7% in the age group of 16-20, respectively[17,18]. Aycan et al. reported *Demodex* prevalence in 20% of the ≤20 age group and in 53.5% of the 21≤ age group[19]. In the present study parasite was observed in 21% of the women aged 35.8±10.3. An analysis of the findings is likely to suggest that, similar to this study[19], the prevalence of the parasite increases among middle-aged and older-aged groups.

There are various researches about the epidemiology of different types of *Demodex.* Akdeniz et al. found that the density of *D. folliculorum* among diabetic patients was significantly higher than control group[20]. Özçelik et al. found the parasite among 12.76% of the 47 patients suffering chronic kidney failure[21]. Türk et al. examined the eyelashes of a total of 96 people (48 healthy and 48 with blepharitis) and found *D. folliculorum* in 11 out of 37 (29.72%) patients with blepharitis, in 1 out of 11 (9.09%) patients with blepharoconjoncktivitis , and in two out of 48 healthy (% 4.16) people[22]. In another study Ding and Huang examined the outer ear canal secretion among 613 healthy high school students and found *Demodex* in 11.58% of them[23]. Aycan et al. examined a total of 197 patients (117 with rosacea, 29 with acne vulgaris and 51 with other allergitic problems) using SSSB method, and found mite among 97 (49.23%) of them[7]. Lazaridou et al. [24] examined pivotal role of chronic sun exposure in the pathogenesis of rosacea. Demodex folliculorum represents a significant cofactor that may contribute to the transition of the disease from a vascular to an inflammatory stage. The low positive results of direct and indirect immunofluorescence do not support a potential autoimmune role in the development of rosacea. Horvath at al. [25] found Demodex folliculorum or Demodex brevis in 17.7% of the samples, more frequently in males (21.9%) and in older adults (20%). Use of make-up seems to reduce the likelihood of Demodex carriage, while pet ownership, use of shared items and living in close contact with older adults had no significant influence of presence of mites.

The relevant literature as far as the researchers analyzed does not include any research about the epidemiology of *Demodex* in the perinea area of the women. Yet, Uğraş et al. reported to have evaluated the specimens obtained from the perianal area of 100 men and found no *Demodex* presence[26]. As a result of the present study, we found 21.1% *Demodex spp.*, 1.6% mite, 3.05% *Enterobius vermicularis* eggs, 0.2% *Taenia* spp. eggs, and 0.2% *Phthirus pubis,* in the women perinea. Saygı et al. reported *Demodex* spp. in perianal area material using cellophane tape method[6]. Similarly, Aycan et al. reported mite[7]. Söylemez et al. reported *Demodex* spp. specimens were taken from perinea areas of 200 men aged 19 - 34 using SSSB method, covered with entellan, the examination revealed the presence of *Demodex* spp. in the specimen from perinea in the rate of 42.0% [27]. These findings are similar to the results obtained in the present study. It is proposed that the employees in gynecology clinic and patients should be informed about parasites and protection methods.

Conclusion

It was concluded that it should be taken into consideration that species of *Demodex* can be found in the women perinea region, thus specimens should be taken from patients consulting with pruritus or allergic reactions in order to diagnose the parasite, and treatment protocol should be planned in this direction. In addition, experimental studies may be planned to investigate the relationship between the parasite intensity in perineum region and pathogenity.

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Influences of weight loss on hematological parameters in male judokas

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Abstract

The purpose of this study was to evaluate the effect of weight loss on hematological parameters in male judokas.

Twenty Serbian male judokas were examined in the early morning of the first day (pre-values) and the last day (post-values) of a 10-day pre-competition training period. Of the 20 subjects, 10 needed to reduce weight (WR group), and the other 10 did not (control group). Blood samples were collected from all subjects on the first (initial measurement) and last (final measurement) days of the 10-day training program, at 07.00am. Venous blood samples were drawn from the cubital vein, and the red blood cell count (RBC), hemoglobin (Hb), hematocrit (Hct), ferritin (Ferr) level, mean corpuscular hemoglobin concentration (MCHC), corpuscular volume (MCV), potassium (K), sodium (Na) and lipid profile were measured.

At the initial measurement, no significant differences were noted in measured hematological parameters. Compared with basic data and control group, decrease in Hb, Hct, RBC, Ferr and MCHC was noted in WR group. Also, Hct and MCV statistically significantly decreased in control group. The lipid profile was unchanged in both groups, except for the triglycerides which decreased in WR group, after the final measurement. Also, K significantly decreased compared with basic data in WR group.

The most obvious finding in the study was that red blood cell count is highly respondents to physical activity, especially in WR group. Weight loss before competition induces alteration in hematological parameters, which can lead to the decline of functional state and exercise ability of male judokas. Judokas are advised not to lose weight before a competition.

Key words: Judo, Body weight, Exercise

Introduction

Judo is a modern combat sport created in Japan in 1882 by Dr Kano Jigoro. Its most prominent feature is its competitive element, where the object is to either throw or takedown one's opponent to the ground, immobilize or otherwise subdue one`s opponent with a grappling maneuver, or force an opponent to submit by joint locking or by executing a strangle hold or choke (Drid et al., 2011).

Judo competitions are divided according to weight categories (Franchini et al., 2011). There are seven weight categories for both male (<60kg, 66 kg, 73 kg, 81 kg, 90 kg,100 kg and >100 kg) and female judo competitors (<48 kg, 52 kg, 57 kg, 63 kg, 70 kg, 78 kg and >78 kg). Judo athletes attempt to maximize the amount of lean tissue, minimize the amount of body fat, and minimize total bodyweight. Judo sport is an athletic mode with a high demand of physiological parameters in competition elevated physiological demand is due to the high intensity (Radjo et al., 2011; Trivic et al., 2011).

Water is a critical element of the body, and adequate hydration is a must to allow the body to functioning. Up to 75% of the body's weight is made up of water. Most of the water is found within the cells of the body (intracellular space). The rest is found in the extracellular space, which consists of the blood vessels (intravascular space) and the spaces between cells (interstitial space). Dehydration occurs when the amount of water leaving the body is greater that the amount being taken in. Hydration, or maintain a proper level of fluid in the body, is an important aspect of sports nutrition because of the loss of water and sodium trough sweating during physical activity. Maintaining proper hydration is not only a physiological necessity but also adds to a performance advantage and reduces risk of medical problems or injuries due to fluid loss (Naghii, 2000; Von Duvillard et al., 2004). Dehydration results in

muscle strength, difficulty concentrating, irritability and headache. It is important for athletes in any age group needing or desiring to lose or gain weight to be properly supervised by nutritionist as well as a physician, because unhealthful dietary practices can lead to long term physical disorders. Food restriction resulted in significant decreases in body weight. In addition, it had significant influence on triglyceride and free fatty acid (Filaire et al., 2001). Restricting food and fluid intake is the most common method of weight loss in judo. This kind of weight loosing is dangerous because much of weight loss will be lean muscle rather that fat, which can affect athletic performance.

Rapid weight loss is highly prevalent in judo competitors and it is very difficult for judokas to know with certainly in which category they will perform the best, and often they evaluation are not objective. It is well know, that judokas typically lose weight rapidly before competitions by a reduction in food intake, sweating trough intensive exercise in plastic suits to promote water loss, fluid restrictions and even the use of diuretics.

Such body weight reduction may affect on plasma and blood volume (Bijlani et Sharma, 1980), and have immediate effects on sport performance (Fogelhom, 1994). Baker et al. (2007) demonstrated that performance on test vigilance, short term memory, and ability to calculate math problems were reduced with a 2% or greater acute reduction in body mass associated with water deprivation and fluid loss. Rapid weight loss did not affect judo-related performance in experienced weight-cyclers when the athletes had 4 h to recover (Artioli et al., 2010).

An inadequate dietary intake is believed to be one of the major factors associate with iron deficiency (Rodriguez et al. 2009). Therefore, caloric and nutrient intakes are very important in athletes. The emphasis on weight-classes obligates the judo athletes to focus closely on their weight and caloric intake (Boisseau et al., 2005).

Athletes are more vulnerable to iron deficiency because an increase in plasma volume during the training due to the extra-celular fluid transfer to vessels (Mc Ardle et al., 2007) and iron loss due to sweating (Adams et al., 2001), especially in athletes who reduce their weight. Faintuch et al. (1998) explained two types of anemia in athletes: a) pseudo-anemia resulted from an increase in plasma volume during a sport performance b) real anemia resulted from a decrease in iron store. As the athlete's performance depends on the transfer of maximal oxygen to active muscles, the athletes are more sensitive to the effects of anemia and iron deficiency than common people.

Detecting iron deficiency in athletes is of great importance due to its fairly high incidence as well as to adverse effects on health. Iron deficiency, anemia is unequivocally associated by symptoms like weakness, pallor, and fatigability. The aim of this study was to evaluate the effect of weight loss on hematological parameters, lipid profile and electrolytes in male judokas involved in weight reduction program and compare them with control group.

Material and methods

Study subjects

Twenty male judokas participated in this study and all of them were member of Serbian national team. Ten subjects who required weight reduction to meet their class requirements were defined as the weight reduction (WR) group (age, 21.9 ± 3.1 years; body height, 175.7±9.4 cm) , and ten subjects without a need of weight reduction were defined as the control group (age, 22.4 ± 3.6 years; body height, 176.9±9.3 cm). All subjects were informed about requirements of the study and written consent was obtained from all of them before the study.

Procedure

Blood samples were collected from all subject on the first (initial measurement) and last (final measurement) days of 10-day training period, at 07.00pm. Blood samples were taken from the antecubital vein inside of the elbow into plain vacutainer tubes. The site was cleaned with germ-killing medicine (antiseptic). The health care provider wrapped an elastic band around the upper arm to apply pressure to the area and made the vein fill with blood. Haemoglobin (Hb), hematocrit (Hct), red blood cells count (RBC), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), ferritin (Ferr), transferrin (sTfR), iron, potassium (K) and sodium (N) in serum were measured.

Total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and non HDL-C were measured to exam lipid profile of male judokas.

The subjects didn't take food twelve our before blood testing. Complete blood tests were done on instrument SAFIR firm Abot. Biochemical parameter has been providing on instrument ADVIA 1800 firm Bayer Siemens. All parameter has been providing with original bar code reagents- firm Bayer Siemens.

Statistical analysis

All values were presented as means (M) and standard deviation (SD). Differences between Pre and Post values for each biochemical parameters were tested with repeated measures for analysis of variance (ANOVA). The differences were considered to be statistically significant at $p<0.05$.

Results

Changes in body weight for judokas before and after training program are listed in Table 1.

Table 1. Body weight of judokas involved in weight reduction and control group.

Parameters	Group	Initial measurement	Final measurement
Body weight (kg)	WR	82.0±20.5	77.6±19.3*[a]
	Control	80.9±16.8	80.6±16.3

*Legend: WR (weight reduction) group, n = 10; control group, n = 10; * p<0.05, compared with pre-value; [a] p<0.05, compared with control group. Values are presented as Mean ± SD*

Table 2. Hematological variables and electrolytes in male judokas before and after weight reduction program

Variable	Group	Initial measurement	Final measurement
Erythrocytes (10^{12}/L)	WR	5.09±0.19	4.75±0.39*
	Control	4.89±0.19	4.79±0.19
Haemoglobin (g/L)	WR	151±6	139±9 [a]
	Control	151±4	142±5
MCV (fL)	WR	89.5±2.6	89.9±3.2
	Control	88.1±1.7	88.6±2.1 [a]
MCH (pg)	WR	29.7±0.6	29.3±0.9
	Control	29.3±0.8	29.1±0.7
MCHC (g/L)	WR	334±3	333±3 [a]
	Control	336±2	335±2
Hematocrit (l/l)	WR	0.44±0.03	0.43±0.03 [a]
	Control	0.44±0.01	0.43±0.02 [a]
Ferritin (µg/L)	WR	77.6±9.5	71.2±12.9 [a]
	Control	111.1±56.5	127.6±85.8*
Transferrin (g/L)	WR	2.5±0.2	2.6±0.3
	Control	2.6±0.3	2.7±0.3
Iron (µmol/L)	WR	12.00±3.35	11.58±3.06
	Control	12.97±4.12	13.02±5.09
Sodium (mmol/L)	WR	139±2	138±2
	Control	139±1	139±1
Potassium (mmol/L)	WR	4.4±0.1	3.3±0.4*
	Control	4.4±0.1	4.4±0.1

*Legend: MCV – mean corpuscular value; MCH – mean corpuscular haemoglobin; MCHC – mean corpuscular haemoglobin concentration; WR (weight reduction) group, n = 10; control group, n = 10; * p<0.05, compared with pre-value; [a] p<0.05, compared with control; Values are presented as Mean ± SD*

Table 3. Effects of the basic training program on serum lipid and lipoprotein levels

Variable	Group	Initial measurement	Final measurement
Total cholesterol (mmol/L)	WR	3.98±0.72	4.34±1.01
	Control	4.39±0.94	4.94±1.46
Triglycerides (mmol/L)	WR	0.74±0.20	0.94±0.28*
	Control	0.90±0.28	0.95±0.25
High density lipoprotein (mmol/L)	WR	1.42±0.36	1.44±0.39
	Control	1.40±0.20	1.40±0.23
Low density lipoprotein (mmol/L)	WR	2.28±0.48	2.49±0.77
	Control	2.66±0.92	3.02±1.22

*Legend: WR group, n = 10; control group, n = 10; * p<0.05, compared with pre-value; Values are presented as Mean ± SD*

Based on the results (Table 1) we can see that body weight was significantly decreased in WR group after the final measurement in compared with pre values and control group.

It can be seen (Table 2) that no statistically significance difference were found on initial measurement between WR and control group in analyzed variables, except in higher number of RBC and lower Ferr concentration level in WR group. Compared with basic data and control group, decrease in Hb, Hct, RBC, Ferr and MCHC was noted in WR group. Also, Hct and MCV statistically significantly decreased in control group.

As observed in Table 2 serum potassium concentration level has had decreased in WR group after the training program, although the serum potassium was unchanged in control group. Variation in serum sodium concentration was also observed in WR group, but there were no significant differences after the second measurement in compared with pre-value and control group.

No change (Table 3) in TC, HDL-C and LDL-C were noted during the study. Values for the lipolytic variables were in agreement with the references value of normal population, but significant decreased in TG were noted after the final measurement in compared with pre-values.

Discussion

As the Iron store affect the athlete's performance it is important to screen the athletes vulnerable to anemia as well as iron management (Romagnoli and Cristani, 2006).

After the final measurement in most parameters in WR group (RBC, Hb, Hct, MCHC, Ferr) was noted statistically significance alteration. Number of erythrocytes, haemoglobin and hematocrit concentration, ferritin and mean corpuscular haemoglobin concentration was statistically decreased after the final measurement in compared with control group. Training treatment in control group induce statistically decrease in haematocrit and mean red cell volume. These results showed that most analyzed parameters are strongly reacting to apply training in booth groups. No differences in MCH, transferrin, Iron was found between the WR and control group.

All parameters of red blood cells have a strongly reaction on high intensive training (Connes et al., 2007) whereby they reduction line to anemia, and demand adequate treatment, resting and nutrition with necessarily supplementation. The results of the present study support the findings reported by number of authors (Degoutte et al., 2006), that the major red blood cell variables are changeable in athletes after physical activity. Reduced Hb, Hct and RBC levels observed in WR judokas can case so called "athletes pseudoanemia", which can mainly be attributed to an exercise-induced plasma volume expansion (Schumacher et al., 2002).

It has been suggested that exercise has no effect on serum sTfR level (Malczewska et al., 2000), which is in accordance with obtained results of the research. Iron and especially ferritin, the iron storage protein, has been demonstrated to be reduced in athletes, due to higher iron turnover and increased synthesis of iron-containing proteins with altered intestinal absorption and an increased loss trough sweat, the intestines and kidneys (Newhouse and Clement, 1988). Based on the obtained result it can be seen that the serum Ferr level was de-

creased after the final measurement in WR group, especially after the final measurement.

Electrolytes such as sodium (Na) and potassium (K) are lost as a consequence of sweating during exercise, and sweat Na concentration can vary considerably among individuals (Patterson et al., 2000). Significant potassium loss occurred in WR group can be results of the use laxatives and diuretics, which may cause potassium deficiency. It is important to note that during the research we didn't control their nutrition.

Potassium is the major ion in the intracellular fluid. For most individuals, the normal dietary intake of minerals is adequate to maintain sodium and electrolyte balance, however for athletes especially to one who are involved in weight reduction program, additional salt sometimes should be ingested. Even mild potassium deficiency can lead to fatigue and decreased performance (McKenna, 1992), while a significant deficiency can lead to cardiac problems. Disturbance in muscle electrolytes play an important role in the development of muscular fatigue. Profuse sweating can lead to significant fluid and electrolytes losses, and there are some indications that Na and K loss is a contributing factor in the etiology of heat-related whole body muscle cramps (Stofan et al., 2005).

Conclusion

Many biochemical parameters respond to physical activity, but in the short term and with a very large homeostatic potential, so that changes are happening during physical activity and returning to the physiological limits in a very short period. It can be concluded that red blood cells variable highly responded to physical activity in judo, especially in WR group. For this reasons, red blood cells variables especially in judokas which reduce their weight, should be closely monitored, to avoid depletion and initiate therapy whenever is necessary. Sports nutritionists should educate athletes, especially the one who are involved in weight reduction, about the relationship between iron deficiency and sport performance. In addition, they should provide instruction about increase iron dietary intake, if there is a need, in order to achieve best results. Weight loss can be beneficial if it involves losing excessive body fat without reducing lean muscle mass or causing significant dehydration. After the training or competition especially in athletes who reduce their weight, any remaining body water and electrolyte deficit need to be replaced with a particular emphasis on salt intake in order to help retain and distribute the ingested fluid, so that all fluid compartments are restored sufficiently. Judokas are advised not to lose weight before a competition.

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Non-Pharmacological Treatment Of Diabetic Polyneuropathy By Pulse Electromagnetic Field

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Abstract

Background: In recent years it has been shown that nonpharmacological therapy has its adventages in treating diabetic polyneuropathy (DPN) because of the local treatment posibility, as well as, safety and low prices. Pulsed electromagnetic field (PEMF) of low frequency improves pain, paresthesias and vibration sensation. The results of the treatment depend on the parameters of the field. The aim of this study was to examine the effect of PEMF of different low – frequencies on neuropathic symptoms.

Methods: The prospective controlled study included a group of 71 patients with diabetic polyneuropathy electrophysiologically confirmed. The patients were randomly divided into two groups: group with pulsed electromagnetic field therapy of 10 Hz (n = 28) and group with pulsed electromagnetic field therapy of 25 Hz (n = 43). Neuropathic symptoms were evaluated before and after the treatment by using Michigan Neuropathy Screening Instrument (MNSI) questionnaire and Numerical Raiting Scale (NRS).

Results The results of neuropathic questionnaire showed a considerable decrease of neuropathic symptoms and signs after the therapy, p<0,001. There wasn`t a significant difference in results of neuropathic questionnaire compared to the low – frequency pulsed electromagnetic field therapy, χ^2 = 1,657, df = 4, p = 0,799. The analgetic effect of PEMF frequency of 10 Hz and 25 Hz was significantly different. NRS pain scale has shown rather lower values after the therapy among the patients that were treated with PEMF of 25 Hz, p<0,001.

Conclusion. Although the precise mechanism of effect of pulsed electromagnetic field of low-frequencies at neuropathic symptoms hasn`t been completely known, its application helps in decrease of neuropathic symptoms.

Key words: electromagnetic fields, neuropathic pain, diabetes

Introduction

Because of partially explained and multifactorial pathogenetic mechanism of diabetic polyneuropathy (DPN), treatment of neuropathic symptoms is now implemented using analgesics, anticonvulsant drugs, antidepressants or, as one of the pathophysiological concepts, using aldose reductase inhibitors and alfalipoic acid (1). Nonpharmacological therapy has been less studied (2) and these are studies which refer to that application of transcutaneous electrical nerve stimulation (TENS), monochromatic infrared energy (MIRE), low power laser and pulsed electromagnetic fields (PEMF) of low frequencies. PEMF has analgesic, vasoactive, neurostimulating and trophic effects, while through depolarization, repolarization, and hyperpolarization of neurons modulate neuropathic pain (3,4,5,6). After reviewing known research of the application PEMF in the treatment of DPN, the results showed: in the study, Weintraub & Cole (7) application of the frequencies below 30 Hz, induction of 2 mT (miliTesla) and the analgesic effect was achieved in 50% of respondents; Musaev et al. (8) recorded analgesic effect using frequencies of 10 Hz in relation to the application rate of 100 Hz, 8 mT induction; Wrobel et al. (9) applied frequency from 180 to 195 Hz and the results of analgesic effects of PEMF are the same as in the group with placebo.

Generally, when it comes to treatment of diabetic polyneuropathy by physical agents, it must be assumed that patients with diabetic polyneuropathy often have damage to the protective sensibility, autonomic nervous dysfunction and microangiopathy. PEMF as athermic therapy proved to be

safe in the treatment of diabetic polyneuropathy. The results of several studies with different dosage of PEMF application protocols (5,10), suggest that dosing of magnetotherapy in the treatment of DPN is not fully defined. The aim of this reserch was to test the effects of different low frequences of pulsed electromagnetic field in treating simpthoms of diabetic polyneuropathy.

Methods

Subjects

A prospective controlled clinical trial, according to the method before and after, included a group of 71 patients, aged 18 to 65, with diabetic polyneuropathy. The study was conducted at the Clinical Center of Montenegro, Center for Physical Medicine and Rehabilitation in the period from 2009 to 2010. The study was approved by the local ethics committee.

Including criteria for participation in the study were: distal simetric polyneuropathy type, confirmed by electrophisiological examination and well regulated glicemia.

Excluding criteria were: contraindications for PEMF, manifest feet ulcerations and other causes of peripheral nerve dysfunction on lower limbs, patients who have already been treated by another therapy.

Evaluation measures

Michigan Neuropathy Screening Instrument (MNSI) questionnaire was used for testing neuropathic symptoms. The questionnaire was designed by MDRTC (Michigan Diabetes Research and Training Center) and includes 15 questions about the presence of symptoms of neuropathy, history of ulcerations or amputation on a foot, circulation disorders and the patient's awareness about the presence of the polyneuropathy (11). The maximum number of positive responses is 15. The result greater than 3 is indicative for the treatment of polyneuropathy. For purposes of this study we omitted the questions “Have you ever been advised that you have neuropathy” and “Have you ever had an amputation” because the inclusion criteria incuded the diagnosis of polyneuropathy.

Numerical Raiting Scales (NRS) were used assess levels of pain before (pre) and after (post) PEMF exposure. The scaling of the pain: 0-4 mild, 5-6 moderate and >7 severe. The number that was chosen by the patient is the score for intensity of the pain.

Neuropathic signs were explored by modified Neuropathy Disability Score (NDS). NDS is used to describe the features of the participants, as well as, presence of risc factors for foot ulceration. Review of vibratory sensibilities was carried out by neurological fork 125 Hz in the lower extremities, and the diagnose is registered on both toes; superficial sensibility to touch was performed by sharp metal needle for a rough touch and woolen cloth for soft touch. Details were recorded for the region of feet. Testing of thermal stimuli was carried out through the tube with hot and cold water in the region of the dorsum of feet and big toe. The ankle jerk reflex was examined by using neurological hammer. The results are scored like this: 0 - normal, 1 - a response that deviates except for a reflex action where, next to 0 and 1, there is also mark 2 - absent reflex activity. The maximum sum is 10, whereas the result greater than 6 indicates a possible risk of feet ulceration.

Procedure

In 28 selected patients PEMF treatment with frequency of 10 Hz was applied, while the remaining 43 patients had therapy with PEMF frequency of 25 Hz. Patients in whom PEMF frequencies of 25 Hz were applied are included in a prospective study which takes two years and monitors the effects of physiotherapy on the distal symmetrical sensorimotor polyneuropathy in patients with diabetes mellitus. A group of 43 patients was formed by using 'at random' method. A group of 28 patients was formed so that each new patient involved in the study, regardless of any other criteria, received PEMF therapy of frequency of 10 Hz. The device used in the treatment was Magno Multi produced by JENA, dual channelled. Characteristics of the device are: a frequency of 1 Hz to 50 Hz, induction of 0.5 mT to 10 mT. The patient is comfortably located in the position between sitting and lying, lower legs and feet are in the toroidal applicator, the coil.

Results of treatment by various frequencies were accompanied by values of MNSI questionnaire and NRS scores.

In statistical analysis, standard deviation and arithmetic mean were calculated among the descriptive statistical parameters. For the test of sta-

tistical significance Wilcoxon Signed Ranks Test, Student's t-test and Chi-Square test were used at significance level of 0.05.

Results

Clinical caracteristics

HbA1c values show regulated glycemia at the time of treatment; triglyceride levels were increased; among the possible factors of risk of ulceration of the feet, there were: the duration of diabetes more than 10 years and the value of NDS test higher than 6.

The statistical significance was tested by W test and there was no significant difference in given characteristics between two groups, before therapy, p>0,05 table 1

Therapy effects measuring

The outcome of MNSI questionnaire before and after therapy has shown significant difference (6,56 ± 1,50 : 2,76 ± 0,86). After the therapy the score of MNSI questionnaire was from minimal outcome 1 to maximal outcome 5. Crostabulation analysis was done to show the percentage of the number of patients with marks from 1-5 table 2. The importance of the results is tested by Chi-Square test. In relation to the applied frequencies of PEMF (10 Hz and 25 Hz) there was no significant difference in the outcome of MNSI questionnaires, $X^2 = 1.657$, df = 4, p = 0.799. The scaling of the pain by NRS before and after therapy has shown significant improvement when bouth frequences PEMF are applied, p<0,0001 (table 3). The scaling of the pain (NRS) after the therapy has

Table 1. Caracteristic of patients before therapy

Caracteristics	PEMF of 10Hz	PEMF of 25 Hz
Number of patients	28	43
Age (years)*	61,39 ± 7,79	60,44 ± 9,44
Duration of diabetes (years)*	11,42 ± 5,80	11,93 ± 6,29
Cholesterol (mmol/l)*	5,65 ± 0,89	5,62 ± 0,88
Triglicerides (mmol/l)*	2,15 ± 1,14	2,21 ± 0,87
Glycosylated hemoglobin (%)*	7,22 ± 1,19	7,37 ± 1,35
Neuropathy Disability Score*	6,96 ± 0,83	6,90 ± 1,28

**Data are means ± SD (range), PEMF pulsed electromagnetic field*

Table 2. Results of MNSI questionnaire after differently dosed therapies

	MNSI score 1 Number	%	MNSI score 2 Number	%	MNSI score 3 Number	%	MNSI score 4 Number	%	MNSI score 5 Number	%	Total Number	%
PEMF 10 Hz	1	3,6 %	9	32,1%	15	53,6%	2	7,1%	1	3,6 %	28	100%
PEMF 25 Hz	2	4,7%	16	37,2%	17	39,5%	6	14,0%	2	4,7%	43	100%
	$X^2 = 1.657$*, df = 4†, p = 0.799‡											

*MNSI - Michigan Neuropathy Screening Instrument * Chi-Square test , †degree of freadom,‡ p>0,05*

Table 3. The scores of the NRS pre and post electromagnetic therapy with different frequency

	NRS pre*	NRS post*	T †	Df ‡	p∫
PEMF 10 Hz	7,250 ± 1,456	4,107 ± 0,737	12,050	27	0.000
PEMF 25 Hz	7,116 ± 1,313	2,488 ± 0,592	27,261	42	0.000

*Numerical Raiting Scales (NRS), Pulsed electromagnetic field (PEMF) * Data are means ± SD (range), † The Student's t-test, ‡ degree of freadom, ∫ p<0,0001*

Table 4. Comparasion of different effects of therapy using NRS pre and post therapy

	Group of patients	Number	T*	Df †	p
NRS pre	PEMF 10 Hz	28	0,402	69	0,689‡
	PEMF 25 Hz	43			
NRS post	PEMF 10 Hz	28	10.208	69	0,000∫
	PEMF 25 Hz	43			

** The Student's t-test, † degree of freadom, ‡ p>0,05, ∫p<0,0001*

shown significant difference between the effects of 10 HZ PEMF frequence and 25 Hz frequence $p<0.0001$, table 4, figure 1.

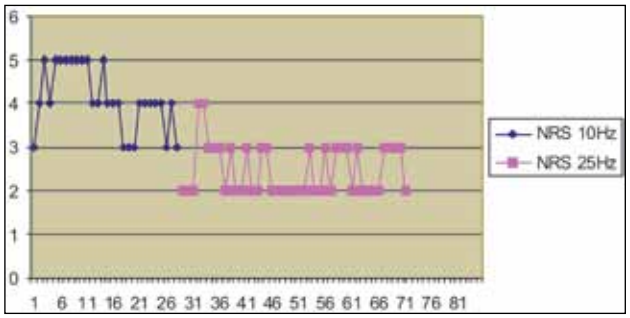

Figure 1. The scaling of the pain post PEMF therapy with 10 Hz and 25 Hz

Discusion

Results found in study, show that various low-frequency PEMF has significant therapeutic effect on neuropathic symptoms in patients with diabetic polyneuropathy. The results are difficult to compare to other studies because of different therapeutic models and variable frequencies. PEMF frequency of 10 Hz, in one larger study (8), had a important effect in regression of neuropathic symptoms. In the same study, in addition to PEMF, active exercise program was a part of the therapeutic protocol. A study which examined the effect of PEMF frequencies below 30 Hz concludes that a better response to therapy was obtained in patients with severe form of symptomatic polyneuropathy (9). Our results correlate with the above mentioned studies on the application of PEMF low frequencies up to 30 Hz.

The results of several studies with different dosage of PEMF application protocols (7,12), suggest that dosing of magnetotherapy in the treatment of DPN is not fully defined. In the treatment we gave the advantage to frequencies up to 30 Hz but with the dilemma of whether the lower frequency of 10 Hz frequency therapy is more effective than PEMF of 25 Hz.

By analyzing our group of respondents, it is clear that this is a group of patients with possible risk factors for developing foot ulcers (duration of diabetes for over 10 years, NDS> 6), so it can be said that according to the symptoms and clinical course those were the patients with chronic sensorimotor polyneuropathy. Musaev et al. examined the effect of PEMF frequencies of 10 Hz and 100 Hz in patients with diabetic polyneuropathy who were divided into groups according to the Thomas Dyke classification of diabetic polyneuropathy. The results showed that PEMF frequencies of 10 Hz has a therapeutic effect in patients with the early signs of diabetic polyneuropathy with predominant sensory symptomatology (8), which could indicate that with the duration and progress of the desease, frequency PEMF of 10 Hz do not have the same effect as in the initial stages of their desease. The MNSI questionnaire is used in the study. It contains the questions that are dealing with different neuropathic simpthoms and sensibility. Comparing the effect of PEMF frequencies of 10 Hz and 25 Hz, our test results of the neuropathic symptoms by using MNSI questionnaire, showed no significant differences in therapeutic effects and also, that the frequency of 10 Hz PEMF, reduce neuropathic symptoms where the chronic diabetic polyneuropathy is present. When you look at the results of the assessment (table 3), the largest representation of patients is in the column with testing grade 3 (53.6% and 39.5%), indicating that the largest proportion of patients in both groups had neuropathic symptoms of significantly lower intensity. Examining analgetic effects of different frequences of magneti field, NRS pain scaling has shown that PEMF frequences of 25 Hz have significant better analgetic effect within chronical senzomotoric DPNE compared to 10 Hz frequences. The mechanism of how PEMF acts on neuropathic symptoms is not fully explained (13,14,15).

Magnet reduces blood viscosity, improves arterial and venous circulation, improves oxygenation and metabolism of blood (16,17,18,19). Webb et al. (17) suggest that the frequencies of 12 Hz PEMF improve local circulation on the foot and reduce tissue hypoxia in patients with diabetes mellitus, leading to reduction of ischemic pain.

In the treatment of diabetic polyneuropathy one can not ignore that the degenerative changes in nerve fibers in DPN are a specific process: both large and small nerve fibers are affected, the regeneration process does not follow the basic physiological mechanisms that are present in nerve injury, while the clinical picture often does not reflect the findings of electrophysiological studies (20,21,22,23).

The limitations of this study: we had no control group because the study examined the difference between the two therapeutic doses. Although the study was designed to examine the dosage of different frequencies of magnetotherapy in neuropathic symptoms, we believe that the study with a longer duration and electrophysiological testing would give its contribution to the responses of the mechanism of action of low frequency PEMF on signs of diabetic polyneuropathy.

Conclusion

The study suggests that the pulse electromagnetic field of different low frequencies reduces neuropathic symptoms in diabetic polyneuropathy. The study has also shown the PEMF frequences.

Results found in study, show that various low-frequency PEMF has significant therapeutic effect on neuropathic symptoms in patients with diabetic polyneuropathy.

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Comparison of a standard and a "one day diagnostic" approach to the investigation of infertile couples

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Abstract

Introduction: Investigation is often a long and exhausting process which is conducted on the basis of a "step by step " system. It is usually implemented over a longer period of time, month after month, with one diagnostic test per month or less. It is frustrating and inconvenient for patients, both in terms of time spent and obtained results.

Objective: To assess the advantages of the current diagnostic method of a couple infertility over the standard method, according to the rate of pregnancy, two years after completing diagnostic and treatment.

Methods: In each group, there were 70 patients younger than 38 years failing to conceive after 12 months. Our study group consists of patients who underwent one-day diagnostic procedures (including hormones, semen analysis, ultrsonography, hysteroscopy and transvaginal laparoscopy), whereas the control group consists of patients in whom some of the current methods of diagnostic were performed, and who were offered the possibility of a diagnostic completion and subsequently evaluation of the existing problems and possible therapeutic solutions.

Results: Evaluation of the success of different diagnostic procedures, the standard and the *one day diagnostic method,* according to the rate of pregnancy, 12 months after completing diagnostic- therapy, showed no statistically significant difference in pregnancy rate ($\chi 2$ p = 0.175) between the study group (21.43%) and the control group (32.85%), as well as after 24 months (the study group 47.1%, the control group 60.0%). Findings indicate that the total time to achieve pegnancy was 11.7 ± 6.1 (2-24) in the study group, whereas in the control group it was (KG) 22.2 ± 15.72 (4-82). Multivariate (ANOVA) analysis showed that the difference in the required time was statistically significant, p = 0.001.

Conclusions: Time to achieve pregnancy in patients who were tested with a "one day diagnostic" approach is shorter, namely achieving pregnancy was earlier in relation to the time needed for investigation.

Key words: infertility, laparoscopy, vagina, hysteroscopy, diagnostic

Introduction

Most international teams conduct investigation of infertile couples through five basic tests that are considered diagnostic fundamentals in this area: a semen analysis, confirmation of the presence of ovulation, hysterosalpingography (HSG), laparoscopy, and post-coital test(1). Testing is often a long and an exausting process that is carried out on a "step by step" basis. Firstly,it is usually implemented over a longer period of time, month after month, with one diagnostic test per month or less. Furthermore, it is frustrating and inconvenient for patients, both in terms of the time spent and obtained results.

Although laparoscopy has been considered the "gold standard" for detecting the diseases in the pelvic cavity, it requires general endotracheal anesthesia and it is performed in the operating room, not without risk and thus considered invasive and most uneconomical diagnostic- therapeutic procedure for the investigation and treatment of a couple infertility. Hysterosalpingography (HSG) is widely used as a first-line diagnostic method, but in more than one third of cases in which the HSG result is estimated as normal, the patient has a false belief about the absence of problems. These women are wrongly treated as those with a normal uterine cavity and undergo unjustifiably long, expensive and exhausting investigation of a couple infertility.

According to some clinicians, the main advantage of HSG is that it provides data on both the uterus and fallopian tube patency, in contrast to hysteroscopy, which only assesses the uterus cavity. However, there is an impression, especially now when there is the practice of introducing transvaginal laparoscopy, that HSG is a stepback. Nowadays mini-hysteroscopies with optics whose diameter is less than 3 mm are used, thereby reducing invasiveness and a need for dilatation of the cervical canal, as well as the use of anesthesia.

Transvaginal laparoscopy (TVL) is a novel technique for the exploration of the pelvic cavity that takes advantage of a mini-endoscopic technology and a liquid medium for visualization of a tubo-ovarian structure and a peritoneal pelvic cavity. Abdominal cavity is accessed through the puncture spot of the pouch of Douglas by applying sophisticated and highly secure technology, using an endoscope of a small diameter. To examine infertility, TVL is combined with a hysteroscopy and hromopertubation, and these procedures are performed in most cases on an outpatient basis, under local anesthesia, analgesia or brief sedation and together represent a transvaginal endoscopy (TVE).

In much of the recent literature, the terms of one-stop management have been used (2-4). Possessing advanced and highly sophisticated diagnostic possibilities ensures a complete evaluation of a female reproductive system that can be achieved in a fast, highly reliable and a secure way. Such a diagnostic of a couple fertility, would prevent delays in making an accurate diagnostic and thus adequate treatment would be carried out according to the infertility assessment in the shortest time possible. In this way, it will contribute to the preservation of their physical and mental health, improved social functioning and a work performance.

As for the principle of a *one day diagnostic* (including transvaginal ultrasound, hysteroscopy and transvaginal laparoscopy with salpingoscopy), it enables, with a great success, a complete insight into the fertility of couples in the shortest time possible, and consequently the effective ways of their treatment. Moreover, the use of hysterosalpingography (HSG), as a standard diagnostic method (including X-rays), is reduced as well as the number of the unnecessary laparoscopy in healthy women by about one third.

With the aim of a clinical implementation, the present study assesses the advantages of this current approach of the "one-day diagnostic" of infertile couples over the standard diagnostic method, in relation to the pregnancy rate after two years of monitoring.

Methods

The study was carried out as a prospective study in the study group, while in the control group it was partly prospective and partly retrospective. In both groups, there were 70 female patients with regular findings of their partners' semen analysis.

Our **study group** consists of female patients, with the problem of a couple infertility (inability to conceive after 12 months of unprotected intercourse), younger than 38 years, in whom the suitability for submission to a one-day diagnostic procedure was assessed (in order to obtain general data concerning a female patient -the length of a couple infertility, a menstrual cycle pattern, and previously undertaken diagnostic -therapeutic procedures).

The female patients who met the criteria for inclusion, came at the scheduled appointment bringing the results of their hormone analysis and their husbands' semen analysis. The required hormonal analyses were:follicle stimulating hormone (FSH), luteinizing hormone (LH),estradiol (E2) and prolactin (PRL) – from 3rd until the 5th day of cycle, and progesterone (PROG) from 21st until 23rd day of cycle.

As for the medical findings for the preoperative treatment, a basic blood analysis was done as well as the negative vaginal smear test.

The female patients, who did not fulfill diagnostic criteria for the one day diagnostic method or did not want to accept this option, were advised on the needs and possibilities of a further diagnostic and treatment with the standard diagnostic approach.All the female patients were given antibiotic prophylaxis (doxycycline tbl., in overall five tablets, starting one day before the intervention). Upon tranvaginal ultrasound examination, hysteroscopy and transvaginal laparoscopy were performed under general intravenous anesthesia. Bowel preparation was not required.

Hysteroscopy and transvaginal laparoscopy were performed in the operating room. As for hysteroscopy, we used 4.9 mm 30° hysteroscope

(Karl Storz,Germany) with saline solution (NaCl) as a distension medium. In cases where polyps, submucous myomas smaller than 2.5 cm, adhesions or septum were spotted, the very same were eliminated in the same procedure by using the Gynecare Versapoint Bipolar Electrosurgery System (Johnson and Johnson).

Transvaginal laparoscopy was performed through the puncture spot of the pouch of Douglas. The puncture was performed by the specifically designed system of troacar needles (Karl Storz, Germany). Both the needle and dilating troacars were taken out, and 2.9 mm 30° endoscope 30 cm long, with the outer covering, attached to a videocamera, was placed into the abdominal cavity.The correct position was checked and then the irrigation system was opened. Then, about 100 ml prewarmed Ringer lactate was inserted.

The fallopian tube patency was checked by inserting the Foley balloon catheter (8 fr) into the uterine cavity through which the diluted solution of methylene blue dye was instilled. Medical findings obtained upon performing transvaginal laparoscopy was entered into the database alongside the respective result of the possible pathohistological examination.

All results obtained during the examination were exposed to a female patient or a couple. Taking into account the previously taken results, a further plan of action was formed, and subsequently potential therapeutic guidelines and expected possibilities of a conception in individual cases were presented.

If one day investigation proved the necessity of the abdominal surgical approach, surgery was scheduled.

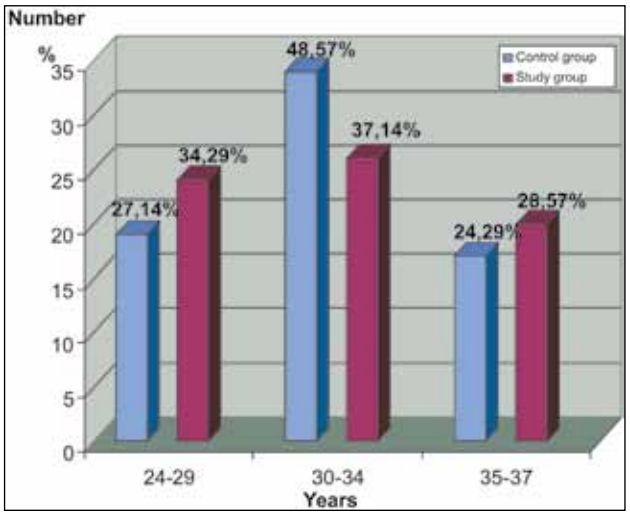
The control group consists of patients with the problem of a couple infertility (inability to conceive after at least 12 months of unprotected intercourse), younger than 38 years who were selected after obtaining the data of some previous diagnostic methods, and thus they were offered the possibility to complete diagnostic evaluation and subsequently the evaluation of existing problems and possible therapeutic solutions. All the data of the previous studies were obtained from medical records and were introduced into the database.

All the patients were followed up for 24 months after completing diagnostic and possible operative treatment and then contacted after24 months for taking insight into the number of conceived pregnancies.

Data from the questionnaires and the results of the performed diagnostic and therapeutic procedures were recorded in a specially designed database and further processed on a computer using an ACCESS database and statistical programs in EXCEL. During statistical analysis, obtained by these tests, the following statistical methods were used: univariate statistical methods (absolute number, number of respondents, mean, median,standard deviation), multivariate statistical methods (multifactorialanalysis), tests of statistical significance: student t-test, parametric X^2 - test.

Results

The average age of patients in the study group was 31.47 ± 3.83 years(24-37) and 31.61 ± 3.28 years (24-37) in the control group. There was no significant difference in the patients' age in both groups (p = 0.813). Graph 1. shows the distribution of patients by the group age (the studied and control group).



Graph 1. Distribution of women by age in the study and control group

The average length of married life until the ending of therapeutic-diagnostic procedure was 56.23 ± 32.03 months (95% CI 48.49 to 63.87) in the study group, whereas in the control group it was 61.87 ± 30.24 (95% CI 54.66 to 69.08) and there were no statistically significant differences in this parameter between groups (p = 0.286). Mi-

nimum and maximum length of the marriage in the study group was 15 and 203 months, while in the control group it was 13 and 148 months.

The average length of a marriage prior to the first examination in the control group (usually semen analysis or HSG) was 45.62 months (11-32 months), whereas the finalization of the diagnostic - therapeutic process took on average11.8 months (1-39 months)

Whilst in the study group, the average length of marriage prior the first examination, either matched the length of a marriage (in cases when the examination and treatment were completed), or it was1 to 4 months shorter, as on average was necessary for the implementation of the proposed surgical treatment, Table 1. There was a statistically significant difference in the length of time from the first examination until the completion of diagnostic -therapeutic procedure between the control and study group.

The evaluation of different diagnostic approaches, a standard and a "one day diagnostic" method, according to the pregnancy rate at least12 months after completing diagnostic-therapy showed no statistically significant difference in the pregnancy rate ($\chi 2$ p = 0.175) between the study group (21.43%) and the control group (32 , 85%), as well as after 24 months (study group 47.1%, control group 60.0%), Table 2.

However, analysis of the total percentage of women who conceived in relation to the total time of an infertile couple investigation, indicates a difference between the study and control group, Figure 2. We observed a greater number of achieved pregnancies in the study group, after 6, 12,18 and 24 months of a couple infertility investigation, but these differences were not statistically significant.

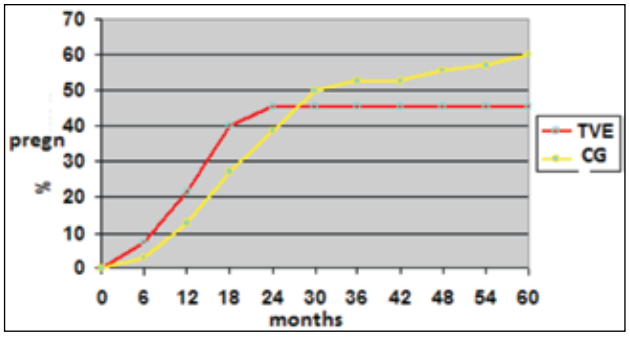


Figure 2. Women who achieved pregnancy during treatment

TVE- study group, CG-control group

There is evidently more conceived pregnancies during the first 12 months of the investigation in the study group (in most cases completed until then) than in the control group.

With the aim to evaluate two diagnostic-therapeutic approaches to a couple infertility – the

Table 1. The length of marriage and investigation of a couple infertility in groups

	Study group	Control group	P
Length of marriage* (month)	56,23 ± 32,03 (15 – 203)	61,87 ± 30,24 (13 – 148)	Ns
Time prior to The first investigation (month)	56,1 ± 31,29 (13-203)	45,62 ± 31,51 (11 - 132)	Ns
Time after completion of The first investigation of Diagn. /theraupetic Procedures (month)	0,42 ± 0,33 (0-4,5)	11,8 ± 10,78 (1 – 39)	P<0,001

* *the completion of diagnostic and therapeutic procedures*
Legend: month - months, NS - not statistically significant

Table 2. Pregnancy rate in the study and control group after 24 months

		Group		Total
		Study	Control	
Pregnant	NOT (no, %)	37 (52,9%)	28 (40,0%)	65 (46,4%)
	IS (no, %)	33 (47,1%)	42 (60,0%)	75 (53,6%)
Total		**70 (100,0%)**	**70 (100,0%)**	**140 (100,0%)**

standard (performed by a "step by step" system) and a contemporary one-day diagnostic method, in terms of overall time of procedure, it was found that the total time from the first investigation to pregnancy in the study (TVE) group was11.7 ± 6.1(2-24), whereas in the control group it was (CG) 22.2 ± 15.72 (4-82). Multivariate (ANOVA) analysis showed that the difference in the required time was statistically significant, p = 0.001.

The analysis of the cumulative percentage of pregnant women between the two groups is shown in Figure 3 and there is a statistically significant difference (p <0.001) in the time of achieving pregnancy.

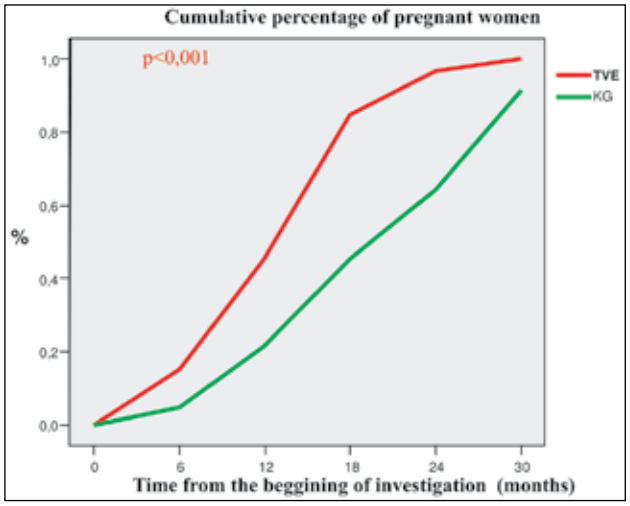


Figure 3. He cumulative percentage of pregnant women in months, in the study and control group

Discussion

Nearly half of the patients (48.57%) in the control group aged 30-34 years and 37.14% in the study group. About a quarter of patients in both groups (24.29% and 28.57% control study group) were over 35 year.

Bearing in mind that a female fertility declines progressively after 35 years, and particularly after 40 years, it is necessary to act quickly and appropriately. It is thus essential to provide effective diagnostic, which will offer, as soon as possible, all relevant data necessary to determine further guidelines for the treatment of an infertility, while the fertility rate is still acceptably high.

It takes about 3.7 to 4.6 years before investigation of a couple infertility begins in our surroundings, and from 4.6 to 5.1 (± 2.5) years of marriage until the completion of diagnostic - therapeutic procedures. How to interprete these data?

Is the period before the first examination too long, as well as the investigation itself and treatment in our surroundings? It is an ongoing question whether to wait or react. Specifically, we are aware that the initiation time for the infertility investigation (5) is crucial and that it is necessary to gain a greater significance, in order to avoid under treatment or over treatment. On the other hand, there are literature reports that more and more couples, who are well informed, address relatively early experts in infertility which results in the increase of assisted reproduction treatments, which these couples require. In this way, ART becomes the first-line therapeutic approach, but with all the risks and expenses it carries, as well as with its relatively high achievements (6). What we find in the literature (7) is that it is sometimes very difficult to convince patients to wait for the ART, unless after detailed instructions and examination, it becomes the method of choice. In our surroundings, both married couples and doctors, are hesitant to start the investigation on infertility, although it is known that the question of subfertility can be raised after 6 months of inability to achieve pregnancy (8.9). It is professionally accepted, and in order to avoid too much and too early treatment, to start with the first examination of a couple infertility after six moths. Thus, it definitely indicates a strong need to work on educating the wider population, as well as gynecologists on the necessity and benefits of timely and early initiation of a couple infertility investigation.

The optimal approach in the management of female infertility requires that the timing and method of the routine investigation are beneficial for the couple by avoiding both under and over treatment. Unfortunately, as for our surroundings, a couple infertility diagnosis and consequently reliable treatments are frequently unduly and excessively delayed.

The duration of infertility has been used as a major factor for timing routine exploration and starting treatment. It has been assumed that the longer the interval, the lower is the probability of conception, but on the other hand, investigations are usually not advised before 1 year of failing the pregnancy.

Individual approach, based on age, length of marriage, the data on the regularity of the menstrual cycle, previous gynecological diseases and

operations, determine the time for the initiation of an endoscopic and general evaluation of female infertility, not earlier than 6 months but not later than 12 months.

Evaluation of different diagnostic approaches, a standard and a "one day" diagnostic method, according to the rate of pregnancy after 12 months of completing diagnostic- therapy, showed no statistically significant difference in pregnancy rate between the study group (21.43%) and control group (39.7%) as well as after 24 months (study group 47.1%, control group 60.0%)

However, analysis of the total percentage of women who achieved pregnancy, according to the total time of a couple infertility investigation points out difference between study and control groups. The greater number of achieved pregnancies were observed in the study group after 6,12, 18 and 24 months from the initiation of a couple infertility investigation, although these differences were not statistically significant. There is also evidence for more pregnancies achieved during the first 12 months of investigation (which were in most cases already completed) in the study group in relation to the control group.

The analysis of the cumulative percentage of pregnant women between the two groups showed a statistically significant difference ($p < 0.001$) in the time to achieve pregnancy, in favour of patients who were investigated by a "one day diagnostic" approach.

By taking insight into all the results of achieved pregnancies in the study and the control group, practically the same success (conceiving pregnacy) was observed, since a professional team of doctors, who sooner or later, has all the relevant facts, determines further treatment. But, on the other hand, what is significantly different, it is the length of the time required to achieve this aim. To evaluate two diagnostic-therapeutic approaches to a couple infertility – the standard (a "step by step" system) and the "one day", in terms of total time of procedure from the initiation of investigation, it was found that the totall time to achieve pregnancy in the study group was significantly shorter (TVE - 11.7 ± 6.1months (2-24), by KG - 22.2 ± 15.72 months (4-82)).

With a view of the "step by step" system of investigation of the standard approach to the evaluation of a couple infertility, the cumulative percentage of pregnant women was significantly lower, compared with the results obtained in the study group. The overall time of achieving pregnancy is higher, namely achieving pregnancy was earlier in relation to overall time of the whole procedure, in the group of women who had a "one day" approach to investigation. As the participation of women of advanced reproductive age is high (24-28% over 35 years), and thus the initiation time and the length of investigation and treatment are essential to the outcome, this contemporary concept is time saving. It was also determined that in the contemporary "one day diagnostic" approach pregnacies are achieved significantly earlier, which certainly has its positive psychological and cost-benefit effect (11-19).

Conclusions

The proposed new approach to the investigation of a couple infertility will ensure short duration of investigation, highly accurate, minimally invasive, with no particular interference with professional activities, and will provide the maximum possible number of required data, necessary for the treatment of a couple infertility. This concept would be performed by combining transvaginal endoscopy,hysteroscopy, TVL, hromopertubation in a minimally invasive form, within a new conceptual approach, called a "one-day diagnosis of infertility.

The time to achieve pregnancy, in patients who underwent "one day diagnostic" approach is shorter, namely achieving pregnancy is earlier in relation to the total time of the whole procedure. As for the total time of this approach, from the initiation of the first examination to achieved pregnacy, it is significantly shorter, and consequently has a variety of health, social and emotional benefits.

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Analysis of patients with upper gastrointestinal bleeding: a study from Anatolian, Turkey Seasonal Distribution of Gastrointestinal Bleeding

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Abstract

The aim of our study was to analyze if we have a seasonal or circadian distribution of acute upper gastrointestinal bleeding (AUGIB) patients, and to evaluate the laboratory and demographic risk factors on mortality rates.

We scanned all of the files of the patients who had been diagnosed with AUGIB, for a ten year period. Datas' about seasonal distribution, circadian rhythm, admission hemoglobin, blood urea nitrogen and demographic variables were extracted from the charts.

We didn't observed a seasonal distribution for AUGIB inspite of we excluded the drug effect by analyzing its seasonal distribution. Also our patients were admitted mostly nights which was compatible with the literature. Whereas our admission rate between 24 and 06 hour period was low. Admission low hemoglobin level, impaired blood urea nitrogen and creatinine level, and patients with advanced age has a higher mortality rate (p=0.03, p=0.003, p=0.02, p=0.001 respectively).

Climatic factors effect on the seasonal distribution among AUGIB patients is not observed. Other risk factors (mental-physical) should also be evaluated. Low hemoglobin level, impaired renal functions and advanced age are bad risk factors for prognosis.

Key words: Peptic ulcer, gastrointestinal hemorrhage, seasonal variation, circadian rhythm, mortality.

Introduction

Acute upper gastrointestinal bleeding (AUGIB) is a common health problem for the emergency physicians, inspite of the improvements for diagnosis and treatments, which has a hospital mortality of approximately 10% and can rise to 30% for the ones who bleed as in-patients [1]. Relationship between AUGIB and seasonal-circadian rhythms have been investigated in the last 50 years and the results are variable. An increased incidence in winter, spring and autumn, [2]decrease in summer, [3]and no seasonal influence at all [4] have all been reported. Whereever the mechanism for the seasonal variation is unclear. We presented our results and compared them with the literature and analyzed the admission demographic-laboratory characteristics and mortality.

Material - method

We scanned all of the files of the patients who had been diagnosed as AUGIB (K92.2 with ICD-10 cod) in Sivas medicine faculty emergency service and were then referred to gastroenterology ward between 1 January 2000 and 31 December 2010. The diagnosis were confirmed by endoscopic results or from the epicrisis for them who didn't underwent endoscopic examination. For each case the demographic data's (age, sex), admission laboratory results (hemoglobin, platelet, blood urea nitrogen, creatinine, hepatic markers, Prothrombin Time (PT), Partial Thromboplastin Time (PTT), International Normalized Ratio), symptoms, admission hour, day, month and year were extracted from the charts. Seasonal periods were divided as usual; spring (March to May), summer (June to August), autumn (September to November), and winter (December to February). Two-tail Chi-square test was used to examine the differences for seasonal distribution-gender. Mann

whitney U test was used to compare the risk factors for mortality.the mean values for risk factors were calculated with independent T test. SPSS15.0 (Statistical Package for Social Sciences) was used for all statistically analyses. A $p<0.05$ was considered statistically significant.

Results

Demographic and laboratory distribution of AUGIB cases:

We examined 491 charts of AUGIB which could be achieved. As most of the studies, the AUGIB rate was more common in the men population; 314 (%64) male and 177 (%36) female. Age range of the patients was between 14 and 96 years. Mean age of all patients was 58.4±17.7 years (60.7 years women, and 57.0 years for men). Most of them (70%) were over 50 years. The admission clinical and laboratory results are shown in Table 1.

The inpatient mortality risc factors were calculated and shown in Table-2.

The seasonal and circadian rhythm of AUGIB:

The mean patient admission rates for each month were as follows; January 25, February 28, March 37, April 32, May 44, June 35, July 52, August 57, September 54, October 58, November 36, and 32 patient had admitted in December. Our data on the seasonal variation of AUGIB shows a greater incidence in autumn (n=148, 91 male - 57 emale) and summer (144, 95 male - 49 female). The lowest rate was in winter with 85(54 male -31 female) patients. In spring the number of the patients was 114 (74 male - 40 female). Statistical difference of the patients distribution according to the seasons was significant (χ^2=21.1, p=0.001) and the low admission rate in winter was statistically different when compared with spring, summer and

Table 1. Demographic and laboratory results of acute upper gastrointestinal bleeding

Clinical or laboratory characteristics		N %	Mean±SD
Admission complaints	Hematemesis	121 (24.7%)	
	Melena	186 (37.9%)	
	Hematochesia	15 (3.1%)	
	Syncope	41 (8.4%)	
	Haematemesis and melena	75 (15.2%)	
	Other	53 (10.7%)	
Physical signs	Abdominal pain	98 (20.%)	
	Nausea-vomiting	223 (45.4%)	
Laboratory Characteristics	Helicobacter pylori	10 (2%)	
	Hepatitis B	25 (5.1%)	
	Hepatitis C	26 (5.3%)	
	Hepatitis B+C	3 (0.6%)	
	Hemoglobin		10,11±2.8
	Blood urea nitrogen		32,5±24,6
	Creatinine		1,15±0.8
	Platelet		233.570±98.582
	International Normalized Ratio		3,5±5,38
	Mortality	19 (3.9%)	

Table 2. Risk factors for mortality

Risk Factors	Mean Value±SD Among Ex Patients (n=19)	Mean Value±SD İn Discharged Patients (n=472)	p
Haemoglobin (gr/dl)	8.65±2.4	10.17±2.8	0.03
Blood Urea Nitrogen (mg/dl)	47.0±28.16	32.0±24.3	0.003
Creatinin(mg/dl)	1.6±1.3	1.1±0.8	0.02
Age(year)	71.1±10.8	57.9±17.8	0.001

autumn seasons. Gender had not an effect on the seasonal distribution (p>0.05) (Figure1).

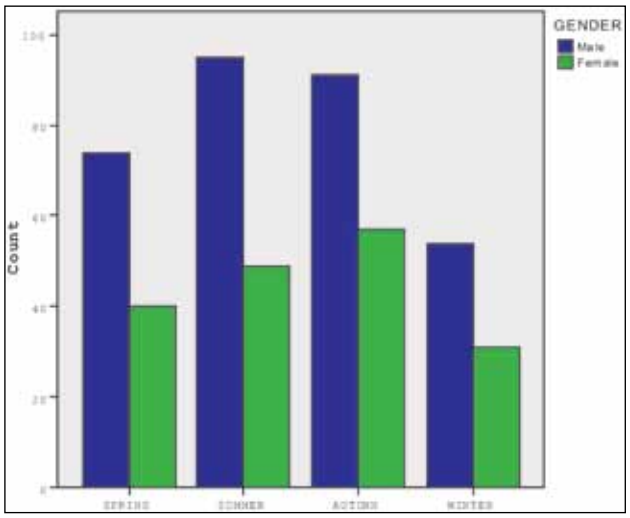

Figure 1. Seasonal distribution of the patients according to their sex

The patients admission rates were classified in four six hour periods and it was significantly low between 0-6 hours (n=67). Whereas the numbers between 7-12, 13-18 and 19-24 were nearly similar (n=143, n=133, n=148 respectively) (Figure 2).

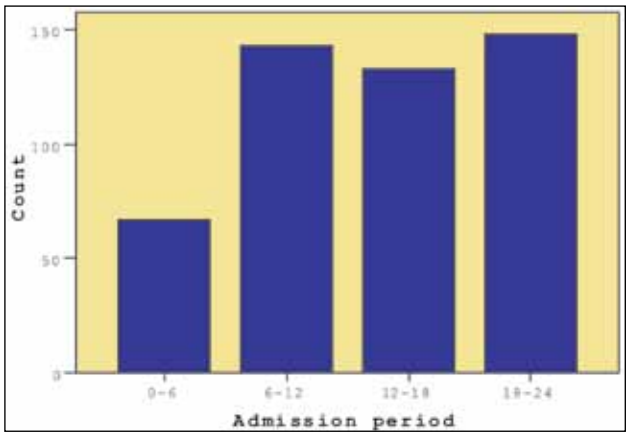

Figure 2. Numbers of the patients according to their admission time periods

The endoscopic examination results of AUGIB:

From 491 patients 413 underwent endoscopic examination. Endoscopic examination was not made in some patients while there wasn't an endoscopic device in a time period in our university or some patient had refused the examination. Gastric and duodenal ulcer concomitation rate was the most frequently seen result among endoscopic examination in spring, summer and autumn seasons. Whereas gastric ulcer (n=11) was seen more in winter (Figure 3).

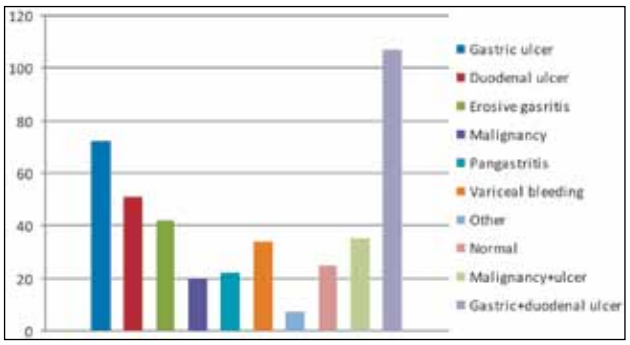

Figure 3. Endoscopic examination results

It is known that some kind of drugs increase the AUGIB rate. Among our 490 patients 306 were current drug users at the admission time. Acetylsalicylic acid was the most used (n=88) drug before nonsteroidal anti inflammatory drugs (n=60). Twenty two patients could not be protected from AUGIB in spite of they were using proton pump inhibitor or H2 receptor blocker for peptic ulcer complaints (Figure 4)

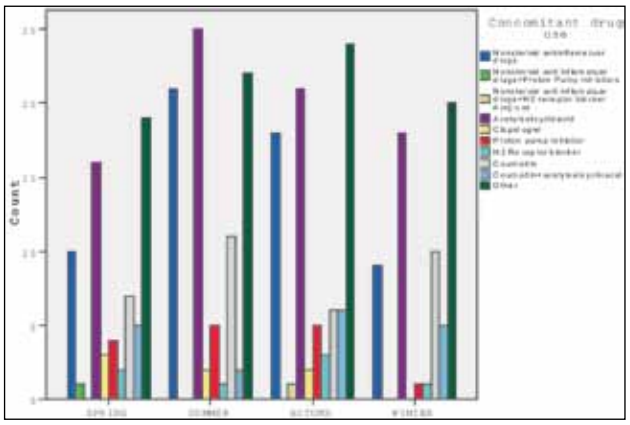

Figure 4. Concomitant drug use at the admission time in acute upper gastrointestinal bleeding

Inorder to evaluate the drug effect on the seasonal distribution; we have compared the two groups who were using a predisposing drug for AUGIB or not at the admission time. We didn't found any significant effect of the drugs on the seasonal admission rate for AUGIB (p>0.05) (Table 3).

Table 3. Risky drug effect on the seasonal distribution

Seasonal Distribution	Risky drug user patients (n)	Non-user patient (n)	Total Number (n)
Spring	42	72	114
Summer	61	83	144
Autumn	54	94	148
Winter	42	43	85
Total	199	292	491

$\chi^2 = 1.42$ $p = 0.23$

Discussion

In the present study we evaluated the seasonal effect, clinical and laboratory characteristics among AUGIB patients in Sivas, by analysing the charts of the patients, who were admitted between 2000-2010 in a university hospital emergency department. The resident population of Sivas and the surrounding cities where patients were admitted is nearly 1.5 million people.

Like most of the studies [2,5]the male population rate was higher than female and the mean age was comparable with some studies [6-8]. The gender had not an effect on the seasonal distribution [7,9].

Melena and haematemesis are the invariable physical signs for upper gastrointestinal bleeding. The vomitus can be bright red (fresh) or coffee ground (altered blood). Melena consists of the passage of black tarry stools caused by bacterial degradation of haemoglobin and is generally due to UGI sources of bleeding, although small bowel and proximal colonic lesions can also be the cause.[10,11]Tsai et al. observed melena (58.1%) as the most common presenting symptom of major gastrointestinal hemorrhage. Haematemesis and melena's rate was 20.2% and haematemesis alone was 10.5%. [2] Melena was our most observed physical sign (37.9%) and haematemesis followed it with 24.7%. Hematochezia usually suggests a lower GI source of bleeding, since blood from an upper source turns black and tarry as it passes through the gut, producing melena. However, up to 5% of patients with bleeding ulcers have hematochezia. Our rate was 3.1% and is comparable with this. The rest complaints which referred our patients to emergency department were syncope (8.4%), and other complaints like vertigo, fatigue, palpitation (10.7%).(Table 1)

There is wide variation in mortality for AUGIB reported by different centers. Due to the variation in study methods; population mean age, comorbidities, endoscopic results and inclusion criterias, comparison of mortality rate is difficult. In a review it is established that mortality rates differ between 3 and 14% according to the different population based surveys. In our study it was 3.9% and is at the lower limit.[13]Numerous prognostic factors and classifications (BLEED, Rockall..) have been described in literature to be associated with a lethal outcome. Kalula et al [12] made bivariate analysis and found that patient over 60years or with a haemoglobin level below 10gr/dl had a poor outcome. In our study mean haemoglobin level was significantly low (8.65gr/dl) and the mean age was high (71.1±10.8years) among the patients who died. In Blatchford classification blood urea nitrogen increase is among the risk parameters. [14]Serum creatinine level is also found as a risk factor for overall mortality by Zimmerman et al [15]. Both of the renal functions were significantly increased among the patients who died in our gastroenterology ward (Table2).

Several studies are made about the seasonal fluctuations of AUGIB. In most studies seasonal fluctuations effect is observed, [2,16-19] but some studies didn't show any significant seasonal variation in the incidence of AUGIB [4,20-23]. Beside this in a study in Greece [19], seasonal fluctuation with low prevalence in winter and an increase in spring and autumn, with two peaks in April and October, was observed. Nomura et al[24] found a seasonal distribution among the gastric ulcer patients, with an increase in winter, but the duodenal ulcer distribution did not show any difference. The high incidence in winter is explained by some investigators with different reasons. While Langman et al. [25] reported that the intake of salicylate drugs increases in winter, Xirasagar et al.[26] and Zimmerman et al.[27] attributed it to the use of non-steroidal anti-inflammatory drugs which may be associated with increased ulcerative bleeding

and this could be because of an increase in the hemorrhage rate in winter. Natelson [28] showed that cold increases the mucosal damage to the duodenum of mice, Moshkowitz [29] explained it with the increase-decrease of H pylori infections in winter and summer. The seasonal distribution of our study included a low prevalence in winter like Thomopoulos et al. [19]. Inorder to exclude the risky drug effect we analyzed their seasonal distribution and didn't found any difference (Table 3, Figure 4).

Moore et al [30] reported that the gastric acidity increases from the evening to the night and decreased during that from the early morning to the hours before noon. This circadian rhythm is known as risk factor for AUGIB time. Du et al. [9]observed a circadian rhythm of AUGIB in Beijing. The admission rate in their study was high between 20-24h, 16-20h and 0-4h time periods respectively. Siringo et al. [31] analyzed circadian occurrence of variceal bleeding in patients with liver cirrhosis and observed that most of the haematemesis occurred at 21 and 24h. Most of our patients' admission time resembled these studies. Whereas our admission rate between 0-6h periods was low. This can be due to the transport problems to the hospital.

Jureidini et al [5] analyzed 100 patients with AUGIB. Among their endoscopic results peptic ulcer (duodenal ulcer 36%, gastric ulcer 12%, and erosive gastritis 19%) was the most common cause. Also Chassaignon et al [6] observed peptic ulcer (ulcers 34%, gastritis 21%) as the most common result at endoscopic examination. Sezgin et al [7] analyzed the results according to the season and combined gastric or duodenal ulcers as peptic ulcer. Sezikli et al [32] compared the endoscopic results of two time periods 1993-2008. They observed that peptic ulcer was high in all seasons and time periods. Duodenal and gastric ulcer concomitation was with 76.9% the most common result in 2008. Our results resembled the literature, we observed also a high frequency of concomitant gastric and duodenal ulcer (25.9%) bleeding rate (Figure3).

At the end of our study we observed that admission low hemoglobin level, increase age, impaired renal functions are risk factors for mortality, compatible with the literature. Whereas we didn't found any seasonal distribution of AUGIB which was found in most studies. While this was an retrospective study we could not determine the risky drug dose taken daily. A prospective study with all of the stress factors (mental and physical) and climatic factors included can give a better result .

Acknowledgment

The authors gratefully acknowledge for the assistance from the Archieve department Cumhuriyet University Medicine Faculty Hospital.

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Endothelial dysfunction and interaction between inflammation and coagulation in sepsis and systemic inflammatory response syndrome (SIRS)

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Abstract

Pathophysiological mechanisms that are responsible for the development of systemic inflammatory response syndrome (SIRS), as well as sepsis, are extremely complex. They are based on the release of potent bioactive cytokines, chemokines, as well as on the activation of components of complement. All these complex reactions lead to certain changes in endothelium, and they also affect the regulation and lead to activation of coagulation (extrinsic and intrinsic pathway). They also activate the process of fibrinolysis which all contribute to coagulation abnormalities, and consequentially has impact on the development of multiple organ dysfunction. Endothelium is a bond between complex inflammatory reactions and activation of coagulation and it has a central role in activation and modification of haemostatic abnormalities during the systemic inflammation. Modification of inflammatory response by activation of coagulation also occurs by various mechanisms. These mechanisms include the reactions in which protease activated receptors, activated protein C, antithrombin and many other molecules are involved. The aim of this review is to illustrate the complex interaction between inflammation and coagulation with the focus on the significance of endothelium as the bond and the base of these complex reactions. The contribution of understanding and monitoring of coagulation activity parameters as well as biomarkers of endothelial dysfunction could find its place in potential new therapeutic approaches.

Key words: Endothelium, Coagulation, Sepsis, Systemic inflammatory response syndrome

Introduction

Endothelium is a structure built from endothelial cells that line the inside of blood vessels. It is composed of approximately 1-6x10^{13} endothelial cells that cover an area of 1 to 7 m^2 of human body. The endothelium has many pivotal functions in physiology of humans and the most important ones are regulation of the blood flow and the tone of blood vessels, as well as the regulation of vascular permeability and the coagulation activation (1-3). Endothelial cells synthesize many bioactive substances, like prostaglandins, growth factors and many other bioactive molecules.

The systemic inflammatory response syndrome (SIRS) to different stimuli is defined as the presence of two or more criteria from following: Body temperature greater than 38 ◦C or less than36 ◦C; heart rate greater than 90 beats/min; respiratory rate greater than 20 breaths/min or hyperventilation with a PaCO2 less than 32 mmHg; white blood cell count > 12000/mm 3, <4000/mm 3 ,or with >10% immature neutrophils. The etiology of SIRS can differ from infection (then it is recognized as sepsis), to pancreatitis, trauma and tissue injuries, burns, ischemia and hemorrhagic shock, as well as organ damages caused by immunologic process or by exogenous administration of mediators of inflammation (4,5).

Pathophysiological mechanisms that are responsible for the development of SIRS, as well as sepsis, are extremely complex. They are based on the release of potent bioactive cytokines, chemokines, as well as on the activation of components of complement (6).

All these complex reactions lead to certain changes in endothelium, like swelling and detachment of endothelial cells which leads to extravasation of fluids to interstitium. Besides these structural changes, many functional changes occur as well, such as the expression of adhesion molecules which results with leukocyte trafficking and platelet adhesion. Furthermore, endothelial cells also have the ability to express adhesion molecules and to release their own mediators of inflammation. These complex reactions of systemic inflammation also affect the regulation and lead to activation of coagulation (extrinsic and intrinsic pathway), and they also activate the process of fibrinolysis (7,8), which all contributes to coagulation abnormalities, and consequentially has impact on the development of multiple organ dysfunction (9,10).

The effects of inflammation in sirs and sepsis on coagulation

Impairments of activation of coagulation are very frequent in the population of critically ill patients. These abnormalities have different manifestations, ranging form mild activation of coagulation, which can be detected only by very sensitive haemostatic markers, over the decrease in platelet count or prolonged coagulation times to very serious and life-threatening conditions like disseminated intravascular coagulation (DIC) (9,11). Epidemiological research shows that these abnormalities are clinically significant in 50-70% cases and that 35% patients with sepsis has positive DIC criteria (12,13).

In physiological conditions the activation of coagulation is blocked with many mechanisms in which endothelial cells have pivotal role. They produce prostacyclines and nitric oxide (NO), as well as many other vasoactive substances that prevent the adhesion of platelets and keep the tone of blood vessels , which all keep the physiology of microcirculation regulated (14).

During inflammation, the physiology of endothelial cells is affected by many proinflammatory mediators which favor process of coagulation. In these conditions, endothelial cells express specific cell adhesion molecules (CAM), such as selectins (E,P,L), integrins (β1,β2), and the immunoglobulin superfamily (intercellular adhesion molecule [ICAM]-1, vascular adhesion molecule [VCAM]-1, etc.), which all have important roles in interactions of endothelial cells with leukocytes. These molecules, in addition to their impact on inflammation, have a significant effect on the coagulation process (8,15,16).

One of the main mechanisms that activates coagulation during systemic inflammation is tissue factor (TF) mediated thrombin generation. Tissue factor plays a central role in the initiation of coagulation in the conditions of inflammation and is released when the integrity of blood vessels is disrupted or when endothelial cells and cells that circulate in blood (predominantly monocytes and macrophages) start expressing IL-6 dependent tissue factor expression. Further on, tissue factor binds to factor VIIa and that leads to a cascade of reactions which results with conversion of fibrinogen to fibrin (17, 18).

Inflammatory process activates platelets by the influence of inflammatory mediators, or directly with endotoxins. Thrombin is strong activator of platelets as well. The expression of P-selectin on the surface of activated platelets leads to adhesion of platelets to endothelial cells and leucocytes and stimulates coagulation (18-20). The important role in the formation of clots on damaged endothelial surface has the release of Von Willebrand´s factor (vWF). The release of vWF takes place whenever endothelial layer is activated or injured, and VWF level is marked as the biomarker of endothelial injury (21).

Microparticles that are fragments of activated and apoptotic cells, as well as apoptotic cells contribute to development of procoagulant state and to the activation of thrombin (22-24).

As already mentioned, the activation of coagulation is inhibited in physiological conditions, and endothelial cells have a pivotal role in this inhibition. There are three important anticoagulant pathways that regulate the activation of coagulation and these are: antithrombin (AT), tissue factor pathway inhibitor (TFPI) and protein C (25,26).

Antithrombin (AT) prevents coagulation by inactivation of thrombin, factors Xa, IXa, XI and XII as well as the bond of factor VIIa with tissue factor (27). The level of antihrombin is decreased in sepsis and in systemic inflammation, because of impaired synthesis, as well as because of degradation by elastase released from activated neutrophils and

also because of the consumption which is a result of thrombin generation (17, 28). Literature data imply that during sepsis proteoglycans that are important for the regular function of antithrombin system are suppressed or inactivated (27, 29, 30).

Tissue factor pathway inhibitor (TFPI) inhibits tissue factor activation of factors X and IX (26). The significance and precise role of TFPI in the regulation of coagulation in sepsis and systemic inflammation is not completely clear.

Protein C is inactive zymogene that is present in plasma in concentration of 4 mcg /ml. It is activated by the thrombin-thrombomodulin (TM) bond (27). Activated protein C (APC) acts with its co-factor protein S to prevent coagulation by proteolytical degradation of co-factors Va and VIIIa (17). The endothelial protein C receptor (EPCR) accelerates the activation of protein C, and binding of APC to this receptor may amplify its cytoprotective effects. When APC dissociates from EPCR and binds to protein S (PS) the anticoagulant effect dominates (31).

In systemic inflammation, TNF-α, IL-1β and lipoplysacchardies can suppress thrombomodulin which affects the activation of protein C and procoagulant state is being favourised (31). The level of protein C is low in inflammatory states, because of impaired synthesis and increased consumption as well as because of amplified degradation with proteolytic enzymes (17). Sepsis can also induce resistance toward APC by mechanisms which are dependent on factor VIII levels (released from endothelial cells), but these mechanisms still need further clarification (17, 33).

However, it is very hard to determine if activation of coagulation is the cause of organ dysfunction or if it is just a consequence of a systemic inflammation.

Fibrinolytic system, with its main enzyme plasmine, also has a very important role in the coagulation process. Inhibition of the fibrinolytic system is a key element of the pathogenesis of fibrin deposition during severe inflammation (34).

Inflammatory process is characterized with increased level of plasminogen activator inhibitor 1 (PAI-1), TNF-α and IL-1β. Endothelial cells have a very important role in modifying the fibrinolytic process during sepsis and systemic inflammation, because they synthesize profybrinolitic factors as well as PAI-1 (22). The result of these processes is inhibition of fibrinolytic system, and insufficient fibrin removal, with consequential development of microvascular thrombosis (12). Madoiwa et al. showed in thir study on 1627 patients that the levels of PAI-1 were significantly higher in the group of patients who had sepsis and DIC in comparison to the group of non-septic DIC patients. The level of this biomarker in the group of patients with sepsis and DIC correlated with mortality rate (35).

The effects of coagulation in sirs and sepsis on inflammation

The activation of coagulation yields proteases that influence inflammation by binding to protease activated receptors (PARs). These receptors are localized on endothelial cells, mononuclear cells, platelets, fibroblasts and smooth muscle cells (34). There are four different types of PARs, and their most important characteristic is that they function as their own ligands (36). PAR-1, PAR-2, and PAR-4 are thrombin receptors, while PAR-1 is also receptor for tissue factor-factor VIIa complex, as well as for factor XA (26). Factor Xa, thrombin and fibrin can activate endothelial cells, and that impacts the synthesis of IL-6 or IL-8 (34). Binding of the tissue factor-factor VIIa complex to PAR 2 influences the inflammatory response by macrophages, neutrophils and by producing proinflammatory cytokines (TNF-α i IL-1β) (26).

Activated protein C (APC) also has a very important role in modification of inflammatory response. The influence of APC to the inflammatory process most likely occurs by EPCR (17,37). APC -EPCR bond influences gene expression profiles of cells by inhibiting endotoxin-induced calcium fluxes in the cell. There is also evidence that binding APC to EPCR can activate PAR-1 and consequentially modify cytokine production. APC also alters inflammation by inhibition of leukocyte trafficking and their adhesion to endothelium. Protein C also inhibits the apoptosis of endothelial cells (17,18).

Activation of coagulation modifies inflammation also by antithrombin. Antithrombin induces prostacyclin release form endothelial cells (38). Prostacyclins reduce adherence of neutrophils to the wall of blood vessels and decrease the production and release of cytokines and chemokines in from endot-

helial cells (17,38). Activated platelets contribute to local inflammatory process by the secretion of chemokines and IL-1 which activate leukocytes and promote neutrophil and monocyte adherence. After that, activated neutrophils release elastases, which destroy thrombin and cleave TFPI. The endogenous controls for thrombin generation are furthermore disrupted by the loss of thrombin and TFPI and that leads to a vicious cycle of systemic inflammation and coagulation abnormalities (39).

In general, the release of proteases increases inflammatory response by different proinflammatory mediators, which on the other hand show procoagulant effect that can lead to DIC. Endothelium is a bond between complex inflammatory reaction and activation of coagulation and it has a central role in activation and modification of haemostatic abnormalities during the systemic inflammation (15).

Potential therapeutical approaches

Since the activation of endothelium, which is followed by disruption of coagulation, is recognized as one of the most important pathophysiological mechanisms that lead to organ dysfunction in systemic inflammation and sepsis, studies are aimed toward potential therapeutic models that could suppress or annihilate this effect. International guidelines for management of severe sepsis and septic shock from 2008. (40) suggest that adult patients with sepsis induced organ dysfunction associated with a clinical assessment of high risk of death, most of whom will have APACHE II score $\geq$ 25 or multiple organ failure, receive recombinant human activated protein C rhAPC if there are no contraindications (Grade 2B except for patients with in 30 days of surgery where it is Grade 2 C). Relative contraindications should also be considered in decision making. These guidelines are mostly based on PROWESS study (The Prospective Recombinant Human Activated Protein C Worldide Evaluation in Severe Sepsis), which showed 6,1% in total mortality reduction, but also illustrated raise of risk of serious bleeding for 1,5% in group of patient who were treated with rhAPC in contrast to group of patients who received placebo (41). Another study significantly contributed to these guidelines and that is ADDRESS study (Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis). This study evaluated the use of rhAPC in patients with severe sepsis associated with either single organ failure or an APACHE II score below 25. The study was canceled, after enrolling 2,640 patients because there was no indication of a positive effect (42). Bearing these results in mind, the use of rhAPC in septic patients still stays a matter of dispute. Two large multicenter, randomized, double-blind trials investigating the use of rhAPC in septic shock are currently in progress, and the results from those studies will certainly give a contribution to new therapeutic concepts (43,44).

Besides studying the use of rhAPC, there are other research projects aimed towards improving the prognosis of systemic inflammation by modifying coagulation.

Experiments that were performed on animals and humans showed that the inhibition of tissue factor pathway prevented endotoxemia induced activation of coagulation (15, 17, 32, 45, 46).

Other studies suggest that administration of inactivated factor VIIa, ATIII, APC, or TFPI blocked activation of the coagulation and inflammatory pathways, reduced organ damage, and improved survival in animal model of sepsis (16,32,33,47).

The effects of antithrombin on animal models of septic shock pointed out the protective role of antithrombin in septic shock (38,48). However a large, multicenter, randomized controlled trial didn´t show significant reduction in mortality in patients with sepsis who were treated with antithrombin (49).

Considering the fact that some trials failed to demonstrate that the use of TFPI and antithrombin reduces mortality in the group of septic patients (49-51), as well as considering the present controversy about the use of rhAPC, further trials and studies aimed towards new therapeutic approaches that can modify the coagulant response and activation of endothelium during systemic inflammation and sepsis are required.

Conslusion

Systemic inflammation and sepsis definitely lead to activation of coagulation, and this process also noticeably affects inflammatory activity, whereby there is an extensive cross-talk between these two processes. The endothelium has a central role in these complex activities. There are many trials

aimed in the direction of new therapeutic approaches that could decrease the mortality in septic patients by modifying endothelial dysfunction and consequential proinflamatory and procoagulant events. Monitoring of coagulation activity parameters as well as biomarkers of endothelial dysfunction have significance, not only because of risk evaluation and categorization of patients in the means of disseminated intravascular coagulation (DIC) and multiorgan dysfunction syndrome (MODS), but because of identification of subgroups of patients who could also benefit from certain therapeutic approaches.

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Relationship between coping strategies with stress and sport confidence

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Abstract

Stress and sport confidence have been researched by many scientist for years. Because, both of these variables could affect performance of athletes. Sport confidence might be affected by coping preferred strategies or higher sport confidence could result in choosing more logical coping strategies. Therefore the aim of this research is to find the relationship between coping strategies and sport confidence. The Coping Inventory and Sport Confidence Inventory were used. Analysis showed that sports confidence significantly correlated with refuge in religion, external assistance, cognitive restructuring, active plan. Males had significantly higher points on refuge in religion, emotional escape and biological and chemical escape. Moreover, significantly higher scores were found in external assistance scores for females. A significant difference in terms of sports year and educational level were also detected. Results were discussed according to the relevant literature.

Key words: Coping with stress, sport confidence, athletes

Introduction

Stress which is a term that is used by everybody in daily life is a feeling that is felt when people perceive a threat to their physical and psychological wellbeing (Atkinson, 1999: 489). Stress has appeared to be as an old feeling as human being and there have been many researches on it. Hard and competitive Industrial life of 21st century we have experienced so far caused that stress appeared to more distinct and it affects people's life (Cartwright & Cooper, 1997: 3). Due to this effect, different behaviors related to situations people experience are observed and coping strategies with stress have emerged. Coping strategies are behaviors or psychological reactions that are seen in order to decrease, deplete or resistance to emotional tension which has been resulted from stress factors (Koc & Tutkun, 2001). In this respect, coping strategies can be listed as follows.

Emotion focused strategies

Seeking external assistance: This strategy is related to finding a solution by an external source. There is a tendency to external assistance.

Refuge in religion: It refers to refuging to a divine power, praying and getting strength from faith.

Emotional escape: It involves abstracting themselves from the cause of stress and this is the way of coping stress.

Biochemical escape: In this technique, there is a tendency of physical metabolism to change. Some of these tendencies could be smoking, drinking alcohol and taking medicine or drugs.

Problem focused strategies

Active planning: It involves actively doing something, getting the job done, increasing active effors, making plans, focusing on present and the problem by rational methods.

Cognitive restructuring: Accepting the problem and trying to find solutions. This strategy emphasizes people's point of view rather than activities related to changing the situation (Koc & Tutkun, 2001).

Confidence is one of the most important factors of psychological well-being in sport context. An enhanced confidence which result from physical activities is an index for the promotion of exercise and sport participation. Sport confidence is the belief that a person doing sports possesses about their ability to be successful in sport in general (trait sport confidence) and in specific sport competitions (state sport confidence) (Vealey 1986 as cited in Callow & Hardy, 2001: 3). Performance goals could provide standards that can increase sport-confidence whereas outcome goals could undermine sport-confidence (Martin & Gill, 1991: 150).

There have been many research related to stress and sport confidence. Differences in the selec-

tion of sport confidence sources may be partially explained by individual differences in perceptions of success, or goal orientations (Magyar & Feltz, 2003; Magyar & Duda, 2000). It has been stated that competitive orientations contribute very little to an athlete's level of state sport-confidence (Martin & Gill, 1991: 150). Previous results show that there was a significant difference between male and female elite soccer player's sources of sport confidence of mastery, demonstration of ability, physical and mental preparation, physical self preparation, social support, coaches' leadership, vicarious experience and environmental comforts (Adegbesan, 2007).

It was initiall thought that there might be a relationship between coping strategies with stress and sport confidence. Sport confidence might be affected by coping preferred strategies or higher sport confidence could result in choosing more logical coping strategies. Therefore the aim of this research is to find the relationship between coping strategies and sport confidence.

Method

Measures

The Coping Inventory. In order to determine participant's coping strategies, the Coping Inventory was used (Ozbay & Sahin, 1997). The Coping Inventory has two 6 subscales (active plan , refuge in religion, external assistance, emotional escape, biological and chemical escape, cognitive restructuring).The scale has 43 items, and each item is scored on a fivepoint Likert scale (0 " always false" to 4 " always true").

Sport Confidence Inventory: The TSCI (Vealey, 1986) is a scale consisting of 13 items. Participants are asked to report the intensity of their self-confidence for various aspects of performing on a 9-point Likert scale which range from 1 (low) to 9 (high).

Results

The relationship between sportive confidence and behaviors of overcoming stress is examined in Table 1. The analysis revealed that there was a positive relationship among the behaviors of sportive confidence, refuge in religion, external assistance, active planning, cognitive restructuring and overcoming stress. In other words, it could be said that when there was an increase in the attitudes of external assistance, active planning, cognitive restructuring, overcoming stress and refuge in religion, an increase was also observed in sportive confidence. A meaningful relationship was not found among emotional escape, biological and chemical escape, sportive confidence and behaviors of overcoming stress.

Table 1. The relationship between sportive confidence and behaviors of overcoming stress

Correlations

		Sport confidence
refuge in religion	Pearson Correlation	,082*
	Sig. (2-tailed)	,025
	N	736
external assistance	Pearson Correlation	,088*
	Sig. (2-tailed)	,016
	N	736
active plan	Pearson Correlation	**,167****
	Sig. (2-tailed)	**,000**
	N	**736**
emotional escape	Pearson Correlation	,033
	Sig. (2-tailed)	,367
	N	736
biological and chemical escape	Pearson Correlation	**-,008**
	Sig. (2-tailed)	**,833**
	N	**736**
Cognitive Restructuring	Pearson Correlation	,086*
	Sig. (2-tailed)	,020
	N	736

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table 2. T values related to the difference between female and male behaviors in overcoming stress

	gender	N	Mean	Std. Deviation
refuge in religion	male	429	2,43	,85
	female	306	2,23	,97
external assistance	male	429	2,49	,63
	female	306	2,62	,68
active plan	male	429	2,65	,61
	female	306	2,72	,53
emotional escape	male	429	1,70	,60
	female	306	1,93	,55
biological and chemical escape	male	429	1,04	1,04
	female	306	,84	1,04
Cognitive Restructuring	male	429	2,40	,71
	female	306	2,31	,68

	t-test for Equality of Means		
	t	df	Sig. (2-tailed)
refuge in religion	2,94	733	,003
external assistance	-2,82	733	,005
active plan	-1,49	733	,136
emotional escape	-5,19	733	,000
biological and chemical escape	2,52	733	,012
Cognitive Restructuring	1,70	733	,089

The difference between attitudes of female and male subjects in overcoming stress is examined in Table 2. The analysis conducted revealed that the average score of male participants in refuge in religion was X=2,43 and the standard deviation was S=85, whereas female participants' average score in refuge in religion was X = 2,23 and standard deviation was S=97. A meaningful difference (t(773)=2,94, p<0,01) was found in favor of male participants when t test was used to determine whether there was a difference between the mean of scores.

At the end of the analysis the male participants average score in external assistance was found X=2.49 and the standard deviation was S=,63 whereas female participants' average score and standard deviation were found as X=2,62 and S=,68 respectively. A meaningful difference [$t_{(733)}$= -2,82, p < 0,01] was found in favor of female participants when t test was used to determine whether there was a difference between the mean of scores.

The analysis carried out revealed that male participants' average score in active planning was ($\overline{X}$ = 2,65) and the standard deviation was (S=,61). Female participants' average score and standard deviation scores were ($\overline{X}$ = 2,72) and (S=,53) respectively. T-test conducted to determine whether there was a difference between these average scores showed that the difference was not meaningful at the level of [$t_{(733)}$= -1,49, p > 0,05].

At the end of the analysis the male participants mean score in emotional was $\overline{X}$ = 1,70, and the standard deviation was (S=,60); whereas female participants' mean and standard deviation were found ($\overline{X}$ =1,93 and S=,55 respectively. A meaningful difference [$t_{(733)}$= -1,49, p < 0,01] was found in favor of female participants when t test was used to determine whether there was a difference between the mean of scores.

At the end of the analysis the male participants mean score in biological and chemical escape was found $\overline{X}$ = 1,04, and the standard deviation was found (S=1,04); whereas female participants' mean and standard deviation were found as ($\overline{X}$ = 84 and S=1,04 respectively. A meaningful difference [$t_{(733)}$= 2,52, p < 0,05] was found in favor of female participants when t test was used to determine whether there was a difference between the mean of scores

The analysis carried out revealed that male participants mean in cognitive restructuring was ($\overline{X}$ = 2,40) and the standard deviation was (S=,71). Female participants mean and standard deviation scores were ($\overline{X}$ = 2,31) and (S=,68) respectively. t-test conducted to determine whether there was a difference between these average scores showed that the difference was not meaningful at the level of [$t_{(733)}$= 1,70, p > 0,05].

The difference between behaviors of overcoming stress and educational level is presented in table 3. The analysis revealed that the average score of secondary level educated participants who seek refuge in religion was ($\overline{X}$ =1,70) and the standard deviation was (S=1,15). The average score of the Participants who have received higher education was ($\overline{X}$ =2,40) and their standard deviation was ($\overline{X}$ =2,40). The average score of the graduate Participants was ($\overline{X}$ =2,74), and the standard deviation was (S=,86). One way ANOVA carried out to determine whether there was a difference between educational level and behaviors of overcoming stress showed that there was a meaningful difference [F(2-735)= 23,852, p < 0,01] in terms of average of educational level. The difference was found to be in favor of graduate and higher education level participants.

The analysis revealed that the average score of secondary level educated participants who performed the behavior of external assistance was ($\overline{X}$ =2,77), and the standard deviation was S=,59), The average score of the Participants who have received higher education was S=,59), and the standard deviation was . S=,59), The average score of the graduate Participants was ($\overline{X}$ =2,68) , and the standard deviation was (S=,80. One way ANOVA carried out to determine whether there was a difference between educational level and behavior of overcoming stress showed that there was a me-

Table 3. F values related to the difference between education level and behaviors of overcoming stress

Descriptives					ANOVA				
		N	Mean	Std. Deviation	Sum of Squares	df	Mean Square	F	Sig.
refuge in religion	1. secondary education	71	1,70	1,15	36,74	2	18,372	23,852	,000
	2. higher education	633	2,40	,84	564,57	733	,770		1<2
	3. graduate	32	2,74	,86	601,32	735			1<3
	Total	736	2,35	,90					
external assistance	1. secondary education	71	2,77	,59	4,90	2	2,449	5,803	,003
	2. higher education	633	2,51	,65	309,30	733	,422		
	3. graduate	32	2,68	,80	314,20	735			1>2
	Total	736	2,54	,65					
active plan	1. secondary education	71	2,73	,49	2,12	2	1,058	3,160	,043
	2. higher education	633	2,66	,59	245,28	733	,335		
	3. graduate	32	2,92	,60	247,39	735			
	Total	736	2,68	,58					
emotional escape	1. secondary education	71	1,93	,62	1,40	2	,702	2,006	,135
	2. higher education	633	1,79	,59	256,53	733	,350		
	3. graduate	32	1,74	,60	257,93	735			
	Total	736	1,80	,59					
biological and chemical escape	1. secondary education	71	,98	1,24	2,35	2	1,177	1,074	,342
	2. higher education	633	,94	,99	803,17	733	1,096		
	3. graduate	32	1,22	1,55	805,53	735			
	Total	736	,96	1,05					
Cognitive Restructuring	1. secondary education	71	2,26	,67	3,01	2	1,507	3,104	,045
	2. higher education	633	2,36	,71	355,84	733	,485		1>2
	3. graduate	32	2,63	,54	358,85	735			1>3
	Total	736	2,36	,70					

aningful difference [F(2-735)= 5,803, p < 0,01] in terms of average of educational level. The difference was found to be in the favor of secondary school graduates rather than the participants who received higher education.

According to the analysis of results the average score of secondary level educated participants who performed the behavior of active planning was ($\overline{X}$=2,73), and the standard deviation was S=,49), The average score of the Participants who have received higher education was ($\overline{X}$=2,66), and the standard deviation was . S=,59), The average score of the graduate Participants was($\overline{X}$=2,92), and the standard deviation was (S=,60. One way ANOVA carried out to determine whether there was a difference between the average scores of educational level and behaviors of overcoming stress showed that there was a meaningful difference[F(2-735)= 3,160, p < 0,05] in terms of average of educational level.

According to the analysis of results the average score of secondary level educated participants who performed the behavior of emotional escape was ($\overline{X}$=1,93), and the standard deviation was S=,62), The average score of the Participants who have received higher education was ($\overline{X}$=1,79), and the standard deviation was . S=,59), The average score of the graduate Participants was ($\overline{X}$ =1,74), and the standard deviation was (S=,60. One way ANOVA carried out to determine whether

her there was a difference between the average scores of educational level and behaviors of overcoming stress showed that there was a meaningful difference [F(2-735)= 2,006, p < 0,05] in terms of average of educational level.

According to the analysis of results the average score of secondary level educated participants who performed the behavior of "biological and chemical escape" was ($\overline{X}$=98), and the standard deviation was S=1,24), The average score of the Participants who received higher education was ($\overline{X}$=,94), and the standard deviation was . S=,99), The average score of the graduate Participants was($\overline{X}$=1,22), and the standard deviation was (S=1,55. One way ANOVA carried out to determine whether there was a difference between the average scores of educational level and behaviors of overcoming stress showed that there was a meaningful difference [F(2-735)= 1,074, p < 0,05] in terms of average of educational level.

According to the analysis of results the average score of secondary level educated participants who performed the behavior of "cognitive restructuring" was ($\overline{X}$=2,26), and the standard deviation was S=,67), The average score of the Participants who have received higher education was ($\overline{X}$=2,36), and the standard deviation was .S=,71), The average score of the graduate Participants was ($\overline{X}$=2,63), and the standard deviation was (S=,54. One way ANOVA carried out to determine whether there was a difference between the average scores of educational level and behaviors of overcoming stress showed that there was a meaningful difference [F(2-735)= 3,104, p < 0,05] in terms of average of educational level. The difference was found in favor of the participants who were secondary school graduates rather than the graduates and the ones having received higher education.

The difference between number of years spent in sports and overcoming stress behaviors is analyzed in table 4. The analysis of the results revealed that the average score of participants who spent 1-5 years and showing the behavior of taking refuge in religion was ($\overline{X}$=2,22), and the standard deviation was (S=,95). The average score of participants who spent 11-15 years was ($\overline{X}$=2,52), and the standard deviation was (S=,87). The average score of participants who spent 16-20 years was ($\overline{X}$=2,55), and the standard deviation was (S=,90).

One way ANOVA carried out to determine whether there was a difference between the average scores of behaviors of overcoming stress according to the number of years spent in sports showed that there was a meaningful difference [F(3-735)= 3,440, p < 0,05] in terms of educational level averages. The difference was found in favour of participants who spent 11-15 years in sports rather than participants having 1-5 years sports experience.

The analysis of the results revealed that the average score of participants who spent 1-5 years and showing the behavior of external assistance was ($\overline{X}$=2,7) and the standard deviation was (S=,66). The average score of participants who spent 6-10 years was ($\overline{X}$=2,60), and the standard deviation was (S=,64). The average score of participants who spent 11-15 years was ($\overline{X}$=2,56), and the standard deviation was (S=,63). The average score of participants who spent 16-20 years was ($\overline{X}$=2,49), and the standard deviation was (S=,85).

One way ANOVA carried out to determine whether there was a difference between the average scores of behaviors of overcoming stress according to the number of years spent in sports showed that there was a meaningful difference [F(3-735)= 2,109, p >0,05] in terms of number of years spent in sports.

The analysis of the results revealed that the average score of participants who spent 1-5 years and showing the behavior of external assistance was ($\overline{X}$=2,62)and the standard deviation was (S=,55). The average score of participants who spent 6-10 years in sports was ($\overline{X}$=2,69), and the standard deviation was (S=,56). The average score of participants who spent 11-15 years in sports was ($\overline{X}$=2,74), and the standard deviation was (S=,65). The average score of participants who spent 16-20 years was ($\overline{X}$=2,86), and the standard deviation was (S=,86).

One way ANOVA carried out to determine whether there was a difference between the average scores of behaviors of overcoming stress according to the number of years spent in sports showed that there was a meaningful difference [F(3-735)= 1,876, p>0,05] in terms of number of years spent in sports.

Table 4. F values related to the difference between years spent in sports and behaviors of overcoming stress

					ANOVA			
		N	Mean	Std. Deviation	Sum of Squares	df	Mean Square	F	Sig.
refuge in religion	1.1-5 year	260	2,22	,95					
	2. 6-10 year	341	2,38	,87	8,36	3	2,787	3,440	,017
	3. 11-15 year	116	2,52	,87	592,95	732	,810		1<3
	4. 16-20 year	19	2,55	,90	601,32	735			
	Total	736	2,35	,90					
external assistance	1.1-5 year	260	2,47	,66					
	2. 6-10 year	341	2,60	,64	2,69	3	,898	2,109	,098
	3. 11-15 year	116	2,56	,63	311,51	732	,426		
	4. 16-20 year	19	2,49	,85	314,20	735			
	Total	736	2,54	,65					
active plan	1.1-5 year	260	2,62	,55					
	2. 6-10 year	341	2,69	,56	1,89	3	,629	1,876	,132
	3. 11-15 year	116	2,74	,65	245,51	732	,335		
	4. 16-20 year	19	2,86	,86	247,39	735			
	Total	736	2,68	,58					
emotional escape	1.1-5 year	260	1,85	,57					
	2. 6-10 year	341	1,79	,59	3	1,381	3,984		,008
	3. 11-15 year	116	1,78	,61	732	,347			1>4
	4. 16-20 year	19	1,38	,74	735				2>4
	Total	736	1,80	,59					
biological and chemical escape	1.1-5 year	260	,93	,98					
	2. 6-10 year	341	,94	1,04	4,02	3	1,340	1,224	,300
	3. 11-15 year	116	1,12	1,21	801,51	732	1,095		
	4. 16-20 year	19	,78	,89	805,53	735			
	Total	736	,96	1,05					
Cognitive Restructuring	1.1-5 year	260	2,33	,73					
	2. 6-10 year	341	2,36	,65	,83	3	,277	,566	,638
	3. 11-15 year	116	2,41	,54	358,02	732	,489		
	4. 16-20 year	19	2,48	1,57	358,85	735			
	Total	736	2,36	,70					

The analysis of the results revealed that the average score of participants who spent 1-5 years in sports and showing the behavior of emotional escape was ($\overline{X}$=1,85), and the standard deviation was (S=,57). The average score of participants who spent 6-10 years in sports was ($\overline{X}$=1,79), and the standard deviation was (S=,59). The average score of participants who spent 11-15 in sports years was ($\overline{X}$=1,78), and the standard deviation was (S=,61).). The average score of participants who spent 16-20 years in sports was ($\overline{X}$=1,38), and the standard deviation was (S=,74).

One way ANOVA carried out to determine whether there was a difference between the average scores of behaviors of overcoming stress according to the number of years spent in sports showed that there was a meaningful difference [F(3-735)= 3,984, p<0,01] in terms of the number of years

spent in sports. .the difference was found in favor of participants who spent 1-5 and 6-10 years in sports rather than participants having 16-20 years sports experience.

The analysis of the results revealed that the average score of participants who spent 1-5 years in sports and showing the biological and chemical escape was ($\overline{X}$=,93), and the standard deviation was (S=,98). The average score of participants who spent 6-10 years in sports was ($\overline{X}$=,94), and the standard deviation was (S=1,04). The average score of participants who spent 11-15 years in sports was ($\overline{X}$=1,22), and the standard deviation was (S=1,21).). The average score of participants who spent 16-20 years in sports was ($\overline{X}$= ,78), and the standard deviation was (S=,89).

One way ANOVA carried out to determine whether there was a difference between the average scores of behaviors of overcoming stress according to the number of years spent in sports showed that there was not a meaningful difference [F(3-735)= 1,224, p>0,05] in terms of the number of years spent in sports

The analysis of the results revealed that the average score of participants who spent 1-5 years in sports and showing the cognitive restructuring was ($\overline{X}$=2,33), and the standard deviation was (S=,73). The average score of participants who spent 6-10 years in sports was ($\overline{X}$=2,36), and the standard deviation was (S=,65). The average score of participants who spent 11-15 years in sports was ($\overline{X}$=2,41), and the standard deviation was (S=,54).). The average score of participants who spent 16-20 years in sports was ($\overline{X}$=2,48), and the standard deviation was (S=1,57).

One way ANOVA carried out to determine whether there was a difference between the average scores of behaviors of overcoming stress according to the number of years spent in sports showed that there was not a meaningful difference [F(3-735)= ,566, p>0,05] in terms of the number of years spent in sport

The difference between age and behaviors of overcoming stress is presented in table 5. The analysis revealed that the average score of the participants showing the behavior of refuge in religion and who were 14-18 years old was ($\overline{X}$ =1,57), and the standard deviation was (S=1,22. The average score of the participants in 19-23 age group was ($\overline{X}$=2,40), and their standard deviation was (S=,83. The average score of participants in 24-28 age group was ($\overline{X}$=2,49), and the standard deviation was (S=,87). The average score of participants in 29-33 age group was ($\overline{X}$=2,58), and the standard deviation was (S=1,11).one way ANOVA conducted to determine whether there was a difference between the average scores of overcoming stress behavior according to age revealed that there was a meaningful difference[F(3-735)= 17,142, p < 0,01] in terms of age range. It was seen that the difference was in favor of 19-23, 24-28 and 29-33 age groups rather than 14-18 age group.

The analysis revealed that the average score of the participants showing the behavior of external assistance and who were 14-18 years old was ($\overline{X}$ =2,69), and the standard deviation was (S=,56). the average score of the participants in 19-23 age group was ($\overline{X}$=2,54), and their standard deviation was (S=,66). The average score of participants in 24-28 age group was ($\overline{X}$=2,46), and the standard deviation was (S=,66). The average score of participants in 29-33 age group was ($\overline{X}$=2,94), and the standard deviation was (S=,71). One way ANOVA conducted to determine whether there was a difference between the average scores of overcoming stress behavior according to age revealed that there was a meaningful difference[F(3-735)= 2,927, p < 0,05] in terms of age range. It was seen that the difference was in favor of 29-33 age group rather than 24-28 age group.

The analysis revealed that the average score of the participants showing the behavior of active planning and who were 14-18 years old was ($\overline{X}$ =2,71), and the standard deviation was (S=,42). the average score of the participants in 19-23 age group was ($\overline{X}$=2,66), and their standard deviation was (S=,59). The average score of participants in 24-28 age group was ($\overline{X}$=2,70), and the standard deviation was (S=,59). The average score of participants in 29-33 age group was ($\overline{X}$=3,17), and the standard deviation was (S=,50). One way ANOVA conducted to determine whether there was a difference between the average scores of overcoming stress behavior according to age revealed

Table 5. F values related to the difference between age and behaviours of overcoming stress

Descriptives					ANOVA				
		N	Mean	Std. Deviation	Sum of Squares	df	Mean Square	F	Sig.
refuge in religion	1. 14-18 age	58	1,57	1,22					
	2. 19-23 age	534	2,40	,83	39,47	3	13,157	17,142	,000
	3. 24-28 age	134	2,49	,87	561,84	732	,768		1<2
	4. 29-33 age	10	2,58	1,11	601,32	735			1<4
	Total	736	2,35	,90					3>1
external assistance	1. 14-18 age	58	2,69	,56					
	2. 19-23 age	534	2,54	,66	3,72	3	1,242	2,927	,033
	3. 24-28 age	134	2,46	,66	310,47	732	,424		
	4. 29-33 age	10	2,94	,71	314,20	735			4>3
	Total	736	2,54	,65					
active plan	1. 14-18 age	58	2,71	,42					
	2. 19-23 age	534	2,66	,59	2,70	3	,901	2,695	,045
	3. 24-28 age	134	2,70	,59	244,69	732	,334		
	4. 29-33 age	10	3,17	,50	247,39	735			4>31,2,3
	Total	736	2,68	,58					
emotional escape	1. 14-18 age	58	1,83	,64					
	2. 19-23 age	534	1,83	,57	2,94	3	,979	2,812	,039
	3. 24-28 age	134	1,69	,61	255,00	732	,348		1,2>3,4
	4. 29-33 age	10	1,50	,87	257,93	735			
	Total	736	1,80	,59					
biological and chemical escape	1. 14-18 age	58	,94	1,31					
	2. 19-23 age	534	,98	1,05	1,53	3	,510	,464	,707
	3. 24-28 age	134	,90	,92	804,00	732	1,098		
	4. 29-33 age	10	,68	,92	805,53	735			
	Total	736	,96	1,05					
Cognitive Restructuring	1. 14-18 age	58	2,23	,66					
	2. 19-23 age	534	2,38	,67	1,33	3	,443	,907	,437
	3. 24-28 age	134	2,34	,82	357,52	732	,488		
	4. 29-33 age	10	2,47	,65	358,85	735			
	Total	736	2,36	,70					

that there was a meaningful difference [F(3-735)= 2,695, $p < 0,05$] in terms of age range. It was seen that the difference was in favor of 29-33 age group rather than 14-18, 19-23 and 24-28 age groups

The analysis revealed that the average score of the participants showing the behavior of emotional escape and who were 14-18 years old was ($\overline{X}$ =1,83), and the standard deviation was (S=,64). the average score of the participants in 19-23 age group was ($\overline{X}$ =1,83), and their standard deviation was (S=,57). The average score of participants in 24-28 age group was ($\overline{X}$ =1,69), and the standard

deviation was (S=,61). The average score of participants in 29-33 age group was ($\overline{X}$=1,50), and the standard deviation was (S=,59).one way ANOVA conducted to determine whether there was a difference between the average scores of overcoming stress behavior according to age revealed that there was a meaningful difference [F(3-735)= 2,812, p < 0,05] in terms of age range. It was seen that the difference was in favor of 14-18 and 19-23 age groups rather than 24-28 and 29-33 age groups

The analysis revealed that the average score of the participants showing the behavior of biological and chemical escape and who were 14-18 years old was ($\overline{X}$=,94), and the standard deviation was (S=1,31).the average score of the participants in 19-23 age group was ($\overline{X}$=,98), and their standard deviation was (S=1,05). The average score of participants in 24-28 age group was ($\overline{X}$=90), and the standard deviation was (S=,92). The average score of participants in 29-33 age group was ($\overline{X}$=,68), and the standard deviation was (S=,90).one way ANOVA conducted to determine whether there was a difference between the average scores of overcoming stress behavior according to age revealed that there was not a meaningful difference[F(3-735)=,464, p > 0,05] in terms of age range.

The analysis revealed that the average score of the participants showing the behavior of cognitive restructuring and who were 14-18 years old was ($\overline{X}$=2,23), and the standard deviation was (S=,66). the average score of the participants in 19-23 age group was ($\overline{X}$=2,38), and their standard deviation was (S=,67). The average score of participants in 24-28 age group was ($\overline{X}$=2,34), and the standard deviation was (S=,82). The average score of participants in 29-33 age group was ($\overline{X}$=2,47), and the standard deviation was (S=,65).one way ANOVA conducted to determine whether there was a difference between the average scores of overcoming stress behavior according to age revealed that there was not a meaningful difference [F(3-735)=,907, p > 0,05] in terms of age range.

Table 6. F values related to the difference between sports type and behaviours of overcoming stress

Group Statistics

	Sports Type	N	Mean	Std. Deviation
refuge in religion	team	529	2,30	,93
	individual	207	2,47	,84
external assistance	team	529	2,55	,66
	individual	207	2,54	,63
active plan	team	529	2,67	,60
	individual	207	2,70	,54
emotional escape	team	529	1,81	,60
	individual	207	1,78	,58
biological and chemical escape	team	529	1,00	1,05
	individual	207	,84	1,04
Cognitive Restructuring	team	529	2,35	,71
	individual	207	2,39	,66

Independent Samples Test

	t-test for Equality of Means		
	t	df	Sig. (2-tailed)
refuge in religion	-2,29	734	,022
external	,237	734	,813
active plan	-,723	734	,470
emotional	,475	734	,635
biological and	1,891	734	,059
Cognitive	-,649	734	,517

The difference between sports type and behaviors of overcoming stress are presented in table 6. The analysis revealed that the average score of team sport in terms of refuge in religion behavior was ($\overline{X}$= 2,30) and the standard deviation was (S=,93). The average score of individual sport in terms of refuge in religion behavior was ($\overline{X}$= 2,47) and the standard deviation was (S=,84). t test used for the equality of average scores determining whether there was a difference between average scores revealed that there was a meaningful difference at the level of [$t_{(734)}$= -2,29, p<0,05] in favor of individual sports type.

The analysis revealed that the average score of team sport in terms of external assistance behavior was ($\overline{X}$= 2,55) and the standard deviation was (S=,66). The average score of individual sport in terms of refuge in religion behavior was ($\overline{X}$= 2,54) and the standard deviation was (S=,63). t test used for the equality of average scores determining whether there was a difference between average

scores revealed that there was not a meaningful difference at the level of [$t_{(734)}$=,237, p>0,05].

The analysis revealed that the average score of team sport in terms of active planning behaviour was ($\overline{X}$ = 2,67) and the standard deviation was (S=,60). The average score of individual sport in terms of active planning behavior was ($\overline{X}$ = 2,70) and the standard deviation was (S=,54) . t test used for the equality of average scores determining whether there was a difference between average scores revealed that there was not a meaningful difference at the level of [$t_{(734)}$=,723, p>0,05].

The analysis revealed that the average score of team sport in terms of emotional escape behavior was ($\overline{X}$ = 1,81) and the standard deviation was (S=,60). The average score of individual sport in terms of refuge in emotional escape behavior was ($\overline{X}$ = 1,78) and the standard deviation was (S=,58). t test used for the equality of average scores determining whether there was a difference between average scores revealed that there was not a meaningful difference at the level of [$t_{(734)}$=,475, p>0,05].

The analysis revealed that the average score of team sport in terms of biological and chemical escape behavior was ($\overline{X}$ = 1,00) and the standard deviation was (S=,1,05). The average score of individual sport in terms of biological and chemical escape behavior was ($\overline{X}$ = ,84) and the standard deviation was (S=1,04). t test used for the equality of average scores determining whether there was a difference between average scores revealed that there was not a meaningful difference at the level of [$t_{(734)}$=1,891, p > 0,05].

The analysis revealed that the average score of team sport in terms of cognitive restructuring behavior was ($\overline{X}$ = 2,35) and the standard deviation was (S=,71). The average score of individual sport in terms of cognitive restructuring behavior was ($\overline{X}$ = 2,39) and the standard deviation was (S=, 66). t test used for the equality of average scores determining whether there was a difference between average scores revealed that there was not a meaningful difference at the level of [$t_{(734)}$=,649, p>0,05].

Discussion and conclusion

As a result of the current study, it was found that there is a relationship between sports confidence and coping with stress. Analysis showed that sports confidence significantly correlated with refuge in religion, external assistance, cognitive restructuring, active plan. The most significant correlation was found to be between active plan which is one of the strategies for coping with stress and sports confidence (Table 2). Active plan has also been suggested to be the most preferred strategy to cope with stress. This positive correlation suggests that active plan increases as sports confidence increases or sports confidence increases according to increase in active plan. This result is desirable in terms of sportive performance.

According to t-test analysis between males and females for strategies for coping with stress it was found that males had significantly higher points on refuge in religion, emotional escape and biological and chemical escape. Moreover, significantly higher scores were found in external assistance scores for females. Although some literature shows the opposite (Bulut, 2005; Uçman, 1990), relevant literature also suggest difference between genders according to coping strategies with stress (Avşaroğlu & Üre, 2007).

Wood (2009) suggested that males are admonished, "don't be a sissy," "go after what you want," "don't cry." Males are usually advised to be strong, independent and successful. It could be thought that males in our study scored higher in refuge in religion, emotional escape and biological and chemical escape due to Wood's suggestions above.

In addition according to a study conducted with female managers by Iwasaki et al., (2005) females were found to be getting external assistance for coping strategies. Females appeared to be socializing and spending time with their families and friends to cope with their stress. This result matches up with the result of the current study. Furthermore, Gender main effects revealed that female athletes demonstrated a significantly greater reliance on sources associated with mastery, physical self-presentation, social support, environmental comfort and coach's leadership than male athletes (Kingston, Lane & Thomas, 2010). Supportingly, Çoruh (2003) also suggested that females utilized refuge in religion, external assistance and emotional escape.

When analyzing the results of ANOVA for strategies for coping with stress in terms of education level, it was found that there was a significant difference between education levels (Table, 4). This significant difference was found to be between secondary education and higher education. It could be interpreted that when an individual's education level is low (secondary education) they get more external assistance compared to participants of higher education (higher education). This might be due to capability of people of higher education for coping with stress without external assistance.

In addition, a significant difference was also observed for cognitive restructuring between educational levels. This significant difference was due to the fact that cognitive restructuring points increased as educational level increased. In this respect, it could be proposed that people might benefit from higher education. Higher education could result in better cognitive abilities. Maybe therefore cognitive restructuring points were higher in high education groups. Supporting this result, Kolayis and Sari (2011) suggested that higher educational level might be positively affecting cognitive process of athletes.

According to ANOVA analyses to find out if there is a difference among strategies of coping with stress in terms of sports year, there is a difference among the groups of sports age. Sports age group of 16-20 was found to be significantly higher than the sports age group of 1-5 and 6-10 (Table 5). Emotional escape is not a desirable way of coping with stress. Therefore, more experienced athletes do not prefer emotional escape to lower their level of stress. This is the reason why experience is one of the determinants of sportive performance. According to Koc and Tutkun (2001) Policemen who work between 1-5 and 10-15 were found to be using active plan as a strategy to cope with stress.

According to ANOVA analyses to find out if there is a difference among strategies of coping with stress in terms of age, there is a difference among age groups. Age group of 29-33 was found to be significantly higher than the age groups of 14-18, 19-23 and 24-28. These results appear to be parallel with the results of sports age. Because, emotional escape is not recommended as a strategy for coping with stress. According to the relevant literature, active plan is one of the best strategies to cope with stress. It was found that more experienced athletes do not prefer emotional escape (table, 4) and older athletes were found to preferring active plan. Considering the relationship between age and experience, these results are supporting each other.

When examining the points for strategies of coping with stress between individual sports and team sports. Points of refuge in religion for individual athletes were found to be significantly higher than points of team sports' athletes. This might be due to the fact that athletes of individual sports don't have teammates in the field and do not have another person to compensate their mistakes. The findings of this research could contribute to the relevant literature (Deklava et al., 2011, Özkahraman et al, 2011, Kılıç et al. 2011).

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Wound healing in different types of incisions used in septoplasty: experimental model

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Abstract

The aim of this paper was to find regularity in the healing of different types of incisions in the nasal septum of rabbits in the postoperative period after septoplasty. Three types of incisions were applied: a crosswise, a spiral and a parallel incision.

The test subjects' material consisted of three groups of rabbits, each group with five specimens of both genders with 2.5 ± 0.15 kg weight. Changes were monitored during postoperative period after one, four and seven days from operations. The thickness of the mucosa in the followed time intervals was measured separately and the data were used to determine the dinamics of change of the operated structures. It was found that each applied method of incision had specific histological features and that the extent of trauma was proportional to the change in mucosal thickness.

Key words: Crosswise incision, Spiral incision, Parallel incision, Septoplasty, wound healing

Introduction

Deviated nasal septum is a relevant cause of poor nose function and paranasal sinus diseases. Followed by an infection, deviated nasal septum is more susceptible to epistaxis, the worsening of breathing function, the sense of smell damage and the ventilation of paranasal sinuses and the middle ear (via the Eustachian tube).[1-4]

Septoplasty is one of the oldest operating methods. Besides septotomy and submucosal resection of the septum, which involve removing the septal cartilage, all other types of septum incisions could be classified into three groups. These are crosswise (C), spiral (S) and parallel (P) incisions (Figure 1).[5, 6]

The aim of our work was to find regularity in the healing of different types of incisions in the nasal septum of rabbits in the postoperative period after septoplasty. Three types of incisions were applied: a crosswise, a spiral and a parallel incision.

Material and methods

Material. Each method of incision was applied to a unique group of rabbits. We used 60 rabbits (Ornitolagus cuniculus) of both gender, weighing from 2500 to 2800 grams. The three previously described techniques for the incision [6] of the nasal septum cartilage were applied to the animals used in experiments.

Methods - surgical approach. After intramuscular administration of Ketamine Hydrochloride in a dose of 40 mg/kg for the purpose of anaesthesia, the skin incisions were made in the medial nose region and pre-maxilla region (a lateral incision from the upper third part to the just above the lip corner line) and the triangular trepanation of the rabbit's maxilla, slightly lateral from the nasal fissure and nasal cavity was opened). Luxation of the nasal concha revealed in the full view the entire half of the nasal cavity and the nasal septum. The planned incision of the nasal septum was then carried out. At the end of the procedure, the nasal bones were repositioned.

The animals were painlessly euthanized on the 1st, 4th and 7th day, postoperatively. The septums were excised, stained with HE staining and processed in sequences. We followed the changes in epithelial part, subepithelial part (including the perichondrium) from the samples and measured the mucous thickness at the incision and around it. Through the analysis of the followed structures at and around the incision, we arrived at certain

regularities in the mucous appearance depending on the type of the applied incision.

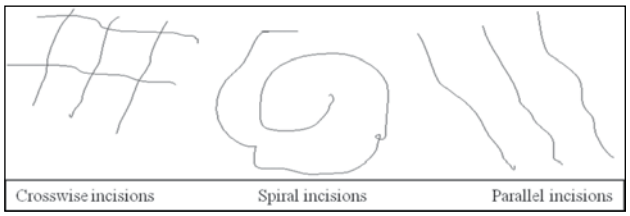


Figure 1. Types of incision – shematic presentation of three used techniques for the incisions: crosswise incisions, spiral incisions and parallel incisions

Methods – histochemical approach. Preventive antibiotic theraphy was applied postoperatively to rule out the influence of infection in the final analysis. After the pain-free euthanasia of the animals, the same approach was used to excise the nasal septum completely. The materials from the excisions were fixed in formalin and treated with HE, AB-PAS and Van Gieson staining according to the standard protocols. Mucosal thickness was measured with ocular microscope using objective with 10x enlargement.

Methods – statistical analysis. The data were compiled with the software package GraphPad Prism 4. Descriptive statistics were reported as mean and standard deviation for continuous data. Comparison of the variables among the experimental groups was made with one-way ANOVA (Kruskal-Wallis test) and t-test. A value of $p<0.05$ was considered statistically significant.

Results

In the analysis of the postoperative material that was isolated in the same way by conventional HE methods we can distinguish the inflammatory reaction of all observed structures. At the level of mucosa, there is hyperemia which is reflected in repletion of blood vessels with blood elements, light perivascular transudation and development of edema and cellular infiltration of the tissue. At the level of perichondrium, we notice edema and thickening of its fibers.

In samples with parallel incisions (**Figure 2, Graph 1, Graph 2**), the tissue edema exhibits the lowest development at the 4th postoperative day in comparison to samples from other groups.

In cases of spiral incisions (**Figure 3, Graph 1, Graph 2**), the appearance of a large exudate under the mucous membrane was detected, especially at the level of perichondrium during the fourth day, while on the seventh day the exudate was reduced in the volume with limitation mainly to perichondrium. The mucosus membrane shows signs of decreased intensity of the inflammation.

In cases of crosswise incisions (**Figure 4, Graph 1, Graph 2**), a substantial thickening of mucosa and perichondrium was visible, with all the elements of the inflammatory reaction.

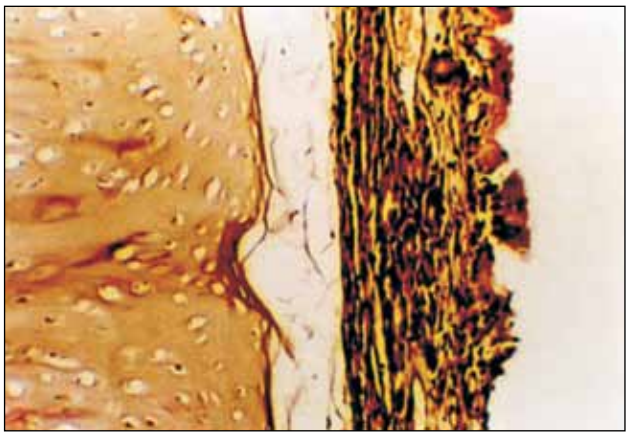


Figure 2. Parallel incision on the forth postoperative day. Van Gieson staining (enlargement 100x)

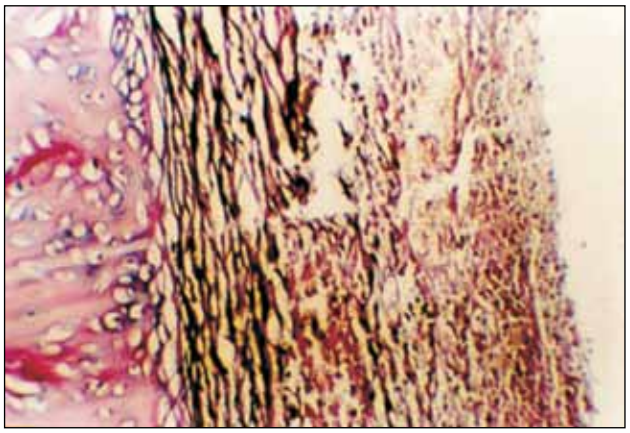


Figure 3. Spiral incision on the forth postoperative day. A large exudate in mucosae and perichondrium is noticeable. Van Gieson staining, (enlargement 100x)

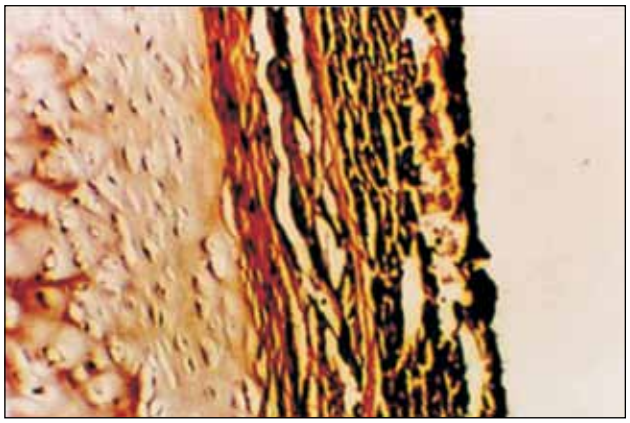
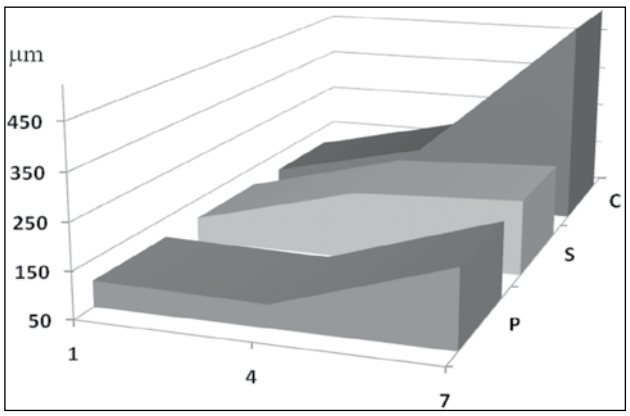
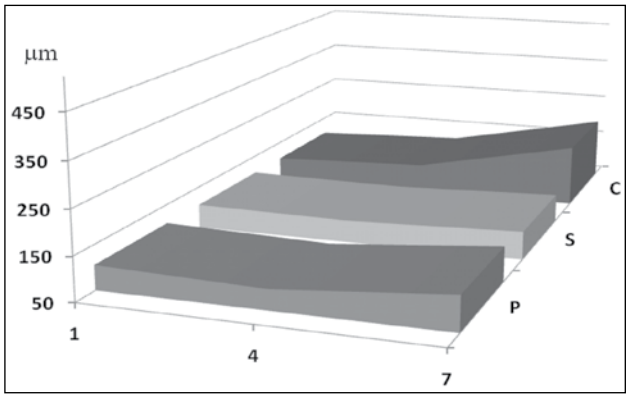


Figure 4. Crosswise incision on the forth postoperative day. A small exudate in the perichondrium is observed but there is a greater inflammatory reaction in both mucosa and perichondrium compared to parallel incision. Van Gieson staining, (enlargement 100x)



Graph 1. The change dynamics in mucosal thickening around the incision, on the 1st, 4th and 7th postoperative day for the crosswise (C), spiral (S) and parallel (P) incisions. The thickening was expressed in microns



Graph 2. The change dynamics in mucosal thickening at the incision on the 1st, 4th and 7th postoperative day for the crosswise (C), spiral (S) and parallel (P) incisions. The thickening was expressed in microns

Table 1. Presentation of mucosal thickening measurements obtained at the place of incision and around the incision for the groups that were measured on the 1st, 4th and 7th postoperative day, and for which different types of incisions were used (C - crosswise, S - spiral and P - parallel). The thickening was expressed in microns

At the incision			
	1st day (µm)	**4th day (µm)**	**7th day (µm)**
C	109	188	509
S	105	199	212
P	104	99	213
Around the incision			
C	106	119	195
S	106	102	115
P	106	96	129

The data obtained by measuring mucosal thickening (**Table 1**) at the incision on the first, fourth and seventh postoperative day were statistically analyzed and the following results were obtained.

After the first postoperative day, there is no statistically significant difference between experimental groups, ($F = 1.85$, $p > 0.05$). But after the fourth postoperative day, we examined significant difference ($F = 288.21$; $p < 0.001$). We also compared results from each experimental group. There was no statistically significant difference observed between groups using the crosswise (C) and spiral (S) incisions; ($t = -2.51$, $p > 0,05$). Between methods using S and P incisions or between C and P incisions, there were significant differences in the mucosal thickness at the incisial part of the tissue ($t = 20.94$, and $p > 0.001$; $t = 19.61$, $p > 0.001$). There was also statistically significant difference ($p > 0.001$) for the groups with used P incisions in comparison to the remaining two used methods in the part of the tissue around the pace of incisions on the fourth postoperative day.

The results obtained after the seven days from the applied methods were significantly different in comparison to the all experimental group ($F = 793.52$, $p < 0,001$). The statistically significant difference between S and C groups was detected ($p < 0.001$). The differences between the S and P groups were not statistically significant.

Discussion

The septal mucosa of rabbits was chosen due to its similarities with human respiratory epithelium.[7] As experiment specimens, rabbits are suitable because with them there is no deviated nasal septum nor habitual deformities that would have an impact on the appearance of the nasal septum. [8, 9,13]

This paper exhibits the characteristics of examined tissue depending of the applied method of incision. Regardless of the method applied to human material during septoplasty, these incision deficiencies are not so visible at first view because an anterior nasal package (tamponade) is used in septoplasty. After detamponade however, it can be expected that a tissue which exibits a larger trauma and the tendency to massive scaring postoperatively, will secondarily result in renewed deformation.[10, 11]

The application of different types of cartilage incisions during septoplasty aims to remodel and reset the nasal septum in medial position.[12] We examined the effects of crosswise (C), spiral (S) and parallel (P) incisions on regularity in the healing of the nasal septum from the rabbits used in the study. The applied types of incisions have shown the significant influence on the postoperative development and provided different effects on wound healing. Massive tissue injury caused by used different procedures during operation, conditions with the massive inflammatory reactions, the expected massive scars are suspected to have influence on uncertainty of the postoperative courses. We have shown that using the parallel incisions during septoplasty have faster healing period after the intervention it self. This effect was aspecially examined in the area it produced incision. The biggest tissue trauma occurs with crosswise incision.

Conclusion

These data can be valuable in rhinology (septoplasty and septorhinoplasty) for the assessment of the choices of incision methods used during the operation. Due to the small number of the examinees, futher experiments and cochort studies are recommended for data confirmation and future implementation in practice.

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An Examination of Food Craving and Eating Behaviour with regard to Eating Disorders Among Adolescent

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Abstract

The purpose of this study was to determine the prevalence of night eating syndrome and binge eating disorder in sample of adolescents and also to compare the food craving and eating disorder groups. A total of 563 adolescent male and female high school students (mean age: 16.7±1.3 years for males and 16.6±0.6 years) were randomly selected in Ankara, capital city of Turkey. The participants were administered the Dutch Eating Behaviour Questionnaire, the Weight and Lifestyle Inventory, the Questionnaire on Eating and Weight Patterns –Revised and the Food Craving Questionnaire-Trait. Fourteen female participants (3.7%) reported NES, while 4.5% reported binge-eating symptomatology. Ten male participants (5.5%) reported NES, while 2.7% reported binge-eating symptomatology. Of those reporting the latter, 7 met criteria for purging bulimia nervosa (1.6% of females and 0.5% of males) and 11 met criteria for nonpurging bulimia nervosa (2.6% of females and 0.5% of males). Seven participants reported both night eating and binge eating. As predicted, participants who reported night eating syndrome and binge eating disorder had significantly higher total food craving scores, restrained eating, emotional eating and external eating scores than those not reporting disordered eating. The current study suggests that binge eating disorder and night eating syndrome are strongly significant problem among adolescents. Our findings indicated that the experience of food craving is an important factor in adolescents with binge eating disorder and night eating syndrome. Finally, these eating problems may contribute to the development and/or maintenance of obesity.

Key words: adolescents, binge-eating disorder, disordered eating, eating disorders

Introduction

According to the World Health Organization, approximately 155 million school-aged children are currently overweight or obese worldwide.[1] The incidence of childhood and adolescent overweight in the Turkey is increasing at an rapidly rate. Recent data indicate that the proportion of overweight or obese children of both genders increased markedly in different areas in the world, including Turkey. It is estimated that today, 13.8% of Turkish children are overweight or obese.[2,3] Childhood and adolescent obesity and overweight have a significant impact on later mortality and morbidity in adulthood. Many of the metabolic and cardiovascular complications and some forms of cancer associated with adult obesity have their onset in.[4]

Therefore, individuals who binge eat seem to be a relevant target for intervention programs, particularly because cessation of binge eating is often effective in stabilizing weight, thereby preventing future weight gain and perhaps promoting weight loss.[5] Binge eating as a distinctive pattern of eating in the obese was also first recognized in 1959. In an early case study, Stunkard[6] described an obese man who experienced uncontrolled ingestion of enormous quantities of food in a short period of time. The "binges" were terminated when a point of physical discomfort was reached and were thought to be triggered by "life stress." Spitzer et al.[7] confirmed that approximately 30% of individuals presenting to weight control programs report what has been termed binge eating disorder (BED). The criteria for BED consist of: a) episodic overeating, defined as eating an amount of food in a short period of time that is definitely larger than most people would eat for at least twice weekly on average for 6 months; b) a sense of loss of control over the binge; c) distress related to the binge; and d) three

of five items that include rapid eating, eating until uncomfortably full, feeling depressed or guilty after bingeing, eating when not physically hungry, and eating alone. BED is distinguished from bulimia nervosa (BN) by the absence of inappropriate compensatory behaviors to prevent weight gain including fasting, purging, and excessive exercise and is a provisional eating disorder diagnosis.[8]

Overweight and obesity present one of the biggest physical health threats to binge eaters. Obese BED patients face the same threats to health as non-binging obese patients, such as increased risk of coronary heart disease, diabetes, hypertension, hyperlipidemia, gallbladder disease, respiratory disease, cancer, gout and arthritis.[9-12] The problem of physical health sequela related to BED is compounded by evidence suggesting a link between BED and poorer weight-related treatment outcome. Specifically, the higher drop-out rates and lower weight losses experienced among those with BED appear to be mediated by psychological dysphoria.[14]

The prevalence of Binge-Eating Disorder, based on the criteria proposed in the Diagnostic and Statistical Manual of Mental Disorders, ranges from 2.0% to 4.0% in female community members and from 0.5% to 1.5% in male community members.[8,15,16] Among individuals attending weight control programs (N = 1785; 89.0% women), the rate for Binge-Eating Disorder is estimated at 28.8% whereas, for individuals seeking bariatric surgery (N = 92; 71.7% women), the rate of Binge-Eating Disorder is estimated at 46.7%.[7,15,16] Furthermore, at a subclinical level, 41.9% of female high school students (French et al., 1998) and 58.8% of female university students report binge eating, making binge eating a prevalent phenomenon.[17]

The Night Eating Syndrome (NES) was first described in 1955 as a stress-related eating disorder consisting of morning anorexia, evening hyperphagia, and insomnia.[18] The presence of nocturnal ingestions (awakening to eat) was added to these criteria later . NES has also been associated with depressed mood; it is generally lower in persons with NES, compared to controls and often worsens in the evening and,[19] Striegel-Moore and collegues[20] highlight that varying NES diagnostic criteria have appeared in the literature over the past 50 years, and suggest that further information on the nature and prevalence of NES in diverse populations is needed. In a study of general psychiatric outpatients (of all body mass indices), Lundgren and colleagues[21] found that 12.3% of patients met criteria for NES, a rate that is significantly higher than the prevalence of NES in the general population (1.5%)[22] and similar to the prevalence of NES among obese samples (6–16%).[23]

Food craving is thought to mediate uncontrolled eating behavior, such as seen in obesity, binge eating disorder, and bulimia nervosa.[24,25] In overweight dieters, this craving for food is thought to be involved in the inability to comply with a low-calorie diet, resulting in relapse to initial over-eating patterns.[26] Also, in non-clinical samples, food craving has been found to be related to body weight, suggesting a ubiquitous role of craving in food consumption.[27] Research that investigates the relationships between food cravings and binge eating is necessary to understand the role of food cravings in the mechanisms that control appetite and eating in women with eating disorders. The scarce research done to this date with clinical samples has nonetheless yielded important findings. Bulik et al.,[28] found that cue-exposure/response prevention interventions may reduce craving reactivity in bulimic patients. In comparison to asymptomatic individuals, women with a history of anorexia nervosa who binged and purged were more likely to report "uncontrollable desires to eat certain foods or types of food" and "strong urges to eat a specific food".[29] Waters, Hill, and Waller[25] found that experiencing "a strong urge or desire for a particular food" was followed by bingeing about 50% of the time. Similarly, Engelberg, Gauvin, and Steiger[30] reported that whereas dietary restraint did not necessarily precede binge eating, elevated restraint preceded "strong" cravings and the probability of bingeing.

Although there is a further wave of articles exploring night eating syndrome, binge eating disorder and food craving with adolescents around the world, there is no study with this group in Turkey. Some evidence provides support for these different propositions for the relationship between social physique anxiety, exercise behavior and eating attitudes on the Western culture samples. However, there is no attempt to test these propositions on the Eastern cultures. The aims of this study were (a) to determine the prevalence of NES

and BED in Turkish adolescents in Ankara and (b) to determine the effect and importance of different risk factors (food craving, restrained eating, emotional eating and external eating) of NES and BED in Turkish adolescents.

Methods

Participants

Participants were 563 students from Ankara, capital city of Turkey. The mean age was 16.7±1.3 years for males and 16.6±0.6 years for females. The participants attended eight different schools in Ankara, an area that is representative for most parts of the Turkey. The questionnaires were administered under the supervision of four master students at the respective school and a researcher. Questions could be asked to the researcher, to make sure that the children understood the meaning of each item. After completing the questionnaire, each child was taken out of the class to a private place where his/her body weight and height was measured.

Assessment Measures

Night Eating Syndrome

Contained within the Weight and Lifestyle Inventory is the night eating syndrome questionnaire (NESQ).[31] The NESQ is a 13-item screening measure, with Likert scores of 0–4. It assesses the core behaviors listed in the provisional criteria and also the associated symptoms of cravings, mood, and control over eating behavior. Scores range from 0 to 52. The Cronbach's alpha in this study was 0.82.

Binge Eating Disorder (BED) and Bulimia Nervosa (BN)

The The Questionnaire on Eating and Weight Patterns -Revised (QEWP-R) is a commonly used screening instrument to identify and diagnose individuals with BED and bulimia according to DSM-IV criteria. The QEWP-R assesses the type and frequency of behaviors associated with overeating, binge eating, and weight control strategies.[32] The QEWP-R is a 28-item, criterion-based instrument that assesses the essential DSM-IV-TR diagnostic criteria for purging and nonpurging BN, as well as, BED. This questionnaire has been used in multisite field trials to diagnose BED, Purging Bulimia Nervosa, and Nonpurging Bulimia Nervosa. In such trials, the QEWP-R was used to distinguish among binge eaters, nonbinge eaters, and bulimics on both weight and eating variables, including BMI, weight history, age of onset of obesity, dieting, and weight cycling.[7,15]

Restrained Eating, Emotional Eating and External Eating (Dutch Eating Behavior Questionnaire-DEBQ)

This questionnaire consists of 33 items, which measured emotional (13 items), external, and restrained eating (both 10 items). All items had to be rated on a five-point scale from 1 (never) to 5 (very often). Examples of items were: “Do you have a desire to eat when you are irritated?” (emotional eating), “If foods smells and looks good, do you eat more than usual?” (external eating) and “Do you try to eat less at mealtimes than you would like to eat?” (restrained eating). The DEBQ scales have high internal consistency, high validity for food consumption, and high convergent and discriminative validity.[33] The reliability and validity of DEBQ for Turkish population is determined by Bozan, Bas and Asci.[34]

Food Craving (FC)

Just like to the original Food Craving Questionnaire-Trait (FCQ-T),[35] the FCQ-T consists of 39 items that originally can be allocated to 9 subscales, each reflecting a dimension concerned with possible precipitants and consequences of food craving. These subscales are (1) intentions and plans to consume food (3 items); (2) anticipation of positive reinforcement that may result from eating (5 items); (3) anticipation of relief from negative states and feelings as a result of eating (3 items); (4) possible lack of control over eating (6 items); (5) thought or preoccupation with food (7 items); (6) craving as a physiological state (4 items); (7) emotions that may be experienced before or during food cravings or eating (4 items); (8) environmental cues that may trigger food cravings (4 items); and (9) guilt that may be experienced as a result of cravings and/or giving into them (3 items). Individuals have to indicate, using a Likert scale ranging from 1 (never or not applicable) to 6 (always), the degree to which each item

would be generally true for them.[36] The reliability and validity of FCQ-T for Turkish population is determined by Bas and Cakir.[37]

Body Mass Index (BMI)

Height and weight were measured; height with a vertical altimeter (sensitivity of 1 mm) and weight with a precision balance (sensitivity of 0.1 kg). The Centres for Disease Control 2000 growth charts for children and adolescents were used to identify body mass index (BMI) percentiles. BMI between 85th and 95th percentile was defined as overweight and BMI at or above 95th percentile was defined as obesity.[38] Weight and height percentiles were obtained from charts of growth curves for Turkish children.[39]

Statistical Analysis

SPSS 11.0 was used for data analysis. All variables were normally distributed. A one-way analysis of variance was used to compare those reporting NES, recurrent binge eating, and non-eating disorders. The assumption of the homogeneity of variances was met for all variables. The Scheffe' post-hoc procedure was used since it is considered stringent and can be used with equal and unequal sized groups. Independent samples t-tests were used to compare continuous variables in subjects endorsing BED. Pearson's correlation was also applied. The significance level was set at $p<0.05$.

Results

Prevalence of NED, BED and other eating disorder

Of the 380 females,7.7% (380/29) endorsed symptoms consistent with an eating disorder. Fourteen female participants (3.7%) reported NES, while 4.5% reported binge-eating symptomatology. Also, of the 183 males,7.6% (183/14) endorsed symptoms consistent with an eating disorder. Ten male participants (5.5%) reported NES, while 2.7% reported binge-eating symptomatology. Of those reporting the latter, 7 met criteria for purging bulimia nervosa (1.6% of females and 0.5% of males) and 11 met criteria for nonpurging bulimia nervosa (2.6% of females and 0.5% of males). Seven participants reported both night eating and binge eating (1.6% of females and 0.5% of males). In addition, 2 participants reported both night eating and purging bulimia nervosa (0.5% of females and no males), and 4 participants reported both binge eating and purging bulimia nervosa (1.1% of females and no males) (Table 1).

Differences of food craving and eating behaviours in adolescent with NES, BED and No-Eating Disorder

Post-hoc analyses revealed that BMI in participants who engaged in BED and NES had significantly different than the no eating disorders (No-ED) group ($p<0.001$). Also, participants who reported binge eating had significantly higher BMI than participants with NES ($p<0.001$). As predicted, participants who reported BED and NES had significantly higher restrained eating [$F(2,560)=43.391$, $p<0.001$], emotional eating [$F(2,560)=26.714$, $p<0.001$] and external eating scores [$F(2,560)=18.763$, $p<0.001$] than those not reporting disordered eating.. Participants who reported binge eating had significantly higher emotional eating and three individual food craving (FC) factors (FC-Positive reinforcement, FC-Relief from negative feelings, FC-Emotions experience) than participants with NES. Post-hoc analyses re-

Table 1. Prevalence of Night Eating Syndrome And Binge Eating Disorder

Eating Disorder	Female (n=380)		Male (n=183)		Total (n=563)	
	n	%	n	%	n	%
Night eating syndrome (NES)	14	3.7	10	5.5	24	4.3
Binge eating disorder (BED)	17	4.5	5	2.7	22	3.9
Purging bulimia nervosa	6	1.6	1	0.5	17	3.0
Nonpurging bulimia nervosa	10	2.6	1	0.5	11	2.0
Night eating and binge eating disorder	6	1.6	1	0.5	7	1.2
Night eating and purging bulimia nervosa	2	0.5	-	-	2	0.4
Binge eating and purging bulimia nervosa	4	1.1	-	-	4	0.7

vealed that total food craving scores in participants who engaged in binge eating and night eating were not significantly different from each other, but both groups were significantly different than the No-ED group ($p<0.001$) (Table 2).

From the analysis of the correlations among the variables, there was significantly correlation between body mass index and restrained eating (Pearson's correlation coefficient=0.17; P=0.000), emotianal eating (Pearson's correlation coefficient=0.10; P=0.014), external eating (Pearson's correlation coefficient=0.14; P=0.002) and total food craving scores (Pearson's correlation coefficient=0.22; P=0.000). Also, there was significantly positive correlation between food craving total score and restrained eating (Pearson's correlation coefficient=0.37; P=0.000), emotional eating (Pearson's correlation coefficient=0.46; P=0.000) and external eating (Pearson's correlation coefficient=0.46; P=0.000) scores (Table 3).

Table 2. Reported Food Craving, Body Mass Index, Restrained Eating, Emotional Eating and External Eating among Reporting Night Eating Syndrome, Binge Eating Disorder or No-Eating Disorder

Variables	BED (n=22)		No-BED (n=541)		NES (n=24)		No-NES (n=539)		No-ED (n=539)		F	Post-hoc comparisons
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
BMI	27.6	5.3	21.9	3.4	24.6	3.0	22.0	3.6	21.8	3.4	34.034	NES and BED>NED BED>NES
Restrained eating	3.9	0.7	2.5	0.9	3.9	0.7	2.5	1.0	2.5	0.9	43.391	NES and BED>NED
Emotional eating	3.8	0.9	2.2	1.1	2.9	1.1	2.3	1.1	2.2	1.1	26.714	NES and BED>NED BED>NES
External eating	3.8	0.9	2.8	0.9	3.5	0.9	2.8	1.9	2.7	0.9	18.763	NES and BED>NED
FC-total score	134.7	37.2	84.0	27.5	118.4	36.9	84.5	28.4	82.7	26.3	51.920	NES and BED>NED
FC-Intent and plan	10.6	3.6	5.9	2.7	9.5	3.5	6.0	2.8	5.8	2.6	49.373	NES and BED>NED
FC-Positive reinforcement	16.8	5.4	10.7	4.2	14.0	5.5	10.8	4.3	10.6	4.1	26.985	NES and BED>NED; BED>NES
FC-Relief from negative feelings	9.6	4.0	4.7	2.3	7.5	3.8	4.7	2.4	4.6	2.1	61.693	NES and BED>NED BED>NES
FC-Lack of control over eating	22.6	5.7	15.2	5.3	20.0	6.2	15.3	5.4	15.1	5.2	28.884	NES and BED>NED
FC-Thoughts, preoccupation	23.0	7.0	15.7	5.7	22.0	7.1	15.8	5.7	15.5	5.5	28.516	NES and BED>NED
FC-Craving-physiological state	14.0	5.4	8.3	4.1	12.0	4.6	8.4	4.2	8.1	4.0	28.342	NES and BED>NED
FC-Emotions experience	13.0	5.6	7.2	3.3	10.7	4.8	7.3	3.4	7.1	3.1	43.492	NES and BED>NED BED>NES
FC-Cues that trigger cravings	13.3	3.9	8.2	3.3	11.4	3.7	8.2	3.4	8.0	3.2	37.292	NES and BED>NED
FC-Guilt giving into cravings	11.8	3.9	8.0	3.0	11.3	3.3	8.1	3.1	7.9	2.9	30.790	NES and BED>NED

NES;Night Eating Syndrome, BED;Binge Eating Disorder, No-ED; No Eating Disorder, FC; Food Craving, BMI; Body Mass Index. F ratios are from ANOVA

Table 3. Correlations among Body Mass Index, Restrained Eating, Emotional Eating, External Eating, Food Craving

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13
1 BMI	1,00												
2 Restrained eating	0,17*	1,00											
3 Emotional eating	0,10*	0,41*	1,00										
4 External eating	0,14*	0,30*	0,55*	1,00									
5 FC-total score	0,22*	0,37*	0,46*	0,46*	1,00								
6 FC-Intent and plan	0,18*	0,29*	0,37*	0,38*	0,85*	1,00							
7 FC-Positive reinforcement	0,21*	0,30*	0,37*	0,38*	0,81*	0,67*	1,00						
8 FC-Relief from negative feelings	0,27*	0,32*	0,34*	0,35*	0,80*	0,71*	0,64*	1,00					
9 FC-Lack of control over eating	0,12*	0,31*	0,40*	0,43*	0,85*	0,71*	0,59*	0,59*	1,00				
10 FC-Thoughts, preoccupation	0,15*	0,31*	0,44*	0,43*	0,86*	0,72*	0,61*	0,55*	0,78*	1,00			
11 FC-Craving-physiological state	0,22*	0,28*	0,30*	0,31*	0,80*	0,65*	0,65*	0,69*	0,56*	0,59*	1,00		
12 FC-Emotions experience	0,24*	0,35*	0,43*	0,36*	0,82*	0,64*	0,64*	0,75*	0,63*	0,62*	0,63*	1,00	
13 FC-Cues that trigger cravings	0,21*	0,33*	0,34*	0,39*	0,83*	0,66*	0,66*	0,66*	0,70*	0,63*	0,62*	0,74*	1,00
14 FC-Guilt giving into cravings	0,13*	0,30*	0,40*	0,38*	0,80*	0,68*	0,61*	0,56*	0,63*	0,73*	0,64*	0,57*	0,59*

***Correlation is significant at the 0.01 level*

Discussion

A major aim of this study was to examine the presence of disordered eating patterns, specifically BED and NES, in Turkish adolescents. In this sample, the overall prevelance of binge eating disorder and night eating syndrome among adolescents was 3.9% and 4.3%, respectively. Research has shown that adolescent and preadolescent children engage in binge eating behaviour, and that this behaviour may be related to increased psychopathology, body dissatisfaction, dieting behaviours, and increased weight.[40] The population-based prevalence of binge eating (objective overeating with a sense of loss of control over what or how much one is eating) among youths is as high as nearly 30% for boys and 46% for girls in other ethnic studies.[41] Also, one recent European study of 126 children and adolescents ages 10-16 seeking inpatient treatment for obesity found that 36.5% had engaged in binge-eating episodes over the previous month.[42] However, of the 126 patients, 6.1% reported binge-eating at least two times per week as required to meet the DSM-IV criteria of binge-eating disorder. Females and males had similar rates of binge eating, or 37.3% and 35.3% respectively. Obese bingers were younger than obese nonbingers, with mean ages of 12.24 years and 13.23 years respectively. Unlike obese adults, obese bingers and obese non-bingers in this population did not differ significantly in degree of overweight. In addition, estimates of the prevalence of NES have ranged from 6%[43] to 64%[18] among patients seeking weight loss, and prevalence estimates of NES have also been reported in the following groups: 1.5% among the general population,[22] 12.3% among an outpatient psychiatric population,[44] and 3.8% among a type 2 diabetic population.[45] Subjects who were not obese or overweight were more likely to perceive their night eating as nonproblematic. Moreover, depending upon the definition, night eating is often noted in adolescent girls without psychological distress. A study of 9-19 years old females noted that 50-70% of subjects described eating more than 25% of total daily calories after the evening meal. Furt-

hermore, occasional episodes of night eating were more common (typically by a factor of 10) compared to multiple episodes of night eating a week.[46]

Binge eating was also correlated with depressive symptoms, body mass index (BMI), and ideal–actual weight discrepancy in another study of adolescent girls.[47] Similarly, we found a significant association between the binge eating disorder and the BMI. Also, the present study indicated that body mass index was significant correlated with food craving and night eating syndrome. Alike, Gendall et al. showed that body mass index was found to be associated with binge eating in cravers.[48]

Food cravings were found to be frequently associated with binge eating.[48] Binge eating is defined as the consumption of large amounts of food in a short period of time.[8] Bruce and Agras[14] reported that binge eating occurs in healthy people and eating-disordered groups. Models of binge eating have included food cravings as a potential trigger for overeating.[49] The present study is the first to compare food cravings across binge eating disorder and night eating syndrome. Our data suggest that the overall general experience of food cravings is different between those with eating disorder symptoms and those without. Total food craving scores were significantly higher in persons with night eating syndrome or binge eating disorder than those not reporting eating disorder symptoms. These results were congruent with the observation by Jarosz et al.[50] that positive association between food craving and night eating syndrome and binge eating disorder are confined to sample of obese women.

Formally proposed in the late 1970s, the dietary restraint model purports that individuals who chronically attempt to maintain strict dietary control are at high risk for becoming temporarily disinhibited in maintaining their control, which often results in a binge eating episode.[51-54] In other words, this model describes a self-fueling cycle in which temporary caloric restriction and homeostatic imbalances, which are common in individuals struggling with eating disorders, causes cravings to eat. Food cravings, in turn, can drive individuals to binge eat.[55] Overall, the present findings suggest that dietary restraint lead to food cravings in individuals with night eating syndrome and binge eating disorders. Also, food cravings are associated to binge eating in adolescents diagnosed with bulimia nervosa. The results were similar to the observation by Cepeda-Benito and Gleaves[56] that positive association between dietary restraint and food craving is confined to samples composed of unsuccessful dieters.[57] While a number of studies have found an association between dietary restraint and food craving,[57-59] others have not.[60,61]

The present findings suggest that emotional eating lead to food cravings in individuals with night eating syndrome and binge eating disorders. Also, the present study indicated that food craving was significant correlated with emotional eating and external eating. Considering the possible factors triggering binge episodes, some studies focused on the role of emotional states.[62,63] The study of the emotional eating, defined as ‘‘eating in response to a range of negative emotions such as anxiety, depression, anger, and loneliness to cope with negative affect’’ suggested that episodes of binge eating are often precipitated by stress and negative affects, and that binge eating appears to be associated with a subsequent decrease in negative affect.[64-66] However, there is accumulating evidence that emotional and external eating may refer to independent constructs and that the mechanism that underlies emotional eating might differ from the mechanism that underlies external eating. Thus, only emotional eating, and not external eating, seemed to be the pre-eminent moderator variable of the relationship between daily hassles and snacking.[67]

The study's limitations; different important data of this study were self-reported. Future studies are needed to replicate these findings, to understand why this population is at increased risk for NES or BED, and to determine the effects of NES or BED on health outcomes among adolescents.

In conclusion, the current study suggests that binge eating disorder and night eating syndrome are strongly significant problem among adolescents, especially overweight adolescents. Our findings indicated that the experience of food craving is an important factor in adolescents with binge eating disorder and night eating syndrome. Body mass index was positively correlated with food craving, binge eating disorder and night eating syndrome. Finally, these eating problems may contribute to the development and/or maintenance of obesity. Food cravings as a single construct with

nine multidimensional factors was significantly different in those with eating disorders compared to those not reporting disordered eating. Our work suggests that the experience of food cravings is an important factor in adolescents with disordered eating patterns that merits further investigation. Also, a short-term internet-facilitated program can promote weight maintenance and reduce binge eating in motivated adolescents.

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Clinical and socio-demographic characteristics of tension type headache in working population

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Abstract

Tension-type headache (TTH) is the most common primary headache, whose clinical characteristics are described in detail, which resulted in definition of current diagnostic criteria, given in International Classification of Headache Disorders- second edition. For the time being, there is an insufficient number of epidemiological studies on tension type headaches in our environment. The aim of this paper is to determine socio-demographic and clinical characteristics in employed that suffer from TTH. The research has been conducted using General questioner and Questioner about characteristics of headaches on sample of 1022 employed people age 20 to 65.

According to our research, 51.8 % of employed people that suffer from tension-type headache has rare episodic, 44.2% frequent episodic, and 4% chronic TTH. Among those that suffer from chronic TTH there was not a single person that belonged to the youngest age group (20-30), while 66.7% belonged to the group with patients who were between 41-50 years of age. In our research, prevalence of rare and frequent episodic tension-type headache grew beginning with the youngest group, culminating with middle group (41-50 years), and then it showed tendency to subside. Among patients with TTH significant percentage of patients are smokers, when it comes to marital status, there is a significant percentage of the divorced, and very often we find presence of this type of headache in their relatives, as well as presence of some other chronic disease. In our research there is prevalence among women, and the ratio is 5:3. Questioner about characteristics of a headache gave us answers characteristic for this particular group. Mental strain and fatigue have been reported as the most common triggers in connection to TTH.

TTH is a very common headache type in working population, participating in this research. All of them filled the questioner at their place of work and are considered to be conditionally healthy. Active search for those suffering from TTH and a timely and proper health care can improve patient's health and lower economic cost due to headache.

Key words: Tension-type headache, socio-demographic characteristics, employed population

Introduction

Working population is the carrier and the backbone of every society. This population is a reproductively active part of any society. With these aspects in mind, it can be said that they are the most important group in any society. Never the less, there is still discrepancy between the society's expectations and investments when it comes to the working population. The common practice is to pay attention to health of this population when it comes to risky occupations and regular medical checkups. The care about an employee who has a primary headache begins only when they themselves go to see a doctor. There are certain professions that have higher risk of headache occurrence (1).

Tension-type headache is the most common primary headache. It is a non specific headache that does not have vascular causes nor is associated with organic damage (2). The word "tension" implies that this headache type can be caused by strain and stress, which again means that many people with this headache type avoid seeing their doctor (3). On the other hand, the word "tension" can be misunderstood, even by doctors, to imply a headache caused by high blood pressure.

Tension-type headache typically causes pain that spreads like a band, on both sides of the head, starting at forehead and progressing towards the occiput.

It often radiates towards neck muscles, and it can even radiate towards trapezius muscles, muscles of the shoulder girdle of scapular and interscapular region (4, 5). TTH pain is of mild or changing intensity, and it is described as tension, pressure or dull pain. Anamneses gives distinctive pain description – the feeling that the head is "pressed as in a vice", "inability to think clearly", "and the numbness and tingling in the head", feeling as if there was "a casque on the head". When the headache is holocephalic, the patients describe the accentuated sensitivity of the vertex of the head while combing (6). Migraine like pain in one side of the head, pulsating pain, nausea, vomiting and photophobia are not usually present.

Diagnostic criteria for a tension-type headache can be found in new International classification of headache disorders (ICHD-II 2004).

According to frequency of attacks, tension-type headache can be:

1. Rare episodic tension-type headache – with TTH attacks that occur less than once a month, that is less than 12 days a year.
2. Frequent episodic tension-type headache - with TTH attacks that occur 1 to 15 times (days) a month, that is at least 12 days, and not more than 180 days a year.
3. Chronic tension-type headache - with TTH attacks that occur, in average, 15 or more times (days) a month.

Tension-type headache starts a bit later than a migraine, in the second half of the third decade of life and it gets less frequent as person grows older (7, 8).

The purpose of this paper

The purpose of this paper is to establish socio-demographic and clinical characteristics of tension-type headache in working population.

Methods and materials

The research has been conducted on 1022 employees in the area of Novi Sad (Republic of Serbia) that have adequately filled in the questioners, and returned them the following day(s).

The following have been used as research instruments:

I. General Questioner – which contains general questions, and questions related to gender, age, company status, marital status, family status, level of education, overtime work, smoking, headache in relatives, presence of chronic disease in the examinees. The last two questions of the general questioner are related to presence of headaches in the last year and the last month. The examinees that have answered affirmatively to the question whether they have had a headache within the last year and/or last month have become part of the next research.
II. Questioner about headache characteristics – which contains questions related to: the year of life when the first headache occurred, the frequency of headache attacks, localization, intensity and quality of pain, associated symptoms, the presence of prodrome and aura, headache triggers. The last two questions in this questioner were for female examinees only, and they were related to the connection between menstrual period and/or menstrual cycle and headaches. Following the ICHD-II criteria, the questions in the questioner have been selected in such a fashion that examinees' answers help establish the diagnoses about the headache type.

During the statistical analysis the headache questioner has been divided in five parts:

- A part about general headache characteristics that is related to the year when the headache first occurred, the frequency of headache attacks, localization and intensity and the quality of pain.
- A part about associated symptoms that is related to aggravation of the condition after physical exercise and avoidance of physical exercise due to aggravation of the condition, the presence of nausea, vomiting, photophobia, phonophobia, tension of pericranial muscles, motor weakness, visual, sensory and speech symptoms
- A part about presence of the headache, prodrome and aura trigger that is related to consummation of specific foods or drinks, mental strain, fatigue, strong

odors, changes of atmospheric pressure, menstrual cycle or other triggers.
- A part about presence of prodrome and aura that is related to presence of prodrome and visual and sensory aura
- A part about the influence of menstrual period and/or menstrual cycle on headache that was meant for female participants only, and its purpose was to establish whether the headache is connected to the menstrual cycle, whether it occurs during the menstrual period only, or in other periods as well, and whether it occurs in pre-menstrual or post-menstrual period.

The data was analyzed using discriminative analysis, and other parametric procedures and methods. Univariate analyses included Roy's test, Pearson's contingency coefficient (χ), and the multiple correlation coefficient (R). Calculation of discrimination coefficients discriminates characteristics that determine specificity of subsamples. The purpose of the mathematical and statistical analysis was to determine characteristics of each subsample and the homogeneity and distance between subsamples in relation to the discriminative characteristics.

The collected data were checked for possible formal or logical errors. The data obtained through the statistical analysis are presented in tables and figures, accompanied by comments.

The results

Out of 1022 employees, 224 (22%) fulfilled criteria for tension-type headache.

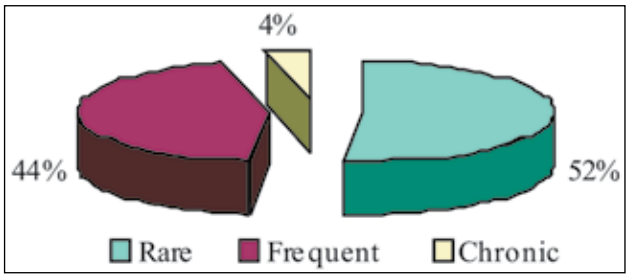

Chart 1. Prevalence of certain sub-types of TTH

Among employees suffering from tension type headache 116 of them (52%) developer rare episodic tension type headache, 99 of them (44%) developed frequent episodic tension type headache, and 9 of them (4%) developed chronic tension type headache, as in Chart 1.

Gender difference in prevalence of TTH is present in complete sample examined, and it is 5:3 for females. That is prevalence of TTH in women is 24.6%, and in men 15.6%.

Table 1 shows prevalence of certain tension headache subtypes in certain age groups. It can be seen that tension type headaches are most frequent in age categories between 31 and 40 and 41 and 50 years of age. There are no patients suffering from tension type headache in the youngest 20-30 years of age, and the oldest tested group.

Table 1. Prevalence of TTH in different age categories

	20-30		31-40		41-50		51-60		61-65	
	n	%	n	%	n	%	n	%	n	%
Rare TTH	15	12.9	42	36.2	46	39.7	12	10.3	1	0.9
Frequent TTH	15	15.2	33	33.3	38	38.4	13	13.2	0	0.0
Chronic TTH	0	0.0	1	11.1	6	66.7	2	22.2	0	0.0

Table 2. Number and percentage prevalence of certain subtypes of TTH related to smoking, presence of headaches in relatives and the presence of chronic disease

	Rare TTH		Frequent TTH		Chronic TTH	
	n	%	n	%	n	%
Smokers	45	38.8	46	46.5	6	66.7
Non-smokers	71	61.2	53	53.5	3	33.3
Relatives with headache	44	37.9	52	52.5	6	66.7*
Relatives without headache	72	62.1*	47	47.5	3	33.3
With chronic disease	31	26.7	31	31.3	5	55.6*
Without chronic disease	85	73.3*	68	68.7	4	44.4

Table 2 shows significant percentage of smokers among patients suffering from tension type headache. Furthermore, the percentage of smokers is the smallest among those suffering from rare episodic tension type headache (38.8%), greater number of smokers can be found in patients suffering from frequent tension type headache (46.5%), and the greatest number of smokers is among those suffering from chronic tension type headache (66.7%). It can also be noticed that we very often found presence of headache in their relatives, as well as presence of some chronic disease.

Table 3 shows that for certain headache characteristics $p > 0.1$ which means that the relevant difference between three TTH sub-types for location of pain has not been perceived (Location 0.180). Never the less, the most frequently mentioned pain location during the testing for all three subtypes, is bilateral.

Also, Table 3 shows that for certain headache characteristics $p < 0.1$ which means that there is relevant difference between some of the TTH sub-types for: age when the first headache occurs (0.019), frequency of headache attacks (0.000), attack time (0.000), intensity of pain (0.007), and quality of pain (0.007).

In Table 4 we can see that for some joined symptoms $p > 0.1$ which means that the relevant difference between three TTH sub-types for: presence of vomiting (0.249), phonophobia (0.258), tension and soreness of muscles (0.260) has not been perceived.

Table 3. The importance of difference between certain sub-types of TTH in relation to headache characteristics

	c	R	F	p
The beginning of headache	0.194	0.188	4.047	0.019
Frequency	0.806	0.983	3064.987	0.000
Attack time	0.562	0.660	84.755	0.000
Location	0.148	0.124	1.730	0.180
Intensity	0.230	0.211	5.133	0.007
Quality	0.227	0.211	5.122	0.007

Table 4. The relevance of difference between certain TTH sub-types in relation to presence of associated symptoms

	χ	R	F	p
Aggravation due to physical exercise	0.151	0.153	2.647	0.073
Avoidance of physical exercise	0.170	0.173	3.416	0.035
Nausea	0.229	0.236	6.533	0.002
Vomiting	0.111	0.112	1.401	0.249
Photophobia	0.233	0.239	6.750	0.001
Phonophobia	0.109	0.110	1.362	0.258
VSS Symptoms	0.273	0.283	9.698	0.000
Musculature	0.109	0.110	1.356	0.260
Motor weakness	0.176	0.179	3.659	0.027

Table 5. The importance of the difference between certain TTH subtypes in relation to the attack triggers

	χ	R	F	p
Food	0.078	0.078	0.677	0.509
Drinks	0.149	0.151	2.596	0.077
Anxiety	0.136	0.137	2.128	0.122
Fatigue	0.145	0.147	2.438	0.090
Strong odors	0.086	0.086	0.836	0.435
Atmospheric pressure	0.149	0.151	2.595	0.077
Menstrual period	0.062	0.062	0.423	0.655
Other triggers	0.042	0.042	0.194	0.824

Furthermore, Table 4 shows that for some joined symptoms $p < 0.1$ which means that there is relevant difference between some of the TTH sub-types for: aggravation due to physical exercise (0.073), avoidance of routine activities (0.035), presence of nausea (0.002), presence of photophobia (0.001), temporary visual, sensory and speech VSS symptoms (0.000), occurrence of weakness and numbness (0.027).

Table 5 shows that for certain attack triggers $p > 0.1$ which means that the relevant difference between three TTH sub-types for: food consummation (0.509), mental strain (0.122), strong odor influence (0.435), menstrual period (0.655), and other triggers (0.824) has not been perceived.

Furthermore, for certain attack triggers $p<0.1$ which means that there is relevant difference between some of the TTH sub-types for: drinks consummation (0.077), fatigue (0.090), influence of atmospheric pressure (0.077).

Discussion

Tension-type headache is the most common primary headache. There is an insufficient number of epidemiologic studies on tension type headaches in our country, for now, although it is the most frequent primary headache Earlier research based on the old headache classification indicates prevalence of 12.1 - 72.8%. A survey in USA indicated prevalence of 38.3% (9). Dutch researchers (10) conducted a study which evaluates epidemiological aspect in Dutch citizens at their work place and the effect of the headache on the economic expenses. The study has been conducted in a company with 1781 employees. The prevalence of tension type headache in this study was 17%. In our research conducted among conditionally healthy participants prevalence of 22% has been established, with the most common rare episodic TTH, and the least common chronic TTH. Never the less, according to our research, 51.8 % of employed people that suffer from tension-type headache has rare episodic, 44.2% frequent episodic, and 4% chronic TTH. Prevalence of tension type headache in our tested sample of employees is within the bound most often mentioned in the literature.

Chronic tension type headache prevalence grows with years of age, and the episodic tension type headache prevalence decreases with the years of age (11). In our research among those that suffer from chronic TTH there was not a single person that belonged to the youngest age group (20-30), while 66.7% belonged to the group with patients who were between 41-50 years of age. In our research, prevalence of rare and frequent episodic tension-type headache grew beginning with the youngest group, culminating with middle group (41-50 years), and then it showed tendency to subside.

According to Olesane and al, peripheral nociceptive mechanisms prevail at the beginning in patients with episodic TTH. Repeated episodes lower the pain threshold and heighten the pericranial sensitivity which is present during headache attack and several days after it (12). Furthermore, through facilitation, that is excitation of nociceptive neuron circles of the brain stem and other parts of the CNS, the inhibitory activity of antinociceptive system is lowered, which means that chronic tension-type headache occurs through central mechanisms (13, 14). Chronic TTH has a significant impact on every day life of the person affected, but on the economy of the society as a whole as well (15). That is why it is important to diagnose the presence of the TTH type and treat it adequately.

Gender difference in headache prevalence tips to the female end of the scale and is most often mentioned in relation to migraine (16) but is also present in the tension type headache prevalence. Among the grown-ups, there are more women suffering from headaches, and the most often mentioned ratio in the data available is 5:4. (17). In our research, there is greater gender difference in patients with tension type headache. That is, Tension type headache prevalence in women in our research is 24.61%, and in men it is 15.6%, which means that the ratio is 5:3 and female gender is worse off in this research. Using the criteria of the International Classification of Headache Disorders, reliable and precise diagnoses can be established, and with very little expense, even in undeveloped countries. Precisely defined diagnostic criteria give opportunity for involvement of the greater number of nurses with higher degree education in the very process of diagnosis (18), as well as diagnostic tools development with the use of the new information technologies. (19).

In our research, the use of the questioner about headache characteristics, has given data typical for

this group of patients for both, TTH generally, and for certain TTH sub-types. Tension type headache is characterized by attacks that are mild to moderate, non pulsing bilateral headaches, and different attack duration, from half an hour up to a week. Furthermore, it can be noted that the employees: aged 41-50, smokers, divorced, with associated chronic disease and having relatives with headaches are at greater risk of chronic TTH. Mental strain and fatigue have been reported as the most common trigger. Headache was the most frequently mentioned problem in relation to burnout (20). Stress is undoubtedly the most common precipitating trigger factor in over 80% of those suffering from TTH. Emotions have biochemical effect on the body and mental stress alone can cause muscle contraction through limbic system (21). The studies have shown that when compared to the control group the patients suffering from TTH have been through similar stressful life situations, but they took them harder, and they had less effective defense mechanisms (3, 22). What basically needs to be done with these patients is to clip and reduce headache attacks, prevent the excessive use of medicaments, recognize, in time, the associated pathologies, prevent episodic headache turning into chronic TTH. For these purposes non-medicamentose and medicamentose treatments can be used, as well as prophylactic treatments. Psychotherapy, relaxation methods and psychopharmaca can be very useful addition to analgesic therapy, and sometimes they can be the main therapy (23, 24).

Conclusion

Clinical and socio-demographical tension type headaches among the working population in our environment do not basically have greater differences in relation to the criteria set by current headache disorder classification and the results from the other research. In order to improve health of the people suffering from TTH, it is necessary to actively search for them.

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Multi Drug Abuse and Sinus Node Dysfunction

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Abstract

Drug abuse is a major public problem not only due to its negative impact on social life but also its detrimental effect on health. Neuropsychiatric drugs used for accompanying psychiatric disorders may act synergistically to increase the harmful effects of recreational drugs. We describe a previously healthy young male patient suffered from sinus node dysfunction caused by multiple drug abuse with resultant implantation of a pacemaker, and discuss mechanisms of the sinus node injury caused by drugs used by this patient. Sinus nodal dysfunction should be considered in patients with syncope caused by recreational drugs.

Key words: Sinus node dysfunction, drug abuse, cannabis, ecstasy, permanent pacemaker

Case Report

A 25-years-old male admitted to our emergency department with 3 episodes of syncope happened in the last 2 months. He had no previous medical history of syncope (i.e. sleep apnea, vasovagal syncope), shortness of breath, or myocarditis. Also he had no family history for syncope. On admission, his initial blood pressure, heart rate and respiratory rate were 127/67 mmHg, 61 beats/minute, and 17/minute; respectively. No important findings were noted on physical examination. Normal sinus rhythm was present on ECG. He was taking several medicaments for depression, and was using recreational drugs and alcohol. For depression, he used venlafaxine HCl 150 mg qd for 8 months, olanzapine 5 mg qd for 3,5 months, mirtazapine 30 mg qd for 2 months, and sertralin HCl 50 mg qd for 4 months. He was using cannabis and ecstasy for 5 years. He hadn't used any recreational drug or alcohol in the past six months. As he had a history of syncope, he was subsequently hospitalized and monitorized. Complete blood count, full biochemistry including thyroid function tests, urinalysis and urine specimen for delta-9-tetrahydrocannabinol (THC) and plain chest x-ray were obtained, and caroticovertebral Doppler ultrasound, transthoracic echocardiography and myocardial perfusion scintigraphy were performed. In all of these investigations, results were found within normal ranges. While he was being monitorized, a total of 53 episodes of sinusal pauses occurring at nighttime with durations varying between 2,5 to 6,8 second were observed (Figure 1). At the same time, heart rate varied between 28 bpm to 98 bpm. To further investigate cardiac conduction, an electrophysiologic study (EPS) was performed. During EPS, basal intracardiac intervals were found as prolonged with AH duration was 82 ms, HV duration was 54 ms, AV-Wenckebach duration was 320 ms, sinus node recovery time (SNRT) and corrected SNRT was 3425 and 680 ms, respectively. Although we were unable to find any reversible reason, we considered that sinus node dysfunction was the responsible event for syncope episodes, and sinus node dysfunction was caused by previous drug abuse. As he didn't use any drugs or recreational drugs in the past 6 months, node damage was thought as permanent rather than reversible. Subsequently, a permanent dual chamber pacemaker was implanted. No further syncope episodes were noted during follow-up, and he was discharged from hospital on the 8th day of his admission.

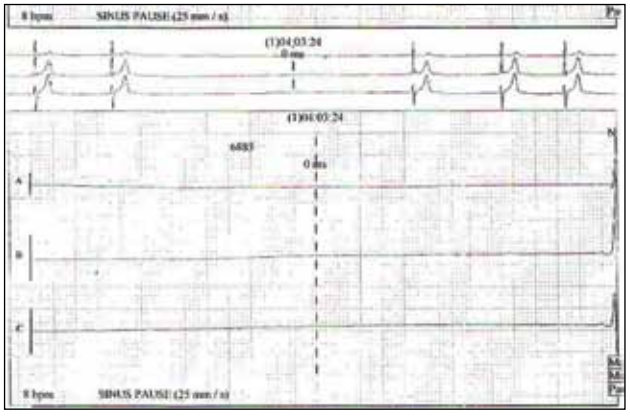

Figure 1. Sinus pause recorded for 6.8 seconds at 04:03 (at sleep)

Discussion

Conduction system of the heart is modulated by both sympathic and parasympathic nervous system. Sinus node is innervated by postganglionic adrenergic and cholinergic nerve termini, which are both found abundantly.

Sinus node dysfunction is a common clinical syndrome. It consists of electrophysiological abnormalities, insufficient discharge rates, inability to conduct impulse to atria, insufficient secondary pacemaker activity and an increased susceptibility of atria toward tachyarrhythmia. Sinus node dysfunction may be caused by a variety of intrinsic and extrinsic reasons. Intrinsic causes, such as idiopathic degenerative disorder and ischemic heart disease tend to disrupt SA nodal anatomy (including surrounding atrial tissue) or physiology, while SA nodal structure is normal in extrinsic causes of dysfunction, such as drugs or hyperkalemia. Histopathologic specimens obtained from patients with SA nodal dysfunction shows loss of nodal cells along with fibrosis, amyloid deposition in nodal area, and hypoplasia of SA node. Idiopathic degenerative disease is the most common etiological factor that causes SA nodal dysfunction; this is followed by diseases caused by ischemia [1]. Other potential causes include collagen vascular disorders, infiltrative cardiomyopathies such as amyloidosis and sarcoidosis and inflammation.

The most common causes of SA nodal dysfunction without structural anomalies include drugs and conditions that affect autonomic nervous system. Some drugs may directly effect nodal tissue functions, while others effect indirectly via altering autonomic nervous system stimuli [2].

History obtained from our patient revealed usage of extended release formulation of venlafaxine 150 mg qd for 250 days due to major depression. Venlafaxine is an antidepressant drug with a normal maximal daily dose of 225 mg. Infrequent side effects include, first-degree atrioventricular block, bundle branch block and sinus arrhythmia. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), bradycardia and death were also reported.

Our patient had used cannabis previously for five years in different doses for 1-2 times in a week; however he did not use the drug for one year. Cannabis has more than 400 chemical ingredients, of these 60 are physioactive agents and known as cannabinoids. Plasma half-life of cannabis is 20-30 minutes, and could be detected for a few days in urine of intermittent users for up to two months in urine of heavy users [3]. Autonomic nervous effects of cannabis are biphasic. By acting on sympathetic nervous system, it causes an increased heart rate and blood pressure; in higher doses it acts on parasympathetic nervous system and inhibits sympathetic nervous system and causes decreased heart rate and blood pressure [4].

A synergistic effect is observed on myocardium when cannabis is taken along with alcohol or other drugs (especially amphetamine). With severe tachycardia triggered by this synergistic effect; ischemia, myocardial infarction and even death could be seen [5].

Our patient was also using ecstasy (3-4 methylene dioxymetamphetamine) in a dose up to 7-8 tablets a week. Ecstasy is a derivative of amphetamine and has similar effects. Both amphetamine and ecstasy have an indirect effect on sympathetic nerve terminus by stimulating the liberation of norepinephrine, dopamine and serotonin. Toxicity of amphetamine increases if it is taken along with alcohol. Chronic usage of cocaine and amphetamine lead to repetitive coronary artery spasms and may result with endothelial dysfunction, coronary artery dissection and accelerated atherosclerosis. Another cause of ischemia in some organs is necrotizing vasculitis in small to medium sized arteries caused by both drugs. High doses of amphetamine blocks fast sodium and potassium channels and inhibits calcium entry into myocytes, with resultant disruption of electrical activity and contractile functions of myocardium. Class I antiarrhythmic (and so, proarrhythmic) effects possessed by this drug, it alters cardiac conductivity and may cause sinusal arrest and atrioventricular blocks. Benzodiazepines and alcohol augments the toxic activity of this drug on cardiac tissue and central nervous system.

Our patient used olanzapine 10 mg qd for 3,5 months. This drug belongs to thienobenzodiazepine class of atypical antipsychotic drugs. Oral olanzapine was associated with orthostatic hypotension and tachycardia.

Along with aforementioned drugs, our patient used mirtazapine 30 mg qd for 2 months and ser-

traline 100 mg qd for 4 months. Mirtazapine is an antidepressant, and frequently reported side effects include hypertension and vasodilatation, while infrequent adverse effects reported so for consists of bradycardia, hypotension and syncope. Sertraline is a selective serotonin reuptake inhibitor, whose side and adverse effects include postural hypotension and syncope.

In United States, drug abuse causes approximately 40 million cases of severe disorders and injuries annually. Many recreational drugs are easily obtainable in western countries, and this situation an epidemic of drug abuse. In United Kingdom, 25% or all population used one or more of these drugs in a part of their lives. Even more frequent usage of antidepressants along with illicit drugs causes permanent sinonodal disruption with resultant syncope episodes.

Sinus node dysfunction results from total or subtotal destruction of sinus node area or nodal-atrial continuity; and inflammatory and degenerative changes of neurons supplying nodal tissue. Obstruction of sinus nodal artery is also an important etiologic cause. Patients with SA node dysfunction could be categorized as those with intrinsic abnormalities and those with autonomic dysfunction, depending on aforementioned mechanisms. In some patients, sinus node dysfunction may be caused by a combination of both causes.

All drugs used by our patient have bradycardia and syncope as reported side effects. When all drugs used by our patient are considered, the cause of SA node dysfunction in our patient seems to caused by both an intrinsic disruption of SA node along with autonomic dysfunction. Alcohol used by our patient may also be responsible for increasing the effects of these drugs.

Although transient and permanent atrioventricular blocks were reported frequently in literature, reported sinus nodal dysfunction cases are scarce. As the usage of these drugs becomes more and more widespread, we fear that the number of young patients with sick sinus syndrome shall increase.

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Exraocular sebaceous carcinoma

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Abstract

Introduction: Sebaceous glands are spread almost all over the skin. The spectrum of changes with sebaceous differentiation involves numerous entities including sebaceous carcinoma as a rare malignant tumour. Sebaceous carcinoma makes 1% of skin cancer, and it can be ocular and extraocular. Extraocular sebaceous carcinoma makes a quarter of this number (0.25% of skin cancer). The clinical appearance of sebaceous carcinoma may resemble many benign and inflammatory changes, which contributes to the longer time required to set the correct diagnosis and initiate appropriate treatment. Tumour lobules consist of predominant atypical basaloid cells and centrally positioned sebaceous cells.

Case report: Female 56-year-old patient noticed a nodule 2 cm in size on her left shoulder. The nodule was not attached to the skin surface and also appeared not to be firmly attached to deeper structures of the shoulder. Subsequently, the nodule was surgically removed. Gross examination revealed clearly demarcated, lobular, yellow, medium firm node of homogeneous appearance. Surgically removed material was fixed in 4% formalin, embedded in paraffin, and 5μm thick sections were stained with standard HE method and immunohistochemical markers, CEA and EMA. Tumour tissue was clearly demarcated, without capsule, located only in the dermis and it was not in contact with the epidermis. Sebaceous carcinoma tissue consisted of basaloid cells on the periphery of tumour lobules, as well as of large centrally localized cells with vacuolated cytoplasm showing sebaceous differentiation. A small number of mitosis, keratin masses and focal necrosis were noted. Tumour tissue showed CEA negativity and EMA positivity. The diagnosis of well differentiated sebaceous carcinoma was confirmed.

Discussion: Our patient's age was in line with literature data. Extraocular sebaceous carcinoma in the area of arms and shoulders, as in our case, is present in 3.9% of all sebaceous carcinoma. The nodule appeared to be unattached to the skin and to deeper skin structures, which is in accordance with data in available literature, as well as with histological appearance in our case showing the presence of cancer only in the dermis without its connection to deeper skin structures. Sebaceous carcinoma tumour tissue is comprised of irregular lobules that may resemble the structure of unchanged sebaceous gland. Although the morphological features of sebaceous carcinoma are well-known, differentiation of sebaceous carcinoma to other tumours of the skin and skin adnexa, malignant melanoma or metastasis of visceral tumours with clear cell morphology could be problematic. Sebaceous carcinoma is CK and EMA positive and CEA negative which distinguishes poorly differentiated SC and tumours of sweat glands, the majority of hematopoietic malignancies and mesenchymal tumours.

Conclusion: Regardless of the rare occurrence of sebaceous carcinoma, it is necessary to include this tumour in the differential diagnosis of the skin lesions. The particular significance of this tumour is in the differential diagnosis of well demarcated lesions, given the fact that they are usually clinically diagnosed as benign changes.

Key words: sebaceous adenocarcinoma, skin, EMA, CEA

Introduction

Sebaceous glands are spread almost all over the skin, mostly in the scalp and neck (1, 2), usually near the hair follicles (2). They are comprised of lobular secretory component consisting of alveoli and short excretory duct continuous with the hair follicle (3). Alveoli are peripherally lined with a thin layer of flattened to cuboidal basaloid cells with scant cytoplasm, and in the inner portion of lobules are polygonal, voluminous mature sebaceous cells (3). Modified and ectopic sebaceous glands arise independent of follicular structures (3), such are the

glands of the penis, vagina, breast areola, Meibomian glands of the eyelid, glands on the border of lips and surrounding skin, in the mucosa of the mouth (Morbus Fordyce) (3, 4). Lesions with a sebaceous differentiation include a number of entities (2, 5). Sebaceous carcinoma (SC) is a rare malignant tumour, originating from sebaceous glands (6). Most patients with this tumour present are between the ages of 60 and 80 years, equally in both genders (4, 6). Clinically and macroscopically, SC is described as a firm, pink to tan, sometimes ulcerated nodule or plaque (5, 6). Cancer is made of irregular lobules located in the dermis, sometimes penetrating the subcutaneous adipose tissue (1). The appearance of cancer lobules, in terms of cellular arrangement, greatly resembles the appearance of normal ones (4). Tumour lobules consist mainly of atypical basaloid cells with increased number of mitosis and in lesser number of centrally placed sebocytes whose abundant cytoplasm and vacuoles are filled with lipid content, which suppress the nucleus and give it a distinctive scalloped appearance (2, 4, 5). Depending on degree of basaloid cell differentiation, SC is classified as well, moderately or poorly differentiated (4, 5). In the tumour tissue sebum and keratinized debris can be seen (5). SC may have a diffuse or nodular growth, and rarely gives metastasis in regional lymph nodes, while metastatic potential does not depend on the localization of the tumour (1).

SC are divided into ocular and extraocular (1). Ocular SC account for about 75% of all diagnosed SC and are in fourth place among the tumours of the eyelids (3, 6). SC in ocular region are painless, slow-growing lesions, usually on the edge of the eyelid, and originate from Meibomian glands, the glands of Zeis or sebaceous glands of the eyelid (4). The diagnosis is made much later than the first appearance (1-2.9 years) because of the clinical similarities to benign changes of the eyelid (4). SC of either extraocular or ocular localization is often misdiagnosed as basal or squamous cell carcinoma (1, 5). Extraocular SC represents about 25% of all SC. As sebaceous glands are present in almost all regions, SC arises in various sites (4), of which the most common is skin of the head and neck (89%) and to a lesser extent, external genitals, shoulders and arms, hip and leg, and the cases of SC in descending colon and ear occurred (1, 6). So far, identified risk factors for SC were older age, radiation exposure, mutation of Rb and p53, HIV, HPV (7), and genetic predisposition (6). Extraocular SC is not uncommon in the area of lesions where sunlight exposure is well known risk factor, and most of extraocular SC arises on sun-exposed areas. However, areas with high incidence of SC like face and neck are both sun-exposed and have plenty sebaceous glands so it may not be possible to confirm a connection between SC and sunlight or ultraviolet radiation exposure (4, 7). Appearance of sebaceous tumours with visceral malignancies was observed in 1972. and called Muir-Torre syndrome (2) According to the study of Dasgupta et al. in 30% of patients had 2 or more previously diagnosed malignancies (6).

Case report

A female patient aged 56 years presented with a slow-growing firm, nodule of about 2cm in size on her left shoulder. Node was not attached to the skin and seemed unattached to deeper structures of shoulders.

Macroscopically, nodule was well demarcated, and the cut surface was lobular, yellow, and showed homogeneous appearance (Figure 1).

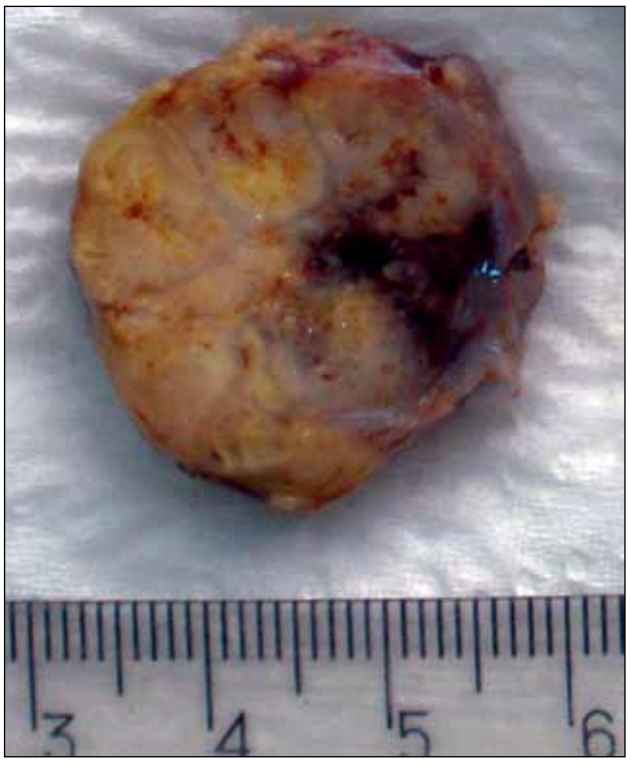

Figure 1. Gross appearance of the tumour.

Histologically, a tumour nodule was present in the dermis of the skin and it had no contact with the epidermis. Tumour tissue had no capsule although it was well demarcated by the compressed surrounding connective tissue without conspicuous infiltration. Tumour was comprised of basaloid cells with central sebaceous differentiation (Figure 2).

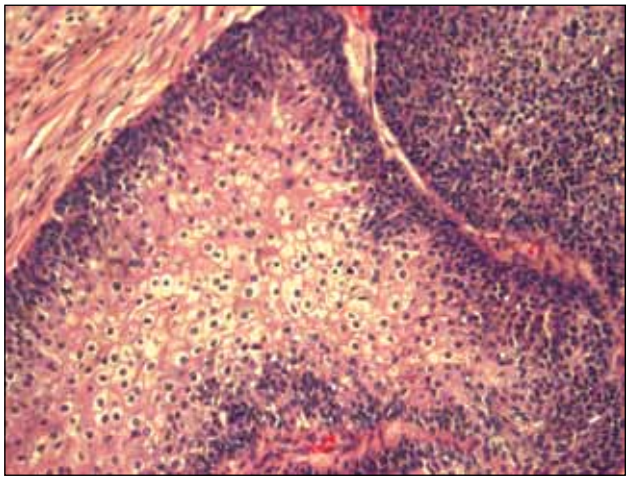

Figure 2. Microphotograph of tumour lobe comprised of basaloid cells with central sebaceous differentiation (HE, x200)

In a small number of tumour cells mitosis were apparent. In the area of tumour tissue keratin masses and smaller foci of necrosis were present.

The material was subsequently stained using immunohistochemical methods, and showed CEA negativity and EMA positivity of the tumour tissue (Figure 3, Figure 4).

The diagnosis of well differentiated sebaceous carcinoma was established.

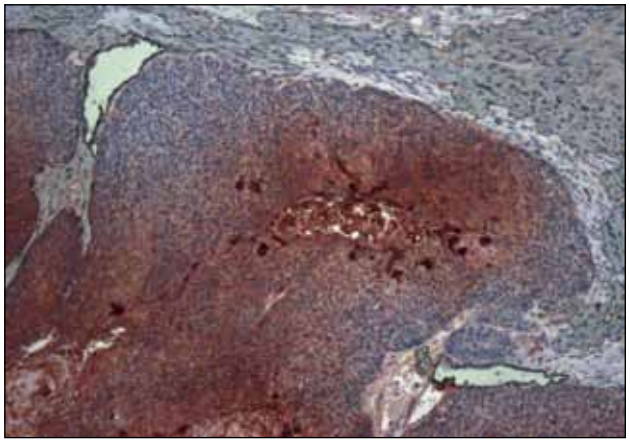

Figure 3. Well demarcated tumour tissue with centrally placed cells showing strong EMA positivity (EMA, x200)

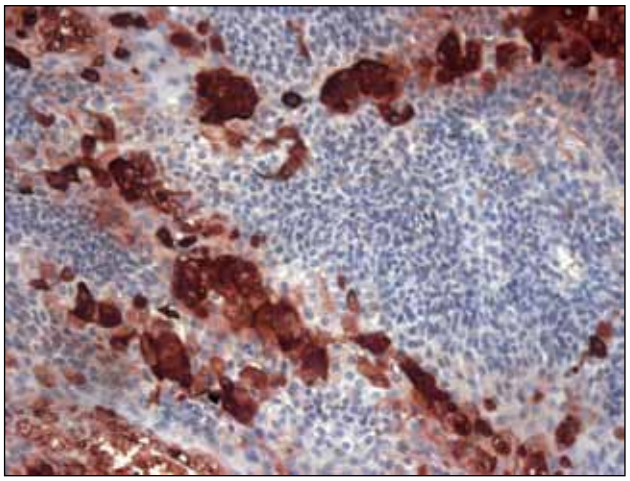

Figure 4. EMA positive cells scattered among EMA negative basaloid cells (EMA, x200)

Discussion

The clinical appearance of SC may resemble some benign and inflammatory lesions, which contributes to the longer time required to set the correct diagnosis and treatment (3, 7). The age of our patient is consistent with the data that SC is more common in people in the sixth, seventh and eighth decade of life (2, 6). Most authors reported that the incidence of SC is equal in both sexes (3, 4, 8), although, according to some authors, as well as in our case, it is more common in women (7). SC makes 1% of all skin cancer, (8) and extra ocular SC constitutes one-fourth of this number (2, 8). According to Dasgupta et al. extra ocular SC is present on the face in 26.8% (excluding eyelids, lips and external ear), on the trunk in 13.3% , on the hairy part of head and neck in 8.7%, in the area of arms or shoulders in 3.9%, in the outer ear 3.2%, on the leg or hip 1.6%, in the lips 0.8%, in 1.1% of cases in another part of the body including the genitals, reproductive organs and the descending colon (6).

SC often occurs in parts of the body that are exposed to a greater extent to the direct impact of sunlight (7). The data of Dowd et al. are in favour of this fact, stating that 25% of patients diagnosed with SC had previously diagnosed solar elastosis, and 43% of patients had SC on parts of the body that are typically due to occupational or orientation, as in our case, to a greater extent exposed to sunlight (4). Extra ocular SC is clinically presented, as in our patient, as a nodule of pink to yellow-brown colour. In our case the change was not ul-

cerated, which otherwise may be the case in SC (3, 8). Change was not attached to the skin and deeper skin structures, which is in consistency with the literature, as well with the histological appearance in our case which showed the presence of cancer only in the dermis without spreading into deeper structures or the epidermis. Histologically, the tumour tissue of SC is irregular, containing multiplied altered lobules and according to differentiation of basaloid cells SC is classified as moderately or poorly differentiated (1, 4). Well differentiated cancers can mimic pyogenic granuloma, blepharitis, hemangioma or other benign changes. SC lobules are made of two or three types of cells (3, 4). On the outer parts of the lobules, there are atypical basaloid cells of unequal size and shape. Toward the centre of the lobules, intermediate type of cells appear. These cells are the transitional forms, in the sebaceous differentiation, to the third type of cells, mature sebaceous cells that have abundant, vacuolated cytoplasm, and scalloped nuclei (1, 4).

Although the morphological features of SC are well-known, it should be thoroughly considered in the differential diagnosis with other entities with sebaceous differentiation, to other adnexal tumors, squamous or basal cell carcinoma, malignant melanoma or metastatic visceral tumors with clear cell morphology (1, 4). Face and neck are most common place for occurrence of sebaceous hyperplasia (SH) and sebaceous adenoma (SA) as well as for SC. SH is by nature a benign sebaceous lesion with a multiplied lobules with up to two layers of peripherally positioned basaloid cells, unlike SA where there are more than two layers of basaloid cells (4). Proliferation of basaloid cells in over 50% of the cell population can lead to doubts about the existence of the BCC or SC. While SH is located in the dermis, SA and SC can be located exclusively in the dermis or spread to epidermis (3). Compared to the SH and benign sebaceous adenoma, SC shows infiltrative growth in the deeper structures or epidermis, vague limitation, large, pleomorphic basaloid cells, hyper chromatic and scalloped shape of nuclei, increased mitosis which are often atypical (1, 5). Extra ocular SC show all these characteristics, often with squamous metaplasia and necrosis of tumour tissue, aggressive growth and pagetoid spread (3). Differentiating various sebaceous entities is mainly possible in routine histological specimens stained with hematoxylin and eosin, but the additional histochemical and immunohistochemical methods are very useful in eliminating diagnostic dilemmas (3, 4). Sebaceous cells are positive when stained with histochemical methods for visualization of intracytoplasmic lipids (Oil Red O, Sudan IV) (1), which can be used on frozen sections to differentiate poorly differentiated SC and SC with pagetoid spread (1). Due to the rare availability of frozen sections, these methods are rarely applied (3). Mature sebocytes and SC are CK and EMA positive and CEA negative (1, 3) which stand out poorly differentiated SC from most mesenchymal and hematopoietic malignancies. It was observed that the central-mature sebocytes show high EMA positivity and basaloid cells CK positivity and EMA negativity (1).

Comparing different sebaceous entities and neoplasia, it was observed that SH and SA in contrast to SC show a greater degree of cellular atypia, nuclear expression of p53 and Ki67 positivity, as well as reduced expression of Bcl-2 (7). T-antigen (Thomsen-Friedenreich antigen) is shown as a marker of sebaceoous differentiation (1, 3), while Ashraf et al. showed that it is positive in normal skin and in SC, while it is negative in entities that may mask the diagnosis of SC, like SA, and BCC with sebaceous differentiation (1). The differentiation of the SC and BCC with sebaceous differentiation or SCC with clear cell component is particularly problematic (4, 5). Poorly differentiated cells can give the false low-power impression of a peripheral palisade, thus mimicking BCC, but a number of atypical mitosis should point to the SC (4). To determine the existence of SC it is important to find the typical signs such as atypical or scalloped nuclei, vacuolated cytoplasm, or observe artefacts of tumour retraction from fibromyxoid stroma which indicates BCC. Several immunostains have been find to be useful in distinction between SC and BCC: EMA and podoplanin are distinctively positive in SC (negative in BCC) (3, 5), same as positive androgen receptors and a higher Ki-67 proliferative index (7, 8). In support of poorly differentiated SC in relation to the sweat glands tumours or extramammary Paget's disease speak CEA negativity, while negativity to melanocytic markers exclude melanoma (5). In addition to immunohistochemical methods, ductal structure and satellite metastatic changes speak in favour of apocrine tumours.

Conclusion

Regardless of the rare occurrence of SC, it is necessary to include this tumour in the differential diagnosis of skin lesions. The particular significance of this tumour is in the differential diagnosis of well demarcated lesions, because they are usually clinically misdiagnosed as benign changes.

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Efficiency of Levosimendan therapy in heart failure: Is it efficient on patients with cardiac dyssynchrony?

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Abstract

Aim: Levosimendan is a new inotropic drug used in acute heart failure for its cardiac contractility increasing effect without increasing myocardial oxygen consumption. Longer QRS duration is an important prognostic indicator independent of the underlying heart disease. In heart failure, presence of a QRS duration ≥ 120ms is regarded as an indicator of cardiac dyssynchrony. In our study, we investigated the efficiency of levosimendan in cardiac dyssynchrony patients whose QRS duration in ECG is accepted ≥ 120ms.

Methots: Fifty-one acute heart failure patients with left ventricular systolic dysfunction were accepted into the study. Patients were divided into two groups as those with QRS duration ≥ 120ms to the study group and QRS duration < 120ms to the control group, based on surface ECG. Levosimendan therapy was administered to both groups in addition to standard therapy for a duration of 24 hours. Serum MMP-9 and TIMP-1 levels of two groups observed in blood samples taken before and after the therapy were compared.

Results: There is no significant difference between the datum (preliminary) levels of serum MMP-9 and TIMP-1 in both groups. However, serum MMP-9 level is higher and serum TIMP-1 level was lower in the study group. While serum MMP-9 level significantly degraded in the study group after therapy, increase in serum TIMP-1 level did not reached a significant value (p=0.036, p=0.053). When we compared the differences between before and after therapy levels, no significant difference was observed between the two groups.

Conclusion: For heart failure patients with estimated left ventricular dyssynchrony according to surface ECG, levosimendan therapy is as efficient as it is with patients without dyssynchrony. For patients with high preliminary (initial) neurohumoral indicator levels, this therapy also effectively decreases these values.

Key words: Heart failure, levosimendan, matrix metalloproteinase, tissue matrix metalloproteinase inhibitor, cardiac dyssynchrony.

1. Introduction

Heart failure (HF), is a progressive, chronic syndrome defined with deterioration of cardiac functions and increase in neurohumoral activity (1-2). QRS duration is an important prognostic indicator even in persons without structural heart diseases. Prolonged QRS duration in heart failure is associated with increased mortality and sudden cardiac death (3). Structural alterations in the left ventricule leads to conduction delay and prolongation of QRS duration on surface ECG by causing dyssynchronous contraction. Prolongation of QRS durations detected on surface ECG is an important indicator showing left ventricular dyssynchrony (4). Levosimendan's efficiency in acute HF therapy has been showed with large-scale studies (5-15). Additionally, it effects MMP's reducing serum levels that show increased serum levels in HF (16-18). In our study, we investigated the efficiency of levosimendan in cardiac dyssynchrony patients with acute heart failure whose QRS duration in ECG is accepted ≥ 120ms.

2. Materials and Methots

2.1. Patients

Fifty-one patients whose left ventricular ejection fraction was <%35 New York Heart Association (NYHA) with class 3 and 4 heart failure disease and irresponsive to traditional heart failure treatment were admitted to the study. Patients who suffered from unstable angina or myocardial infarction within the previous 2 weeks, those with obstructive cardiomyopathy or uncorrected valvular stenosis disease, symptomatic primary lung disease, whose systolic blood pressure is < 80 mmHg or > 200 mmHg, whose resting heart rate is >115/min., those who use immunosuppressive drugs, whose creatinine is > 2.5 mg/dL, aspartate aminotransferase and alanine aminotransferase values are double the normal values, and serum potassium level is <3.5 or >5.5 mmol/dL, and with acute and chronic infectious and inflammatory diseases were excluded from the study. This study has been approved by the local ethics committee (document dated 11.08.2005 and with protocol number 2005/095). A "patient consent form" was filled and signed by each patient.

Patients who qualified for the pre-evaluation requirements were picked randomly and based on surface ECG, patients with QRS duration ≥ 120ms were designated as the study group (n=22), and patients with QRS duration <120ms were designated as the control group (n=29). Age, gender, coronary artery disease history, hypertension, diabetes mellitus, prescribed medication, HF class according to NYHA, blood pressure, blood rate and ECG information of all patients were noted.

In addition to the traditional treatment consisting of beta blocker, ACEI, furosemide and spironolactone, levosimendan was applied for a duration of 24 hours by intravenous administration via infusion in a dose of 0,1 mcg/kg/dk. During levosimendan infusion, no situation that required discontinuation of infusion or a dose decrement was encountered and as no mortality was observed, the research was completed with 22 patients from the study group and 29 patients from the control group. Blood samples were collected from the patients twice in order to examine serum MMP-9 and TIMP-1 levels, once prior to levosimendan administration and once immediately following the termination of infusion. Blood samples were centrifuged on 2500 rpm for 10 minutes and stored in -80 Celsius degrees. After the study, samples stored in the deep freezer were examined in order to check MMP-9 (Human pro-MMP-9, R&D Systems, Minneapolis) and TIMP-1 (Human pro-TIMP-1, R&D Systems, Minneapolis) levels in Haematology Laboratory on Microplate Reader MPR A4I device using the ELISA (enzyme-linked immunosorbent assay) method.

2.2. Electrocardiographic Analysis

Patients' electrocardiographic examination was performed with the available ECG equipment (ELI-250, Mortara Instruments, Wisconsin, USA). ECGs were recorded at a speed of 50 mm/second. QRS duration was measured manually using a digital caliper and magnifying lens in the electrocardiograms performed on admission. QRS duration was determined in the single lead which had the longest QRS. Maximal QRS width in any lead was measured from the first to the last sharp vector crossing the isoelectric line. Electrocardiographic data were analyzed by 2 independent observers blinded to all other patient's data, and an average of two measurements was accepted as final result.

2.3. Echocardiographic Analysis

Patients' echocardiographic examination was performed with available ultrasound equipment (GE-Vivid 3 with a 3.5 MHz transducer, Wisconsin, USA). Left ventricular ejection fraction (LVEF) was measured by Simpson's rule. Examination was performed by two blinded echocardiographists, thirty minutes and an average of two values were obtained for each examination.

2.4. Statistical analysis

Normal distribution was assessed by Kolmogorov-Smirnov one sample test. Wilcoxon and Mann Whitney U test were used for numeric variables. Chi Square and Marginal homogeneity tests were applied for categorical variables. A p value <0.05 was accepted as significant.

3. Results

A sum of 51 patients concluded the study. Mean QRS duration of the study group was 123.1 ± 2.6 ms, and 96.3±3.8 ms for the control group. Prior to the study, all demographic qualities and laboratory results between the two groups were similar (Table 1). After the treatment, a significant decline in serum MMP-9 level (p=0,036) and an insignificant increase in serum TIMP-1 level (p=0,053) was observed in the study group (Table 2). When we compared the differences between before and after therapy levels, no significant difference could be detected between the two groups (Table 3).

Table 3. Comparison of differences obtained from the blood parameters after the study in both groups

	QRS ≥120 ms mean ± SD / n	QRS <120ms mean ± SD / n	P*
MMP-9	1088.3±2024.5	417.5±1920.4	0.254
TIMP-1	-656.0±4363.8	-1019.9±3935.0	1.000

*MMP: matrix metalloproteinase, TIMP: matrixmetalloproteinase tissue inhibitor, *Mann Whitney U test*

Table 1. Demographic and clinical features of both groups

		QRS ≥120ms mean ± SD / n (%)	QRS <120ms mean ± SD / n (%)	p
Age (year)		62.7 ± 14.3	66.1 ± 11.7	0.523*
Male/ Female (n, %)		16 (72.7) / 6 (27.3)	20 (68.9) / 9 (31.1)	0.770**
Hemoglobin (mg/dl)		12.5 ± 1.5	12.3 ± 1.6	0.783*
İschemic DCMP (n, %)		5(22)	7(24)	0.903**
Non – İschemic DCMP (n, %)		17 (78)	22 (76)	
Hipertension (n, %)		13 (59)	16 (57.1)	0.890**
Diabetes Mellitus (n, %)		7 (31.8)	10 (35.7)	0.773**
Sistolic BP (mmHg)		100.4±9.9	103.4±10.4	0.248*
Diastolic BP (mmHg)		67.2±9.3	67.4±7.3	0.737*
Heart rate		97.8±13.1	93.1±13.1	0.244*
NYHA class 3 (n, %)		10 (45.4)	11 (37.9)	0.589**
NYHA class 4 (n, %)		12 (54.6)	18 (62.1)	
Af (n, %)		10 (45.5)	12 (41.4)	0.771**
MMP-9		4963.2±1363.9	4852.6±1206.1	0.332*
TIMP-1		4046.6±3591.7	4171.5±2692.7	0.864*
Echocardiographic features	LVESV (ml)	154.3 ± 59.0	138.5 ± 51.1	0.274*
	LVEDV (ml)	207.0 ± 71.1	183.5 ± 61.1	0.199*
	LVEF (%)	25.5 ± 5.4	25.6±5.6	0.901
Drug use	Beta blocer (n, %)	14 (63.6)	23 (79.3)	0.214**
	ACEİ (n, %)	17 (77.2)	16 (55.1)	0.102**
	Furosemid (n, %)	20 (90.9)	25 (86.2)	0.606**
	Spiranolakton (n, %)	18 (81.8)	16 (55.1)	0.046**
	Digoksin (n, %)	9 (40.9)	15 (51.7)	0.443**

*DCMP: dilated cardiomyopathy, BP: blood pressure, NYHA: New York Heart Association, MMP: matrix metalloproteinase, TIMP: matrixmetalloproteinase tissue inhibitor, LVEF: left ventricule ejection fraction, LVESV: left ventricule end sistolic volüm, LVEDV: left ventricule end diastolic volüm, ACEİ: angiotensin converting enzyme inhibitor, Af: atrial fibrilation. *Mann Whitney U test and **Chi square test*

Table 2. Comparison of blood parameters before and after the treatment in both groups

	QRS ≥120ms mean ± SD / n			QRS <120ms mean ± SD / n		
	Before treatment	After treatment	p*	Before treatment	After treatment	p*
MMP-9	4963.2±1363.9	3874.8±1018.1	0.036	4852.6±1206.1	4435.1±1383.4	0.304
TIMP-1	4046.6±3591.7	4702.7±2424.3	0.053	4171.5±2692.7	5191.4±2792.6	0.214

*MMP: matrix metalloproteinase, TIMP: matrixmetalloproteinase tissue inhibitor, *Wilcoxon test*

4. Discussion

Acute heart failure, during which typical symptoms and findings of HF appear suddenly or gradually, is a clinical syndrome that requires immediate treatment and causes significant morbidity and mortality (19). Levosimendan, the new member of positive inotropic drug group which is used in the treatment of decompensated heart failure due to left ventricular systolic dysfunction, exhibits a double action with its calcium sensitizer and K channel activation characteristics (20-21). Levosimendan effects and reduces serum levels of MMP's which show increased serum levels in HF (16-18). Thus, it reduces the negative impact of these substances, whose level has been increased during heart failure. MMP-9 levels that were higher in the study group before treatment, were significantly reduced after the treatment (Table 2). However, when we compared the differences of values before and after the treatment, it was determined that there were no differences between the two groups (Table 3).

QRS duration is an important prognostic indicator in heart failure patients and among this group of patients, prolonged QRS duration is associated with increased mortality (22-23). For HF patients with NYKC advanced to class 3 and 4, LVEF<%35 and with QRS duration ≥ 120ms , guidelines suggest a cardiac resynchronization therapy (24). Studies show that there is a weak or moderate connection between mechanical dyssynchrony and electrical dyssynchrony (25-28). However, Neto NR *et al.* (29) showed that there is a strong connection between mechanical and electrical dyssynchrony in patients with prolonged QRS duration who have especially a classical LBBB pattern. Moreover, Tournoux *et al.* (28) showed that this connection is even more strong in patient group with non-ischemic cardiomyopathy heart failure. 68% of the patients in our study group had LBBB pattern and 78% was non-ischemic cardiomyopathy derived.

The most important result obtained from this study is that; the new inodilator drug levosimendan can show the same effect in the heart failure patient group with left ventricular dyssynchrony defined by prolonged QRS duration according to surface ECG. Here, levosimendan appears more efficient than the study group. One of the reasons for this, is that in a condition which aggravates heart failure such as left ventricular dyssynchrony, basal neurohumoral indicators are higher and post-treatment reduction present a more significant result. The second reason, according to the result obtained from the study conducted by Yontar O.C. *et al.* (30), treatment efficiency may be increased as a result of levosimendan treatment reducing the prolonged QRS duration.

5. Conclusion

Levosimendan therapy positively affects neurohumoral system and ventricular dyssynchrony and remedies heart failure patients.

6. Study Limitations

In this study, several limitations can be mentioned. First, the number of patients in the study is relatively low. Second, the follow-up period is short and third, cardiac dyssynchrony which is determined according to surface ECG cannot be confirmed echocardiographically.

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Corpus cavernosum electromiografic parameters in men with preserved erectile function

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Abstract

Summary: Assessment of genital autonomic nerves has an important role in sexual dysfunction evaluation. Corpus cavernosum electromyography is important in diagnosis of neurogenic erectile dysfunction.

Objective: Assessment of methodological validity of corpus cavernosum electromyographic parameters in clinical following of erectile function in men without erectile dysfunction. Validation of corpus cavernosum electromyography as a method for assessment of autonomic inervation and smooth muscles of corpus cavernosum.

Material and methods: Our research has been conducted as prospective, controlled, opened and randomised study, and involves 50 men with preserved erectile function, older than 20 years. Research has been conducted in Urology Clinic, Clinical Center of Vojvodina, in two years time frame (jun 2009 till july 2010). All patinets had erectile function assessment, using International index of erectile function and corpus cavernosum electromyography conducted.

Results: In observed group all patients had preserved (65.2%) to mild (32.8%) erectile function. Corpus cavernous electromyographic parameters were constant in all subjects. Average amplitude in this group was 328.70 ± 125.28 μV, maximal amplitude 484.95 ± 287.03 μV, minimal amplitude 203.30 ± 46.48 μV, midle wave 58.84 ± 27.08 μV and polyphase waves 3.35 ± 0.79.

Conclusion: Using corpus cavernosum electromyographic parameters in group of patients with preserved erectile function shows validity of this method in clinical assessment of erectile function and its recovery after radical prostatectomy, but just in case when assessing nerve component of erectile function. Only few articles about this topic could be found and we conceder that it is important to define those values in order to compare them to pathological ones.

Key words: Electromyography; Penis; Erectile Dysfunction

Introduction

Erection is a neurovascular phenomenon under hormonal control. Erectile dysfunction (ED) is defined as permanent inability to achieve and maintain erection appropriate for sexual intercourse. Recent epidemiological data show high prevalence (25-52%) and incidence (25-30‰) ED worldwide. It is estimated that by 2025. approximately 322 million men will suffer from ED [1].

Penis is innervated by somatic and autonomic nerves. Somatic inervation (nervus dorsalis – branch of pudendal nerve) provides penile inervation with sensor fibers and perineal muscles with motor fibers. Autonomic nerve fibers are simpathic and parasimpathic. Cavernosal nerves are branches of pelvic plexus, which form simpathic and parasimpathic fibers after leaving appropriate segments of spine and travel on lateral side of bladder and posterolateral to prostate. Cavernosal nerves together with capsular arteries and prostate veins form neurovascular bundle, 2-3 cm distally from prostatovesical junction. Neurovascular bundle is located in lateral pelvic fascia, between prostatic and levator fascia [2]. After penetration of urogenital diaphragm those nerves pass behind artery and nervus dorsalis penis, and than proceed to cavernosal and spongious body, regulating penile blood flow during erection and detumescence. Fibers of cavernosal nerves end on arteriolar and trabecular smooth muscle. Iatrogenic surgical injuries of those nerves (radical prostatectomy, bladder and rectal surgery, retroperitoneal lymphadenectomy) can lead to iatrogenic ED [3,4,5]. Stimulation on cavernosal nerves and pelvic plexus leads to erection, while stimulation of simpathicus leads to detumescence.

Assessment of genital autonomic nerves has a important role in sexual dysfunction evaluation.

Lately few tests have been developed for genital autonomic nerves, among which corpus cavernosum electromyography (CC-EMG) is one of most important. CC-EMG represents direct recording of cavernosal activity. First time it was conducted with usage of electrical electrodes during detumescence with visual stimulation and published by Wagner and al. [6]. They found that in normal electrical activity from cavernosal bodies, in flaccid state, rhythmical, slow electrical waves can be registered followed by intermittently higher activity. Characteristics of those electrical potentials are maximal amplitudes which are between 120-500 μV, with average length of those potentials cca 12 seconds [7].

It is generally accepted that CC-EMG in healthy men provides reproducible electrical activity [8]. Its diagnostic application in clinical practice was difficult because of very little knowledge in field of electrophisiology of corpus cavernosum muscles, lack of standardisation, technical difficulties and also followed with result interpretation problems. It is considered that CC-EMG gives information about smooth muscles and autonomic nerve system of the penis, and from that reason it is considered as a diagnostic method.

Objective

Assessment of methodological validity of CC-EMG in clinical following of erectile function in men without erectile dysfunction. Validation of CC-EMG as a method for assessment of autonomic inervation and smooth muscles of corpus cavernosum.

Material and methods

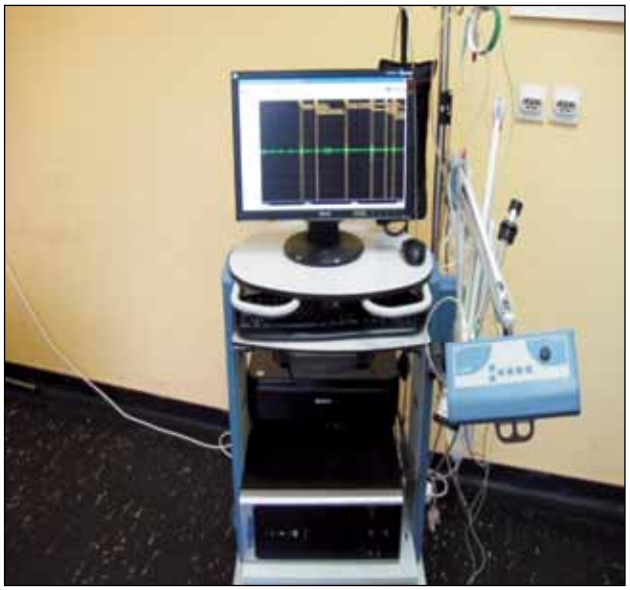
Our research has been conducted as prospective, controlled, opened and randomized study, and involves 50 men with preserved erectile function, older than 20 years. Research has been conducted in Urology Clinic, Clinical Center of Vojvodina, in two years time frame (Jun 2009 till July 2010).

Assessment of erectile function

Each subject, during first examination had detail anamnesis taken and physical examination. Evaluation algorithm of erectile function or dysfunction included medical, sexual and psychosexual history taken. After this, all subjects had erectile function questionnaire – IIEF-5 (International Index of Erectile Function). Four questions have been taken from erectile function domain, while fifth question is related to sexual satisfaction. Each question brings 1-5 points. Minimal number of points is 5, maximum 25. Severity of ED is classified according to IIEF in five categories: serious (5-7), moderate (8-11), mild to moderate (12-16), mild (17-21), without ED (22-25).Exclusion criteria are: erectile dysfunction, diabetes mellitus, neurological conditions of central and/or peripheral nervous system, elderly people (older than 70 years), impossibility of interpretation and acquiring CC – EMG writing.

Corpus cavernosum electromyography – CC-EMG

In initial measurement, all subjects were conducted to CC – EMG assessment on Solar® urodinamic machine, with software appendix for electromiography of corpus cavernosum Solar Neuro Modul® - Medical Measurement Systems (The Netherlands) (Picture 1).

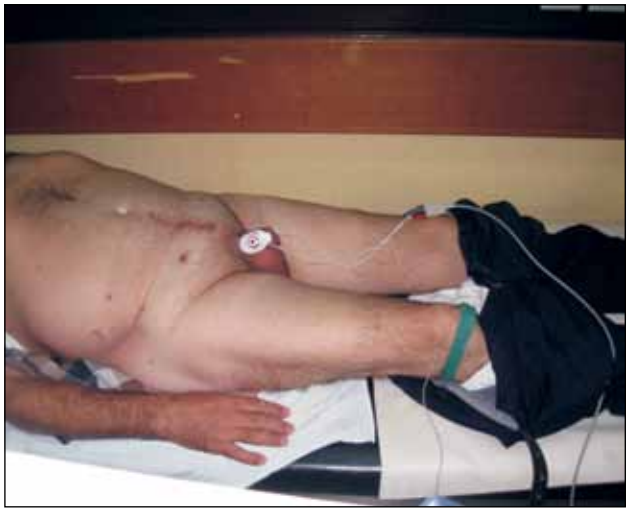


Picture 1. Solar Neuro Modul

For CC-EMG potential registration, we used superficial electrodes from same manufacturer. Examinations were conducted ambulatory in Clinical Center of Vojvodina in Novi Sad. In dark, closed room, in period fro 10 – 12 h, with examiner present. Air temperature was between 22

-24 ºC. All subjects had breakfast two hours before examination and not to consume coffee, tea or psycho stimulative substances. Also they were told not to expose to any demanding physical activity day before examination.

Subjects were positioned in semi lying position (30◦ angle) and suggested to relax as possible. Skin beneath electrodes was previously cleaned with abrasive medium applied on gauze- Nuprer gelom (*Weaver and Co.,USA*). After abrasion the surface was cleaned with alcohol to improve electrode adhesion. Electrodes were positioned to lateral sides of penis (left and right cavernosal body, middle third). Referent electrode was positioned to knee (Picture 2).

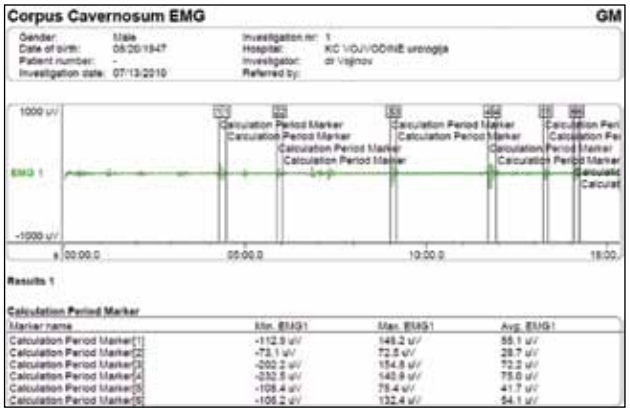


Picture 2. Subject and electrode position

Recording started 10 – 20 minutes after electrodes positioning, to achive maximal relaxation of the subject. Recording lasted 20 minutes in flaccid state. Signals were simultaneously recorded and stored in electronic form in device, so further analysis can be done.

In the beginning the recordings were assessed globally. Attention was directed to quality of recordings (noise and artifacts), basic waves characteristics and shape of corpus cavernosum potential. Recordings with stable basic waves, reproducible corpus cavernosum potentials have been taken as good quality recordings. In case the findings were impossible to analyze, those subjects were excluded from trial.

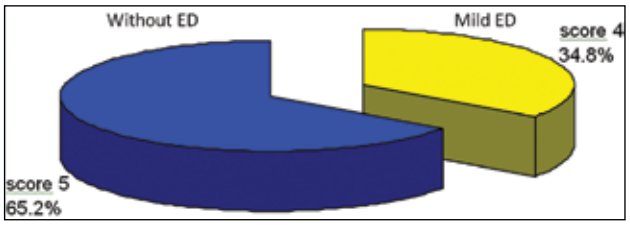
Based on recorded CC - EMG curve, following parameters were determined: amplitude of single complex (minimal, maximal and average amplitude in microV), middle wave, number of waves in complex and also there polyphasewaves (Picture 3).



Picture 3. CC-EMG of the subject with preserved erectile function, after processing

Results

After completing CC-EMG measurements, data on our participants are presented below. In Graph 1 we present the ED score in erectile function assessment in our participants. Table 1 shows the values of electromyographic parameters of corpus cavernosum function in participants with preserved erectile function.



Graph 1. Assessment of erectile function (ED scor)

Discussion

Spontaneous CC – EMG can be registered in vast majority of subjects. On the other hand number of subjects (healthy or with ED), could not have those potentials registered, or only few potentials can be registered. In literature possible causes of this can be [9]: excessive relaxation, although some subjects have structural and functional changes in simpathic inervation and/or smooth muscles of corpus cavernosum [10].

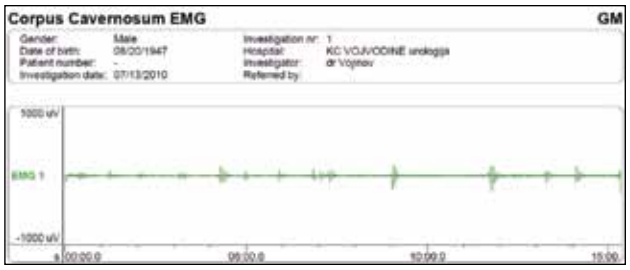
First group of subjects had average values of potentials before operative procedure (minimal, maximal and average amplitude, middle wave, number of waves in complex, can be found in

Table 1. Electromyographic parameters of corpus cavernosum function with preserved erectile function

CC-EMG parameters	Number of waves	Average amplitude	Minimal amplitude	Maximal amplitude	Middle wave	Polyphase waves
Mean ± **SD**	5.2 ± 0.8	328.7±125.3	203.3±46.5	484.9±287.0	58.8±27.1	3.4±0.8

physiological range. Frequency wasn't processed, because this parameter wasn't reproducible.

Slow waves were registered in all subjects and had regular rhythm. Those parameters were constant in all subjects. Average amplitude in this group was 328.70 ± 125.28 μV, maximal amplitude 484.95 ± 287.03 μV, minimal amplitude 203.30 ± 46.48 μV, midle wave 58.84 ± 27.08 μV and polyphase waves 3.35 ± 0.79. (Picture 4).



Picture 4. Normal findings of CC EMG

Some characteristics in normal CC - EMG, in healthy men can be defined. Recordings mainly show basic line with slow or continued waves, whose amplitude doesn't exceed 75 μV, with frequency of 4-8x/min**.** This basic activity is interrupted with significantly stronger electrical activity, so called action potentials, which are influenced by state of relaxation of the patient: better relaxation – less potentials, which implicates stress dependency. Maximal amplitude (from positive to negative peak) varies between 75 and 500 μV. Duration of potential which is poliphasic is in average 12 seconds [11]. Synchronization of those potentials is published in studies in which signals were recorded with two positions of cavernosal body with multichanel machine [12]. It is important to say that some of subjects with physiological findings on CC-EMG have abnormal signals: almost without signal on anarchism, also signal desinhronisation, which was noticed in a number of our subjects (excluded from trial).

Corpus cavernosum is composed of smooth muscles, which create electrical waves, as all smooth muscles do. This implies that there is precise relation between electrical activity of CC and autonomic nervous system integrity (preoperatively). It is assumed that this relation exists between functional status of smooth muscles of corpus cavernosum and cavernosopathy, which can't be assessed by other methods, except CC –EMG. In a study by Shafik et al. in 2004 year included 68 subjects, from which there have been 18 healthy volunteers with preserved erectile function [13]. Healthy volunteers had waves in form of slow waves and occasional action potentials. Those waves had regular rhythm and identical shape from both electrodes in each patient, and were reproducible. Those findings correlate to findings in our research.

In literature there are many debates about normal CC – EMG. Recorded signals from different centers have similarities, bat are insufficient to make quantitative comparison. This is a cause of measurement and interpretation lack. Variation of majority of parameters is wide, so it is hard for normative values to be established [14]. Fabra et al. performed two independent recordings in 36 healthy subjects and a single recording in 324 patients with erectile dysfunction. Conclusion was that CC - EMG has limited value in differentiation of potent end ED subjects [15]. This conclusion is not surprising, regarding that requirement for equipment standardization is not fulfilled.

Despite this some characteristics of normal CC- EMG, in potent subjects can be defined.

After literature insight, we can conclude that onley representative potentials of CC can be analyzed. Amplitude, length and polyphase waves of the CC potential are reproducible, while frequency (No. of CC/ in time unit) is not. [9].

Fact that some parameters are reproducible, and other are not, can be explained by physiological mechanism of creation. Evidence from earlier studies show that CC potentials reflect simpathic modulated activity of CC smooth muscles[16]. It is estimated that CC potentials present superposed membrane charging, caused by calcium passage through calcium channels in CC smooth muscles. Amplitude depends on quantity of smooth muscles in cavernosal bodies and synchronization of

electrical activity of those smooth muscles, which again depends on simpathic impulses and intracellular communication [17]. Although physiological mechanism is not well understood, all reproducible parameters reflect physiological characteristic of smooth muscles and simpathetic inervation. Length is not reproducible, because it depends on relaxation (simpathetic tonus).

Majority of researchers interested in neurophysiology, understands necessity for assessment of genital autonomic nerve system integrity. This system plays significant role in means sexual response, and CC-EMG represents method for autonomic inervation of penis assessment.

Conclusion

Using CC-EMG in group of patients with preserved erectile function shows validity of this method in clinical assessment of erectile function and its recovery after radical prostatectomy, but just in case when assessing nerve component of erectile function. Only few articles about this topic could be found and we conceder that it is important to define those values in order to compare them to pathological ones.

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Body mass index in Turkish female adolescents: The role of emotional eating, restrained eating, external eating and depression

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Abstract

The purpose of this study was to determine the association between body mass index, depression, emotional, external and restrained eating behavior in adolescent females. The present study examined the relations between body mass index, emotional eating, restrained eating, external eating and depression level in female adolescents. The participants were 644 females aged between 16 and 18 years (mean age 16.71, standard deviation 0.73 years), from one of several randomly selected universities in Ankara, capital city of Turkey The participants were administered the Dutch Eating Behaviour Questionnaire and Beck Depression Inventory. Restrained eating ($r=0.32;p<0.05$), emotional eating ($r=0.37;p<0.05$), depression level ($r=0.36;p<0.05$) and age ($r=0.16;p<0.05$) all showed significant correlations with BMI, but external eating ($r=0.05;p>0.05$) was not significantly correlated with BMI. Also, there were significantly differences in body mass index, restrained eating, emotional eating, external eating, depression level and age between the normal weight group and the overweight group. Three factors were found as significantly associated with body mass index. Emotional eating stood out as the major risk factor for body mass index in female adolescents. Second and third important factors are found as restrained eating and depression level. In conclusion, obesity in adolescence might be relationship between emotional eating, restrained eating and depression level among female adolescents. Emotional eating appear to be a major contributor to obesity in the adolescent group in this sample. At this point we can recommend developing interventions for obesity prevention and treatment targeted at emotional eating.

Key words: BMI, Restraint Eating, Depression, Emotional Eating, External Eating

Introduction

Childhood and adolescent obesity is rapidly becoming a major health problem. Obesity is a complex and increasingly prevalent disorder that can confer a number of medical, social, and psychological difficulties. This rapid increase in the prevalence of obesity has led the World Health Organization (1) to declare a global obesity epidemic. Therefore, this is a matter of concern because obesity increases risks for many serious and morbid conditions, such as diabetes mellitus, hypertension, dyslipedemia, coronary artery disease and some kinds of cancer (2). It is known that changes in lifestyle, dietary habits, physical activity and social and cultural environments are associated with the occurrence of obesity (1). Martorell, Khan, Hughes and Grummer-Strawn (3) reported that women in Turkey have the highest proportion of overweight (31.7%), as well as the highest proportion of obesity (18.6%).

Three types of eating behavior that are thought to be associated with excessive food intake, body mass index, and binge eating are: eating in response to negative emotions (emotional eating), eating in response to the sight or smell of food (external eating), and (paradoxically) dietary restraint, which is, eating less than desired to lose or maintain body weight. These three eating behaviors are derived from, respectively, psychosomatic theory, externality theory, and restraint theory (4,5,6,7).

The psychosomatic theory focuses on "emotional eating", which states that emotional eaters do not eat in response to internal signals, feelings of hunger and satiety but in response to their emotions. In case of emotional arousal or stress, emotional eaters respond by excessive eating, while normally emotional arousal and stress would result in loss of appetite. A second theory, focusing on external eating, states that certain people are more

sensitive to external food cues than others, and eat in response to those stimuli, regardless of their internal state of hunger and satiety. According to a third theory, the restrained eating theory, dieting can cause overweight through bingeing. People who diet suppress their feeling of hunger cognitively and eat less. However, when cognitions are undermined (disinhibition), restrained eaters are more likely to overeat than non-dieting individuals; this is called counter-regulation (5,7,8).

However, support for the Psychosomatic Theory has not been consistent. Emotional eating was not related to body mass index (BMI) in a British adolescent sample, however findings did show that perceived fatness was related to emotional eating (9). A study of binge-eating and obesity found that emotional eating was positively associated with binge-eating, and binge-eating was predictive of obesity (but negative affect alone was not related to BMI) (10). In a sample of 9–12-year olds from Belgium, Braet and van Strien (11) found that overweight and obese children scored significantly higher on emotional eating than normal weight children.

The correlation between dietary restraint and body mass index was found in several studies on adolescents. Stice (12) reported that dieting was positively related to weight gain over a 9-month period among 369 female adolescents aged 16 to 19, but there was also a quadratic component to this effect wherein extreme dieting predicted weight loss. Likewise, Goldfield et al. (13) found that a relationship was also found for dietary restraint and weight status whereby higher restraint scores were associated with greater adiposity. Conversely, McGuire et al. (14) reported that fexible and rigid restraint scales were not differently associated with weight and behaviors in this heterogeneous sample of adults who were attempting to lose weight.

Previous research suggests that obesity and depression are positively associated (15). However, the strength of association between obesity and depression varies considerably between studies (16,17). Obese females were more likely to report more serious emotional problems, hopelessness, and a suicide attempt in the last year, when compared to their normal weight peers (18). Similarly, anxiety disorders were associated with higher weight in adolescent females (19). In contrast, community-based, cross-sectional studies (20,21) indicate no difference in the incidence of depression between overweight and normal-weight children and adolescents. As obesity in adolescence continues to rise, it is paramount to study its association with adolescent psychopathology given the high prevalence of both obesity and affective problems in girls. Some evidence provides support for these different propositions for the relationship between body mass index, depression level and eating behaviours on the Western culture samples. However, there is no attempt to test these propositions on the Eastern cultures. The purpose of this study was to determine the association between body mass index, depression, emotional, external and restrained eating behavior in adolescent females.

Methods

Participants

The participants were 644 females aged between 16 and 18 years (mean age 16.71, standard deviation 0.73 years), from one of several randomly selected universities in Ankara, capital city of Turkey. Of the 750 distributed surveys, 106 were had missing information; therefore we used 644 surveys for present analyses (response rate 85.9%). Measurement and data collection were conducted during a 6 month period between January and June 2009. The questionnaires were administered under the supervision of four master students at the respective universities and a researcher. Questions could be asked to the researcher, to make sure that the adolescents understood the meaning of each item. After completing the questionnaire, each adolescent was taken out of the class to a private place where her body weight and height was measured. The adolescents were grouped into two categories, normal-weight and overweight in accordance with the cut-off points of 5th to ≤85th, >85th percentiles. BMI between 5th to ≤85th percentile was defined as normal weight and BMI at or above >85th percentiles was defined as overweight. Mean body mass index was 21.42±2.29 kg/m^2; 57.8% of females had a BMI 5th to ≤85th (normal weight) and 42.2% of females had a BMI >85th (overweight).

Measures

Dutch Eating Behavior Questionnaire-DEBQ

This questionnaire consists of 33 items, which measured emotional (13 items), external, and restrained eating (both 10 items). All items had to be rated on a five-point scale from 1 (never) to 5 (very often). Examples of items were: "Do you have a desire to eat when you are irritated?" (emotional eating), "If foods smells and looks good, do you eat more than usual?" (external eating) and "Do you try to eat less at mealtimes than you would like to eat?" (restrained eating). The DEBQ scales have high internal consistency, high validity for food consumption, and high convergent and discriminative validity (22). The reliability and validity of DEBQ for Turkish population is determined by Bozan, Bas, & Asci.(23). Cronbach's alphas were: 0.97 (emotional eating), 0.91 (external eating) and 0.90 (restrained eating).

Beck Depression Inventory-BDI

Depression was measured with the 21-item Beck Depression Inventory (24). The BDI measures the severity of depressive symptomatology. Items are scored on a 4-point scale. One item about weight loss was excluded from the analysis and the sum of the remaining 20 items was calculated. A higher score indicates more severe depression. Scores below 10 are considered normal; a score of 10 or more indicates mild to moderate depression (25). The reliability and validity of the instrument for Turkish university student were determined in a recent study carried out by Hisli (26).

Body Mass Index

Adolescent's body weight was assessed in light clothes and without shoes to the nearest 0.1 kg with a regularly calibrated digital medical scale (Tanita, Body Composition Analyzer, BC-418MA, United Kingdom). Adolescent's height was measured without shoes to the nearest 0.1 cm with a regularly calibrated stadiometer. The BMI was calculated (kg/m^2) for each adolescent. The Centres for Disease Control 2000 growth charts for children and adolescents were used to identify BMI percentiles (27). Weight and height percentiles were obtained from charts of growth curves for Turkish children (28).

Data Analysis

Descriptive statistics for the sample were obtained by computing means and frequencies of demographic data. Statistical significance was accepted at $p<0.05$ for all analysis. Bivariate relations between the study variables with Pearson's correlation coefficients. T-tests were used to test for mean differences between body mass index groups and depression level groups. Logistic regression analysis was used to identify the certain risk factors of body mass index. Analyses were completed using the Statistical Package for the Social Sciences (SPSS, version 16.0)

Result

T-tests revealed significant differences in body mass index (t=-32.98, p=0.000), restrained eating (t=-8.05, p=0.000), emotional eating (t=-11.04, p=0.000), external eating (t=-3.84, p=0.000), depression level (t=-11.97, p=0.000) and age (t=-3.81, p=0.000) between the normal weight group and the overweight group (Table 1).

Table 1. Characteristics of the sample

Variables	Normal Weight N=372		Over weight N=272		Difference	
	Mean	S.D.	Mean	S.D.	t	p
BMI	19,87	1,11	23,54	1,71	-32,98	0,000
Restrained eating	2,33	1,03	2,99	1,06	-8.05	0,000
Emotional eating	1,96	1,01	2,83	0,96	-11.04	0,000
External eating	2,87	0,81	3,13	0,92	-3.84	0,000
Depression	3,01	3,21	11,02	12,36	-11.97	0,000
Age	16,61	0,63	16,84	0,83	-3,81	0,000

Table 2 presents Pearson correlation coefficients between all the variables in the present study. Of special interest for our purposes are the correlations between BMI and the measures for restrained eating, emotional eating, external eating depression and age. Restrained eating ($r=0.32;p<0.05$), emotional eating ($r=0.37;p<0.05$), depression level ($r=0.36;p<0.05$) and age ($r=0.16;p<0.05$) all showed significant correlations with BMI, but external eating ($r=0.05;p>0.05$) was not significantly correlated with BMI. Of further interest are the significant interrelationships between depression level, restrained eating, emotional eating and external eating ($p<0.05$).

T-tests revealed significant differences in body mass index ($t=-10.12$, $p<0.05$), restrained eating $t=-5.33$, $p<0.05$), emotional eating ($t=-9.91$, $p<0.05$), external eating $t=0.-9.75$, $p<0.05$), depression level ($t=-46.41$, $p<0.05$) and age $t=-5.27$, $p<0.05$) between the low depression level group and the high depression level group (Figure 1).

In the examined regression analysis for body mass index, three factors were found as significantly associated with body mass index. Emotional eating stood out as the major risk factor for body mass index in female adolescents. Second and third important factors are found as restrained eating and depression level. (Table 3).

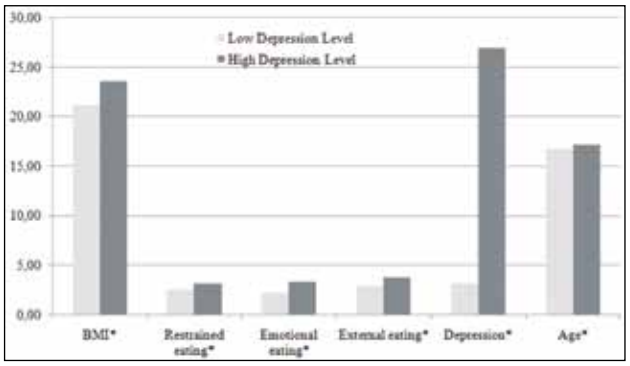

*Figure 1. Body mass index, restrained eating, emotional eating, external eating, depression and age for low and high levels of depression. (*p<0.05)*

Discussion

The relationship between depression level and emotional eating showed that BMI is a moderator of this significant positive relationship. Furthermore, there were differences found in level of emotional eating by overweight and normal weight participants; and the proportion of emotional eaters was higher in the overweight group than in the normal weight group. These findings are inconsistent with those that have found an association between weight and emotional eating, e.g., (29). In their study, emotional eating was not re-

Table 2. Pearson correlation coefficients.

		1	2	3	4	5	6
1	BMI	1,00					
2	Restrained eating	0,32**	1,00				
3	Emotional eating	0,37**	0,48**	1,00			
4	External eating	0,05	-0,08**	0,25**	1,00		
5	Depression	0,36**	0,19**	0,36**	0,33**	1,00	
6	Age	0,16**	-0,07	0,16**	0,09*	0,18**	1.00

**p<0.05*
***p<0.01*

Table 3. Logistic Regression Model Predicting Body Mass Index entered in successive blocks

Model for Prediction of Body Mass Index								
	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.	
							Lower	Upper
Restrained eating	0.311	0.099	9.804	1	0.002	1.365	0.311	0.099
External eating	-0.081	0.128	0.398	1	0.528	0.922	-0.081	0.128
Emotional eating	0.458	0.103	19.630	1	0.000	1.582	0.458	0.103
Depression	0.124	0.019	41.835	1	0.000	1.132	0.124	0.019
Age	0.192	0.131	2.144	1	0.143	1.212	0.192	0.131

lated to body mass index (BMI) in a British adolescent sample, however findings did show that perceived fatness was related to emotional eating (29). Conversely, in a two-year prospective study of 231 adolescent females from private California high schools looking at risk factors for binge eating, itself a verified risk factor for obesity, it was found that emotional eating predicted binge eating onset (10). This study by Stice, Presnell and Spangler (10) provides indirect evidence that emotional eating may influence the development of obesity; however, its generalizability was limited by including primarily subjects from high socioeconomic status (SES) homes. Another study, by Striegel-Moore et al. (30) examined the correlates of emotional eating in young girls focusing on race, adiposity, and food intake. The positive correlation between emotional eating, body mass index, depression level and restrained eating was clear in our study. Similarly, Based on Bruch, H. (5) theories one should expect a positive relation between overweight and emotional eating. However, the few studies that have investigated this relation in children and adolescents did not support the hypotheses in all aspects (29). In a study by Wardle *et al.* (29) average body mass index (BMI) was higher in restrained, and lower in external eaters, whereas no relationship was found between emotional eating and BMI. In other study, being overweight was positively related to restrained eating, but negatively related to external eating (only for girls) and non-related to emotional eating (31). Similarly, to the psychosomatic theory (5), significantly association between emotional eating and overweight or BMI was found in our study. This findigs is in line with previous adolescent studies, in which significant correlations were found between emotional eating and overweight or BMI (32,33). Emotional eating and obesity, it was made apparent that individual food choice is an important factor in this relationship, and that consumption, often involved high-calorie food (34). There have been several reviews of studies concerning emotional eating in relation to body weight (32,33). These studies have almost always dealt with negative emotions such as depression or fear (35,36) and have mainly compared obese and normal-weight subjects (37). Similarly, our findings indicated that overweight females have higher scores on emotional eating than normal weight adolescent females. Dennis and Goldberg (38) found that, compared to non-obese women, obese women tend to eat more in response to emotional arousal and to have more negative self-images. Emotional eating is found to occur more frequently in the obese population such that overweight individuals report engaging in more emotional eating than normal-weight and underweight individuals (39,40).

A cross-sectional study conducted by Hays et al. (41) show that disinhibition was a significant predictor of weight gain and BMI based on recalled weight history data, whereas restraint was not an independent predictor of weight change. One potential explanation for these findings is that restrained eaters may be eating less than they want but apparently not less than they need (42). These findings suggest that disinhibition may be a stronger predictor than restraint on weight and weight gain over time. Participants who engaged overweight in the present study have been found report higher restrained eating compared to normal weight group. Also, there was positive correlation between BMI and restrained eating. The results from the present study are similar to those by Snoek et al. (43) which surveyed adolescents and found that restraint were related to BMI.

The absence of difference between people with overweight and those with normal body weight in their degree of external eating may seem remarkable in view of the recent resurgence of interest in the possible role of external food cues in development of overweight (7,8). In the study by Wardle (9), overweight women were no more external than were those with normal body weight. Pothos, Tapper and Calitri (44) reported that for females there was a negative correlation between BMI and external eating and for males a positive correlation between BMI and both external eating and emotional eating, a finding which broadly replicates recent research with Dutch participants (44). In contrast, we not found a significant association between BMI and external eating, but significant association both emotional eating and restrained eating. Braet and Van Strien (11) investigated emotional, external, and restrained eating behaviour in 9-12 year-old obese ans non-obese children. Using parental reports of eating beha-

viour, they found that the obese children scored significantly higher on tha scales for emotional, external, and restrained eating behaviour. They also found that emotional and external eating were both related to increased caloric intake, as might be expected, suggesting that they may be potential predictors of greater weight gain in the longer term. These result provide some support for both with psychosomatic and restraint theories.

One exception is a longitudinal study (45) where the results were negative for cross-sectional analyses, but if obesity persisted over all four time points (between childhood and late adolescence), there was a slightly higher prevalence of depression. Another study found a small correlation between BMI and depressive symptoms in girls but not boys (46). In an earlier study, depression in adolescence was observed to be associated with an increased BMI in adulthood, even when participants with childhood obesity were excluded at baseline (47). A recent study showed that depressed adolescents were at increased risk of obesity in a 1-year follow-up (48). The present study demonstrates that the level of depression level among overweight females was very high than normal weight adolescent females. Also, there was significant correlation between depression, emotional eating and body mass index. Pine, Cohen, Brook, & Coplan (49) studied 4700 adolescents in 1983 and again in 1992 to determine whether baseline depressive symptoms would predict elevated adulthood BMI. Baseline depression levels predicted significantly elevated adulthood BMI, although the effect was small and no longer significant when adjusting for covariates. In other study, researchers(50) found that the effect of adolescent depression on 20-year weight change depended on baseline relative body weight. Among adolescents in the highest BMI quintile, those who were depressed were significantly more likely to gain at least 10 kg over 20 years compared to non-depressed adolescents.

This study has several limitations. The sample did not include males. Future studies should investigate a wider demographic sample. Also, study limitations include the use of self-reported data, which a common limitation of many research. Therefore, an important strength of our study is that it addressed the issues of BMI and, depression level, restrained and emotional eating in a predominantly Turkish adolescent female sample. In conclusion, obesity in adolescence might be relationship between emotional eating, restrained eating and depression level among female adolescents. Emotional eating appear to be a major contributor to obesity in the adolescent age group in this sample. At this point we can recommend developing interventions for obesity prevention and treatment targeted at emotional eating. Therefore, longitudinal researches are needed to explore the linked between obesity and emotional eating, restrained eating, external eating and depression level.

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Healthcare Workforce Trends in Changing Socioeconomic Context: Implications for Planning

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Abstract

Introduction: A key international issue in the health policy is the capability of the healthcare system to maintain and improve population health given the contextual challenges, including health workforce problems. Considering the possibility of the replication of strategically relevant contextual changes in transitional countries, it seemed important to ensure future health workforce planning is built on past successes and to avoid repeating mistakes.

Objective: The study aimed at assessing the impact of key social and economic events on the development of the healthcare workforce by use of Joinpoint Regression Programme to analyse the main healthcare workforce (physicians and nurses) trends in Serbia between 1961 and 2007, and to yield recommendations for a more socially accountable approach to healthcare workforce planning.

Methods: A literature search was done to identify the key social and economic changes in Serbia between 1961 and 2007. To capture the impact of key socioeconomic events on the development of healthcare workforce the joinpoint regression analyses was conducted to assess changes of healthcare workforce density rates per 100,000 of population (1961-2007) in the public sector. Estimates of jointpoint regression models included the annual per cent change and the average annual per cent change with the respective 95% confidence interval.

Results: The joinpoint regression analysis demonstrated a significantly diverse trend over time in the ratio of general practitioners, medical specialists, and nurses to population ($p<0.05$). The average annual per cent change of specialist and nurse density was higher (4.6% and 3.6%, respectively), while the growth of general practitioner density was much more limited (1%). In Serbia, the main drivers for healthcare workforce policy changes include shifts from decentralisation to centralisation and private practice development, social and financial crises, and economic and constitutional reforms. The following policy implications were based on the evidence of some compatibility in the projections of observed density rates with links to socioeconomic events: a higher growth of workforce density rates occurred with decentralisation (general practitioner's by 33%, specialist's by 169% and nurse's by 221%), while a lower growth of workforce density rates was observed in centralisation and their decrease with a stronger financial control (general practitioner's by -6%, specialist's by 29% and nurse's by 24%).

Conclusion: Making socially accountable policies in transitional countries requires capacity building for integrative workforce planning and management among health managers at all levels in the system. This study has highlighted several key lessons learned and policy implications, built on efforts, success and mistakes in health workforce policy making, local and global.

Key words: Socioeconomic Factors, Human Resources Planning and Development, Healthcare Workforce, Log-Linear Models.

Introduction

A key international issue in the health policy is the capability of the healthcare system to maintain and improve population health given the contextual challenges including health workforce problems.[1-3] Despite the evidences of direct link between positive health outcomes and the density of professional healthcare workers, many countries are still reporting a "health care crises".[1,4] Some of them do not have enough number of professional healthcare workers that is equal to "a threshold below which high coverage of essential interventions, including those necessary to meet the health-related millennium development goals, is very unlikely"[1]. Those countries, in most cases are among

developing or low developed countries that have suffered from major socio-political and financial upheaval, which has set off the transition toward market oriented health care provision or induced the economic and organizational crises in the health sector.[2,4] An important aspect of the health sector crises is the mismatch between the need for healthcare workers and their density, which in fact, reflect an inappropriate workforce distribution and planning[3]. A number of experts agree that strategic workforce planning, which considers the interplay among social, political, geographical, technological and economic risks in the changing context will lead to increased capability of policy makers to respond effectively to international issues and pressure, and the greater engagement and accountability of stakeholders regarding human resources for health mobilisation.[2,3,5-8]

In the Republic of Serbia, the health system reform as a planned struggle toward better performance and more efficient use of healthcare resources within the financial framework of healthcare budgets has started in 2003.[9] However, since than numerous healthcare institutions have been continuously reporting personnel shortages or surpluses in relation to the national standards and demand for healthcare services. In terms of healthcare worker to population ratio there is apparent geographical variation in distribution of nurses and physicians (per districts the ratio varied in the range 1-4)[10] as well as in their effectiveness and efficiency[11]. Recently, over 1700 general practitioners and 10 000 nurses were registered as unemployed and were seeking the job in health sector (in 2007).[10] Regardless of that, approximately 1800 students enrolled at the first year of medical studies, whereas about 5700 students at secondary and post secondary nursing schools.[10] To address appropriately those healthcare workforce misbalances, we require better understanding of the traditional approach toward health workforce planning, its roots and rationale. Considering the possibility of the replication of strategically relevant contextual changes in future, it seemed important to build future health workforce planning on past successes and to avoid repeating mistakes.

Objective

In order to make recommendations for more socially accountable health workforce policy this study objective was twofold: to assess the impact of key social and economic events on the development of the healthcare workforce and to analyse the main healthcare workforce (physicians and nurses) trends in Serbia between 1961 and 2007.

Methods

In order to identify the record of health workforce policy making in Serbia between 1961 and 2007, we reviewed all health related legislation, expert analyses, reports and reviews, published by 2010 with key words "Serbia, health policy, labour policy, healthcare workers planning, health workforce strategies, health planning, physicians/nurses planning and development, and socioeconomic factors". Most relevant documents were retrieved from the Consortium of Libraries of Serbia, PubMed, and the personal libraries of the authors.

The impact of key social and economic events on the development policy of the healthcare workforce in Serbia between 1961 and 2007 was assessed by the jointpoint regression modelling of the healthcare workforce density. The Joinpoint Regression Programme[12,13] was applied to find the best-fit model line ($P<0.05$) through the physician and nurse density trends per 100,000 of population in the period between 1961 and 2007. It allowed us to explore the underlying socioeconomic factors associated with significantly different segments of the trend line. Time trends in log-rate of the annual density were explored using the following formula: $\ln(y)=bx$, where x represents years, b is the regression coefficient and y is the healthcare workforce density rate. [12,13] Each of the three models of the general practitioner, specialist and nurse time-series could have a maximum of four joinpoints (five line segments). Estimations included the annual per cent change (APC) and the average annual per cent change (AAPC) with the respective 95% confidence intervals (CIs). The AAPC is the summary measure for APCs between 1961 and 2007. It is a weighted average of all APCs within one model, with the weights equal to the length of the APC interval. Therefore, the AAPC is valid even if the joinpoint

regression analysis indicates that there were changes in the trend between 1961 and 2007. The zero APC or AAPC (stated as a null hypothesis) is equivalent to the trend in healthcare workforce density rates that is neither increasing nor decreasing. Statistically significant differences between AAPCs would occur if the 95% CIs did not overlap.

The Institute of Public Health of Serbia provided data on the healthcare workforce employed in the public sector[14], and the Statistical Office of the Republic of Serbia[15] provided population data from census data (1961, 1971, 1981, 1991, and 2002) and mid-year estimates for other years. In the Serbian context, general practitioners are general medicine physicians. Specialists refer to those who specialised in general medicine, surgery, gynaecology, paediatrics and other medical disciplines. The term "nurses" covers the gamut of nursing specialties, including midwives and laboratory, dental, and X-ray technicians with primary, secondary and collegiate levels of qualification. To obtain the most consistent longitudinal data series possible, we focused only on physicians (general practitioners and medical specialists) and nurses employed in outpatient and inpatient healthcare institutions in the public sector of Serbia between 1961 and 2007. The changes in the methodology of health worker registration did not allowed us developing a reliable time-series for unemployed or retired health workers, and those who worked in private and other sectors. In addition, the data and the study results refer to the Serbian healthcare workforce and do not include data for Kosovo or Metohia (a United Nations (UN) protectorate).

Results

Socioeconomic and health workforce changes in Serbia (1961-2007)

The significant socioeconomic events in Serbia over the 47 years in question were demographic changes, economic reforms, the intermittent legalisation of private practice, decentralisation and centralisation, significant inflation, social tensions and country disintegration (Serbia was a republic of the former Yugoslavia) (Table 1).

During the 1960s and 1970s, the authority over the production, allocation and utilisation of healthcare resources and expenditures belonged to "self-management communities of interest", which were founded by representatives of the local population and healthcare providers at different administrative levels of parliament.[16] Such devolution resulted in an enlarged network of healthcare institutions and an increase in healthcare workforce density in the public sector. It aimed at providing better accesses to population whose growth rate was positive (Table 1). In the late 1960s, international loans decreased, and the government restricted investments in the healthcare sector and began to closely monitor health workforce and institutional productivity.[17] To optimise operations and more closely resemble the health system organisation of other counties, the state conceded functional regionalisation of the public healthcare sector and developed the "minimum" of guaranteed healthcare benefits.[17] By 1972, many healthcare services within a district were merged into units of larger medical capacities (e.g., primary with secondary institutions; pharmacy care in healthcare centres; and clinics, hospitals and institutes into clinical or clinical-hospital centres with over 400 beds)[17], generating more posts for specialists.

However, the new Constitution (in 1974), its amendments, and the subsequent Labour Law through decentralisation brought a broader autonomy to the management of healthcare institutions, resulting in the split into numerous joint-labour units. In addition to more healthcare workers, more administration and administrative staff positions were also created (Table 1).

In the 1980s, a concrete push for centralised healthcare workforce planning emerged from a stagnating economy, rising national debts and existing tensions between nationalist and separatist elements of the population (Table 1). Further financial restrictions in healthcare and insufficiently regulated private practices forced many healthcare workers to emigrate.[16] By 2000, the long-term development plan for Serbia targeted a gradual decline in healthcare workforce production, a more focused approach to healthcare education addressing the need for highly specific qualifications, reductions in vacancies based on centrally planned healthcare worker to population ratios and an endorsement of private practice.[17]

During the 1990s, the strongly centralised almost autocratic health system faced economic deprivation and influxes of both healthcare wor-

Table 1. Main socioeconomic events from the perspective of healthcare workforce planning and development in Serbia, 1961 – 2007

Period (years)	Local socioeconomic events (Serbia and their effects)
Extensive development: 1961 – 1973	• Positive population growth; "Self-management communities of interest"; • Five-year development plans for the economy (1961 and 1965); • Gradual decrease in international investments (1967, 1969, and 1971); • Introduction of health insurance for farmers; • Regionalisation in health care (1961-1972); • The minimum guaranteed amount of healthcare benefit (1971); • State ownership of healthcare assets and equipment installed; • Private practice prohibited.
Intensive development and stabilisation: 1974-1989	• State Constitution (1974); • Labour Law (1976); Law on Education (1976); • Law on health records and reporting (1978); • Cost-containment in health care (1978); • Separatist and nationalist pressures; • Constitutional amendments limited the autonomy of republics and Serbian provinces (1981); • Inflation increased (1989); • The long-term plan for development of Serbia by 2000 (1982); • Endorsement of private practice for dentists (1987), pharmacists and physicians (1989).
Stagnation and destruction: 1990-1999	• Yugoslavia break-up (1991-1995); • Law on Health Care and Health Care Insurance (1992) -Centralisation and autocracy in health care; • The UN Security Council sanctions (1991-1996) and other international sanctions (by 2001); • Hyperinflation (1992-1994) and stabilisation measures; • Ownership transformation (1997) – private practice in health care. • The UN protectorate of Kosovo and Metohia (1997); • NATO bombing (1999)
Period of reconstruction capacity building / reforms: 2000s	• Political changes with democratic government constitution and onset of economic reform (2001); • Law of Public administration and local government: decentralisation (2002); • State Constitution of Serbia (2006); • Draft of the paper on healthcare policy, vision and reform (2003); • New health system laws (2005): decentralisation in primary health care; • Medical education with accordance to EU standards and Bologna Declaration (2005); • National Economic Development Strategy of the Republic of Serbia 2006 – 2012. • Rationalisation of health personnel (IMF and WB 2005/2006); • Endorsement of licensing for healthcare workers (2007).

kers and patients among refugees and internally displaced persons. Private practice, while permitted, was not profitable due to currency revaluations and hyperinflation and practically did not exist (1992-1996).[18]

The onset of health system reform in 2003 was stimulated by global health initiatives and facilitated by the conditions of international grants and loans.[9] New health-related legislation delegated the authority over primary care institutions to local municipalities (financing remained centralised); defined working conditions, operating standards and healthcare workforce requirements (ratio to population); and proposed performance measures.[19] Apart from that, the reconstruction of public healthcare sector included an action plan for staff rationalisation (in 2005 and 2006) and Ministry of Health introduced strong enrolment criteria for specialist studies.[20]

The Joinpoint Regression Analysis of Healthcare Workforce Density in Serbia (1961-2007)

Over the study period, the AAPC (1961-2007) between general practitioner (1%), specialist (4.6%) and nurse (3.6%) density was significantly different ($p<0.05$) (Table 2). The growth of specialist density and nurse density were high and almost synchronised (by 660% and 445%, respectively), while general practitioner density showed much more limited growth (by 55%). The nurses to physicians ratio (general practitioners and specialists) increased from 1.8:1 in 1961 to 2.4:1 in 2007 ($p=0.008$). However, the ratio of specialists to general practitioners gradually increased from 0.6:1 in 1961 to 3.2:1 in 2007 ($p<0.0001$).

The best-fitted regression models of log-rates per 100,000 population had five joinpoint segments (and four joinpoints) for all observed health worker categories pointing to the compatibility in the projections of observed density rates with links to socioeconomic events (Figure 1).

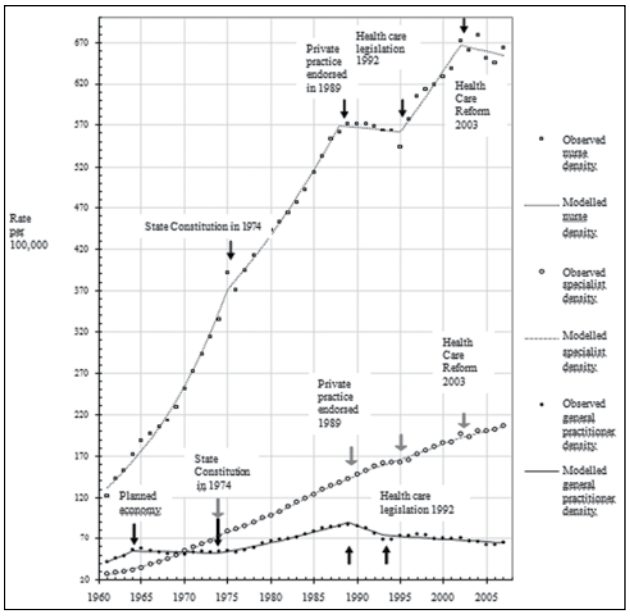

Figure 1. Joinpoints (years) and regression models of healthcare workforce log-rates in Serbia, 1961-2007 (Observed and modelled rates per 100,000 population; the open squares denote nurse, the open circles represent specialist, and the black circles represent general practitioner density, the arrows indicate joinpoints per model)

Between 1961 and 1964, the annual growth in general practitioner density was higher than that of

Table 2. Annual Percentage Change (APC) per joinpoint segments of physician and nurse density rates per 100,000 between 1961 and 2007 in Serbia

	Joinpoint segments		Rates (% change)	APC[a] (95% CI)
General practitioners	1961-2007		42.0-65.2 (55%)	AAPC: 1.0 (0.4;1.5)
	1.	1961-1964	42.0-55.8 (33%)	9.6 (3.6; 15.9)
	2.	1964-1974	55.8-54.1 (-3%)	-0.5 (-1.4; 0.4)
	3.	1974-1989	54.1-86.8 (60%)	3.6 (3.2; 4.1)
	4.	1989-1993	86.8-69.4 (-20%)	-4.7 (-8.3; -0.9)
	5.	1993-2007	69.4-65.2 (-6%)	-0.9 (-1.3; -0.5)
Specialists	1961-2007		27.2-206.7 (660%)	AAPC: 4.6 (4.4; 4.8)
	1.	1961-1974	27.2-73.1 (169%)	8.4 (8.0; 8.8)
	2.	1974-1985	73.1-123.5 (69%)	4.8 (4.5; 5.1)
	3.	1985-1991	123.5-152.7 (24%)	3.4 (2.6; 4.2)
	4.	1991-2002	152.7-196.4 (29%)	2.2 (1.9; 2.4)
	5.	2002-2007	196.4-206.7 (14%)	1.4 (0.7; 2.0)
Nurses	1960-2007		121.8-663.8 (445%)	AAPC: 3.6 (3.3;3.8)
	1.	1961-1975	121.8-391.4 (221%)	7.7 (7.3; 8.1)
	2.	1975-1988	391.4-562.5 (44%)	3.4 (3.0; 3.7)
	3.	1988-1995	562.5-543.8 (-3%)	-0.2 (-1.0; 0.6)
	4.	1995-2002	543.8-673.1 (24%)	2.5 (1.7; 3.3)
	5.	2002-2007	673.1-663.8 (-1%)	-0.4 (-1.4; 0.6)

[a] *APC is significantly different from 0 ($p<0.05$); Figures are rounded.*

specialists and nurses due to investments in economic development and healthcare workforce production (Figure 1, Table 2). However, from 1964 to 1974, this growth stagnated, most likely due to the merging of institutions and their functional reorganisation (Table 1). When provinces in Serbia gained broader autonomy in 1974 in an already decentralised healthcare system, the APC of the general practitioner density rate continued to increase by 3.6% annually over a 16-year period (Table 2). However, after 1989, the APC of the general practitioner density rate significantly decreased at a constant rate of -4.7%. The identified decrease was related to the private practice legalisation, the centralisation of the health system and population dynamics in a disintegrated country (Table 1).

In contrast to general practitioners, the APC of the specialist density rate was less detrimentally affected by the social and economic events in the country (Figure 1, Table 2). The highest APC of the specialist density rate coincided with the extensive development of the healthcare sector (Table 1). Due to several state cost-containment interventions and centralisation (1974 -2002), the APC of the specialist density rate dropped from 4.8% to 2.2%.

The nurse density rate significantly increased by 7.7% per year during the extensive development of the country (1961-1975) and then reduced to half this rate before the disintegration of the country in 1989.

Specialist and nurse density models by joinpoint projections showed similar APC patterns in the first ($p>0.05$) and fourth segments ($p>0.05$) (Figure 1, Table 2). The third joinpoint segment for the general practitioner model matched the second joinpoint segment of the nurse model in 1975-1988 ($p>0.05$) due to broadened autonomy in decision making based on the state Constitution in 1974, its amendments and the modified Labour Law.

Discussion

The joinpoint regression analyses of the healthcare workforce physicians' and nurses' trends in Serbia between 1961 and 2007 outlined the key socioeconomic events that have impacted the development of healthcare workforce. The drivers for policy changes regarding healthcare workforce in Serbia include the following: decentralisation and centralisation, private practice development, social and financial crises, and economic and constitutional reforms. Other studies that make intraregional comparisons of healthcare workforce policies and practices and health systems have identified these same factors as drivers for strategic healthcare workforce planning.[2,5,21-23]

According to a number of authors, decentralisation and financial incentives, among range of initiatives proved to be associated with significant workforce inflow and retain in health sector.[24-26] In Serbia, international financial investment and planned economy development (from 1961 until the beginning of 1970s), and decentralisation (in the period prior to 1981) triggered extensive development of physician and nurse density rates (for example, specialists by 169% and nurses by 221%). It is important to be clear about how the introduction of a new health policy, like privatization or centralization can be translated in public workforce to population ratio. Thus, similar to other countries[27,28], the private practice legalisation (in the late 1980s) in Serbia was characterised by considerable workforce outflow from the public sector (APC were -20% general practitioners, and -3% nurses), while centralization by declined physicians and nurses employment.

A number of publications[21,22,27-31] were warning about direct and indirect health expenditures related to major system-wide changes, still there is a relative paucity of more detailed documentation that describes the return of such investment in practice. For example, observed structural changes in Serbian health system aimed to improve public health sector efficiency. However, the access to healthcare workers had increased with merging of health institutions and their functional reorganisation (in 1960s and 1970s), and it has declined during capacity reconstruction and division of health centres in 2000s, without evidences that those changes has improved efficiency.[32,33] Some authors found that structural adjustments coupled with limited job opportunities and low salaries leave a space for *ad hoc* decision making and conflicts among multiple actors and action plans and can spur workers to switch occupations or work outside the country.[28,34,35] The political instability has been translated in overall social degradation and hyperinflation and economic depriva-

tion several years after the Yugoslavia break-up. In those circumstances and under the pressure of refugees and internally displaced physicians, nurses and patients Serbian health sector capacity has been collapsing.

The correspondence between key events and staffing changes had a ”lag” effect, which likely reflected administrative readiness, flexibility, and the capacity to respond to imposed requirements for change or a number of factors that we were not able to document well (e.g., migration). Other limitations of the study include the potential over- and under-estimating of staff numbers because of workforce-recording errors, such as registration of those at specialist training for several years or at “compulsory vacation” with minimal reimbursement as active workers.

Policy implications

The role of leadership and strategic planning is perhaps the most critical factor for health workforce development. The study provided some evidence that sole compliance with an agreed decision making format in health care was insufficient in both single-party system and *multi-party political system, as well as in centralisation and decentralisation*. The radical shift from general practitioner to specialist population coverage began in 1964, and it has contributed to Serbia having a lower population coverage with general practitioners and nurses and a higher coverage with surgical, obstetric and gynaecologic specialists than the EU.[36] Apart from that, if current policies for human resources for health remain, health worker' unemployment was projected to grow by 2017.[10] Further researches should include the question of the return on investments in health workforce, in terms of their impact on health outcomes or productivity.

The study showed that a major barrier to integrative and strategic planning was poor cooperation among stakeholders, which has been translated into asynchrony among labour, health and educational policies interests and benefits. An unambiguous example of it is that official health personnel registers still lack the valid data about the private-public labour flow and migration. Therefore, in transition economies of low developed and developing countries we advocate for building the competency for health workforce planning as the key factor for making more accountable policies to a future society needs, expectations and challenges.

Despite past[18,32] and current evidences[11,33] insufficient assurance of healthcare quality or productivity and deepening health workforce misdistribution, the traditional healthcare workforce planning approach has not changed in Serbia by now. Even more, it degraded from a preferred provider to population ratio to one derived simply by a prescription in the structure of inputs.[19] Recently, the Ministry of Health has identified four health workforce objectives for the period between 2010 and 2015: improving legislation, developing management capacity, customising training to the real needs of society and strengthening the strategic information for planning.[37]

A final message that can be synthesized from all study findings is the apparent need for competency in strategic human resources for health planning and development at all governing and management levels of the health care system.

As a recommendation, Serbia must move to the complex, flexible and comprehensive healthcare workforce planning methods required for reorganising staff roles, skills and functions in order to achieve a more effective use of current and future health staff. To do so will require a healthcare workforce planning agency within the government structure (i.e., an accountable multistakeholder partnership) that is competent to plan and develop the careful management of guidelines, plans, and strategies for healthcare workforce production, development, deployment, and migration in an expanding labour market (including long-term perspectives) and that has independent expertise in terms of responsiveness for accurate and valid information flow and analysis.

Conclusion

Though strategic, health workforce issues seemed to be a low priority on the national agenda by now. The main lessons learned were that higher physicians' and nurses' deployment pattern has been associated with decentralisation, while their density rates have decreased during centralisation and were stabilised with stronger financial control in healthcare. The identified socioeconomic impacts on health workforce trends provide visible and tan-

gible messages for policymakers. Recommended workforce policy should include anticipation of its impact on health outcomes or productivity. In order to ensure the health care improvement in the future, Serbia needs to move instantly toward more socially accountable, integrative and well coordinated health workforce planning and management.

Acknowledgements

Ministry of Science and Technology of the Republic of Serbia (grant no.175087).

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The influence of physical activity on attention in Turkish children

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Abstract

This study aims to determine the influence of regular physical activity on attention among 4th and 5th graders. A total of 60 4th and 5th graders aged between 9-11 participated in the study. This is an experimental study which employs a pretest-posttest control group design. The experimental and control groups consisted of 30 children each, who did and did not engage in sports activities respectively. The data were collected using personal information form and Bourdon Attention Test, and analyzed using Gretl software package with multiple regression analysis. The results show that physically active children had significantly higher attention levels compared to sedentary children ($p<0.05$). In conclusion, engaging in physical activities regularly and under the supervision of a trainer positively affects attention development in 4th and 5th graders.

Key words: Physical Activity, Sports, Attention, Bourdon Attention Test, Early Adolescence

Introduction

Attention is one of the most important elements of cognitive functioning in education and professional life as well as in most daily activities. As a cognitive skill, attention is defined as a process affecting human behavior by which a sensory stimulus is selectively perceived while others are ignored (1, 2, 3) in order for someone to be able to observe an entity or event that motivates him or her. In other words, it is characterized as being oriented towards (4), focused or concentrated on, or conscious of (5) an object, event, or activity. In light of these definitions, one could say that directing attention on a particular task yields more successful results by making all relevant details noticeable. Attention is thus considered to be a necessary condition for success in a task or activity.

The period between 9 and 11 years of age is an orderly and peaceful transitional stage during which children accumulate, internalize, and balance knowledge. It is also the golden age of balanced development (6). Attention development is especially important during the periods when children learn intensively. Attention is the first step of learning process, and it plays an important role in learning. It also guides the development of cognitive representations starting from early childhood (7). For a student with an active attention level, there is a direct relationship between attention processes, level of interest, previous learning experiences, and level of motivation (8). For primary school students, the level of attention is relatively low, and attention has a shorter span. They could give their attention to an operation for only between 10 to 20 minutes at most (9). Many teachers in Western countries thus complain about increasing concentration problems and attention disorder as well as growing discomfort (10). Recent research has begun to recognize the importance of understanding the mechanisms that underlie attention regulation in order to promote children's academic success (11,12).

Some studies (13, 14, 15) identified a correlation between underachievement and presence of attention problems during primary school years. It is quite likely that these children will develop further problems later in their lives, too. Moreover, the problems of the children who perform poorly at school due to low attention levels is not limited to their academic success, they could also have problems with the concept of the self, language skills, and interpersonal communication. Early

interventions are thus crucial in preventing or at lest minimizing negative consequences. Attention plays an important role in perceiving the external world, learning adaptive behaviors, remembering interests, solving problems as well as in social interaction and various mental processes (16).

Several studies (17, 18, 19) identified a positive relationship between physical activity and academic performance and showed that engaging in physical activities positively affects the cognitive level of school children (20, 21). In a study conducted by Coe et al., it was found that children who were engaging in physical activities outside school hours had higher levels of academic success than those who were not (22). Tantillo et al. (2002) also found that an effective and regular engagement in physical activities has positive effects in children with Attention Deficit and Hyperactivity Disorder (ADHD)(23).

In developed or developing countries sedantary life and obesity is an outstanding health problem. By increasing number of the child in total population, and also weight increased (obesity I-II-III) in body type. Arslan and et al., (2011) are reported positive correlation between number of the child and BMI (24) It is know that lack of PA causes many of cardiovascular diseases(25) (Radjo and et al., 2011). it is know that childhood and the young hood is the period of life in which by proper process of exercise and PA can significantly influence the physical and psychological development(26).

In the western countries, the sports and physical activities programs at school started to draw more attention after many studies showed that physical exercise and sports have a positive impact on cognitive performance and academic success (27, 28, 29).

This study aims to examine whether a 12-week physical activity has an impact on attention development among Turkish children during early adolescence.

Materials and methods

A total of 60 4th and 5th graders aged 11-12 volunteered in this study. This is an experimental study which employs a pretest-posttest control group design. The experimental and control groups consisted of 30 children each, who did and did not engage in sports activities respectively. The experimental group went through a 12-week program, engaging in physical activities (volleyball and gymnastics) three times a week. The control group did not follow a physical activity program. Personal information form was used to collect demographic data, and the Bourdon Attention test was employed to assess attention levels.

The demographic data were collected before the physical activity program began. Students were then given 9 minutes to take the Bourdon Attention Test. During the 8th week of the program, a control test was conducted to assess attention levels. The test was administered for the last time during the 12th week.

The Bourdon Attention Test. The last version of the Bourdon test was developed by Benjamin Bourdon in 1955. The test consists of two forms. The first form involves finding certain letters in a mixed word grid, while the second involves finding certain shapes in a mixed group of shapes. The test requires the full attention of the participants. There are 660 letters in the letter form. The shape form is 1-page long, and consists of 450 shapes. In this form, participants are asked to look for certain shapes among a mixed set of shapes. There is no age limit for the Bourdon test, but participating children should be capable of identifying letters to be able to take the letter test. Correct answers, mistakes, or duration could all constitute the basis of assessment. The number of corrects answers per unit time could also be used for assessment. The letter form of the Bourdon test was employed in this study. Students were asked to find and mark the letters "b, d, g and p" in 3 minutes. The number of correct answers was used for assessment. Each correct answer was worth one point. Unmarked or incorrectly marked letters were considered a mistake. The students were given 3 minutes for each set. The maximum possible score was 110. Higher scores mean higher level of attention in this test.

Statistical Analysis

Gretl statistical analysis software package was used to analyze the data. Cronbach's alpha for a total of 13 variables was calculated to be 0.62. Since a Cronbach's alpha value between 0.6 and 0.8 indicates acceptable reliability, the results of

this study are reliable. This study employs multiple regression analysis. Regression analyses could be used to examine the relationship between two variables as well as the multiple relationships between multiple variables.

This study employs the logarithmic-linear regression analysis model. According to this model, the results of the tests constitute the dependent variables. The students' test scores show the number of mistakes. The test was conducted three times: before the physical activity program began, after the 8th week, and after the 11th week. Two dummy variables were specified to determine the difference between the three tests. The first test was taken as the reference point, and different dummy variables were assigned for the second and the third tests. In this way, the relative difference between the first and the later tests were identified.

Since dependent variables indicate the number of mistakes, a lower number of mistakes was considered to indicate higher levels of attention. Therefore, a negative coefficient for a dummy variable indicates an increase in the level of attention compared to the reference group, while positive coefficients indicate a lessening of attention levels.

Results

The demographic data suggest that 45% of the participants were male, and 55% were female. When asked about the type of sports they played, 30% and 20% responded "volleyball" and gymnastics respectively, while 50% did not engage in any sports activities. As for the mothers' level of education, 8% were primary school graduates, 6% were secondary school graduates, 48% were high school graduates, and 36% were university graduates. As for the fathers' level of education, 3.3% were primary school graduates, 5% were secondary school graduates, 36.7% were high school graduates, and 55% were university graduates.

The F-test suggests that the model is statistically significant. The results of this model are thus reliable for interpretation. The adjusted R^2 suggests that % 47 of the attention measurements are explained by the model. This could be interpreted as an acceptable level of explanation for a regression analysis with cross-sectional data. Dummy variables with a negative coefficient indicate an improvement, while positive coefficients indicate a worsening relative to the reference group. In this study, the R^2 and the adjusted R^2 were calculated to be 0.508501 and 0.469060 respectively, with F(13.162)=12.89262, and P(F)=0.0000.

When the results of the three tests were compared, it was found that children made 58% less mistakes at the 8th week, and 91% less mistakes at the 11th week compared to the first week. It was also found that male children had higher attention levels than female students. While the children of primary school graduate mothers and secondary school graduate mothers had the same attention levels, the

Table 1. Attention Test Regression Results

Independent Variables	Coefficient	Std. Error	t-value	p-value
Constant	291.929	0.849317	34.372	0.00075***
Attention Test 1st Week-8th Week	-0.581004	0.105915	-54.856	0.00001***
Attention Test 1st Week-12th Week	-0.915097	0.1015	-90.157	0.00001***
Gender	0.504078	0.112823	44.679	0.00001***
Mother's level of education: Secondary School	-0.26177	0.304558	-0.8595	0.39133
Mother's level of education: High School	-0.542623	0.273021	-19.875	0.04855**
Mother's level of education: University	-0.663579	0.292617	-22.677	0.02467**
Father's level of education: Secondary School	0.664204	0.876592	0.7577	0.44972
Father's level of education: High School	0.0332665	0.859703	0.0387	0.96918
Father's level of education: University	0.307915	0.861044	0.3576	0.72110
Level of Income (1000-2000 TL)	0.356743	0.188316	18.944	0.05996*
Level of Income (2000-3000 TL)	0.23143	0.207037	11.178	0.26530
Physically Active-Sedentary	-0.832587	0.166937	-49.874	0.00001***
Number of Siblings	0.298186	0.0733722	40.640	0.00008***

** Significant at α= 0.10, ** Significant at α= 0.05, *** Significant at α=0.01,*

level of attention of the children of high school graduate mothers were 54% higher than the children of primary school graduate mothers. Similarly, the children of university graduate mothers had 66% higher attention levels compared to the children of primary school graduate mothers. These results suggest that mothers' level of education play a key role in the attention levels of children.

It was also found that fathers' level of education had no impact on children's attention levels. The children with a monthly household income of 1000-2000TL had 30% higher attention levels than the children with a monthly household income of 1000 TL or below. Therefore, there was an inverse relationship between level of income and level of attention. It was also calculated that children who were engaging in physical activities had 83% higher attention levels than sedentary children. This shows that physical activity plays a key role in increasing attention levels. Lastly, higher number of siblings was found to result in lower attention levels, while every extra sibling decreased the level of attention by 30%.

Discussion and conclusion

This study examines the attention levels of physically active and sedentary early adolescents aged 9-11 living in Izmir. The attention levels of the children who participated in a physical activity program and those who were sedentary, were measured and analyzed using the Bourdon Attention Test.

The findings of this study show that the children who were engaging in physical activities had higher attention levels. In conformity with our hypothesis, a significant relationship was found between the attention levels of the physically active children and the sedentary children ($p<0.05$).

A significant relationship was found between genders ($p<0.05$). Boys had higher attention levels compared to girls. This difference could be explained by the differences in sex-related cognitive abilities. It is therefore important that girls of this age be canalized to activities that improve focusing attention.

Pre-school period is a time when children are open to many stimuli that could boost their intelligence. If guided properly, they keep improving the basic skills acquired during this period for the rest of their life and adopt a more open-minded attitude towards learning (30). Considering the length of time that preschool children spend with their mothers, the attention levels of children whose mothers have a high level of education and awareness, should be relatively higher. A significant relationship was found between mother's level of education and level of attention in this study ($p<0.05$). Our study supports the existing literature in this regard.

In a study, in which Polderman et al. (2011) genetically examine the relationship between attention problems and ADHD symptoms during early adolescence and four academic skills (mathematics, spelling, reading, and comprehension), it was found that comprehension and spelling skills were influenced by environmental factors, while mathematics skills came from shared genes (mother-child)(31). It is therefore very important that the education of girls, who are the mothers of tomorrow, should be taken seriously is as much as that of boys.

It was also observed that there was a significant relationship between number of siblings and level of attention ($p<0.05$). Attention levels went down as the number of siblings increased. No data was found in the literature supporting this inverse relationship. Conducting studies with higher number of participants might shed more light on the issue.

In light of the data, a significant relationship was found between the attention levels of the physically active children and the sedentary children ($p<0.05$). The children who were engaging in physical activities had higher attention levels compared to sedentary children. Similarly, in a study examining the effect of acute treadmill walking on cognitive control, behavioral and neuroelectric indices of attention, and academic performance, Hillman et al. (2009) found that moderately-intense aerobic exercises (walking) could increase the cognitive control of attention among pre-adolescent children(27) Hillman et al. (2008) also found a positive relationship between aerobic exercise and academic performance(28) In a study entitled "Be Smart Exercise Your Heart: Exercise Effects on Brain and Cognition", Hillman et al. (2008) determined that aerobic exercises have a boosting effect on cognitive performance.

Similarly, in a comparative cross-sectional study conducted by Tomporowski et al. (2007), it was found that physically fit children performed

cognitive tasks better and had better neurophysiological activity indicators, compared to the children who are less fit(29). In a randomized clinical experimental study conducted by Davis et al. (2007), it was found that aerobic exercises had a positive influence on children's executive function. In a study entitled "The Relationship between Movement Training, Attention and Memory Development among 8-year-old Children"(32), Akcınlı (2005) showed that movement training had a positive influence on attention and memory development(33). Özdemir (1990) also concluded that the children who were engaging in sports activities had higher attention levels compared to those who do not(34).

Previous findings about the effects of sports and physical activities on attention development among pre-adolescent children support the findings of this study. This study suggests that mothers have an enormous influence on their children's attention development especially during early adolescence, and that high number of siblings is one of the factors that adversely affect attention levels. A positive correlation was identified between physical activity and attention skills. It was also observed that the positive influence that engaging in sports and physical activities regularly had on attention levels also contributed to learning skills of the children. Having children acquire the habit of engaging in sports and physical activities will not only increase their attention levels and boost their academic achievements and learning skills, but it will also help build a society that is more health both physically and psychologically. Conducting similar studies on different age groups might provide further insights on the topic.

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Effect of Punch Strokes on Hearing Levels of Elite Amateur Boxers

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Abstract

Although the injury risks of boxing is well known, this sport continuous to attract athletes and an increase of introduction to boxing is observed in the last decade. In terms of injury locations, head and face are reported as most common sports. Present study aimed to examine the hearing differences of elite amateur boxers as a result of punch strokes in boxing.

Subjects are interested in active boxing for 5-14 years (mean 6.67) and between the age of 18-32 (mean 21.71). Screened group consisted of 21 male boxers. Auditory brainstem responses, pure tone and high frequency audiogram tests were conducted for boxers and unscreened groups in the standard acoustically controlled rooms using Interacoustics Clinical Computer Audiometer.

Mean ± standard deviations are reported. Groups were compared by Student's *t* test $p<0.05$. Auditory brainstem responses and pure tone values were determined in range of I-V inter-pick latency (ms).

There were no statistically significant differences in the hearing level of elite amateur boxers in contrast to non-boxers. It is seen to be important that amateur boxers wear protective materials as a helmet and mouth guard to minimize the risk of injury. The use of protective equipment must be encouraged for boxer's health.

Key words: Hearing, boxer, punch, boxing, sport

Introduction

A combat sport, also known as a fighting sport, is a competitive contact sport where two competitors fight under certain rules of engagement. Boxing is an example of combat sports and the one of the oldest sports. Two opponents make effort for success using their fists (1). Boxing may result in injuries to various parts of the body including injury associated with chronic, repetitive head blows (2). Permanent brain, eye and hearing damage of retired boxers exist as result of the repeated blows against their head (3).

Compulsory helmets and change in the scoring system is an important step to minimize the risk of boxing injury. In the past 30 years, significant improvements in ringside and medical equipment, safety, and regulations have resulted in a dramatic reduction in the fatality rate (4). Nevertheless, especially loss of hearing still occurs in post-traumatic events (5).

Superficial facial lacerations and head injuries are the most common injury reported in boxing (6). The extent of the injuries is correlated to the number of bouts fought. Due to the repeated and numerous blows against their head, hearing problems should not be ignored. In fact, a punch in boxing that turns the head can cause serious hearing problems (7) but the results are not conclusive. Since information on the incidence of hearing injuries in amateur boxing is limited. This study aimed to examine the hearing effects of punch strokes in boxing.

Methods

Participants: Screened group consisted of 21 male boxers of the Turkish national team. Boxers are involved in elite competitions such as World Championships, European Championships and Olympics for more than five years. Comparison group consisted of 21 healthy male, who had no hearing loss and head trauma. The stories and demographic characteristics (age, sports age and gender) were recorded from all participants. Subjects with former hearing problems or disorders that resulted in loss chronic neurological disease, subjects using an autotoxic agent, or with trauma and those with a history of hearing loss in their families were excluded from the study. All subjects

were examined by an otolaryngologist and had a systemic examination.

Tests: The audiometric tests were carried out for all participants in the standard acoustically controlled rooms using Interacoustics Clinical Computer Audiometer Model AC-40 (Denmark). Measurements were made after rest period in a silent environment. To determine the hearing thresholds at 250, 500, 1000, 2000, 4000, (pure tone) 8000, 10000, 12000 and 16000 Hz (high frequency), the standard ascending/descending (after attenuation to inaudibility in 5-10 dB steps, the signal to be increased "until the tone is heard") method was applied to all subjects. Tests were performed in the frequencies at octave intervals from 250 to 16000 Hz and from 500 to 4000 Hz for air conduction and bone conduction, respectively. Hearing loss was defined as a decrease in the threshold sensitivity of 20 dB or greater at one or more test frequencies in relation to the baseline measurement. Auditory brainstem responses (BERA) test, wave amplitudes and interval ranges were evaluated to the all subjects.

This study was performed at a University Medical Center. Informed consent was obtained from the subjects prior to the study. The design and procedures approved by Fırat University Ethical Committee.

Statistical analyses: The Statistical Package for the Social Sciences program was used for data analysis. Results were presented as mean ± standard deviation. Groups were compared by Student's *t* test $p<0.05$. BERA values were determined in I-V inter-pick latency durations.

Results

The screened group consisted of 21 boxers, who were active boxers for 5-14 years (mean 6.67) and were between the age of 18-32 (mean 21.71) (Table 1).

There were no statistically significant differences in I-V inter-pick latency durations in BERA test with the click stimulus of the unscreened and screened groups ($p<0.05$) (Table 2). BERA and high frequency averages were evaluated both the unscreened and screened groups.

In standard audiometry, no statistically significant were found differences in boxer's hearing thresholds than unscreened group. In high-frequency hearing thresholds, an increase was found in 8000, 10000, 12000 and 16000 Hz hearing thresholds of boxers. However, increase in hearing thresholds was statistically significant only in 8000 and 12,000 test frequencies. Other test frequencies were not significant (Table 3).

Table 2. BERA values of control and boxers groups

Tests	Controls	Boxers
BERA test 30 nHL *	5.10 ± 0.64	4.86 ± 0.51
BERA test 40 nHL *	4.88 ± 0.63	4.94 ± 0.59
BERA test 50 nHL *	4.45 ± 0.55	4.50 ± 0.28

** Value of I-V inter-pick latency (ms). Data were given as mean ± standard deviation. Groups were compared by Student's t test ($p<0.05$).*

Table 3. High frequency data of control and boxers groups

Test frequency (Hz)	Mean hearing threshold (dB HL)	
	Controls (21 subjects, 42 ears)	Boxers (21 subjects, 42 ears)
250	14,10 ± 6,34	15,93 ± 8,16
500	11,79 ± 5,04	13,69 ± 7,49
1000	10,48 ± 5,16	9,52 ± 4,79
2000	10,83 ± 5,51	12,02 ± 7,16
4000	11,55 ± 4,62	14,52 ± 10,75
8000	13,45 ± 5,89	19,88 ± 9,21*
10000	20,76 ± 5,77	21,67 ± 9,28
12000	19,00 ± 6,22	28,81 ± 11,14*
16000	24,57 ± 14,87	27,29 ± 14,99

** $p<0.001$ (Students't-test); Mean ± SD*

Discussion

Injuries are common in boxing. This is considered an occupational damage. In fact, ear injuries have represented only a relatively small percen-

Table 1. Descriptive statistics of boxers

	N	Minimum	Maximum	Mean	± SD
Age	21	18.00	32.00	21.7143	4.20883
Sport age	21	5.00	14.00	6.6667	2.76285
Gender	42	1.00	1.00	1.0000	.00000

tage of all problems. In our study, there were no statistically significant differences in the hearing level of elite amateur boxers. Test results are in normal levels. Yet, it is important that amateur boxers wear protective materials as a helmet and mouth guard to minimize the risk of injury.

It is generally considered greater exposure to injury in many boxers in cochlea after blunt trauma. Although injuries of the ear are not threatening life, they may account for significant morbidity. They may cause severe pain, hearing loss, tinnitus, or vertigo. Ear trauma may occur secondary to a number of mechanisms, including blunt trauma (8).

In the literature found 107 injuries were reported from 427 fight participations, corresponding to an injury rate of 250.6 injuries per 1000 fight participations. The most frequently injured body region was the head/neck/face (89.8%), followed by the upper extremities (7.4%). Injury rates for amateur boxers have been reported at 9.1 injuries per 100 personal exposures and 14.0 injuries per 100 boxers respectively (9). The majority of these injuries were lacerations to the head and face. An increasing age and an increasing number of fights were both significant predictors of injury (10). There is only a small risk for serious injury, and that injuries occur in a hierarchy of upper extremity (441, 25%) and head/face (344, 19%) for amateur boxers (11).

In a review of boxing data from the state of Nevada from September 2001 through March 2003, the overall incidence rate of injury was 17.1 per 100 boxer-matches, or 3.4 per 100 boxer-rounds. Facial laceration accounted for 51% of all injuries, followed by hand injury (17%), eye injury (14%), and nose injury (5%) (Fitzgerald 1996).

Brain injury in boxing, both acute and chronic, is the major risk for potential catastrophe. In spite of the perceived brutality associated with the sport, most injuries are minor, although serious injuries and deaths do occur, most commonly due to brain injury (12). Also brain injury from repetitive head blows has been reported in the boxer population (13). Besides permanent brain damage due to repeated and numerous blows to head, severe permanent damage to the hearing organ exists (2). Moreover, hearing disorders such as Tinnitus is a significant symptom that commonly occurs as a result of head or neck trauma can occur in athletes (14).

A study investigated the incidence, pattern, and severity of injuries resulting from participation in amateur boxing. The incidence of injuries in competition was 0.92 injuries per man-hour of play (or 0.7 injuries per boxer per year), while the incidence in training was 0.69 injuries per boxer, per year (15).

Another study related to hearing problems conducted a health management survey to identify the potential causes of boxing injuries. After a fight, many of the corresponding boxers complained from headache/heaviness in the head, tinnitus, difficulty in hearing and vertigo. Some experienced headache, ringing in the ears, and difficulty in hearing and vertigo in their daily lives (7). Our research has supported this temporary condition on amateur boxers. We think that the use of protective equipment must be encouraged for boxer's health.

A study supports the relevance of the neurophysiologic assessment of athletes engaged in violent sports which can cause brain impairment (16). There is increasing evidence that boxing can lead to chronic brain damage, ranging from mild subclinical dysfunction to the slowed motor performance, tremors, memory defects and slowness of thought associated with severe neurological impairment (17).

A review of the available records indicates that there have been a substantial number of fatalities in amateur boxers due to intracranial injuries sustained in the ring in comparison to the numbers of boxers at risk (18). Nonetheless, the rate of boxing-related head injuries, particularly concussions, remains unknown, due in large part to its variability in clinical presentation. Furthermore, the significance of repeat concussions sustained when boxing is being understood (4).

The safety of boxing is an issue that stimulates emotive responses on both sides of the debate, and calls to ban the sport continue. Nevertheless, on the basis of a systematic review, it was concluded that the current evidence, such as it exists, for chronic traumatic brain injury as a consequence of amateur boxing is not strong (19).

Conclusion

In conclusion, it is well known that injuries are common in boxing, occurring most often in head region. Many people have thought that the boxing is so dangerous that it should be abolished. In fact,

compulsory wearing of helmets and other protective materials in amateur boxing competitions are important step to minimize the risk of injury.

Our results have been shown that there isn't any problem seriously in the hearing level of elite amateur boxers due to the use of protective equipments. Although there wasn't increase in hearing thresholds of elite amateur boxer's standard audiometry, we found a statistically significant increase in high-frequency audiometry at hearing thresholds 8000 and 12000 Hz. This situation is to show the less exposure to trauma of boxers due to the use of protective.

On the other hand amateur boxing is different from professional boxing, and has unique rules and equipment. There may be considerably greater exposure to injury in professional boxers in cochlea after blunt trauma. Further comparative studies are valuable to determine the optimal injury prevention strategies in professional versus amateur boxing. We recommend that future research should collect more knowledge on the formation of injury, as this is important for the development of effective injury prevention strategies.

Acknowledgments

I thank to Erol Keleş, MD, Faculty of Medicine, Fırat University, Turgut Karlıdağ, MD, Faculty of Medicine, Fırat University and Dr. Şule Özkara, Faculty of Medicine, Fırat University for their support and comments on this manuscript.

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Endometrial thickness and beginning of bleeding as prospective markers for the risk of surgical intervention after intracervical application of misoprostol in early pregnancy failure

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Abstract

Aim: This study was conducted to examine the effectiveness of misoprostol in early pregnancy failure, based on ultrasound measured endometrial thickness and the beginning of bleeding after the first application of misoprostol.

Materials and Methods: A prospective study was conducted with 250 women due to early pregnancy failure to a maximum of 56 days gestation. Misoprostol was applied intracervically to all patients in the total dose of 1000 μg during the three consecutive days. All patients after the first, second and third administration of misoprostol and 14th day of the first drug administration had ultrasound examinations.

Results: The procedure was successful in 232 (92.8 %) patients. Endometrial thickness ≥ 15.06 mm predicted incomplete abortion with a sensitivity of 84.6 % and specificity of 99.6 % (area under the ROC curve was 0.845). Women in whom the drug after the first application within 4 h, had the successful procedure (p = 0.000).

Conclusion: The endometrial thickness and the beginning of bleeding were reliable prognostic factors of complete / incomplete abortion.

Key words: endometrial thickness, transvaginal ultrasonography, misoprostol, early pregnancy failure

Introduction

Approximately 200 000 early pregnancy failures (EPF) are done annually in Serbia. Standard procedures of dilatation and vacuum aspiration with an instrumental revision of uterine cavity (D&C) are generally used. The incidence of complications is about 1 %, which means that more than 2000 women are treated from direct and early complications of abortion annually. In Serbia abortion is legalized, but there are no standards which refer to the choice of the safest method. Based on literature data, medical abortions are safe and effective alternative to surgical ones, particularly among younger women who have not given birth. (1) Successful medical abortion is defined as the complete removal of products of conception, so instrumental revision is not required (2). Misoprostol (Cytotec) is prostaglandin E1 analogue that has been initially used for the treatment and prevention of gastric ulcer disease. In addition, misoprostol has been investigated as an agent to induce abortion (3 -7). A standard protocol for use of misoprostol alone is not established yet. Based on numerous clinical studies, it was found that the efficiency of misoprostol varies and depends on administration type (oral, sublingual, intravaginal), applied doses, dosing schedules and gestation age. All these studies have demonstrated that misoprostol, alone, was highly effective for first trimester medical abortions; with efficacy rates ranging from 65 to 93 % (8-13). The parameters used for monitoring patients after abortion include levels of serum ß-hCG, transvaginal ultrasonography and assessment of bleeding intensity. An ultrasound measurement of endometrial thickness is a useful parameter for diagnosis of incomplete abortion after a miscarriage in the first trimester of pregnancy, and can be expected to be useful in diagnosis and eventual failure of medical abortion

(14). It is evident that, after expulsion of gestational sac, endometrial thickness decreases with time, but even today there isn't a consensus about the value of endometrial thickness which would be considered the milestone in the diagnosis of complete abortion.

Objective

The aim of this prospective study is to examine the effectiveness of intracervical and intravaginal applications of misoprostol in the total dose of 1000 μg for EPF based on ultrasonography-measured endometrial thickness and the beginning of bleeding after the first application of misoprostol.

Materials and methods

This prospective study was conducted on 250 women who came to GOC CC in Kragujevac, Serbia, due to EPF to a maximum of 56 days gestation. All subjects have previously signed a statement of approval for entry into the study by the principles of good clinical practice. Permission for the study was obtained from the Ethics Committee of the Medical Faculty in Kragujevac and the Ethics Committee of the Clinical Centre in Kragujevac. Misoprostol was applied to all patients in the total dose of 1000 μg during three consecutive days. First and second day the application was carried out intracervically in single dose of 400 μg and the third day intravaginally in fornix posterior, in a dose of 200 μg. All patients after the first, second and third misoprostol administration and 14th day since the first drug administration (when the final assessment of procedure performance was carried out) had ultrasound examinations. Multi-frequency vaginal probe was used (the frequency of 7.5 MHz), and review was carried out in accordance with published recommendations (15). This way it was tested whether there was an expulsion of gestational sac and, if so, the endometrial thickness at each examination was determined. Patients in whom intact pregnancy was diagnosed, which had residual tissue or significantly prolonged / intense bleeding, which presented the clinical picture of incomplete abortion, had the instrumental revision of uterine cavity and the procedure was classified as unsuccessful.

The area under the ROC (Receiver Operating Characteristic) curve was calculated to assess the overall ability of endometrial thickness to predict the need for subsequent D&C, also for the cut-off, sensitivity and specificity. Area under the ROC curve higher than 0.500 is statistically significant. Comparison of quantitative variables in the study groups was done with Mann-Whitney test for independent samples. All other comparisons were performed using Chisquere analysis and Fisher exact test. Statistical significance was determined by the level of $p = 0.05$. For statistical processing of results a commercial software package SPSS (version 13) was used.

Results

Our study included 250 patients age 19 to 43. After the protocol, procedure was successful in 232 (92.8 %) patients. Intact pregnancy was established in 6 (2.4 %) patients. In 7 (2.8 %) patients instrumental revision was done due to the appearance of residual tissue and in 5 (2 %) patients due to intense or prolonged bleeding. Baseline characteristics of patients in the study groups are shown in Table 1.

Table 1. Baseline characteristics of the study groups

	successful procedure (n=232)	unsuccessful procedure (n=18)	p
Maternal age (years ± SD)	27.66 ± 0.36	32.64 ± 1.59	0.002
Gestational ages (TVUS) ± SD)	6.29 ± 0.79	6.25 ± 0.78	0.815
Cervical length measured by TVUS	37.83 ± 3.23	38.14 ± 4.05	0.649
Parity (n [%])			
Nulliparous	116 (95.9 %)	5 (4.1 %)	0.056
Multiparous	116 (89.9 %)	13 (10.1 %)	
Position of the uterus (n [%])			
AVF	181 (92.8 %)	14 (7.2 %)	0.981
RVF	51 (92.7 %)	4 (7.3 %)	

Results of this study showed that women age was a parameter that significantly affects the performance of procedures (p = 0.002).

Gestational age (ultrasound-determined), did not affect the performance of procedures (p=0,815) and it has been shown here that the position of the uterus (AVF/RVF) (p=0,981) and cervical length measured by ultrasound (p=0,649) had no effect on the performance of procedures.

Fischer's exact test has shown that the successfulness of procedure between nulliparous and multiparous women is at the level of p=0.056, which is on the verge of significance. But when we divided the patients in four groups according to previous deliveries and abortions (Table 2), no statistically significant differences between the four groups of women were observed (p=0,347).

In our study, we have questioned whether there was a correlation between the beginning of bleeding after the first dose of the drug application and successfulness of the procedure. The results collected indicate that there was a statistically significant difference between the beginning of bleeding in patients in whom the procedure was successful from those which had unsuccessful ones (p=0.000). After 14 days of the first application of misoprostol endometrial thickness in the case of complete abortion was 12.56±1.1 mm and 21.94±7.2 mm in the case of incomplete abortion, which is a statistically significant difference (p=0.002) (Table 3).

After 14 days of the first application of misoprostol an endometrial thickness of ≥ 15.06 mm predicted incomplete abortion with a sensitivity of 84.6 % and a specificity of 99.6 % (area under the ROC was 0.845, p=0.000) (Figure 1).

Increase in body temperature to 38 º C was registered in 38 (15.2 %) patients.

Antibiotics have been administered during the protocol in 6.8 % of cases.

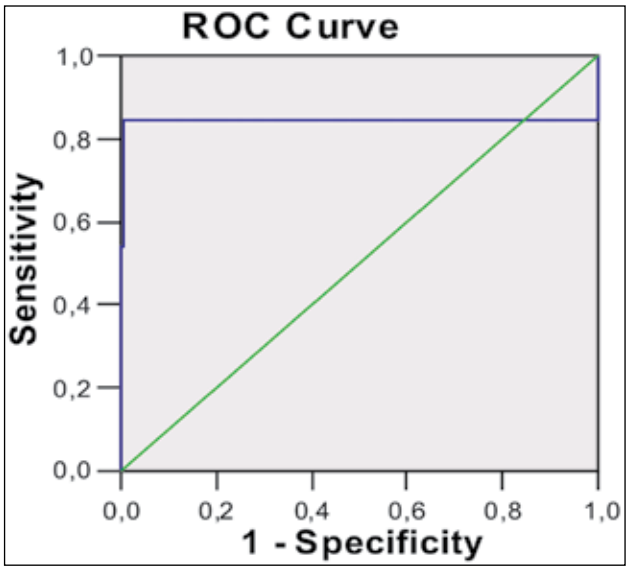

Figure 1. ROC curve for endometrial thickness after 14 days since the first application of misoprostol

Side effects of misoprostol were recorded at 46.85 % and patients: nausea (24.4 %), vomiting (11.6 %) and diarrhea (10.8 %).

Complications such as prolonged bleeding, which requires transfusion infection, sepsis and allergy that have been applied during the protocol are not registered in any of the patients.

Discussion

There are many clinical studies supporting the claim that misoprostol as a stand-alone agent is

Table 2. Influence of previous abortions and births on the successfulness of the procedure

		successful procedure (n=232)	unsuccessful procedure (n=18	p
Nulliparous	who had an abortion	25 (96.2 %)	1 (3.8 %)	0.347
	who had no abortion	91 (95.8 %)	4 (4.2 %)	
Multiparous	who had an abortion	45 (90.0 %)	5 (90.0 %)	
	who had no abortion	71 (89.9 %)	8 (10.1 %)	

Table 3. Statisticaly significant difference in endometrial thickness and starting time of bleeding in the study groups

	successful procedure (n=232)	unsuccessful procedure (n=18)	p
endometrial thickness (mm) ± SD	12.56 ± 1.1	21.94 ± 7.2	0.002
start time of bleeding (h) ± SD	3.90 ± 0.05	5. 07 ± 0.39	0.000

an effective mean of medical abortion. A standard protocol for the use of misoprostol-alone has not yet been established. In this study the application of misoprostol was carried out intracervically. Until now there was no literature data on this type of drug administration.

This procedure was successful in 232 (92.8 %) patients, which is consistent with the results which have been reported by the other authors (8-13, 16-21).

Intact pregnancy was observed in 6 (2.4 %) patients, which is somewhat higher percentage in comparison to studies of other authors, in which about 1 % of such cases were recorded (18, 19).

Results of this study showed that in younger women (<28 years), the procedure was successful, i.e. until that age the mother affects the performance of medical abortion (p = 0.002), which is in contradiction with the results of the other authors (22).

It was not demonstrated that the gestational age (determined by ultrasound) affected the performance of procedures (p = 0,815), which is consistent with results of other authors (19, 23).

As we showed in the results, this study has not shown that the position of the uterus (p = 0,981) and length of cervix (p = 0,649) affect the performance of procedure. There is no literature data about the impact of the uterus position and cervix length in the performance of procedure.

Several large studies showed that multiparous women with previous abortions by D&C have a higher risk of failure of the procedures in relation to nulliparous (11, 12, 24). Our study has not confirmed a statistically significant difference in procedure successfulness between nulliparous and multiparous, however significance of p = 0.056 is on the verge of significance, so based on the results of this study we cannot safely argue that parity has no influence on the performance of procedure. Considering the impact of previous abortion on the procedure successfulness, it was determined that there was no statistical significance in the success of applied protocol in women which previously had abortions compared to those who have not had an abortion (p = 0,347).

In previous years several modalities for monitoring patients after medical abortion were proposed. Some authors believe that the clinical findings are more precise compared to ultrasound measurements of endometrial thickness in order to diagnose the incomplete abortion, from 14-30 days after treatment (25).

Markovic et al. in the study from 2006th found that there is no correlation between the patients' reports of symptoms and the sonographic findings. They found that an intrauterine echogenic mass, with or without Doppler-confirmed flow signals may frequently be detected two weeks after treatment. However, most women with such finding subsequently resumed normal periods and they concluded that this finding could indicate remnants of trophoblastic tissue which spontaneously regresses without the need for dilatation and curettage (26).

According to that, Fiala et al. believe that the most reliable criteria for the diagnosis of complete abortion are levels of serum ß-hCG-a (27).

Machtinger et al. with their research showed that TVUS has a sensitivity of 100 % and specificity of 98.7 % in diagnosing residual tissue after medical abortions and Wong and his colleagues reported similar data (28, 29).

It is evident that, after expulsion of gestational sac, endometrial thickness decreases with time, but consensus has not been established about the value of endometrial thickness which can be considered as the "turning point" cut-off in the diagnosis of complete abortion.

The study conducted by Louis et al. presented data that in the absence of vaginal bleeding, endometrial thickness of less than 15 mm is the ultrasound finding which confirms the complete abortion (30). Some authors suggest that the endometrial thickness of less than 16 mm is a reliable diagnosis of abortion that does not require surgical intervention (31-33).

The study of Sahar et al. came to the conclusion that the endometrial thickness greater than 12 mm is the predictive factor of incomplete abortion with sensitivity of 88.5 % and specificity of 73.7 %. Blumenfeld et al. showed that with the endometrial thickness less than 11 mm there was no need for surgical intervention, if the value is greater than 14 mm the risk is increased by 50 % and with the thickness of the endometrium of 11-14 mm there is no difference in risk (34, 35).

Some authors, however, dispute the existence of correlation of endometrial thickness and the need for surgical intervention because of incomplete aborti-

ons in women treated with misoprostol (36-38).

As shown in the results, there is a statistically significant difference in endometrial thickness, 14 days from the first application of misoprostol, among women who had complete compared to those who had an incomplete abortion ($p = 0.002$), suggesting the existence of links between endometrial thickness and performance procedures.

Based on the results of this study, we can conclude that the endometrial thickness ≥ 15.06 mm is an accurate predictive factor in assessing of medical abortion caused by misoprostol with sensitivity of 84.6 % and specificity of 99.6 % ($p = 0.000$).

Beginning of bleeding after drug administration proved to be a good predictive factor because the highest percentage of success was recorded in women in whom the bleeding began 4 hours after application of the first dose ($p = 0.000$). According to other authors bleeding after misoprostol application has started 2.2 to $4.1 \pm 0.72 \pm 0.79$ h but they have not considered it as a possible prognostic factor in the success of the procedure (23,38).

Misoprostol side effects: nausea (24.4 %), vomiting (11.6%) and diarrhea (10.8 %) were registered in a somewhat lower percentage compared to the data that other authors reported (23, 39).

During the protocol implementation, antibiotics were applied at 6.8 % of patients while serious infections and sepsis were not registered in any case; these complications were reported by other authors in higher percentage (40).

Bleeding that required instrumental revision of uterine cavity was present in 2 % of cases and intense bleeding that required transfusion hasn't been recorded in anyone of the patients, which is different from literature data (41) .

Conclusion

Based on data obtained in this study, we can conclude that medical abortion caused by intracervical application of misoprostol is safe and effective alternative to surgical methods. Endometrial thickness and the beginning of bleeding after the first application of the drug can be used as prognostic factors of success of the procedure

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Seasonal Variability of Parathyroid Hormone and Its Related Biochemical Parameters in Hemodialysis Patients

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Abstract

Objective: We aimed to investigate the seasonal variability of the parathyroid hormone levels and its related biochemical parameters in hem dialysis patients.

Methods: We retrospectively analyzed the data of 81 hemodialysis patients (36 female, 45 male; the mean age: 54, 8±19, 3) between 2008 and 2009 years. We compared the seasonal variability of the mean levels of parathyroid hormone (PTH), calcium (Ca), phosphor (P), and alkaline phosphatase (ALP).

Results: The lowest level of PTH (163 pg/ml (26-1894 pg/ml) was detected during the summer, followed by the fall, and then by the winter (273 pg/ml (23.7-2500 pg/ml); 275 pg/ml (17.9-2122 pg/ml) respectively). The highest level of PTH (292 pg/ml (9, 8-2289 pg/ml) was detected during the spring. Similar to PTH, the peak level of ALP was detected during the summer. The lowest level of Ca was detected during the spring. The level of P did not demonstrate any seasonal variability.

Conclusions: We observed that the level of PTH was showed seasonal variability. The seasonal variability of PTH and its related biochemical parameters should be considered in medical treatment of secondary hyperparathyroidism in hemodialysis patients.

Key word: Hemodialysis, parathyroid hormone, seasonal variability, secondary hyperparathyroidism.

Introduction

In the general population, body composition, organ function, laboratory test results, and disease processes have all been demonstrated to be subject to seasonal variations.[1-6] Similarly it is reported that, blood pressure and biochemical parameters demonstrate seasonal variability in hemodialysis patients.[7-10] It is known that, the synthesis of calcitriol, which is an inhibitor factor in the occurrence of secondary hyperparathyroidism in chronic renal failure, change with diet regimen and exposure to sunlight.[11] Thus, in this study, we aimed to investigate the seasonal variability of the level of PTH and its related biochemical parameters in hemodialysis patients.

Materials and methods

The study protocol was approved at the local ethics committee. This study planned as cross-sectional. We retrospectively analyzed the 2008 and 2009 data of 81 hemodialysis patients (36 female, 45 male; the mean age: 54,8±19,3) who have been received hemodialysis at least 1 year, three times a week. So patient's consent was not requirement. We compared the seasonal variability of the mean levels of PTH, Ca, P, and ALP. The patients with known malignancy and patients treated for osteoporosis were excluded from the study. The patients with secondary hyperparathyroidism were receiving oral vitamin D and phosphor binders according to suggestion of The National Kidney Foundation Disease Outcomes Quality Initiative (NKF-KDOQI) guideline. The seasonal means of PTH, Ca, P and ALP were calculated with SPSS 15.0 software. The levels of Ca and P were measured by the endpoint method, the level of ALP by the clorometric assay method via Modular ISE900 device; the level of PTH was measured by the chemiluminescence method via Architect I 4000 SR device.

Statistical analysis

The seasonal variability of calcium and P were analyzed with repeated variance analysis; the seasonal variability of PTH and ALP was calculated by Friedman test. In addition, the Tukey multiple comparison test was used for assessments of seasonal differences. Ca and P values were recorded as mean ± standard deviation; PTH and ALP were recorded as median (min-max). A value of $p<0.05$ indicates a significant difference.

Results

The seasonal alteration of the levels of PTH, ALP, Ca and P are shown in table 1 and 2. The lowest level of PTH was detected during the summer. The level of PTH was higher during the fall and the winter. The highest level of PTH was detected during the spring. The lowest level of Ca was detected during spring. Then, the level of Ca was next highest during winter, followed by the summer and fall, respectively. Similar to PTH, the lowest level of ALP was detected during summer. The level of P did not demonstrate any seasonal variability (Table 1).

Discussion

The most common cause of secondary hyperparathyroidism is chronic renal failure (CRF). The development of secondary hyperparathyroidism in CRF is very complex. However, it has been known that respectively the most important activation factor and inhibitory factor are calcium and calcitriol (1,25(OH)D) in the pathogenesis of the secondary hyperparathyroidism.[11-12] The synthesis of ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), which are precursors of calcitriol, depends on sunlight exposure and dietary intake.[11] Thus, we aimed to investigate whether there is a seasonal alteration of the level of PTH and its related biochemical parameters in hemodialysis patients.

The seasonal variability of the PTH levels has been reported in several studies.[13-16] However, there are only two studies on the seasonal variability of PTH in hemodialysis patients. Strózecki et al.[17] reported the level of PTH was lower in winter compared to spring, and higher in fall compared to summer; the level of Ca was low in winter, spring, and fall; the lowest level of P was in winter. They suggested that the seasonal variability of PTH was related to sunlight.

In another study involving 26 hemodialysis patients was examined the seasonal variability of the level of PTH and P. In this study, when the patients PTH level was less than 120 pmol/L(n:18), there was no significant seasonal variability of the level of PTH; whereas there was a peak of the level of PTH in summer when the patient's PTH level was higher than 120pmol/L (n:8). They suggested that the lower level of PTH in summer was related to poor intake of calcium, vitamins and other minerals owing to a lack of appetite.[18] However, the number of subjects is not enough for a definite conclusion.

Vitamin D can suppress the secretion of PTH from parathyroid gland. The level of 25-hydroxy vitamin D (25(OH)D), which is a good indicator of vitamin D, reflect the cumulative effects of dietary intake and exposure to sunlight.[19] Brot et al.[20] reported that the level of PTH was found lower during summer compared to winter and spring on perimenopausal women. They suggested that the seasonal variability of PTH might

Table 1. The seasonal alteration of the levels of PTH and ALP

	Winter	Spring	Summer	Fall	p
PTH	275,50 [b] (17,86-2122,00)	292,00 [a] (9,8-2289,0)	163,00 [c] (26,0-1894,0)	273,50 [b] (23,7-2500,0)	0,001
ALP	108,00 [a] (23,9-1325,0)	104,50 [ab] (40,0-1116,0)	99,00 [b] (31,0-1393,0)	109,00 [a] (6,6-1874,0)	0,001

Table 2. The seasonal alteration of the levels of Ca and P

	Winter	Spring	Summer	Fall	p
Ca	8,73 [c] ± 0.74	8,56 [d] ± 0,68	8,95 [b] ± 0,69	9,11 [a]± 0,57	0,001
P	5,07± 1,24	5,31± 1,28	5,41± 1,23	5,17±1,29	0,341

be related to low vitamin D level in winter.[20] In another study, the authors found a negative correlation between PTH and 25(OH)D.[21,22] In addition, several supportive studies showed the seasonal variability of 25(OH)D.[15,23] Christensen et al.[24] reported a negative correlation between the level of 25(OH)D and PTH, and found that the level of PTH was high in the winter and at the beginning of the spring, and was low at the end of the summer. They proposed that the PTH variability was related to the level of 25(OH)D and, when vitamin D deficiency is suspected, the measurement of PTH level may give additional diagnostic information.[23] The variability of PTH in their study was compatible with our results.

The geographic location may affect the seasonal variability of PTH and its related parameters. The Van city in which the study was conducted, with geographic coordinates of 40°58'N latitude and 28°50'E longitude, elevation 1661 m , is among the sunny cities of the Turkey, it is sunny in most of the days of the year. Therefore, the low level of PTH during summer may be caused by an increased level of vitamin D due to excessive sunlight exposure during summer time. The peak level of PTH in spring may be related to late-onset of cumulative effect due to decreased sunlight exposure during winter and fall. However, unmeasured vitamin D level is a deficient part of our study; it would be better, if we analyzed the correlation between the level of vitamin D and PTH.

In our study, the lowest level of calcium was during the spring. Then, the level of calcium was next higher during winter, followed by the summer and fall, respectively. Because of the difference in the mean level of calcium between fall and summer (0.16 mg/dl) is not clinically significant, we say that alterations in the PTH and calsium levels were parallel to each other.

Conclusion

This study has demonstrated that the lowest level of PTH and ALP was during the summer; the highest level of calcium was in spring. The level of P did not demonstrate any seasonal variability. We suggest that the seasonal variability of PTH and the related parameters may correlate with seasonal sunlight exposure and vitamin D synthesis. The seasonal variability of PTH and its related biochemical parameters should be considered in medical treatment of secondary hyperparathyroidism in hemodialysis patients.

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Influence of gender, age and number of prostheses to the adaptation to a complete denture

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Abstract

Objectives: In reconstructive prosthetic dentistry adaptation refers to a process of adjusting to a complete denture and the reactions happening during the process. The prosthodontist has the task to make the period of adaptation as tolerable and short as possible for the patient. The aim of this paper was to research into the possible influence of gender, age and the number of complete dentures on the process of adaptation within edentulous patients, observed and measured against the number of follow-up appointments.

Methods: The research included the total of 139 edentulous patients, of both genders, from 29 to 87 years of age. Patients who came to the Dentistry Clinic of Vojvodina had complete dentures done as a part of prosthetic rehabilitation. Gathered information has been processed by using the χ^2 test with the level of statistical significance $p<0.01$.

Results: After the prosthetic rehabilitation almost half of the patients (49.6%) have never appeared for the follow-up appointment. Closer analysis of the relation between the number of appointments and the gender of patients did not determine any significant difference in statistics regarding the process of adaptation of complete denture. The analysis of the data indicates that there is no significant statistical connection between the age of patients and the number of appointments

Conclusions: The gender and age of patients, as well as the information if the patient has one or two complete dentures, do not have any influence on the adaptation of edentulous patients to complete dentures. Having in mind the constraints of this study, the number of follow-up appointments may be used as one of the indicators of the process of adaptation to complete dentures.

Key words: Adaptation, complete denture, physiology adaptation, follow-up appointments

Introduction

It is certain that damages to any component of a prosthodontic system lead to a number of consequences which affect the functioning of the system, with the possibility of deterioration of the quality of life of edentulous patients. Loss of all the teeth has a negative influence on mastication function, speech, visual effect and overall oral health.[1]

The oldest and the only conservative way to tackle the problem of edentulous patients is by making a complete denture as a form of prosthetics to make up for the missing teeth and the part of alveolar ridge which atrophied. The complete denture, made with the oral tissue functioning, becomes a component of orofacial system, and for that reason represents not only a formal but also a functional reconstruction of certain parts of masticatory organs.

In physiology adaptation refers to the ability of the senses not to react to long-lasting and intensive stimuli, but to adjust to permanent but less intense stimuli which in time become unnoticeable. In reconstructive prosthetic dentistry adaptation refers to a process of adjusting to a complete denture and the reactions happening during the process. The process of adaptation can take place only if the stimuli are of a certain intensity. If the stimuli are too intense, the process of adaptation will not occur. Neuromuscular and sensor systems of oral cavity are not only highly sensitive but also have great capability to adapt. It has been proven that touch receptors adapt the fastest and that the adaptation to the sense of pain is not possible. In order for a process of adaptation to be success-

ful it is necessary to remove the cause of painful sensation.[2] The adaptation of edentulous patients to complete denture is very complex matter in a sense that it concerns the connection with certain factors of general and local character which are frequently combined with pain, mastication difficulties and problems of pronunciation of particular sounds.[3,4,5,6,7,8,9,10,11] The role of the prosthodontist in the process of adaptation and acceptance of complete denture is of high importance. The prosthodontist has the task to make the period of adaptation as tolerable and short as possible for the patient i.e. to fix everything that prevents normal function of a denture. During the follow-up appointments all necessary procedures are done so as to remove the feeling of discomfort and to fulfill the patient's expectations regarding esthetics, retention and the stability of a denture.[12] The aim of this paper was to research into the possible influence of gender, age and the number of complete dentures on the process of adaptation within edentulous patients, observed and measured against the number of follow-up appointments. The null hypothesis was that there are not significant differences about influence of gender, age and the number of complete dentures on the process of adaptation.

Methods

The research included the total of 139 edentulous patients, of both genders, from 29 to 87 years of age. Patients who came to the Dentistry Clinic of Vojvodina had complete dentures done as a part of prosthetic rehabilitation. All the principles of modern prosthetic dentistry have been obeyed. Patients who had only upper or lower complete denture as well as patients with both complete dentures have been part of the research. The research included the analysis of the influence of gender, age and the number of dentures on the process of adaptation observed and measured against the number of follow-up appointments. In order to obtain all before mentioned information patients' index cards have been used. Gathered information has been processed by using the χ^2 test and by applying the non-parametrical correlation (Spearman) with the level of statistical significance $p<0.01$.

Results

The analysis of the gathered information has shown that almost three quarters (73.2 %) of the total number of patients in the research are of female gender, which is significantly larger number in comparison with the number of male patients (χ^2=9.849, p=0.002). More than half of the respondents are patients older than 60, next are patients of 46-60 years of age (63) and the smallest number of patients are younger than 45 years (6) (χ^2=53.194, p=0.000). The number of patients represented in relation to the overall number of complete dentures is: patients with two complete dentures 59 (42.4%) and patients with one complete denture 80 (57.6%).

After the prosthetic rehabilitation almost half of the patients (49.6%) have never appeared for the follow-up appointment and that number is significantly higher than the number of patients who appeared for one or two appointments (38.8%), or three or more follow-up appointments (11.5%) (χ^2=32.216, p=0.000).

The analysis of the number of appointments in relation to the gender of the patients is shown in Table 1. The results show that 26 (51.0%) male patients and 43 (48.9%) female patients after receiving the dentures have never appeared for the follow-up appointment. Within the group of patients with one or two appointments the percentage of patients of both genders is almost the same. Closer analysis of the association between the number of appointments and the gender of patients did not determine any significant difference in statistics regarding the process of adaptation of complete denture among male and female patients (p=0.484).

Number of follow-up appointments measured against the age of patients is shown in the table 2. The percentage of patients with no appointments is very similar in different age groups, from 33.3% in the youngest group (up to age of 45), 44.4% in the middle group (46-60 years of age), to 55.7% in the oldest group (over 60 years of age). The analysis of the data indicates that there is no significant difference in number of appointments between these age groups (p=0.399). Comparison in number of appointments has been done between patients up to age of 60 years and patients older than 60 years. There is no statistical significant difference between these two age groups (p=0.309). The

Table 1. Number of follow-up appointments in relation to gender

Number of follow-up appointments	Man n (%)	Women n (%)	Total number n (%)
0	26 (51.0)	43 (48.9)	69 (49.6)
1-2	19 (37.3)	35 (39.8)	54 (38.8)
3 or more	6 (11.8)	10 (11.4)	16 (11.5)
Total	51 (100.0)	88 (100.0)	139 (100.0)

Table 2. Number of follow-up appointments in relation to age

Number of follow-up appointments	Age categories			Total number n (%)
	Up to age of 45 years n (%)	46-60 years of age n (%)	Older than 60 years n (%)	
0	2 (33.3)	28 (44.4)	39 (55.7)	69 (49.6)
1-2	4 (66.7)	27 (42.9)	23 (32.9)	54 (38.8)
3 or more	0 (0.0)	8 (12.7)	8 (11.4)	16 (11.5)
Total	6 (100.0)	63 (100.0)	70 (100.0)	139 (100.0)

Table 3. Number of follow-up appointments in relation to the number of complete dentures

Number of follow-up appointments	Number of dentures		Total number n (%)
	1 n (%)	2 n (%)	
0	40 (50.0)	29 (49.2)	69 (49.6)
1-2	30 (37.5)	24 (40.7)	54 (38.8)
3 or more	10 (12.5)	6 (10.2)	16 (11.5)
Total	80 (100.0)	59 (100.0)	139 (100.0)

association between the number of appointments and the number of complete dentures (patients have one or two dentures) is shown in the table 3. Half of the total number of 80 patients who have had one complete denture done have never appeared for the follow-up appointment after the prosthodontic therapy. Of the rest of the patients from this group 37.5% had one or two follow-up appointments, and 12.5% had three or more. Among 59 patients with two complete dentures 49.2% of them have never appeared for the appointment after the denture has been made, 40.7% have appeared for one or two, whereas 10.2% have appeared for three or more. The analysis of the number of appointments did not determine any statistically significant difference in ratio to the number of complete dentures (p=0.881).

Discussion

Clinical and laboratory stages in the process of making a denture complement each other, and they, alongside with follow-up appointments afterwards, have the same goal and that is to achieve biological functions of a denture: masticatory, visual and speech function.[2]

Some authors point out in their works that the character of a patient, their attitude towards dentures and their motivation for wearing one may influence the process of adaptation in a way that the process is much shorter with the motivated patients.[8,9] For the patients with negative reactions like rage, anger, dissatisfaction and loneliness it is more difficult to accept dentures or they do not accept them at all.[10] What is important for the adaptation to prosthesis and the success of prosthodontic therapy is subjective assessment of the patient, motivation and functional efficiency.[11] The information from the literature concerning the length of adaptation period varies between two and twelve weeks.[13,14,15] Patients visits continue for as long as patients have the feeling of discomfort and until the complete denture becomes an integral part of the prosthodontic system.[3]

The results from Panek and Jonkman studies show that the gender influences the process of

adaptation of patients with complete dentures. Namely, according to these works male patients adapt easier in comparison to female patients, who are more sensitive to different kinds of stimuli.[1,3,9] However, the results of our research do not correspond with the before mentioned because our results show that there is no statistically significant difference regarding the process of adaptation with patients of different genders. The reasons for these results might be the consequence of the fact that uneven number of patients of both genders participated in this research, the number of female patient being higher.

The age is not considered to be an important factor in accepting or rejecting the denture, nor is that the indicator of the quality of adaptation of patients to complete dentures. Regardless of the age category of patients i.e. whether the patient is older or younger than 60, there are no differences concerning the characteristics of adaptation period.[3,9]

Although it was expected that the patients with one complete denture would overcome the period of adaptation easier and that they would appear for a lesser number of follow-up appointments compared with the patients who had two complete dentures done as a part of prosthodontic therapy, the results did not show that.

Conclusions

The gender and age of patients, as well as the information if the patient has one or two complete dentures, do not have any influence on the adaptation of edentulous patients to complete dentures. There is a necessity for more similar research since there is only a small number of research on this subject. Having in mind the constraints of this study, the number of follow-up appointments may be used as one of the indicators of the process of adaptation to complete dentures.

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Investigation of the Factors Influencing Utilization of Health Services by Women in Turkey

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Abstract

We aimed to determine factors influencing utilization of health services by women in Turkey. Subject group of this descriptive study was 11.058 registered women of the Esentepe Regional Primary Healthcare Center. The sampling method recommended by the World Health Organization for field surveys was used. Survey questionnaires evaluating individuals' socio-demographic characteristics, perceived health status, and utilization of health services were conducted.

Of the women who participated in the survey, 51.9% utilized preventive health services, while 61% utilized therapeutic health services. The use of preventive health services increased by high social status of the head of household at 2.61-fold ($p<0.01$), higher income at 1.91-fold ($p<0.05$), social security at 2-fold ($p<0.01$); besides, the use of therapeutic health services increased by high social status of the head of household at 0.51-fold ($p>0.05$) and social security at 1.75-fold ($p>0.05$). Perceived health status was determined to be ineffective on the use of health services ($p>0.05$).

With the achieved data, we concluded that nurses should give priority to the individuals having low social status; through inter-sectoral collaborations, should lead women to apply to employment institutions; by using opportunities at house environment, should lead women to production process; and also, women with low income should be given the priority in providing preventive healtcare services. Moreover, by establishing cross-sectoral cooperation and consultation, individuals without health insurance should be guided to get a social security card (green card).

Key words: Utilization of health services, socio-economic status, perceived health, nursing

Introduction

Inequality means unnecessary, avoidable and unfair differences, with an ethical dimension, as well. Inequality is not a contemporary issue; inequalities in areas such as education, law, as well as healthcare have been recorded in history[1, 2].

The World Health Organization (WHO) defines inequality in healthcare not only as unnecessary and avoidable, but also as unfair and unjust differences[3]. The phenomenon of inequality in healthcare, has been taking place in the international public health agenda since the mids-1970. In this context, inequalities in health has been one of the focused topics in the 1978 Alma Ata Primary Health Care philosophy and in the 1984 European Region Health for All Targets[1]. In the WHO document, named Health for All in the 21st century, " Health-related differences between socio-economic groups in the countries should be reduced by ¼ until 2020 through improving the level of health in favor of the disadvantageous groups" clause has been written[4].

However, in the light of the known data, it is obvious that inequalities between countries and between different regions within countries, continue to increase nowadays.

As an important indicator of health, infant mortality rate (IMR) varies between 4 and 41 per 1000 live births between developed and developing countries of the world[5]. The infant mortality rate (IMR) of our country is reported as 17 per 1000 live births. Besides inequalities between countries, inequalities within countries are also increasing. The Infant Mortality Rate (IMR) is reported as 39 per 1000 live births in the eastern Turkey, while as 16 per 1000 live births in the western regions of Turkey[6].

Maternal mortality rates also vary between countries. In Africa, as an example to developing

countries, maternal mortality rate is noted on average as 900, while in European countries as 27, and in Asian countries as 450 per 100,000 live births. In Italy, a Western country, the maternal mortality rate is declared as 3 per 100,000 live births, while in Pakistan, an Eastern country, as 320[5]. In Turkey, maternal mortality rate is reported as 28.8 per 100,000 live births[7].

Considerably serious disparities are observed in the utilization of health services worldwide, in Turkey as well[8]. "The inverse care law" describes the bad situation of those who most need medical care due to the poor socio-economic situation but are least likely to receive it[1].

Public health nurses need to know the factors affecting healthcare service utilization of individuals in order to ensure an equal health service for everyone. Factors influencing ustilization of health services can be analysed in three groups as social determinants, health care systems, and individual determinants [9]. Social determinants, health care systems and individual determinants such as age, sex, marital status cannot be changed, however, factors such as individuals' occupation, education level, income status, social security and perceived level of health, can be manipulated so that inequalities in health service utilization may be prevented.

In the studies conducted; it is evaluated that low social status[10, 11, 12], low educational level[13, 14, 15], low income level[15, 16, 17], consequences of being uninsured[18, 19, 20] and perceived good health[16, 21] decrease utilization of health services. In contrast to these, in some opposite studies, it is found out that low educational level increases utilization of health services[22, 23, 24], and perceived poor health[11] reduces utilization of health services.

Due to their duties and responsibilities, public health nurses associate directly with and have an active role in the society, consequently they are important in terms of reducing the growing health inequalities between different socio-economic groups[25]. When Turkish literature is reviewed, even though there are studies dealing with inequalities in health systems and in utilization of health services, very few of them are found to be carried out by nurses. With the data achieved in this study, it is aimed to lead public health nurses to identify the causes of individuals' inadequate and inequal utilization of health services and to give priority to these individuals suffering from these inequalities. Additionally, our data would be important for the nurses to enlighten their nursing care planning process. The objective of this study was to determine the factors influencing utilization of health services by women registered in Esentepe Regional Primary Healthcare Center.

Research Questions

1. Does utilization of health services differ in terms of social status?
2. Does utilization of health services differ in terms of educational level?
3. Does utilization of health services differ in terms of income level?
4. Does utilization of health services differ in terms of social security?
5. Does utilization of health services differ in terms of perceived health status?

Methods

This descriptive study was conducted to examine factors influencing utilization of health services in the period between December 2006 and May 2007, in Esentepe Regional Primary Healthcare Center, Provincial Health Directorate, İzmir. Esentepe Regional Primary Healthcare Center was responsible of four quarters and a total of 81 streets, which totally consisted of 21.226 people, of which 11.058 were women. The population of this study was women who live in Esentepe Regional Primary Healthcare Center. Through the research sampling method used, that was recommended by the World Health Organization for field surveys, 210 women were reached and enrolled[26, 27]. In order to do this all street numbers were identified in the study area. Thirty streets were randomly selected amongst 81 streets in the area. The flat numbers in each street were listed. Choosing a random number out of this list, first household to be surveyed was identified. Seven women consistent with the research criteria were surveyed in each street. For the streets where seven women couldn't be found some other streets which had been chosen before were used.

Inclusion Criteria: Women who don't have any chronic diseases, and who are married and neither pregnant nor puerperium were included in the study.

Data Collection Tools: Questionnaire method was used to collect data. Two different questionnaire forms, one covering individual's socio-demographic characteristics and perceived health status, and the other covering utilization of health services, have been used.

Socio-Demographic Characteristics Questionnaire: It was composed of 5 items that were questioning individual's socio-demographic characteristics and perceived health status.

The Utilization of Health Services Questionnaire: To identify the utilization of health services using the related literature the questionnaire was formed. Opinions of three Public Health Nursing professors and one Public Health profession's were taken for the questionnaire. In order to determine the utilization of health services, a questionnaire including seven questions based on expert opinion, was formed. Preliminary application of the questionnaire was performed with 10 women from Güzelbahçe Regional Primary Healthcare Center, who had the same characteristics of women in the original study.

Application of Data Collection Tools: Data collection tools have been applied to women in each household. In order to fill in the questionnaires, an average of 10 minutes was spent at each seperate house.

Research Variables

Independent Variables

Social Status: Considering the household head's job, social status was evaluated in 2 groups as high social status and low social status. In the high social status, professional groups such as employer, artisan and craftsman, qualified self-employed or freelancer and white-collar employee were included. On the other hand, in the low social status, blue-collar workers, unskilled laborer, marginals and unemployees were included[28].

Education: Education level was evaluated in three groups as 'less than primary school education', 'primary school education' and 'upper primary school education'.

Income: Income status was classified as 'income less than expenditure', 'income equals to expenditure', and 'income more than expenditure".

Social Security: Social security status was defined as 'insured' and 'uninsured '.

Perceived Health Status: We asked the question 'How do you assess your health in general?. In assessing the perceived health status, the replies to this question were grouped in five: 1. Very good, 2. Good, 3. Average, 4. Bad, 5. Very bad. Answers, were categorized in two groups as the first two 'good' responses and the last three 'bad' responses[29].

Dependent Variable: It was determined as the utilization of health services.

Utilization of Health Services: The utilization of health services was assessed through examining the use of 'preventive health services' and 'therapeutic health services'. For preventive health care utilization the question "For the last six months have you consulted a health care center for any reasons other than a health problem?" was asked to women in order to identify how women use services such as immunization, early detection, health education and family planning. For therapeutic health care utilization the question "For the last six months have you consulted a health care center for any health problems?" was asked.

Data Analysis: The study data were evaluated by SPSS 11.00 computer program. Chi-square and logistic regression analysis methods were used to analyze these data[30, 31].

Ethical Issues: The study has been started following the approval of the Board of Ethics, Dokuz Eylul University School of Nursing, Izmir, and carried out by getting written approval from the Provincial Health Directorate, Izmir. The study data of the individuals who agreed to participate in the study were collected after getting their verbal consent.

Results

Socio-Demographic Characteristics of Women

Socio-demographic characteristics of women in the study group displayed that 46.2% were primary school graduates and 59% of their households occupied with lower social status jobs. 57.1% of women had income less than expenditures. 69.5% of women had social security. 38.1% of the participants specified good health perception in general, while 61.9% of women implied worse health perception (Table 1).

Table 1. Distribution of women according to socio-demographic characteristics and perceived health status

Variable	Number	%
Household Head's Job		
Low social status	124	59
High social status	86	41
Educational		
Less than primary school	45	21.4
Primary scholl	97	46.2
Upper primary school	68	32.4
Income		
Income less than expenditures	120	57.1
Income equals to expenditures	90	42.9
Income more than expenditures	0	0
Social Security		
Insured	146	69.5
Uninsured	64	30.5
Perceived Health Status		
Good	80	38.1
Bad	130	61.9
Total	210	100

Utilization of Preventive Healthcare Services by Women

51.9% of women are found to use preventive health services. The reason for 56.0% of these women to use primary healthcare centers was defined as being close to their houses, while 28.7% of the women who did not use preventive health services defined the reason simply as feeling good about herself.

With regard to utilization of preventive healthcare services, we detected statistically significant differences between job of the head of household, income status and social security, however, we detected no statistically significant differences between educational level, and perceived health status (Table 2).

Of the women who participated in the survey, the odds ratios between utilization of healthcare services without any complaints and their socio-demographic characteristics are shown in Table 3. The use of healthcare services of the women was found to be 2.61-fold higher when head of household's job was of high social status compa-

Table 2. Utilization of preventive healthcare services by participants with regard to head of household's job, education, income, social security, and perceived health status

	Utilization of Preventive Healthcare Services				Total		
	Yes		No				
	n	%	n	%	n	%	
Head of household's job							
Low status	54	43.5	70	56.5	124	100	X^2=8.47
High status	55	64.0	31	36.0	86	100	p=0.004
Total	109	51.9	101	48.1	210	100	p<0.01
Education							
Less than primary school	23	51.1	22	48.9	45	100	X^2=1.99
Primary school	55	56.7	42	43.3	97	100	p=0.4
Upper primary school	31	45.6	37	54.4	68	100	p>0.05
Total	109	51.9	101	48.1	210	100	
Income							
Income<Expenditures	56	46.6	64	53.4	120	100	X^2=4.90
Income=Expenditures	53	58.8	37	41.2	90	100	p=0.046
Total	109	51.9	101	48.1	210	100	p<0.05
Social security							
Uninsured	23	35.9	41	64.1	64	100	X^2=8.50
Insured	86	58.9	60	41.1	146	100	p=0.004
Total	109	51.9	101	48.1	210	100	p<0.01
Perceived Health Status							
Good	43	53.8	37	46.2	80	100	X^2=0.17
Bad	66	50.8	64	49.2	130	100	p=0.67
Total	109	51.9	101	48.1	210	100	p>0.05

red to those with low social status, and the difference was statistically significant (p<0.01). Within the context of the relationship between utilization of healthcare services and income level, the use of healthcare services was found to increase 1.91-fold in parallel to higher income (p<0.05), and 2-fold with social security (p<0.05).

Utilization of Therapeutic Health Services by Women

56.2% of the women reported to have complaints in the last 6 months. 61% of these women have utilized healthcare services. 38.9% of these women reported their reason to use primary healthcare centers as being close to their houses. On

Table 3. According to the socio-demographic characteristics of the participants, odds ratios for utilization of preventive healthcare systems

Variable	Utilization Of Preventive Healthcare Systems		p
	OR	95% CI	
Household head's job			
Low social status	1.00[a]		p<0.01
High social status	2.61	(1.29-5.31)	
Income			
Income<Expenditures	1.00[a]		p<0.05
Income=Expenditures	1.91	(1.02-4.10)	
Social security			
Uninsured	1.00[a]		p<0.05
Insured	2.00	(1.39-4.69)	

[a] *Reference category*
CI: Confidence interval

Table 4. Utilization of therapeutic healthcare services by participants with regard to head of household's job, education, income, social security, and perceived health status

	Utilization of Therapeutic Healthcare Services				Total		
	Yes		No				
	n	%	n	%	n	%	
Head of household's job							
Low status	34	47.9	37	52.1	71	100	X^2=11.57
High status	38	80.9	9	19.1	47	100	p=0.001
Total	72	61.0	46	39.0	118	100	p=0.001
Education							
Less than primary s.	19	61.3	12	38.7	31	100	X^2=5.40
Primary s.	42	68.9	19	31.1	61	100	p=0.67
Upper primary s.	11	42.3	15	57.7	26	100	p>0.05
Total	72	61.0	46	39.0	118	100	
Income							
Income<Expenditures	32	55.0	39	45.0	71	100	X^2=2.17
Income=Expenditures	33	52.2	14	47.8	47	100	P=0.14
Total	72	48.1	46	51.9	118	100	p>0.05
Social security							
Uninsured	13	31.0	29	69.0	42	100	X^2=22.8
Insured	59	77.6	17	22.4	76	100	p=0.000
Total	72	61.0	46	39.0	118	100	p<0.001
Perceived health status							
Good	20	64.5	11	35.5	31	100	X^2=0.06
Bad	52	59.8	35	40.2	87	100	p=0.80
Total	72	61.0	46	39.0	118	100	p>0.05

Table 5. According to the socio-demographic characteristics of the participants, odds ratios for utilization of therapeutic healthcare systems

Variable	Utilization Of Therapeutic Healthcare Systems		p
	OR	95% CI	
Head of household's job			
Low status	1.00[a]		
High status	0.51	(0.18-1.42)	p>0.05
Social security			
Uninsured	1.00[a]		
Insured	1.75	(0.95-3.23)	p>0.05

[a] *Reference category*
CI: Confidence interval

the other hand, the reason for the women who did not apply to primary healthcare centers despite their complaints has been reported as a consequence of being uninsured at 47.8% rates.

In terms of utilization of therapeutic health services, we detected statistically significant differences between job of the head of households and social security. However, we detected no statistically significant differences between education, income status and perceived health status (Table 4).

For the study group, the odds ratios of the socio-demographic characteristics influencing utilization of healthcare services due to any complaints are shown in Table 5. The utilization of healthcare services is 0.51-fold higer with high social status of head of household compared to those with low social status, but it was not found statistically significant (p>0.05). The utilization of healthcare services by the insured women was detected as 1.75-fold higher compared to uninsured women, and the difference was not statistically significant (p>0.05).

Discussion

Utilization of Preventive and Therapeutic Healthcare Services According to the Household Head's Job

The utilization of preventive healthcare services by the high social status women was found to be 2.61-fold higher compared to those with low social status (Table 3). Borrel et al. (1999) declared that low social status women utilize healthcare services at low rate. Nesanır et al. (2005), stated that low social status job related factors reduce the use of preventive health services. Similarly, Belek (1999) specified a significant correlation between social status and utilization of the healthcare services. Besides the studies confirming the increase in uti of healthcare services in parallel with higher social status, there are also some studies suggesting no correlation between social status and utilization of preventive healthcare services. In their studies, Borrel at al. (2001) and Berra et al. (2006) detected no difference between social classses and utilization of preventive healthcare services.

In this study, the reasons for inconsiderable use of health services by low social status women may be their priorities of basic needs such as housing, nutrition, hygiene, and security, consequently ignoring preventive healthcare services, or simply being unisured.

Compared to low status women, high status women utilize therapeutic healthcare services at 0.51-fold more (Table 5). Borrel et al. (1999) reported that low social status women utilize therapeutic healthcare services at lower rates. Nesanır et al. (2005) stated that low social status has been influential on the use of preventive health services. Belek (1999) has achieved similar results, as well. On the contrary, Borrel et al. (2001) observed no considerable differences between social classes in terms of utilization of healthcare services.

In this study, the reasons for low status women's less utilization of therapeutic healthcare services may be a conscious choice unless their daily activities are precluded by their complaints or simply due to feeling themselves good. Being uninsured has influenced the use of therapeutic healthcare systems negatively, as well.

Utilization of Preventive and Therapeutic Healthcare Services According to the Educational Status

Women's educational status was found to be ineffective on the preventive and therapeutic healthcare services (Table 2, Table 4). Among the studies dealing with the relationship between education and utilization of healthcare systems, Suominen et al. (2004) emphasized that individuals with high level of education have utilized preventive healthcare services more than those with low educational levels. Aslan et al. (2006) also highlighted women's use of the preventive healthcare services showed an increase in parallel with the educational level. Differently, Grimsmo et al. (1984) noted that educational status had no influence on utilization of healthcare services. Study data of Thi Hong Ha et al. (2002) displayed similarities, as well. It is thought that, the reason for the study group women's educational status being ineffective on the use of the preventive healthcare systems might be that the majority of them was either primary scholl graduate or even less.

Utilization of Preventive and Therapeutic Healthcare Services According to the Income

In this study, statistically significant difference was detected between income level and utilization of healthcare services (Table 2, Table 3). Women with high level income are found to use healthcare systems 1.91-fold more than those with low income (Table 3). Similarly, Thı Hong Ha et al. (2002) reported that individuals with high level income have been using preventive healthcare systems more than destitutes. Unlike our study data, Usta (1999) observed that high level income individuals utilized preventive healthcare services at lower rates. Income level is one of the indicators of socio economic status. As the level of income increases, socio economic status increases incidentally, and as a consequence, appreciation of health status increases. Accordingly, high income level individuals may use preventive healthcare services more.

In this study, we detected no influence of income on utilization of therapeutic healthcare services (Table 4). Kim et al. (2003) indicated less use of healthcare services in parallel to a dicrease in inome status. Usta (1999) observed that women with the highest income status use healthcare systems less frequent than low income status women. Şenol (2006), on the other hand, indicated that high income level individuals utilized healthcare systems at most.

Type of the disease and severity of the observed symptoms are important for the individual to perceive herself as a patient and make the decision to get medical help. In this study, the reason for income status had no influences on utilization of therapeutic healthcare systems might be due to the fact that women with either high or low income levels perceived the symptoms seriously, as it shold be, and reacted accordingly, so that utilized healthcare systems when required.

Utilization of Preventive and Therapeutic Healthcare Services According to the Social Security

Compared to uninsured ones, women having social security used preventive healthcare systems 2-fold more and therapeutic healthcare systems 1.75-fold more (Table 3, Table 5). Aslan et al. (2006) highlighted that women having social security utilized healthcare systems more frequently. Study data of Düzgün et al (2004) and Usta et al (1999) indicated similarities, in this respect. Social security is one of the most important factors influencing utilization of healthcare systems. In this study, an increase in utilization of healthcare systems in parallel to having social security was an expected consequence.

Utilization of Preventive and Therapeutic Healthcare Services According to the Perceived Health Status

Health perception of women did not influence utilization of preventive and therapeutic healthcare systems (Table 2, Table 4). Various data have been achieved in different studies. Bhandari (2001) detected that poor health status group utilized healthcare systems at higher rates. De La Hoz et al. (1996) also implied that individuals with self-perceived health status as bad, applied to healthcare systems more frequently. Usta (1999) reported that women with good health status utilized healthcare systems less than those with poor health. In this study, the perceived health status showed no influences on utilization of either preventive or therapeutic healthcare systems, maybe due to the

women's appreciation of health status, or due to women's personal characteristics, moreover due to women's perceived health status, which was poor for 61.9% of them.

Conclusion

In this study which was conducted to investigate the factors influencing utilization of healthcare services, high social status job of the household head, high income and having social security are found to increase utilization of preventive healthcare services. High social status job of the household head and having social security are also noted to increase utilization of therapeutic healthcare services.

According to our data, low social status is found to decrease utilization of healthcare services. In their responsibility group, nurses should give priority to the individuals with low social status. High level income has been an important factor increasing uti of healthcare systems, therefore, using inter-sectoral collaborations, nurses should lead the low income stustus women to apply to the employment institutions in order to be part of the production process.

Considering the importance of health insurance in the use of health services, social security systems should be improved to encompass the whole community and nurses should take an active role in structuring national healthcare systems. Nurses should educate individuals who do not have health insurance in order to achieve regular healthcare service. In addition, through intersectoral collaborations and consultations, individuals who do not have health insurance should be leaded to get a social security card (green card).

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Knowledge, habits and attitudes of health care workers about hand hygiene

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Abstract

Introduction: Nosocomial infection is a major problem in modern medicine and a source of concern to health workers and the public. Hand hygiene is considered to be the most effective measure to prevent microbial cross-transmission and healthcare-associated infections. The aim of the research was to dermine the differences in attitudes of health workers about the hand hygiene.

Material and methods: The investigation was carried out in the period October 2009 - February 2010, as a a cross-sectional study. The study included 500 healthcare workers of both sex employed at the Clinical Centre of Vojvodina in units of intensive care, surgery, internal medicine, neurology, gynecology and obstetrics, at the Institute for Children and Youth Health Care of Vojvodina in Novi Sad, Institute of Oncology of Vojvodina and Institute for Pulmonary diseases in Sremska Kamenica. A special questionnaire was desingned for the purpose of this research.

Results: The results showed that health workers who participated in the survey had a basic knowledge of hand hygiene. Insufficient level of knowledge of medical staff was shown in terms of modern disinfectants. Conditions for performing hand hygiene depended on the department of the heath institution. Compared to others, in the units of intensive care were easily accessible more modern means for hand hygiene.

Conclusion: Education of health workers on hospital infections is essential for the higher level of quality of health care. This could contribute to reduction of the incidence of hospital infections in our hospital.

Key words: Nosocomial Infection; Health Workers; Hand Hygiene;

Introduction

Nosocomial infection, i.e. hospital-acquired infection (HAI), is defined as a local of systemic disease resulting form an undesired body reaction to the presence of one or more infectious agents or their toxins, whish was *neither present* nor *incubating* at the time the patient was admitted to hospital. In the majority of HAI the typical incubation period is 48 hours, but it can extend even to one year if an implant or prosthesis is present (1).

Patients, hospital staff and environment are major reservoirs of HAI (2). The patient-to-patient transmission via the hands of medical staff implicates five important moments: before touching the patient, before performing aseptic procedures, after contact with body fluids and excretes, after contact with patient and after contact with objects around the patient. Patient's skin can be colonized by numerous organisms, which are necessarily transferred to surrounding surfaces, and hence contaminate the hospital environment. The hands of medical staff get contaminated through the contact with hospital environment and patient's skin during routine activities, sometimes in spite of wearing gloves. It has been established that microorganism can survive on hands a long time after contamination. Without adequate hand hygiene, the pathogens are transmitted from the hands of hospital staff to patients either directly or indirectly via the hospital environment. In that respect, regular and appropriate hand hygiene is the single most effective measure to prevent hospital-associated infections (3, 4).

Hospital-acquired infections are important public health problem worldwide. Their global prevalence cannot be precisely quantified due to widely heterogeneous data obtained by diverse methodologies at different time periods. In the U.S.A.,

hospital-acquired infections are responsible for 1.7 millions infections and 99,000 lethal outcomes yearly (5). The therapy of HAI is expensive, and treatment costs vary from country to country (6). An American research conducted 2001-2006 that included 1,355,347 patients from 55 hospitals indicated that each nosocomial infection had increased the expenses of hospital treatment for 12,197 USD (7).

Numerous research and medical literature strongly indicate association of HAI and severe consequences – medical, economical, ethical, legal (8). Thus, significant effort is aimed at eradication of hospital-acquired infections.

The aim of this research was to establish differences in a view of quality of hand hygiene practice among healthcare workers according to gender, age, profession, department they work in, and years of service.

Material and methods

The research was carried out as a prevalence study on attitude of healthcare workers on the importance of hand hygiene. In the period from October 2009 to October 2010 healthcare workers from three (out of six) hospitals in the territory of South Bačka region were polled. The opinion poll encompassed staff employed in the departments of the Clinical Center of Vojvodina: ICUs, Surgery, Internal Medicine, Neurology, Gynecology and Obstetrics, as well as employees of the Institute for Health Protection of Children and Youth of Vojvodina in Novi Sad, Institute of Oncology of Vojvodina and Institute for Pulmonary Diseases in Sremska Kamenica.

The participation in the poll was voluntary and anonymous.

As a research instrument an epidemiological questionnaire recommended by WHO was used, advised also by the National Expert Committee for monitoring hospital-acquired infections and the Institute of Public Health of Serbia.

The level of knowledge about HAI was compared according to participants' characteristics, i.e. gender, age, profession, years of service and department they are employed in.

With an aim of evaluating the level of knowledge about HAI, an assessment system was designed, including the following four categories: not satisfactory (51% or less correct answers), partly satisfactory (52-70% correct answers), satisfactory (70-89% correct answers), and highly satisfactory (90-100% correct answers).

The data collected during the research were entered into the specifically created database. Survey data analysis encompassed methods of descriptive and inferential statistics. Comparison of numerical characteristics of two groups was performed using Student's t-test, whereas attribute data were analyzed applying chi-square test and Fisher exact test. Statistical analysis was performed using a SPSS 14 for Windows statistical software.

Results

The opinion poll encompassed 500 (83.3%) healthcare workers – 66.4% females and 33.6% males. According to the education level, the participant population included 362 nurses, 100 technicians and 38 medical doctors. The ratio of staff that completed secondary school to medical doctors was 12:1. According to the working place, 73 participants were working in the ICUs, 427 were employed at the departments of Clinics and Institutes involved in this research.

Majority of participants demonstrated satisfactory level of relevant knowledge about HAI, whereas highly satisfactory level (over 90% correct answers) was obtained to questions addressing definition of antimicrobial soap, situations that entail indispensable application of gloves in patients who do not require spatial isolation, and factors possibly affecting the success of hand hygiene.

Satisfactory level of knowledge (83.6%) was observed in questions pertaining to when it is necessary to perform hand hygiene and 87% in analyzing the advantages of alcohol-based formulations over other products for hand disinfection.

Analysis of the obtained results revealed low level of knowledge pertaining to spectrum of antimicrobial activity of alcohol-based formulations. Fifty percent of the respondents were of the opinion that alcohol exhibits no virucidal activity; almost 40% believed that it has no fungicidal effect, and 6.2% of respondents deemed that it shows no bactericidal effect. In respect of the importance of using alcohol as a hand disinfectant, only 34% of

correct answers were recorded within the population of 500 respondents.

T-test revealed statistically significant difference ($p<0.05$) in relation of age of healthcare workers and acquaintance with facts on use of alcohol as a disinfectant. The respondents under 40 years of age gave higher percentage of correct answers as compared to their older peers.

To the question in which situation the hand hygiene will be unsuccessful, 91.6% or respondents stated that wearing jewelry, artificial fingernails and disposing gloves after contact are major factors of inadequate hand hygiene.

Analysis of answers on existence of written protocol for proper hand hygiene and necessity for such protocol in health care settings revealed that 84% respondents stated that written protocols for appropriate hygiene did not exist at their working places, and 100% considered instituting such protocols indispensable.

In respect of the knowledge on existing protocols, our research revealed differences between departments. In the ICUs, every third employee was aware of existence of the protocol, whereas at other departments only every sixth employee was informed about it (Fisher test, $p<0.01$).

Comparison of years of service and knowledge about protocols on proper hand hygiene indicated that respondents with more years of service demonstrated better knowledge on existence of the protocol compared to the other group. Not every twelfth respondent with less than 20 years of service knew about the protocol, whereas same answer was obtained from every twentieth healthcare worker with more than 20 years of service. The difference is highly statistically significant ($\chi^2=16.402$, $p<0.01$).

Analysis of answers pertaining to personal attitude of respondents towards regular and proper hand hygiene, as well as conditions and ways of maintaining personal hygiene in work place revealed that respondents are facing inadequate conditions for proper hand hygiene in the work place. Namely, sinks are not installed in patients' rooms, alcohol-based hand rub dispensers (ABHD) are lacking, and supply of paper towels is not continuous. Thus, in order to perform adequate hand hygiene before and after each patient, medical staff needs to return into their premises. In that respect, heavy workload, lack of paper towels and alcohol, and distance to the closest sink are major reasons for incompliance with proper hand hygiene reported by healthcare workers. Highly statistically significant difference ($\chi^2=11.103$, $p<0.01$) is observed in relation to the intensive care units, which provide better conditions for proper hand hygiene as compared to other departments.

Analysis of answers to the question pertaining to reminding colleagues about washing their hands revealed that every fourth respondent believes that colleagues would not remind him/her about such omission, and 37% stated that they themselves would never pass such remarks to peers.

With respect to the question *how many times a day they forget to wash their hands*, more than a half of respondents considered their hygiene regimen regular, whilst every fourth healthcare worker stated to wash his hands five times a day.

One of the questions in our Questionnaire was *which measures should contribute to more effective hand hygiene in the work place*. 56.4% respondents indicated as most important mounting of bedside alcohol-based disinfectant dispensers and increase of number of conveniently located sinks with liquid soap and towels. The importance of continuing education of medical staff in the field of nosocomial infections is emphasized by 34.4% respondents, some 6% participants consider adequate control of hand hygiene practices in healthcare institutions the most important factor in prevention of infection, whereas 3.2% did not know what would improve the hand hygiene in their work place.

Answers pertaining to conditions and way of maintaining personal hygiene in the work place indicated difficult conditions for maintaining proper hand hygiene due to lack of dispensers and ABHDs, as well as discontinuous supply of paper towels.

Discussion

By launching national campaign for hand-hygiene in healthcare settings entitled „Clean Hands – Safe Hands" Serbia became a member of the Alliance for Patient Safety of the World Health Organization.

Results of our research pertaining to general knowledge of healthcare workers about hospital-acquired infection and regular and proper hand hygiene revealed that our healthcare workers are

educated about HAI and importance of their prevention in view of hand hygiene using soap and water. Our research indicated a strong need for more information and more education on HAI prevention and other available and recommended hand hygiene products. Exploring new methods and techniques of hand hygiene is aimed at increasing safety in providing healthcare. Poor knowledge of medical staff about modern products and methods significantly reduces quality of performed medical procedures, thus increasing risk of HAI outbreak.

Unsatisfactory level of knowledge of novel hand-disinfection products could be partly explained by the fact that, for generations, hand washing with soap and water has been considered well-established traditional way of maintaining hand hygiene. On the other hand, emphasizing the advantages of alcohol-based products as a golden standard for maintaining hand hygiene in healthcare settings dates back only for several decades (9,10). Alcohol-based formulations are still available only at some departments (ICUs) or doctors' premises. Thus, poor information and education in majority of our healthcare workers about novel approach to hand hygiene may be attributed to inaccessibility to such products and to routine hand disinfection habits. Undoubtedly, economic issues are considered an important factor affecting availability of such products to not only employees in medical settings, but also to hospitalized patients, their visitors, students and all persons entering the medical settings for different purposes (11).

Test results for comparison of level of knowledge about HAI according to selected respondent characteristics revealed statistically significant differences with respect to knowledge of HAI and respondents' age, department they work in, years of service, gender and education level. Medical doctors were expected to show better knowledge as compared to staff with secondary education / college; however, the results indicated the contrary, strongly suggesting a repeated research among doctors that will include a larger number of respondents.

The results of this survey indicated that healthcare workers face difficult conditions for proper hand hygiene in their work places. Bischoff reported that, in spite of better working conditions than in our institutions, increased number of accessible sinks did not result in higher hand washing rates (12). Proper hand hygiene practices require the appropriate equipment; however, the issue is to be addressed from different perspectives, such as adequate staffing, education and motivation. The results of chi-square test, considering the parameters age and years of service, revealed no statistically significant differences in a view of conditions and hand-hygiene practices at work place.

Regrettably, the hand hygiene is not performed as often as necessary. In 1981, Albert at al., reported that proper hand washing is performed by only 28% doctors in university hospitals and 14% in private hospitals (13). Almost three decades later, proper hand hygiene by patient contact is still practiced by less than 66% nurses/technicians and doctors (14). American Society for Microbiology conducted a research aimed at discovering how often people are telling the truth about their hand-hygiene habits. Out of the 1000 investigated people 95% claimed they always wash their hands; however, an observation study revealed that only one third of healthcare workers do so (15).

A very simple question – *why healthcare workers do not practice hand hygiene more often* – is very difficult to answer. The respondents in our survey stated the following reasons: being to busy, forgetfulness, lack of ABHD or inaccessible sink with soap. The cited reasons for not practicing hand hygiene comply with similar research worldwide (16, 17).

The research of Borg et al., revealed that in economically underdeveloped countries the insufficient number of hand-wash dispensers and ABHD dispensers is the main reason for the law rate of compliance with hand-hygiene protocols (18). In Western European countries, as well as economically developed countries, heavy workload and skin intolerance are reported as the major reasons of incompliance with protocols (19).

Specific design of this epidemiological questionnaire enables separate monitoring of ICUs and other departments. Highly statistically significant difference was established at the level of satisfactory answers of ICU employees compared to other departments, pertaining to questions on existence of written hand hygiene protocols (Fisher test, $p<0.01$), accessibility of dispensers ($p<0.01$)

and availability of ABHDs ($p<0.01$). The results of this research indicated better conditions for hand hygiene practices in the ICUs then in other departments and hospitals included in this survey.

In the period 1977-2008, more than 20 medical surveys were conducted, offering evidence for *association* between *hand hygiene* adherence and *decreased* rates of *HAI. Some of these studies extended over several years. Majority of research was carried out at ICUs, including pediatric ICUs* (20). All but three of the studies revealed a reverse proportion between hand hygiene promotion and the rate of HAI (21-23). In most countries, the results of these surveys were an initial argument for involvement of national government in addressing this issue by providing financial support for hand hygiene promotion campaigns. An attempt to implement and apply the well-established methods in reducing the rate of HAI initiated the establishment of Alliance for Patient Safety of the WHO and launching of national campaign entitled „Clean Hands – Safe Hands“ in Serbia.

Conclusion

Healthcare workers showed basic knowledge about hand hygiene. Unsatisfactory level of knowledge pertaining to up-to-date disinfectant formulations was observed in all medical staff, both with secondary medical education and doctors. Conditions for practicing proper hand hygiene vary depending upon department. Disinfectants are more accessible at the intensive care units, which is desirable priority in conditions of limited financial assets in our hospitals.

Further education of healthcare personnel on HAI is indispensible, as well as the improvement of hand-hygiene protocols, which should be accessible for each healthcare worker. Equipment policies giving priority to high-risk departments and extending towards low-risk departments and finally to the entire hospital, should be encouraged. The aforementioned measures will increase the quality of medical service, thus contributing to reduced incidence of hospital-acquired infections in our hospitals.

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Association between anticardiolipin antibodies, serum protein C levels and acute myocardial infarction

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Abstract

Objective: Anticardiolipin antibodies and protein C deficiency and/or resistance are among the well-known hypercoagulability syndromes. We wanted to investigate whether serum levels and activity of Protein C and/or anticardiolipin antibodies were different in patients who admitted with acute ST elevation myocardial infarction from healthy controls.

Patients and methods: Fifty patients who admitted to the emergency department within 6 hours of onset of chest pain and diagnosed as acute ST elevation myocardial infarction was included. Complete blood count, biochemistry, CK, CKMB and Troponin T levels were measured after a complete physical examination. Control group consisted of age and sex matched healthy individuals with no symptoms or signs of coronary artery disease or history of coronary artery disease. Protein C activity and anticardiolipin IgM, IgG and IgA were measured in the core laboratory of the hospital.

Results: Protein C activity of the AMI group and the control group did not reveal significant difference although mean Protein C activity was higher compared to control group (148.16±7.51 vs 135.64±4.8; $p>0.05$). Anticardiolipin IgG levels were higher in AMI patients than the controls (10.09±0.62 vs 5.5±0.36 $p<0.01$) as well as anticardiolipin IgM levels (10.27±.13 vs 7.8±0.37 $p<0.01$).

Conclusion: It is important to detect high-risk groups in terms of recurrent thrombosis. Larger studies with standardized measurement of anticardiolipins may clarify whether hypercoagulability should be investigated in at least some high-risk acute myocardial infarction survivors.

Key words: Anticardiolipin antibody, Protein C deficiency, acute myocardial infarction

Introduction

Acute myocardial infarction is an irreversible myocardial damage and necrosis and it is the most serious clinical presentation of coronary artery disease which occurs due to inadequate supply of oxygen to the myocardium because of severe and prolonged ischemia (1,2). Besides atherosclerosis which is the most common cause of coronary artery disease, there are also other conditions which can damage myocardium. Congenital coronary abnormalities, connective tissue disorders including different types of vasculitis, coronary aneurysm/dissection, irradiation, illicit drug usage are some of the causes other than coronary atherosclerosis which may end up with an acute myocardial infarct (3).

Anticardiolipin antibodies and protein C deficiency and/or resistance are among the well-known hypercoagulability syndromes. Protein C deficiency which is associated with venous thrombosis rather than arterial thrombosis can be inherited or acquired in hepatic disease, Warfarin use, inflammatory conditions, pregnancy and hormone therapy (4).

Antiphospholipid antibody syndrome is one of the common causes of acquired thrombophilias which are produced against phospholipid binding proteins or cardiolipin. Some studies related this condition with myocardial infarction (5). We wanted to investigate whether serum levels and activity of Protein C and/or anticardiolipin antibodies were different in patients who admitted with acute ST elevation myocardial infarction from healthy controls.

Patients and methods

Fifty patients who admitted to the emergency department within 6 hours of onset of chest pain

and diagnosed as acute ST elevation myocardial infarction was included. The study which was conducted according to the recommendations of Declaration of Helsinki on Biomedical Research involving human subjects was approved by the local ethics committee. Acute myocardial infarction was diagnosed according to the European definition of myocardial infarction (6). All of the patients has undergone a complete physical examination. Complete blood count, biochemistry, CK, CKMB and Troponin T levels were measured. Disclusion criteria comprised acute coronary syndromes other than acute ST elevation myocardial infarction (unstable angina pectoris, non-ST elevation myocardial infarction, variant angina), stable angina pectoris, diabetes mellitus, autoimmune or immunological disease and active infection. Control group consisted of age and sex matched healthy individuals with no symptoms or signs of coronary artery disease or history of coronary artery disease. Participants who have never smoked or not smoked for last five years were included into the non-smokers group whereas current smokers were included into the smokers group.

Six ml of venous blood was drawn from each participant. Protein C activity was measured (900/1800 ILAB, Roche diagnostics) in the core clinical biochemistry laboratory of the university hospital using 3 ml of blood which was seperated into vacuum tubes containing 0.12 mol/L sodium-citrate. Spectrophotometric analysis of the p-nitroanilin hydrated chromogenic substrate formed by an activator which activates specificaly inactive protein C was performed. Normal protein C antigen level or protein C activity is 70-140%. Below 70% is defined as protein C deficiency.

Rest of the venous sample was used for the measurement of anticardiolipin IgM, IgG and IgA (Biomaster Biokit) in the clinical microbiology laboratory of the hospital using micro ELISA isotypes method. Anticardiolipin IgG, M, A isotypes were expressed as phospholipid units according to Harris criteria (Trinity Biotech, Clark laboratories Inc., USA) as: GPL, MPL, APL. When GPL, MPL and APL levels were less than 12, between 12-13 and >13; IgG, M and A were considered as negative, possibly positive and definitely positive respectively.

Statistical analysis

Standard Package for Social Sciences (SPSS) version 10.0 were used for the statistical analysis of the data. Ki-square test was used for the evaluation of the difference of the mean between two groups. Pearson's correlation coefficients were calculated for the association between anticardiolipin Ig G, and protein C and anticardiolipin Ig G, M and AMI risk factors. Logistic regression analysis was conducted for the corrected coronary risk factors.

Results

Table 1 shows the characteristics of the study population. Mean age of the 37 male and 13 female patients with acute myocardial infarction was 56.12±11.95 whereas mean age of the 35 male and 15 female healthy controls was 53.08±11.92 ($p>0.05$). When smoking status was analysed, rate of smokers were higher in the AMI group not surprisingly (65.2% - 34.8% in AMI vs 37% - 63% in control group $p<0.05$); and the duration of smoking was also longer in AMI survivors ($p<0.05$). LDL levels of the AMI group were higher than the controls (137.3±7.45 vs 108.4±4.64 $p<0.01$); whereas there was no significant difference in terms of HDL ($p>0.05$).

Table 1. Basal characteristics of the study population

	AMI n=50	Control n=50
Age	56,12 ± 11,95	53,08 ± 11,92
M/F	37/13	35/15
Total cholesterol	209,90±8,24	190,96±8,6
HDL	42,44±2,83	42,02±1,60
LDL	137,36±7,45	108,44±4,64
VLDL	34±3,29	36,4±7,08
Triglyceride	155,78±13,89	173,82±35,1
Smoker n (%)	30 (60)	16 (32)

AMI: acute MI, M/F: male/female, HDL: high density lipoprotein, LDL: low density lipoprotein

Analysis of Protein C activity of the AMI group and the control group did not reveal significant difference although mean Protein C activity was higher compared to control group (148.16±7.51 vs 135.64±4.8; $p>0.05$).

Anticardiolipin IgG levels were higher in AMI patients than the control group (10.09±0.62 vs 5.5±0.36 p<0.01). Anticardiolipin IgM levels were also significantly higher compared to the healthy controls (10.27±.13 vs 7.8±0.37 p<0.01). Twelve patients (24%) in the AMI group was detected to have positive aCL-IgG, and 5 patients (10%) has been detected to have aCL-IgM. Four of these patients were positive both for aCL-IgG and IgM. We have not detected any patients positive for aCL-IgA. None of the control group patients were positive for any of the anticardiolipin antibodies. Two patients who were defective in protein C has also been detected to have anticardiolipin antibodies.

In the analysis of the correlations between protein C levels and aCLs, the only significant correlation is between protein C and aCL-IgM. (r:-0.28 p<0.05).

Table 2 and 3 shows the results of the logistic regression analysis for the relationship between classical cardiovascular risk factors and aCL-IgG anda CL-IgM respectively.

Table 2. aCL-IgG and risk factors logistic regression analyses

	p	OR	95% confidence interval	
Smoking	0,147	0,232	0,032	1,67
Age	0,747	0,000	0,000	31,23
Triglyceride	0,867	1,251	0,90	17,368
Total cholesterol	0,671	0,605	0,92	3,97
LDL	0,945	0,915	0,73	11,49
VLDL	0,99	0,129	0,11	1,47

Table 3. aCL-IgM and risk factors logistic regression analyses

	OR	%95 confidence interval	
Smoking	1,31	0,03	3,02
Age	0,31	0,20	8,62
Triglyceride	0,31	0,03	3,02
Total cholesterol	1,31	0,2	8,62
LDL	1,62	0,15	17,10
VLDL	1,83	0,27	12,34

Discussion

This study investigated plasma levels of protein C, one of the most important anticoagulant factors, and serum levels of procoagulant aCLs in addition to the correlation between them, if any. We have detected Ig G and Ig M type anticardiolipin antibodies as independant risk factors for thrombogenesis in a study population without any autoimmune disease, infection, diabetes mellitus or any drugs to cause formation of aCL.

Anticardiolipins are antiphospholipid type immunoglobulins of IgM, IgA, IgG class which are produced against cardiolipins (7,8). In deep vein thrombosis, cerebral thrombosis, spontaneous miscarriages, ocular ischemia, and myocardial infarction, presence of these antibodies were reported (9-11). Acute myocardial infarction and repeated cardiovascular events were correlated with aCLs as well; but these are mostly in the form of case reports and small case studies (12-16). Anticardiolipin antibodies attach to the so-called co-factor proteins; prothrombin, thrombomodulin, protein C, protein S and β_2GPI which has also phospholipid binding properties. For that reason, binding of these to aCLs may attenuate the efficiency of anticoagulant systems. Despite presence of studies in accordance with our's, there are many which did not find any association (13,15-23). Some studies suggest that presence of aCL in healthy individuals predict AMI (24,25). Of course this is related to thrombosis rather than taking a part in atherogenesis pathogenesis (25,26).

Protein C, when bound to thrombomodulin which is a thrombin receptor located on the endothelial surface is converted to the active serin protease activated protein C by thrombin. APC inhibits coagulation by inhibiting FVa and FVIIIa. Cases of intra cardiac thrombus and acute myocardial infarction have been defined in familial or acquired deficiency of Protein C (27,28). We had two young male AMI patients at the age of 30 and 32 in our study population whose protein C activity were 18% and 20% respectively. These two had also aCL IgM and aCL IgG. Takazoe et al. suggested that elevated protein C levels in acute coronary syndromes were due to the need for decreasing hypercoagulability after AMI (29). Some of the scarce studies regarding protein C and AMI relation were supportive to our's (30,29,31) while some were discrepent (32).

It was proposed that activated PC resistance may be induced by an interaction between APC binding sites on FVa and IgG (31). However we were not able to show a significant association between protein C anda CL-IgG.

In conclusion, it is important to detect high-risk groups in terms of recurrent thrombosis. More research especially on the association between anticardiolipin antibodies, coagulation system and fibrinolytic system using standardized measurement will shed light on the suitable methods to determine this risk.

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Cytogenetic Evaluation of Fexofenadine hydrochloride Effects in Human Lymphocytes Culture

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Abstract

Fexofenadine hydrochloride, the major active metabolite of terfenadine, is an antihistamine with selective peripheral H1-receptor antagonist activity. It is a new non-sedating anti-histamine with rapid and long-acting activity. The current study examined the possible genotoxic effects of two concentrations of fexofenadine hydrochloride. Fexofenadine hydrochloride was added to the cultures at the beginning of the cultivation period. Separate cultures for two tested concentrations of fexofenadine hydrochloride (286 ng/ml and 572 ng/ml) were set. Effects of fexofenadine hydrochloride were evaluated by micronucleus cytokinesis-block assay, chromosome aberration analysis, and nuclear division index. The results of this study suggest that fexofenadine hydrochloride in both tested concentrations expresses certain genotoxic effects in human peripheral blood lymphocytes *in vitro*.

Key words: chromosome aberrations, micronuclei, nuclear division index, fexofenadine hydrochloride

Introduction

Fexofenadine hydrochloride, the active acid metabolite of H_1 antagonist terfenadine, has been developed for the treatment of the symptoms associated with allergic rhinitis and chronic urticaria (1). Clinical trials have demonstrated fexofenadine hydrochloride to be safe and effective for treatment of seasonal allergic rhinitis at the dosages of 60, 120 and 240 mg twice daily compared to placebo treatment. In chronic urticaria patients, fexofenadine 180 or 240 mg once daily was significantly effective than with placebo (2, 3). The recommended dose of fexofenadine hydrochloride is 120 mg daily for seasonal allergic rhinitis (either as 120 mg once daily or 60 mg twice daily) or 180 mg once daily for chronic idiopathic urticaria. Fexofenadine has a high margin of safety and is also well tolerated in subjects with renal or hepatic impairment, in children and the elderly. It is highly selective for peripheral H1-receptors and does not cross the blood-brain barrier (4). Recent studies suggest that fexofenadine possesses anti-inflammatory properties by modulating release of proinflammatory mediators (5). Fexofenadine is rapidly absorbed after oral administration and is not affected by food (6). Plasma concentrations reach a peak in about 2.6 hours. In the plasma, about 60-70% of fexofenadine is bound to plasma proteins, mainly albumin and alpha-1-acid glycoprotein. The metabolism of fexofenadine is not dependent on cytochrome P450 activity (7). Approximately 5% of the total dose is metabolized in the liver and only 0.5-1.5 % is converted by cytochrome P450. The rest is excreted in the feces (80%) and urine (12%), with an elimination half-life of 14.4 hours (1, 8).

The carcinogenic potential and the chronic and reproductive toxicity of fexofenadine hydrochloride were based upon carcinogenicity and reproductive toxicity studies conducted with terfenadine, with appropriate pharmacokinetic bridging studies to demonstrate that there was adequate fexofenadine exposure (based on plasma area-under-the-curve [AUC] values). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses up to 150 mg/kg of terfenedine for 18 and 24 months, respectively. In both species, 150 mg/kg of terfenadine produced AUC values of fexofenadine that were approximately 3 times the AUC at the maximum recommended daily oral dose of fexofenadine hydrochloride. In the

terfenadine mouse chronic toxicity/carcinogenicity study doses of 50 and 150 mg/kg/day did not enhance tumor development. Mice receiving 150 mg/kg/day in the diet exhibited a 5% decrease in weight gain compared to controls, indicating that this dose approached the maximum tolerated dose. In the terfenadine rat chronic toxicity/carcinogenicity study, doses up to 150 mg/kg/day administred via the diet for two years showed no apparent carcinogenic effects. Rats receiving 150 mg/kg/day in the diet exhibited a 10% decrease in body weight gain, and an increase in relative liver weights compared to controls. Oral doses of 50-300 mg/kg/day terfenadine did not produce any embryo lethality or teratogenicity in the mouse nor did terfenadine exhibit any teratogenic potential or delay in fetal development in the rat. No evidence of teratogenicity was observed in the rabbit at doses of 0, 30, 100 or 300 mg/kg/day (9).

Generally, except one stydy undertaken by Kasurka et al., there are not any other reports regarding fexofenadine hydrochloride genotoxicity investigating in the *in vitro* chromosome aberration assay utilizing human peripheral blood lymphocytes. The results of this study suggest that fexofenadine hydrochloride has a cytotoxic effect, but not genotoxic effect on human peripheral blood lymphocites cultures (10).

Chromosome aberration analysis in human peripheral blood lymphocytes allows observation of chromosome structure and morphology as indicators of genetic damage (11). Chromosome aberrations analysis is a conventional cytogenetic procedure with the significant clinical application (12) but also frequently used in cytogenetic and genotoxicological monitoring of human populations (13) as well as in genotoxic evaluation of various pharmaceuticals (14, 15) and chemical compounds (16, 17), often being combined with complementary micronucleus cytokinessis-block assay (18). Compared with other cytogenetic tests, micronucleus cytokinessis-block assay provides certain advantages regarding the simplicity of performance, does not require metaphases and enables reliable detection of micronuclei in cultivated human or mammalian cells which have undergone only one division and are recognized by its binuclear appearance (19, 20). Micronuclei are expressed in dividing cells that either contain chromosome breaks lacking centromeres (acentric fragments) and/or whole chromosomes that are unable to travel to the spindle poles during mitosis. Micronuclei provide a convenient and reliable index of both chromosome breakage and chromosome loss (20). As micronuclei derive from chromosomal fragments and whole chromosomes lagging behind in anaphase, the micronucleus assay can be used to show both clastogenic and aneugenic effects (21).

The aim of this research was to evaluate genotoxic and cytotoxic effects of antihistamine fexofenadine hydrochloride in human lymphocyte cultures at concentrations of 286 ng/ml and 572 ng/ml, according to the mean maximum plasma concentrations of fexofenadine hydrochloride following recommended daily oral doses administration.

Materials and Methods

Fexofenadine hydrochloride

For the purpose of the cytogenetic evaluation of fexofenadine hydrochloride effects in cultured human peripheral blood lymphocytes, fexofenadine hydrochloride in the form of tablets (Bosnalijek, Sarajevo, BiH) was used. Tablets were diluted in distilled water and added to the cultures to the final concentrations of 286 ng/ml and 572 ng/ml at the beginning of cultivation. Tested concentrations of fexofenadine hydrochloride were determined according to the plasmatic concentrations that are expected to occur after recommended daily oral doses administration. Untreated cultures were set up as negative controls.

Sample collection and cultivation

The peripheral blood from four healthy volunteers was collected by venipuncture and transferred into heparinized vacutainers (BD Vacutainer Systems, Plymonth, UK). The blood was cultivated according to the standardized procedure described by Moorhead et al. (22). The whole blood cultures, containing 400 µl of peripheral blood added in 5 ml of PB-MAX Karyotyping Medium (GIBCO-Invitrogen, Carlsbad, CA, USA), were set up in 15-ml sterile, plastic tubes with conical bottom (NUNC, Rochester, NY, USA), and incubated at 37°C. Cultivation lasted for 72 hr. Cell division was blocked by the adition of colcemid (GIBCO-Invitrogen) 1.5 hr prior to the end of the cultivation period. For

micronucleus assay, at the 44th hour of cultures initiation, cytochalasin B (Sigma-Aldrich, St. Louis, MO, USA) was added to the final concentration of 3 μg/ml. Cytochalasin B stops dividing cells from performing cytokinesis, thus cells that have completed one nuclear division are recognized by their binuclear appearance. After the cultivation period, cultures were centrifuged for 11 min at 1100 rpm, resuspended in prewarmed hypotonic solution (0.075 M KCl) and, after the centrifugation, fixed in ice-cold glacial acetic acid:ethanol (1:3) fresh fixative. For micronucleus assay, cultures were centrifuged immediately after hypotonic addition, while for chromosome aberration assay, the hypotonic treatment lasted for 20 min. Fixed lymphocytes solution was dropped on ice-cold microscope slides. Air-dried slides were stained with 5% Giemsa stain (Carlo Erba, Milan, Italy).

Informed consent was obtained from all participants of this study. The study was approved by the Scientific Council of the Institute for Genetic Engineering and Biotechnology (Sarajevo, Bosnia and Herzegovina).

Microscopic analysis

Air-dried and coded slides for micronucleus test were analyzed on light microscope (BX51 Olympus, Japan) at 400× magnification. Metaphase slides were analyzed under oil-immersion objective. For each blood sample and tested concentration, 100 metaphase spreads were analyzed. Aberrations were scored according to International System for Human Cytogenetic Nomenclature (23). Verified aberrations were subclassified as chromosome-type (chromosome breaks, acentric and minute fragments), chromatid-type aberrations (chromatid breaks, chromatid minute fragments), aneuploidies and poliploidies. Gaps were not scored as aberrations (24, 25). Binuclear cells with micronuclei were registered. At least 2000 binuclear (BN) cells for each blood sample and tested concentration were scored. The criteria for recognizing and scoring cytokinesis-blocked cells and micronuclei were applied according to Fenech et al. (26). Microscope slides used for micronucleus assay were also used for estimation of dividing lymphocytes by calculating the nuclear division index (NDI) according to Eastmond and Tucker (27). Frequencies of mononuclear, binuclear, trinuclear, and quadrinuclear cells were registred in total number of at least 500 counted cells.

Statistical analysis

Arithmetic means (Xav) and variability measures (standard deviation - s; standard error of the mean – sX_{av}; and coefficient of variation - V) were determined for each fexofenadine hydrochloride treatment and controls in the applied tests. The significance of differences between arithmetic means of results of conducted analysis was determined by two-tailed t-test for independent groups analysis, using Winks 4.5 Professional software (TexaSoft, Cedar Hill, TX, USA).

Results

Individual results of chromosome aberration analysis as well as statistical measures are presented in Table 1. In the current study, it was found that the arithmetic mean of total chromosome aberrations in control samples was 3 per 100 metaphases. The mean for structural aberrations was 1, and the means for acentric fragments/chromosome breaks, chromatid breaks and minute fragment type aberrations were 0.5, 0.5 and 0. The mean for numerical aberrations was 2, and the means for aneuploidy and polyploidy were 2 and 0. Within structural aberrations were 2 acentric fragments/chromosome breaks, 2 chromatid breaks and 0 minute fragment. Within numerical aberrations were 8 aneuploidies and 0 poliploidies. The arithmetic mean for 286 ng/ml fexofenadine hydrochloride treatment was 5.5 for total aberrations, and means for structural and numerical aberrations were 2.25 and 3.25. The means for acentric fragments/chromosome breaks, chromatid breaks and minute fragment type aberrations were 0.75, 1.25 and 0.25. The means for aneuploidy and polyploidy were 1.5 and 1.75. Within structural aberrations were 3 acentric fragments/chromosome breaks, 5 chromatid breaks and 1 minute fragment. Within numerical aberrations were 6 aneuploidies and 7 poliploidies. Treatment with 572 ng/ml of fexofenadine hydrochloride revealed that the arithmetic mean for total aberrations was 6.25 (1.5 for structural aberrations and 4.75 for numerical aberrations). The means for acentric fragments/chromosome breaks, chromatid breaks and minute fragment type aberrations were 0.25, 1

and 0.25. The means for aneuploidy and polyploidy were 3.25 and 1.5. Within structural aberrations were 1 acentric fragments/chromosome breaks, 4 chromatid breaks and 1 minute fragment. Within numerical aberrations were 13 aneuploidies and 6 poliploidies. Summarized results of chromosome aberration analysis for four analyzed blood samples and each treatment are presented in Figure 1. Arithmetic means comparisons showed increase in total frequencies of structural and numerical aberrations, and total aberrations, in samples treated with fexofenadine hydrochloride compared with control samples but t-test analysis revealed no statistically significant differences among total frequencies of structural and numerical aberrations, and total aberrations, in control samples and samples treated with fexofenadine hydrochloride. Frequencies of binuclear (BN) cells with micronuclei in 2000 binuclear cells per sample and each treatment as well as arithmetic means and variability measures are shown in Table 2. In the same table, results and calculated statistical measures for nuclear division index are presented. In controls, the mean for BN cells with micronuclei was 26.5 and the arithmetic mean for NDI was 1.693. In treatments with 286 ng/ml of fexofenadine hydrochloride, the mean for BN cells with micronuclei was 40.5. In the same treatment arithmetic mean for NDI was 1.673. In cultures treated with 572 ng/ml, the means for BN cells with micronuclei and NDI were 51.25 and 1.582. Except binuclear cells with one micronuclei, in cultures treated with fexofenadine hydrochloride were also observed those with two and three micronuclei. Binuclear cell with three micronuclei was detected only in treatment with highest fexofenadine hydrochloride concentration (572 ng/ml). Summarized results of micronucleus test for all treatments are presented in Figure 2. The individual results of nuclear division index in each fexofenadine hydrochloride treatment and control are shown in Figure 3. Two tailed t-test analysis revealed significant difference among arithmetic means of frequencies of BN cells with micronuclei in treatment with 286 ng/ml and the control ($p < 0.05$), as well as in treatment with 572 ng/ml, and the control ($p < 0.005$). T-test analysis revealed no significant differences among nuclear division index arithmetic means in each fexofenadine hydrochloride treatment and control. Comparation of NDI arithmetic means was found decrease of NDI mean in both fexofenadine hydrochloride treatment compared with control treatment (Figure 4).

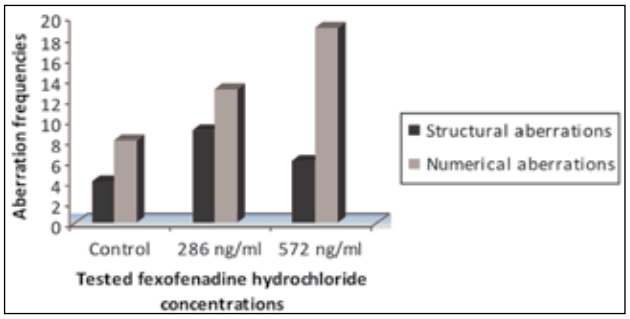

Figure 1. Summarized results of chromosome aberration analysis

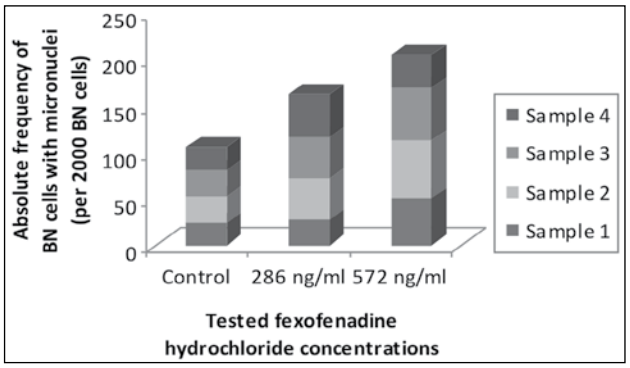

Figure 2. Results of micronucleus assay per each treatment

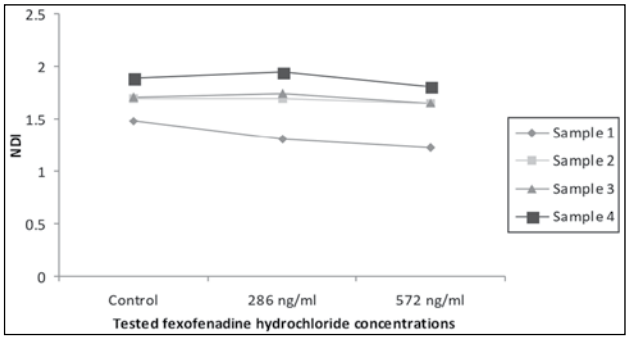

Figure 3. Individual results for nuclear division index

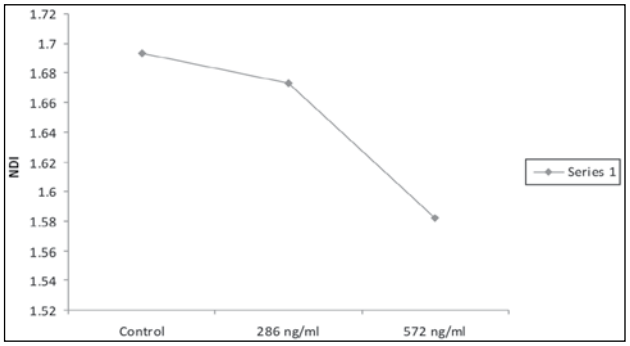

Figure 4. The average results for nuclear division index

Table 1. Individual results and statistical measures for chromosome aberration analysis

Treatment	Sample lable	Structural aberrations (A)				Numerical aberrations (B)			Total (A+B)
	Statistical measures	Acentric fragments/ Chromosome breaks	Chromatide breaks	Minute fragment	Total	Aneuploidy	Poliploidy	Total	
Control	1	1	0	0	1	1	0	1	2
	2	0	0	0	0	1	0	1	1
	3	1	1	0	2	3	0	3	5
	4	0	1	0	1	3	0	3	4
	X_{av}	0.5	0.5	0	1	2	0	2	3
	s	0.577	0.577	0	0.816	1.155	0	1.155	1.826
	sX_{av}	0.288	0.288	0	0.408	0.577	0	0.577	0.913
	V	115.4	115.4	0	81.6	57.75	0	57.75	60.867
286 ng/ml	1	0	0	0	0	2	1	3	3
	2	0	1	0	1	2	2	4	5
	3	1	2	1	4	2	0	2	6
	4	2	2	0	4	0	4	4	8
	X_{av}	0.75	1.25	0.25	2.25	1.5	1.75	3.25	5.5
	s	0.957	0.957	0.5	2.061	1	1.708	0.957	2.082
	sX_{av}	0.478	0.478	0.25	1.03	0.5	0.854	0.478	1.041
	V	127.6	76.56	200.0	91.6	66.667	97.6	29.446	37.854
572 ng/ml	1	0	0	0	0	2	1	3	3
	2	0	1	1	2	5	3	8	10
	3	0	3	0	3	4	1	5	8
	4	1	0	0	1	2	1	3	4
	X_{av}	0.25	1	0.25	1.5	3.25	1.5	4.75	6.25
	s	0.5	1.414	0.5	1.291	1.5	1	2.363	3.304
	sX_{av}	0.25	0.707	0.25	0.645	0.75	0.5	1.181	1.652
	V	200.0	141.4	200.0	86.067	46.154	66.667	49.747	52.864

X_{av}, arithmetic mean; s, standard deviation, sX_{av}, standard error of the mean; V, coefficient of variation

Table 2. Results of micronucleus assay and nuclear division index

Treatment	Sample lable / Statistical measures	Binuclear cells with micronuclei	Nuclear division index
Control	1	24	1.482
	2	29	1.693
	3	27	1.708
	4	26	1.887
	Σ	106	
	X_{av}	26.5	1.693
	s	2.082	0.166
	sX_{av}	1.041	0.083
	V	7.857	9.805
286 ng/ml	1	27	1.309
	2	45	1.696
	3	44	1.744
	4	46	1.941
	Σ	162	
	X_{av}	40.5	1.673
	s	9.037	0.265
	sX_{av}	4.518	0.133
	V	22.314	15.84
572 ng/ml	1	51	1.223
	2	61	1.646
	3	57	1.648
	4	36	1.811
	Σ	205	
	X_{av}	51.25	1.582
	s	10.966	0.252
	sX_{av}	5.483	0.126
	V	21.397	15.929

X_{av}, arithmetic mean; s, standard deviation, sX_{av}, standard error of the mean; V, coefficient of variation

Discussion

The use of antihistamines is relatively common in medical practice. Fexofenadine hydrochloride is an antihistamine which is used in a number of conditions, in spite of the fact that the possible genotoxic potential of this drug is still unknown and at the stage of research. In *in vitro* (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and *in vivo* (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine hydrochloride revealed no evidence of mutagenicity (9). In here presented *in vitro* study, fexofenadine hydrochloride in both tested concentrations has induced increase in frequency of chromosomal aberrations in human lymphocytes culture, but this increase was not statistically significant. The majority of chromosomal aberrations found in this research were numerical aberrations. About numerical aberrations, both aneuploidies and poliploidies were found. By structural aberrations, fexofenadine hydrochloride induced chromatid breaks, chromosome breaks, acentric and minute fragments. The majority of structural aberrations were chromatid breaks. Structural aberrations can lead directly to cell death and are often major contributors to cellular toxicity (28). On the contrary, the results

of micronucleus assay revealed that fexofenadine hydrochloride has induced statistically significant increase in frequency of binuclear cells with micronuclei in both fexofenadine hydrochloride treatment, which indicate certain aneugenic and clastogenic potential of this antihistamine in cultured human peripheral blood lymphocytes. It was also observed in the present study that positive correlation exists between absolute frequency of binuclear cells with micronuclei and fexofenadine hydrochloride concentration. The *in vitro* micronucleus assay is available for assessment of aneugenic and clastogenic activity. It offers the advantage to provide simultaneously information on both cell cycle progression and chromosome/genome mutations (29, 30). In the *in vitro* study conducted by Kasurka et al., the results of chromosomal aberrations assay and micronucleus assay showed that fexofenadine hydrochloride was not genotoxic in concentrations of 50, 100 and 150 μg/ml in treatment lasting for 24 and 48 hr in human lymphocyte culture. The results of nuclear division index and mitotic index in the same study showed that fexofenadine hydrochloride induced dose-dependent decrease of nuclear division index and mitotic index with significant differences for at least one concentration, and suggest that fexofenadine hydrochloride has a cytotoxic effect on human peripheral blood lymphocyte culture (10). In current study, NDI results demonstrated that fexofenadine hydrochloride in both tested concentrations modify proliferation of cultured human lymphocytes. In high concentration of 572 ng/ml fexofenadine hydrochloride induced certain decrease of nuclear division index in all samples treated with fexofenadine hydrochloride compared with control samples. By calculating of nuclear division index arithmetic means, it was found decrease in NDI mean for the both fexofenadine hydrochloride treatment compared with control treatment, but this decrease of NDI mean was not statistically significant.

Conclusion

The results of the applied *in vitro* cytogenetic tests revealed certain clastogenic and aneugenic activity of both fexofenadine hydrochloride tested concentrations (286 ng/ml and 572 ng/ml). This study demonstrated statistically significant increase in frequencies of binuclear cells with micronuclei in comparison with control. Certain, but not statistically significant increase in chromosome aberrations in cultures treated with fexofenadine hydrochloride was evidenced. Frequencies of structural and numerical aberrations, as well as nuclear division index do not statistically differ in comparison with controls. Further cytogenetic analysis are required for clarification and determining of fexofenadine hydrochloride genotoxic and cytotoxic effects.

Acknowledgements

Author would like to thank the personnel of the Institute for Genetic Engineering and Biotechnology in Sarajevo, Bosnia and Herzegovina, where this research has been done.

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Weight Management, Calorie Intake and Body Image Perception among Young Adults

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Abstract

Objectives: To examine eating behaviors of university students, identify recent major food intake patterns, and explore body image perceptions. It also aims to find out any correlation between nutrient intake, body image perception and weight altering intentions.

Design: Cross-sectional study

Setting: Ankara Başkent University, Turkey

Subjects: 503 randomly selected university students

Intervention: A questionnaire examining nutritional habits

Main Outcome Measures: Calorie intake, body image perception in relation to body mass indexes, eating and dieting behaviors and weight management plans.

Analysis: Chi-square analysis and logistic regression

Results: 68.8% of female students, and 69.2% of males with normal BMI, described their bodies as overweight. Consumption of low-calorie type of food, attending to a diet program, gender, and regular exercising are the positive affecting variables in daily calorie intake (kcal/kg/day). In contrast, BMI and fast food consuming are the negative ones.

Conclusion: This is the first study of the perception of body image and calorie-intake of young adults in Turkey. It adds to limited amount of knowledge that is currently available about dietary habits of this age group. Findings suggest that a need for further education is necessary for young people regarding healthy nutrition and weight control behaviors.

Key words: youth, body image, health behavior, Turkey

Introduction

Adolescence is the phase of life that physical and sexual growth occurs, and the changes in body consequently turns into adult formation.[1] This period generates the characteristics of adult life, like weight, height, health status and life style. Nutritional status has importance in the disease prevention as well as growth and development. [2]

Good nutritional habits -as well as adequate and regular exercise- have critical importance for establishing and maintaining good health.[3] Recent evidence suggests that dietary habits during adolescence may predict the occurrence of adult cardiovascular diseases, hypertension, insulin resistance, lipid disorders, obesity, osteoporosis, and may determine risk for adult diet-related cancers. [1, 2, 4-9] University students could be considered in a transitional period between late adolescence and early adulthood. Examining this period could give an idea about the reflections of adolescence nutritional habits to adult life.

Body image has been found to be one of the strongest determinants of adolescent nutritional habits in conjunction with demographic factors. [3,10] Overweight perception is associated with eating and dieting behaviours.[11-14] It is thought that this perception leads to differences in dietary reporting because of the dissatisfaction of the body image.

The objectives of this study are to examine eating behaviors of students in a university in Ankara, Turkey, identify recent major food intake patterns, and explore body image perceptions. This study also aims to find out any correlation between nutrient intake, body image perception and weight altering intentions; which would provide a basis for future public health recommendations on nutrition education or interventions.

Methods

Participants: A sample group of 700 students in a university in Ankara was selected by stratified sampling. Students were selected from different university departments by a systematic circular method. Written informed consent was obtained and participation was voluntary. ***Questionnaire:*** There is a quantity of methods that have been designed to determine nutritional patterns like diet records, diet-history questionnaires, 24 hour recalls, 72 hour recalls or food-frequency questionnaires [4, 15-19] and each of them has its own strength and weakness. [4, 15, 20, 21] As it is difficult to compare these methods, there is not much knowledge about validity of any food questionnaire. [15, 22]

The questionnaire form used in this study was created by authors. Students were asked to write whatever they ate or drunk at breakfast, lunch and dinner, and between the meals, in the last 72 hours, in terms of serving per day. The form also included questions about body image, attitudes towards weight loss or gain, and socioeconomic variables.

Body Mass Index (BMI): The study group was classified into the overweight group and the normal/low weight group according to their calculated BMI (kg/m^2). This classification was based on the hypothesis that BMI's method of determining the fat tissue has reliability and validity in both adolescent and young population and this method has a tendency of being more accurate in comparison with other obesity measurements. [23]

Table 1. Demographic characteristics of participants by gender

Demographic Characteristics	No. (%) of participants		P value
	Female (n=266)	Male (n=237)	
	n (%)	N (%)	
Year at University			0.010
Preparatory year*	59 (22.2)	28 (11.8)	
1st	58 (21.8)	72 (30.4)	
2nd	50 (18.8)	56 (23.6)	
3rd	63 (23.7)	51 (21.5)	
4th	36 (13.5)	30 (12.7)	
Living at home with family			0.003
Yes	151 (56.8)	166 (70.0)	
No	115 (43.2)	71 (30.0)	
Income Groups			0.053
First 20%	64 (24.1)	43 (18.1)	
Second 20%	37 (13.9)	25 (10.5)	
Third 20%	72 (27.1)	92 (38.8)	
Fourth 20%	55 (20.7)	41 (17.3)	
Fifth 20%	38 (14.3)	36 (15.2)	
Mother's education			0.000
Did not complete high school	63 (23.7)	33 (13.9)	
Completed high school	115 (43.2)	81 (34.2)	
Completed university	88 (33.1)	123 (51.9)	
Father's Education			0.075
Did not complete high school	40 (15.0)	28 (11.8)	
Completed high school	71 (26.7)	47 (19.8)	
Completed university	155 (58.3)	162 (68.4)	
Mother's employment status			0.526
Employed	98 (36.8)	95 (40.1)	
Unemployed	168 (63.2)	142 (59.9)	
Father's employment status			0.780
Employed	224 (84.2)	202 (85.2)	
Unemployed	42 (15.8)	35 (14.8)	

**Students of this university attend to a preparatory class in which English language is taught.*

Table 2. Descriptive Characteristics of the Subjects: Age, Height, Weight, Body Mass Index, and Mean Energy Intake and Macronutrient Composition of the Diet (Percent Daily Energy)

Descriptive Characteristics	No. (%) of participants				Total (n=503)		p value
	Female (n=266)		Male (n=237)				
	Mean± Standart Deviation	Range	Mean± Standart Deviation	Range	Mean± Standart Deviation	Range	
Age (years)	21.2±1.6	18-25	21.5±1.8	18-25	21.3±1.7	18-25	0.073
Height (cm)	165.9±5.7	152-182	178.2±7.0	160-196	171.7±8.8	152-196	0.000
Weight (kg)	55.5±8.6	40-117	74.7±12.1	49-122	64.6±14.2	40-122	0.000
BMI (kg/m2)	20.1±2.7	16.0-40.0	23.5±3.4	16.6-42	21.7±3.5	16.0-42.0	0.000
Energy Intake (kcal/day)	1547±697	178-4294	1564±731	342-3744	1555±712	178-4294	0.791
Energy Intake (kcal/kg/day)	28.7±14.0	3.4-81.0	21.4±10.3	3.6-57.6	25.2±12.9	3.4-81.0	0.000
Carbohydrates (%)	44.7±12.0	17.0-77.0	44.2±12.0	9.0-76.0	44.5±12.0	9.0-77.0	0.655
Lipids (%)	27.8±9.4	10.0-56.0	27.8±9.3	9.0-60.0	27.8±9.3	9.0-60.0	0.957
Proteins (%)	27.5±6.9	12.0-51.0	28.0±6.9	13.0-52.0	27.7±6.9	12.0-52.0	0.481
Breakfast (kcal)	344±236	0-1050	355±320	0-1721	349±278	0-1721	0.660
Lunch (kcal)	394±218	0-1130	424±225	0-1150	408±222	0-1150	0.134
Dinner (kcal)	474±240	0-1067	508±275	0-1437	490±257	0-1437	0.134
Intervals (kcal)	112±142	0-977	93±123	0-560	103±134	0-977	0.105

Statistics: Data were analyzed with SPSS version 11.5, SPSS Inc., Chicago, IL, 2002. Chi-square analysis and logistic regression were used where relevant.

Results

Among the randomly selected and invited 700 students, 197 (28.1 %) did not want to participate in the study. Of the 503 participants, 237 (47.1 %) were male, and 266 (52.9 %) were female. Average age was 21.3 ±1.7 years. Demographic characteristics of participants are shown in Table 1.

Descriptive characteristics according to gender are shown on Table 2 in details. Mean BMI was 20.1 (Sd 2.7) in females, and 23.5 (Sd 3.4) in males (P = 0.000). Daily calorie intake per one kilogram of weight was found 28.7 ± 14.0 kcal in girls and 21.4 ± 10.3 kcal in boys (P = 0.000). Of the total energy intake, 44.7% was carbohydrates, 27.8% was lipids and 27.5 % was proteins in girls, and 44.2 %, 27.8 % and 28.0 %, respectively in boys, with no significant difference between genders.

The distribution of the calorie intake according to meals was 349 ± 278 kcal for breakfast, 408 ± 222 kcal for lunch, 490 ± 257 kcal for dinner, and 103 ± 134 kcal for snacks. While the calorie intake at breakfast was similar, it was observed that males took more calories at lunch and dinner (424 ± 225 kcal, 394 ± 218 kcal, P = 0.134 and 508 ± 275 kcal, 474 ± 240 kcal, P = 0.134), and females more at snacks (112 ± 142 kcal, 93 ± 123 kcal, P = 0.105).

Table 3 shows students' self-perception, plans about weight control and related habits. 59.4% of the students defined their bodies as slightly overweight, with no statistically significant difference between genders. Calorie intake of students who define their body as slightly overweight was significantly higher than others (1628.1 kcal/day, F = 3.421, P = 0.009). When the future plans of the students about their body weights were asked, 47.0% of females, and 33.8% of males said they were planning to lose weight. Those who plan to lose weight take calories per day less than others (1447.9 kcal/day, F = 4.249, P = 0.006). 35% of the students exercise regularly, and their daily average calorie intake is less than those who do not exercise (1438.4 kcal/day, t = 2.722, P = 0.007).

Girls consumed more of low-calorie type of food, compared to boys (40.2% and 19.0% respectively, P = 0.000), and the average of daily calorie intake was significantly lower in this group (1352.7 kcal/day and 1678.6 kcal/day respectively, t = 3.014, P = 0.003).

34.2% of students were already in a diet program prepared by a dietician or physician. There

Table 3. Body Image self description, plans about weight control and Daily Calorie Intake Averages of University Students by Gender

	Female		Male		Total		p-value
	n (%)	Mean Calorie Intake	n (%)	Mean Calorie Intake	n (%)	Mean Calorie Intake	
Body image self description							**0.447**
Extremely underweight	14 (5.3)	1377,1	10 (4.2)	1101.0	24 (4.8)	1262,1	F= 3.421 p= 0.009
Slightly underweight	28 (10.5)	1637,0	44 (18.6)	1535.0	72 (14.3)	1574,7	
Ideal	41 (15.4)	1343,3	19 (8.0)	1780.6	60 (11.9)	1481,8	
Slightly overweight	156 (58.6)	1639,3	143 (60.3)	1615.9	299 (59.4)	1628,1	
Extremely overweight	27 (10.2)	1323,1	21 (8.9)	1300.6	48 (9.5)	1313,3	
Plans for the body weight							**0.004**
To lose weight	125 (47.0)	1379,9	80 (33.8)	1554,0	205 (40.8)	1447,9	F= 4.249 p= 0.006
To gain weight	24 (9.0)	1583,4	48 (20.3)	1643,8	72 (14.3)	1623,7	
Preserve actual weight	97 (36.5)	1745,2	59 (24.9)	1624,2	156 (31.0)	1699,4	
No plans	20 (7.5)	1593,1	50 (21.1)	1434,4	70 (13.9)	1479,7	
Regularly exercising							**0.005**
Yes	108 (40.6)	1374,2	68 (28.7)	1540,3	176 (35.0)	1438,4	F= 7.411 p= 0.007
No	158 (59.4)	1666,0	169 (71.3)	1574,1	327 (65.0)	1618,5	
Low calorie food consumption							**0.000**
Yes	107 (40.2)	1352,7	45 (19.0)	1550,4	152 (30.2)	1411,2	F= 9.082 p= 0.003
No	159 (59.8)	1678,6	192 (81.0)	1567,7	351 (69.8)	1618,0	
Already in a diet program							**0.000**
Yes	116 (43.6)	1424,7	56 (23.6)	1734,1	172 (34.2)	1525,4	F= 0.465 p= 0.495
No	150 (56.4)	1642,5	181 (76.4)	1511,9	331 (65.8)	1571,1	
Medical or herbal substance usage without a medical control							**0.000**
Yes	70 (26.3)	1447,9	16 (6.8)	1542,6	86 (17.1)	1465,5	F = 1.657 p= 0.199
No	196 (73.7)	1583,1	221 (93.2)	1566,0	417 (82.9)	1574,0	
Eat-Purge Behaviors							**0.031**
Yes	14 (5.3)	1357,5	4 (1.7)	1134,8	18 (3.6)	1308,0	F= 2.259 p = 0.133
No	252 (94.7)	1558,1	233 (98.3)	1571,8	485 (96.4)	1564,7	
Traditional food consumption in the last 3 days (kebap, lahmacun etc.) at any meal							**0.000**
Yes	137 (51.5)	1647,5	197 (83.1)	1544,2	334 (66.4)	1586,6	F= 1.896 p= 0.169
No	129 (48.5)	1441,4	40 (16.9)	1664,0	169 (33.6)	1494,1	
Fast food (hamburger, pizza etc.) consumption in the last 3 days at any meal							**0.399**
Yes	229 (86.1)	1585,1	210 (88.6)	1588,3	439 (87.3)	1586,6	F= 6.671 p= 0.010
No	37 (13.9)	1314,8	27 (11.4)	1378,9	64 (12.7)	1341,9	

was no statistical difference between calorie intakes of dieting and not-dieting boys, whereas the calorie intake of dieting girls was significantly lower than the not-dieting ones.

The percentage of students who use medical or herbal dietetic substances without medical assessment was 17.1%, and this behavior seemed to be more extensive in females (6.8% compared to 26.3%, P = 0.000). A significant difference for such substance users for calorie intake was not found.

3.6% of students had eat-purge behaviors. 5.3% of girls and 1.7% of boys had such behaviors (P = 0.031). Calorie intake of these students (1308.0 kcal/day) was found to be significantly lower than others (1564.7 kcal/day).

When students were asked whether they ate traditional food (kebab, lahmacun, doner, pide) in the last 3 days, 66.4% of them stated that they ate these foods. Male students' traditional food consumption (83.1%) was significantly higher than females' (51.5%) (P = 0.000). In contrast, western style fast food (hamburger, pizza etc.) consumpti-

Table 4. Odds Ratios (95% Confidence Interval) of University Students' Socioeconomics, Perceptive, Conductive and Behavioral Conditions Related to Their Mean Daily Calorie Intake (kcal/kg/day)

Predictors	Coefficient	Std Error	p-value	95% CI	
				Lower	Upper
Gender	6.823	1.183	0.000	4.499	9.146
Age	0.160	0.248	0.519	-0.328	0.649
Year at University	0.145	0.449	0.748	-0.739	1.028
Mother's Education	-1.695	1.056	0.109	-3.770	0.380
Father's Education	-0.671	0.951	0.481	-2.540	1.119
Mother's Employment Status	0.525	0.482	0.276	-0.421	1.471
Father's Employment Status	0.191	0.512	0.709	-0.815	1.198
Income Group	-0.239	0.415	0.565	-1.054	0.576
BMI Value	-7.224	1.834	0.000	-10.828	-3.621
Body Image	0.213	0.562	0.705	-0.891	1.316
Plans for the Body weight	0.895	0.546	0.102	-0.178	1.967
Regularly exercising	3.627	1.297	0.005	1.080	6.175
Low calorie food consumption	10.876	2.179	0.000	6.594	15.158
In Diet program	9.274	2.122	0.000	5.104	13.443
Medical/Herbal substances	-0.251	1.676	0.881	-3.545	3.042
Eat-Purge	-0.460	2.983	0.877	-6.322	5.401
Traditional food consumption	-0.807	1.255	0.521	-3.274	1.660
Fast Food consumption	-4.081	1.633	0.013	-7.289	-0.874

N=503; R^2=0.841; F Change= 141.75 p= 0.000

on in the last 3 days was high in both sexes (86.1% for females, 88.6% for males, P = 0.399).

The regression analysis showed that consumption of low-calorie type of food (ß = 10.876, 95%CI 6.594-15.158, P< 0.001), attending to a diet program (ß= 9.274, 95%CI 5.104-13.443, P< 0.001), gender (ß = 6.823, 95%CI 4.499- 9.146, P< 0.001), and regular exercising (ß = 3.627, 95%CI 1.080-6.175, P = 0.005) are the positive affecting variables in daily calorie intake (Kcal/kg/day). In contrast, BMI (ß = -7.224, 95%CI -10.828—3.621, P< 0.001) and fast food consuming (ß = -4.081, 95%CI -7.289- -0.874, P< 0.05) are the negative ones (Table 4).

Discussion

This is the first study of the perception of body image and calorie-intake of young adults in Turkey. It adds to limited amount of knowledge that is currently available about dietary habits of this age group. We believe this group already has an established food intake pattern in contrast with teenagers and it may reflect the likelihood nutritional status of adult life.

There are a number of possible limitations of our study. First, the study was conducted in Turkey's capital city, Ankara and may not be generalizable to the rest of the country, especially rural areas. Second, the study included only currently enrolled university students and the results may not be applicable to young people of the same age who do not have a university education. Third, the study was conducted in winter and it may not reflect the seasonable changes of eating patterns of the country. And fourth, as already known, there is always a risk of underreporting calorie intake when people are asked.[2-5,15,24,25] However, strengths of this study are that the total sample was relatively large, the participants were randomly chosen, the rate of recruitment was high (71.9%), and the questions investigating the last three days' food and drink intake were open-ended. One characteristic of the study is that, in the questionnaire more than 200 kinds of food and drink were asked separately, and the standardized portion for each was also noted.

In considering the generalizability of our findings, because of lack of local or national studies, we can compare it with studies from several other countries.

An interesting finding of the study is that 68.8% of female students, and 69.2% of males with normal BMI, described their bodies as overweight. In Middleman et al.'s study [3], among high school students these percentages were 42% for girls and 22.3% for boys. In the same population 61.6% girls and 21.5% of boys were trying to lose weight whereas in our population the percentages were 47% and 33.8%, respectively. Van den Berg reported the relationship between body dissatisfaction and self-esteem as strong and significant in both boys and girls in an adolescent study group.[26] In Vera et al.'s study, differences were found between objective weight status and self-perception of weight in adult population.[27] In longitudinal analyses, he did not find a significant change in the strength of the association as adolescents grew older. We might assume that continuity in such decrease in self-esteem in relation to body dissatisfaction would affect young adulthood as well as later periods in life. A feeling of overweight in BMI normal population reaching almost 70% might be an alarm finding for body dissatisfaction, which could further lead to decrease in self-esteem. Harring reported that American female college students with an inflated body weight perception were significantly more likely to engage in unhealthy weight management strategies and report depressive symptoms than were females with an accurate body weight perception.[28] We might assume that decreased self-esteem and depression might further lead to several social consequences.

Another interesting finding of our study is that self-description of overweight did not decrease calorie intake among the study population. This finding was inconsistent with Middleman's study.[3] 80.1% of their study group dieted or exercised to lose weight, while this rate was 35% in our study. While the ratio of medical or herbal dietary pills or substances usage ratio was 26.3% for females and 6.6% for males in our study, these percentages were 3.5%, 1.3% in their study, respectively. But we also need to take into account that marketing of herbal dietary pills have extensively increased in recent years in our country.

When total energy intake was compared with Hong Kong Chinese people in respect of carbohydrates, proteins, and lipid percentages, our university students seemed to consume more proteins and less carbohydrates, whereas lipid consumption ratio was almost equal (protein, carbohydrate and lipid percentages for Hong Kong Chinese and Turkish people were 18%, 54%, 29% and 28%, 45%, 28% respectively).[9] In Schaefer et al.'s study[15], 66 ± 11 years old people seemed to take more carbohydrates (49%) and lipids (35%) and less proteins (15%) than our subjects. 30.7 ± 10.4 years old Spanish people took more lipids (38%) and less proteins (17%) and lipids ratio was equal (45%).[3] Because of the age differences of the people studied, these comparisons may not give an accurate view to energy intake, but may give light to it by means of cultural differences.

Implications for Research and Practice

The results of this study show that deep attention to youth's eating and dieting practices should be given. The results are remarkable for young people in Turkey, and the findings suggest that a need for further education is necessary for young people regarding healthy nutrition and weight control behaviors.

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Retention of total lower prosthesis using mini dental implants in elderly patients (Report on two cases)

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Abstract

Introduction: A toothless patient is facing serious handicap. He has difficulties by chewing, thus his diet is poor, he often suffers impaired digestion, has problems to speak properly, his visual appearance is compromised as well as his position in the society. Total lower denture does not only replace the missing teeth, it has to provide substitute for a range of supporting tissues diminished due to resorption process, to re-establish the original relations in the region of jaw complex, to support the surrounding soft tissue that had lost their natural support, and, moreover, to be unobtrusive and discrete substitution of lost functions. Most recently, application of titanium endosteal mini implants proved highly applicable in overcoming the unfavorable anatomical conditions, revealing very good results in stabilization and retention of total lower dentures.

Case Report: In this paper, we presented two patients, who came to our Clinic of Dentistry of Vojvodina, Faculty of Medicine Novi Sad, for prosthetic rehabilitation and re-establishment of normal function of dental system. In one patient the flapless („no incision“) technique was applied, whereas the second patient underwent incision, i.e. open surgery technique. In both cases, four mini implants with a *diameter* of *1.8 mm* and a *length* of 10mm were inserted into the toothless lower alveolar ridge. The implants were positioned to fill the space of teeth Nos. 32, 34 and 42, 44

Conclusion: An accurate diagnosis, adequate therapy plan, proper and precise placement, i.e. adequate and appropriate prosthetic solution enables replacement of missing teeth with maximal preservation of anatomical structure and architecture of surrounding soft tissues and bone structures. In toothless persons, especially in the elderly, application of mini implant systems provides an additional stability of mobile dentures, particularly the total lower ones, thus making their lives much more comfortable.

Key words: mini dental implants, total toothlessness, elderly

Introduction

A toothless patient is facing serious personal handicap. He has chewing difficulties, his diet is poor, he often suffers impaired digestion, has problems to speak properly, his visual appearance is compromised as well as his position in the society. Total lower denture does not only replace the missing teeth, it has to provide substitute for a range of supporting tissues diminished due to resorption process, to re-establish the original relations in the region of the jaws, to support the surrounding soft tissues that had lost their natural support, and, also to be unobtrusive and discrete substitution of lost functions. (1)

One of the most important conditions that total lower denture needs to fulfill is to provide an adequate stability and retention. Factors influencing the retention and stability of the denture include the physical and physiological ones. Physiological factors contributing to denture stability, i.e. its firm position in the bed, mainly encompass muscular strength of cheeks, lips and tongue. Their effects are mainly reflected through functions of chewing and speaking, as well as parafunctions. The shape of a toothless ridge can be also considered physiological factor. Physical factors affecting retention and stability of total lower denture are surface tension, viscosity of the saliva, adhesion and cohesion, valve effect and atmospheric pressure. In some cases, especially in the elderly

patients, resorptive changes after tooth extraction result in decrease of height and width of the alveolar ridge. Considering that supporting surface is reduced, decrease in retention and stability of total lower denture is suspected. (1)

In case of unfavorable anatomical conditions, a number of oral-surgical pre-prosthetic procedures are applicable on soft tissues, as well as on bone structures (vestibuloplasty, alveolar ridge augmentation...). These procedures to some extent enable appropriate formation of total lower denture. Considering the old age of the patients, majority of which suffering chronic diseases such as diabetes mellitus, cardiovascular problems, systemic diseases etc., such procedures should be avoided because of the extent of the procedure, possible systemic complications and prolonged therapy period.

Application of conventional implant systems to provide stability and retention of total lower denture, particularly in the elderly, is not advocated because of the following: conventional implants require sufficient bone structure (height, width); in case of lack of bony mass, excessive augmentations of alveolar ridge are indicated, which sometimes require several donor sites to achieve adequate bone volume; augmentation procedures prolong the period of therapy and healing, provoke postoperative swelling and pain, and at least (but not less important) they increase the expenses of prosthetic rehabilitation. (2,3)

Most recently, application of titanium endosteal mini implants proved highly applicable in overcoming the unfavorable anatomical conditions, revealing very good results in stability and retention of total lower dentures.

Mini implants belong to the group of endosteal, titanium, self-drilling, single-phase implants. They are similar to conventional implants, yet being smaller in size and made of titanium admixture (not pure commercial titanium). In most cases, their application is aimed at stabilization and retention of mobile prosthetic constructions. (Four, 5)

Indications for placement of mini implants:

1. Total toothlessness of the lower jaw (impossible implantation of conventional implants due to unfavorable anatomical conditions)
2. Total toothlessness of the upper jaw (unfavorable anatomical conditions)
3. Toothless elderly patients (flapless technique is less traumatic for the patient and minimizes the postoperative discomfort)
4. Persons who reject extensive augmentation procedures
5. Patients who don't want to wait for several months after placement of conventional implants
6. Financial obstacles (patients who can not afford conventional implants)

Case report

In this paper, we presented two patients, who reported at the Clinic of Dentistry of Vojvodina, Faculty of Medicine Novi Sad, for prosthetic rehabilitation and re-establishment of normal function of dental system.

Case No. 1

Male patient, aged 64, reported to our Clinic for prosthetic rehabilitation of total toothlessness of the upper and lower jaw. Clinical examination and analysis of the OPT scan indicated placement of two total acrylic dentures. Considering pronounced atrophy of the lower alveolar ridge and high insertions of mimic musculature we decided to produce total lower denture, stability and retention of which would be improved by placing four mini dental implants with a *diameter* of *1.8 mm* and a *length* of 10mm, by the use of flapless technique.

a) Stages of surgical protocol – flapless technique are as following:

1. Informing the patient about dental implant system
2. Anamnesis, clinical examination and RTG diagnostics
3. Establishing indications, selecting appropriate implants, determining the precise location for the implant
4. Obtaining patient's written consent for surgical procedure
5. Local anesthesia
6. Forming a bone bed in the jawbone to accommodate the dental implant applying a pilot drill directly through the gingiva and the bone - the drilling is performed to only *half* the *implant length* using a physio-dispenser at drilling speed of around 1000 rpm. Four mini implants are

placed in a lower jaw at the place of lower lateral incisors and lower primary premolars.
7. Extracting of mini implants from the sterile package and its gentle manual screwing via plastic cap (mini implants have a self drilling, i.e. self-cutting thread pattern)
8. Continuing screwing using a special set containing three ratchet wrenches, each of them producing increased screwing force. In case of pronounced resistance, make a pause of about 20 seconds (because of horizontal force on bone trabeculae) to prevent compromising of bone circulation, and than carefully continue the procedure. Implant is screwed until polished part has reached the level of alveolar ridge.
9. Control RTG scan

b) Prosthetic protocol includes the following stages:

1. Covering the neck of the implant with silicone blockers to prevent the self-binding acrylic from flowing under the implant head
2. Positioning metal caps onto the inserted implants
3. Making a bed in the denture, which fits to metal caps
4. Mixing the self-binding acrylic and pouring it into the denture holes
5. Placing of denture by the use of liquid self-binding acrylic onto the metal caps and implants
6. After hardening of the acrylic, removing the denture off the implant, while metal caps remain in the denture body
7. Removing of excess acrylic, processing and polishing of the denture
8. Delivery of the denture to the patient

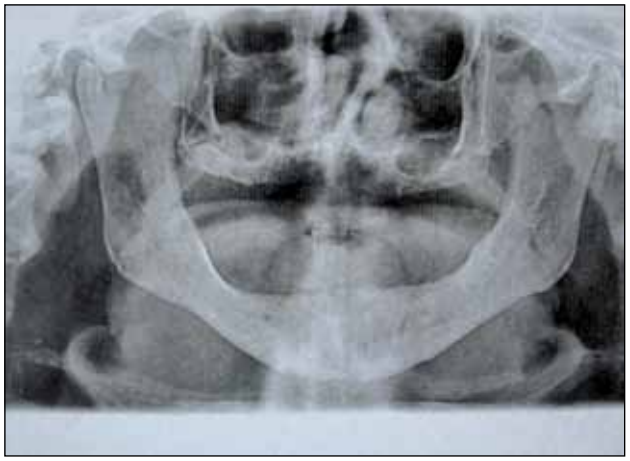

Figure 1. OPT scan

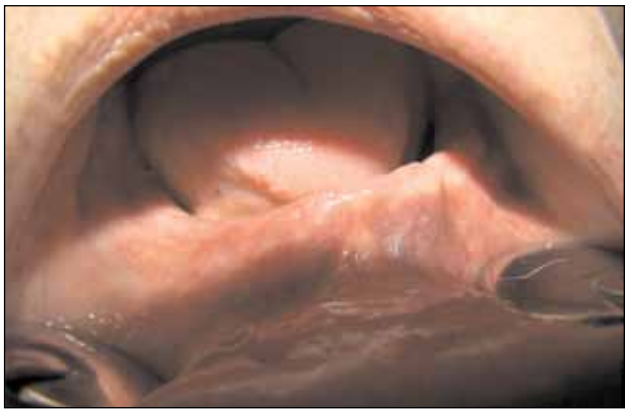

Figure 2. Intraoral finding

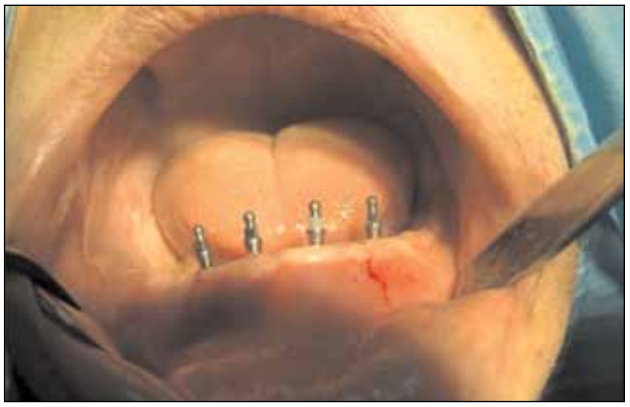

Figure 3. Inserted implants

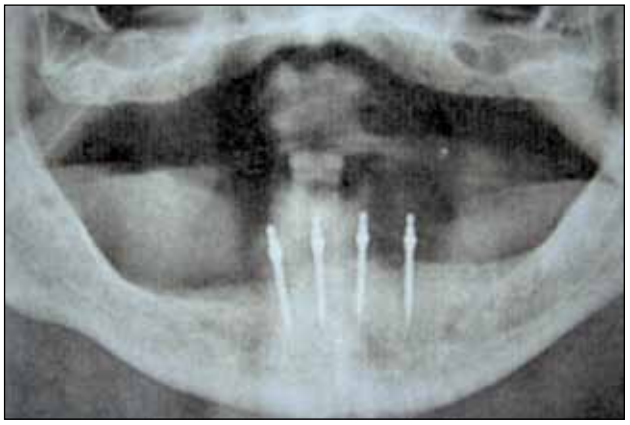

Figure 4. Control OPT scan

Figure 5. Positioned metal caps

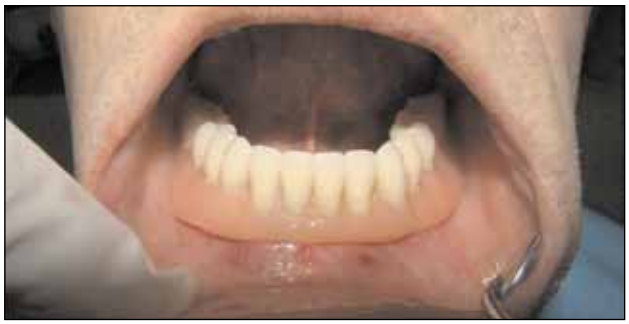

Figure 6. Final appearance of the patient

Case No. 2

Male patient, aged 76, came to our Clinic for complete prosthetic rehabilitation of the upper and lower jaw. Clinical examination and analysis of the OPT scan revealed total toothlessness of the lower jaw and partial toothlessness of the upper jaw. After consulting, definitive therapy plan was made. The upper jaw was rehabilitated using a fixed denture (metal-ceramic bridge), whilst in the lower jaw an implant-supported total denture was made. Considering pronounced and uneven resorption of the lower alveolar ridge and difficulties by positioning a mini implant, we decided to perform placement of four mini implants, with a *diameter* of *1.8 mm* and a *length* of 10mm, employing the so-called open technique. This technique differs from the flapless approach only by the existence of surgical incision.

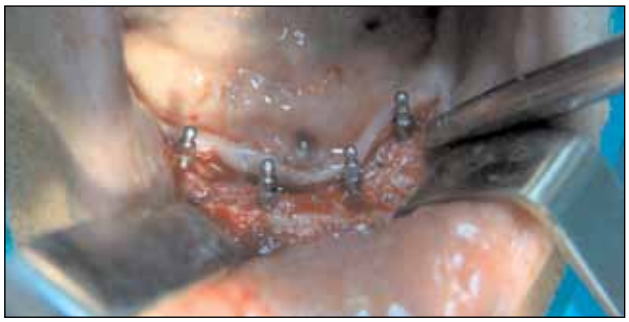

Figure 7. Intraoperative finding

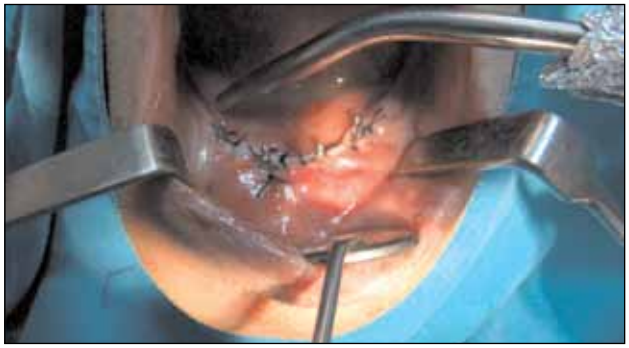

Figure 8. Sutures' position

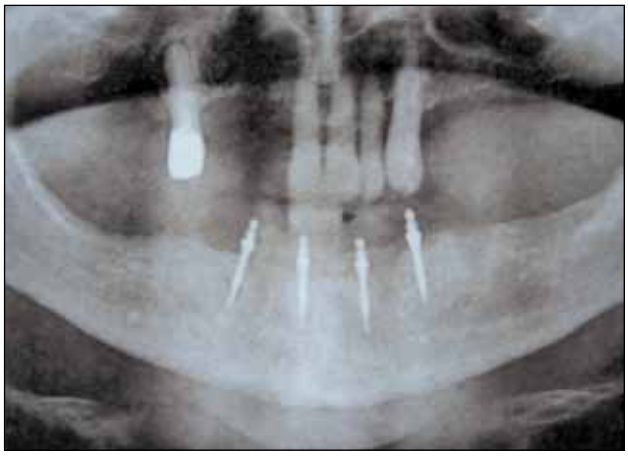

Figure 9. Control OPT scan

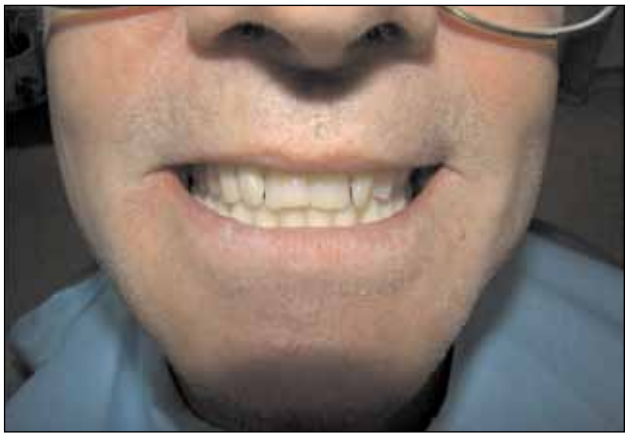

Figure 10. Final appearance of the patient

Discussion

The major advantage of mini implant systems is a minimally invasive surgical procedure and almost negligible postoperative discomfort. Non-invasive surgical procedure implicates the flapless technique („no incision"), direct formation of implant bed through the gingiva and the bone, with minimum damage for surrounding soft tissues of the alveolar ridge. In some cases, such as bony exostoses, uneven resorption of alveolar ridge, knife-edge shaped alveolar ridge etc., the open technique is indicated, i.e. surgical incision with elevation of mucoperiosteal flap. The open, that is, incision technique is more comfortable for the surgeon by providing better visibility of the operation field and better orientation of the implant direction. However, the procedure is more stressful for the patient, is associated with more complicated postoperative course, thus it should be avoided in the elderly patients.

The decision about the need for making an incision before placing mini implants, and the subsequent need for sutures (stitches) after the implants are placed is made on a case-by-case basis. The major factor is the shape of the remaining bony ridge as determined by x-ray. If a patient has been without lower front teeth for a very long time (decades), the bone at the top of the ridge may be quite sharp. Consequently, the pilot drill used to prepare the bone to receive the implant may slip off the top of the ridge when the hole is started. To avoid this problem and to allow the implant to integrate into bone along its maximum length, the dentist makes an incision along the ridge, from about where the canine tooth used to be on one side to the canine position on the other side. This allows the dentist to visualize the bone, and to flatten the sharp ridge slightly in order to drill the pilot holes in precise positions.

Another advantage of mini implant system is the possibility of their immediate load after placement into the bone tissue of the lower jaw (disregarding the technique), which practically means that patient can get the implants and implant-supported total lower denture in just one visit to the dentist. (6, 7, 8)

Mini dental implants are not intended to replace conventional implants. Their application relies on strictly defined indications, which should be carefully considered when planning the prosthetic treatment (9).

Conclusion

Majority of well-established mini implant systems are available at our market. An accurate diagnosis, therapy plan, precise placement, i.e. adequate and appropriate prosthetic solution enable replacement of missing teeth with maximum preservation of architecture of surrounding soft tissue- and bone structures. Furthermore, in toothless persons, especially in the elderly, application of mini implant systems provides an additional stability of mobile dentures, particularly the total lower denture, what makes their lives much more comfortable. Nowadays, modern implantology does not pose the question „is it possible? “, but focuses the research towards finding an answer to the question „how to do it sooner? “

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Organ Donation: knowledge and attitudes of Health College and other departments' students in a Turkish University

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Abstract

Objective: The aim of the study was assess knowledge and attitudes on organ donation both in the Health College and other departments' students of the university.

Methods: The study was carried out among the students enrolled in the Health College (1st group) and the other departments (2nd group) of the same university. A total of 609 university students were taken in the sample group. A questionnaire, with 19 questions, was developed by the researchers after reviewing the literature. Data evaluated with Chi-square and Fisher's exact test.

Results: 90.6% of the students in the 1st group and 83% of those in the 2nd group were informed about organ donation. Willingness to donate was significantly higher among the 2nd group students (46%) than the 1st group (35.6%). However, while 4.2% of the 1st group students said that they carried legal donor cards, only 0.7% of the 2nd group students did so. 44.3% of the 1st group and 70% of the 2nd group said they did not know where to apply to become organ donors. 60.2% of the 1st group and 66.7% of the 2nd group reported that organ donation to be religiously appropriate.

Conclusions: The results of the study indicate the need for more information and education to prepare university students about organ donation. Especially, the next generation of health care professionals must be targeted.

Key words: attitude, midwifery, nursing, organ donation, university students

Introduction

Organ transplantation is one of the most efficient ways to save lives and improve the quality of life for people with end-stage organ failure (1). Improvements in transplantation have greatly increased the number of potential transplant recipients (2,3).

Today, shortage of cadaveric organs for transplantation is a global problem (2). Developed countries generally meet their organ needs through cadaver organs, in developing countries like Turkey; the majority of transplantations are performed with organs taken from living relatives (1, 4). In developed countries 80% of donated organs are from cadavers and 20% are from living persons. On the other hand, in Turkey about 75%-80% are living donors (2, 5, 6). The number of cadaver donors for each million population is 34,6 in Spain, 21,1 in Italy, 20,9 in France, whereas in Turkey it is only 2,4 (2). While organ removals from cadavers have become more successful, at the same time, the number of patients waiting for transplantation increases. Organ donation rates have fallen behind the demand for organs (7, 8). If enough donor organs were available, many thousands of patients in the worldwide could benefit from organ transplantation (9). Currently, in our country, there are about 50,000 people being treated for end stage kidney failure (6).

Several factors; such as experiential, educational, social, cultural, and religious, have been affect the people's attitudes, beliefs, and behaviors toward organ donation and transplantation (10, 11). People's attitudes and beliefs toward organ donation contribute significantly to willingness to donate (9). Especially, education provides to increase people's knowledge and awareness of this issue (6, 12).

The knowledge and attitude of university students, who are key actors in transferring information and raising awareness about organ donation, are considerable (13). Individuals with higher educational levels and younger persons have positive atti-

tudes to be a cadaveric organ donor and in general, university students represent the well-educated and younger population (9, 14). Educated individuals with good social support systems and strong emotional support have a more favorable attitude to organ donation (15). In addition, health care professionals also play an important role in eliminating barriers and increasing organ donation (16, 17). Therefore, assessing the opinion of university students and next generation health care professionals is important for the future organ supply (18).

The aim of the study was to assess knowledge and attitude towards organ donation among the health college students, who will take part in society's health education, and the university students from other departments.

Methods

Study Design, Setting and Sample

The descriptive and cross-sectional study was performed among students enrolled at the health college and other departments (except health-related school, medicine, dentistry, pharmacy etc.) at the university located on the European side of Istanbul. Health college students were the 1st group, and the other departments students were the 2nd group. Between January and March of 2010, a total of 609 university students, 309 of whom were enrolled in the Health College, answered the questionnaire.

Group 1: The questionnaire was only applied to the health college students since the departments of medical, dentistry, pharmacy, and physical therapy schools/faculties are located on a different campus. The health college has two parts: nursing and midwifery. The total number of students is 371. 309 questionnaires were assessed in the study. The questionnaires were handed out to the students at the beginning of a lecture and were gathered after the students completed filling the questionnaires.

Group 2: The same questionnaire was given to students from different departments which were not related to health sciences. The researchers visited on the main campus in order to collect data from students. We tried to include students from various departments in our sample. Students who consented to participate in the study filled the questionnaires. 300 students were enrolled in the second group.

Questionnaire Form

A questionnaire, with 19 questions, was developed by the researchers after reviewing the literature (7, 16, 18, 19). A pilot questionnaire was filled by 20 students at the health college to identify and eliminate bias in the questionnaire design. As a result, minor changes in wording were made. Questions about demographic variables such as age, gender, year in school, and school division (nursing and midwifery), were included along with questions on information about organ donation, source of knowledge, willingness to become a donor and, if not, why, where to apply for become donor, organ donation card holders, and whether they find organ donation religiously appropriate. It took 5-10 minutes to complete the questionnaire.

Ethical considerations

The study was performed in accordance with the principles of the Declaration of Helsinki. Written permission for this study was taken from the health college administration. Students from other departments in the university's main campus accepted to take place in the study comprised the study group. The purpose of the study was explained to all the students as verbally.

Statistical Analysis

Results were expressed as mean, standard deviation, and percentages for categorical data. Categorical variables were compared with Chi-square test and Fisher's exact test. An age variable was evaluated with t-test in the independent samples. P values less than 0.05 were considered significant. The data was analyzed using the Statistical Package for the Social Sciences (SPSS) 15.0 software package.

Results

At the study, we assessed with 609 students. In the 1st group, the mean age was 21.93+2.01, and 97.7% (n=302) of the participants were female. The mean age was 20.85+2.84, and 51.3% (n=154) of the participants were female in the 2nd group. Since the majority of Health College students are female, the number of female students in the 1st group is higher.

We found that the 1st group (90.6%, n=280) was better informed on the subject of organ do-

nation compared to the 2nd group (83%, n=249) (χ^2=7.735, p=0.005). 75.7% (n=212) of the students in the 1st group and 94.7% (n=236) of those 2nd group said that they get information on organ donation from the media. Willingness to donate organs was significantly higher among the 2nd group (46%, n=138) than the 1st group (35.6%, n=110), (χ^2=6.994, p=0.030). However, while 4.2 % (n=13) of the students in the 1st group reported having donor cards, only 0.7% (n=2) of those in the 2nd group did so (Fisher's exact test p= 0.005). 48.5% (n=150) among the 1st group and 39.7% (n=119) among the 2nd group stated being undecided about organ donation. 44.3% (n=137) of the 1st group and 70% (n=210) of the 2nd group said they did not know where to apply to become donors (χ^2=40.897, p=0.0001). 60.2% (n=186) of the 1st group and 66.7% (n=200) of the 2nd group reported that organ donation is religiously appropriate (χ^2=6.319, p=0.042) (Table 1).

Among the participants who did not want to donate their organs; the most frequent reason "no reason" was high in both groups (group 1; 81.6%, n=40, group 2; 97.7%, n=42). "Fear" (32.6%, n=16) and "don't want to destroy the integrity of the body" (22.4%, n=11) were expressed as other major reasons in the 1st group (Table 2).

*Table 2. The reasons for refusal to donate organs**

	1st group (n=49)		2nd group (n=43)	
	n	%	n	%
No reason	40	81.6	42	97.6
Religious beliefs	4	8.1	6	13.9
Fear of torment of the body after death	3	6.1	3	6.9
Fear	16	32.6	2	4.6
Don't want to destroy the integrity of the body	11	22.4	10	23.2

**Marked more than one option. Percentages were calculated based on "n".*

Discussion

Increased knowledge about organ donation and transplantation was predictive of more positive attitudes (9). The present study, most of the students from both groups said that they had knowledge about organ donation. Akgün et al. (13) found that 90.1% of university students have knowledge on organ donation. In another study which includes health college students, it was found that 59.5% of university students have knowledge on organ donation (20). Although the 1st group was found to have significantly more knowledge, it is pleasing to find a higher overall rate of knowledge on organ donation in our study. Increasing knowledge of next generation health care professionals about organ donation and transplantation will hopefully increase the number of future donors. However, Ohwaki et al.(11) reported that increased knowledge alone was not enough to change

Table 1. Students' attitudes on organ donation

	1st group (n=309)		2nd group (n=300)		Total	
	n	%	n	%	n	%
I have knowledge about organ donation	280	90.6	249	83	529	86.9
I don't know about organ donation	29	9.4	51	17	80	13.1
I received information from the media*	212	75.7	236	94.7	448	84.7
I received information from the school*	171	61.1	91	36.5	262	49.5
I'm willing to donate organs	110	35.6	138	46	248	40.7
I don't want to be an organ donor	49	15.9	43	14.3	92	15.1
I'm undecided to donate organs	150	48.5	119	39.7	268	44.2
I'm already a registered donor	13	4.2	2	0.7	15	2.5
I haven't organ donor card	296	95.8	296	98.7	592	97.2
I knew where to apply to become donors	172	55.7	90	30	262	43.0
I don't know where to apply to become donors	137	44.3	210	70	347	57
Organ donation is religiously appropriate	186	60.2	200	66.7	386	63.4
Organ donation is against my religious beliefs	7	2.3	13	4.3	20	3.3
I have no idea	116	37.5	87	29	203	33.3

**More than one option was marked. Percentages were calculated based on "n".*

an individual's behavior and correct knowledge should be needed. We also believed that education is important in improving students' opinions about organ donation.

In our survey, both groups reported the media as the primary source of knowledge. Previous studies have shown that media has been indicated as the most common source of knowledge on organ donation (7, 8, 19, 21). In this study, over half of the 1st group and fewer half of the 2nd group noted school education as their source of information. Salim et al. (22) found that a media (especially television) campaign can significantly influence organ donation awareness, knowledge, and beliefs. Pham and Spigner (23) stated that school-based organ donation education is optimal for the young people. In current study, more than half of the future health care professionals refer to media as their source of knowledge; this issue should become more important in their education.

Students usually have a more favorable attitude to organ donation and transplantation than the general population (15). Two studies among university students in Turkey reported willingness to donate organs to be 49.5% and 23.6% (13, 19). In another study, this rate was 65.5% (3). The current study, less than half of both groups reported that they are willing to donate organs. Although other studies conducted in our country reported similar rates, among our health college students were less interested in becoming donors. Ohwaki et al. (11) found that there was no difference in their willingness to donate organ between medical students and non-medical students. Health care professionals' attitude positively influences the decision of potential organ donors' family members and they play an important role in organ donation (4, 8, 24, 25). Since health college students will take part in educating the society on organ donation in the future, the topic should be included in their curriculum and it should be approached more sensitively. New educational policies should be developed to improve awareness.

Individuals who have a positive attitude toward organ donation are more likely to be willing to donate and/or to sign a donor card (9). Although there is a higher rate of students who are willingness to donate organs in the 2nd group, it is worrisome that only few participants have organ donation cards. Goz et al. (3) found that 6% of students reported to have organ donation cards. A study among medical students in Turkey showed that only 1.2% have organ donation card (26). These findings are compatible with other studies but we think that these rates are too low compared to other countries; 22% in Iran, 31% in Japan, 16% in Italy (25, 27, 28). The rate of students, who express willingness to donate organs, is higher than those carrying donor cards. It is clear that most students do not know where to apply to become donors. It is easier for health college students to reach the relevant information than others but the rate is still not enough. Insufficient information on the organ donation procedure prevents the current sensitivity from being reflected in actual donation.

Religious belief is one of the factors that affect an individual's decision on organ donation (29). Strong religious/spiritual beliefs may be predictive of lower willingness to donate (9). The Islamic religion permits organ transplantation as long as the person is dead at the moment of removal of the tissue or organ (7, 19). In this study, we found that more than half of the both group see organ donation religiously appropriate. These rates are unsatisfactory. We think that this might be a barrier to organ donation and that correct information is necessary. If we want to increase organ donation, religious/spiritual beliefs must be considered.

If we could begin to gain an understanding of why people are resistant to donating organs, it might contribute to an increase in organ donation (4). In this study, most people stated that "no reason" for unwillingness to donate organs in both groups. Lack of awareness for organ donation and transplantation is a common practice. But it is important to educate both young people and adults for organ donation (15). The current study, the second reason is "fear" in the 1st group and "not wanting to destroy the integrity of the body" in the 2nd group. Lack of information, religious reasons, commercial organ use, harming body integrity and thoughts of organs taken before death have all been expressed as reasons to refuse donation in other studies (2, 3, 19). Limited thinking about death could also be reason for not accepting a commitment to organ donation. We think that this hesitation might disappear if people had sufficient knowledge on organ donation. These responses

may be useful in planning education about organ donation and tissue transplantation and it be useful in future studies.

The present study has some limitations. First, the study may represent only our Health College students; it might not be generalized to other nursing and midwifery students. Second, the sample size of the study was too small especially in the second group. Thus, it should be repeated with a larger university population.

In conclusion, there is a growing need for organ donations in the Turkey. The current study, knowledge on organ donation was high. A more positive attitude towards organ donation was expected from nurse-midwife students compared to the general population, but their willingness to become donors is lower. The results of the study indicate the need for more information and education about organ donation for university students, especially future health care professionals. In order to develop of individual and community awareness, education of this population is crucial in countries like Turkey.

Finally, these findings highlight that organ donation should be included in the curriculum for all university students. It is necessary to review the curricula of medical and health science schools/ faculties' and emphasize the importance of organ donation. These subjects should be included in the all university classrooms as part of the compulsory curriculum.

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Laryngopharyngeal reflux in patient with morbus Bechterew: Case report

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Abstract

Laryngopharyngeal reflux is the reflux of gastric contents into the upper airways. Acid content in the throat, mouth and trachea is associated with the emergence of symptoms such as hoarseness, chronic cough, snoring, burning throat, otitis media, irrigative drip and dental caries. The pain behind the sternum and the feeling of heartburn are absent in more than two thirds of patients.

Patients diagnosed with ankylosing spondylitis are predisposed to excessive secretion of gastric acid most likely due to the long-term therapy with NSAIDs. Impaired function of the lower and upper esophageal sphincter is common in patients with autoimmune diseases and results in the return of acid content in the upper airways with concomitant symptoms laringofaringealnog and/or gastroesophageal reflux.

We report a patient with ankylosing spondylitis with symptoms of laryngopharyngeal reflux which is proved with 24-hour pH-metry.

Key words: Laryngopharyngeal reflux, Ankylosing spondylitis, pH metry

Introduction

Laryngopharyngeal reflux represents the return of gastric contents from the stomach through the esophagus into laryngopharinx. It is part of a wider syndrome extraesophageal reflux (EER), which includes the presence of gastric contents, not only in laryngopharinx but also in other parts of the respiratory system: paranasal cavities, middle ear and lower respiratory tracts.[1]

Morbus Bechterew or ankylosing spondylitis (AS) is a complex, potentially debilitating disease that is insidious in onset, progressing in sacroileitis in over several years. Patients with symptomatic AS lose productivity, become unable to work, unemployed and reduced quality of life. The pathogenesis of AS is poorly known. However, immune-mediated mechanisms involving human leucocyte antigen (HLA)-B27, inflammatory cellular infiltrates, cytokines (For example, tumor necrosis factor and interleukin 10), and genetic and environmental factors are thought to play a key role. Detection of sacroileitis by radiography, magnetic resonance imaging, or computerized tomography in the presence of clinical manifestations is affirmative diagnostic for AS , although presence of inflammatory back pain plus at least two other typical features of spondyloarthropathies (for example, enthesitis and uveitis) is highly predictive for early stage AS.

We report a case of a patient with ankylosing spondylitis and symptoms of LPR, which is a reflux disease confirmed by endoscopy and 24 - hour pH-metry.

Case report

A 60 –year –old patient came to the ENT clinic complaining of a one-year constant coughing, hoarseness and occasional complete aphonia, burning sensation in the throat, and snoring.

Otherwise, suffers from ankylosing spondylitis over 15 years with periodic hospitalizations for treatment of primary disease. With regard to the diagnosis she is taking medications from a group of nonsteroidal anti-inflammatory drugs and more types in larger doses (acetylsalicylic acid, ibuprofen, diclofenac etc.).

With indirect laryngoscopic examination (ILS) is found RFS> 11 (Table 1), which suggests a diagnosis of LPR.

Table 1. Scoring system of clinical signs of reflux in the larynx. "Bold" are results in our patient

subglotic edema	**2-yes**; 0 – no
ventricular obliteration	**0 – no;** 2 – partial; 4 - complete
erythema/ hyperemia	**2 - only the arytenoid cartilage**, 4 diffuse
edema of the vocal cords	1- slight, **2-moderate**, 3-serious, 4-polypoid
diffuse laryngeal edema	1- slight, 2-moderate, **3-serious**, 4-obstructive
Hypertrophy of the posterior commissure	1- mild, **2-moderate,** 3-serious, 4-obstructive
granulomas / granulations	2-yes; **0 - no**
dense laryngeal mucus	**2-yes**; 0 - no

After ILS- it is indicated a 24-hour continuous multi-channel pH-metry (pH Digitrapper GastroTrac TM (Alpine Biomed Corp.., USA) and GeroFlex Reusable pH catheter, Dual sensor, 21cm (Alpine Biomed Corp., USA).

Data were analyzed using the program GastroTrac ™ Version 4.3.0.47.

Twenty four hours pH-metric recording confirmed that it is laryngopharyngeal reflux (LPR) with an average pH value in the upper esophageal sphincter of 5.84. A gastroesophageal reflux (GER) is also confirmed in the patient with the criterion values DeMeeseter score is estimated to be 40.7, Johnson-DeMeeseter is 64.8 and Boix-Ochoa 38.5 (Figure 1).

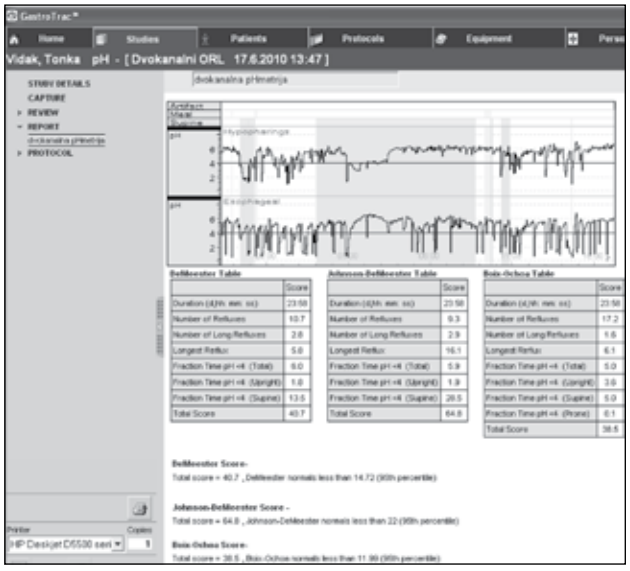

Figure 1. Representation of 24-hour dual-channel pH-metry

Due diagnosed GERD she was admitted to gastroscopy which was performed after a break of 14 days of irregular and subdosed taking proton pump inhibitors (PPIs) during the last two years (Figure 2).

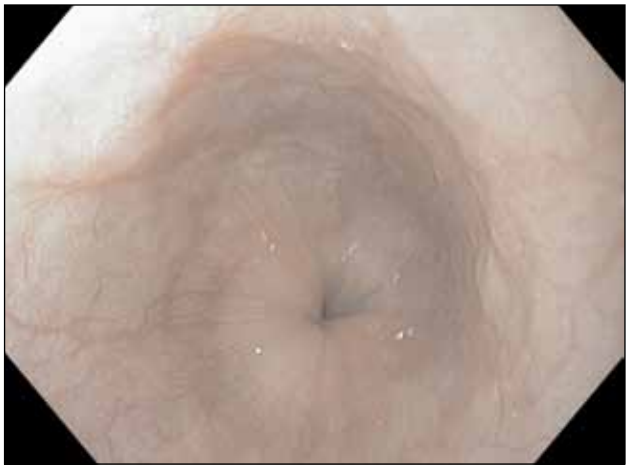

Figure 2. Gastrointestinal display area above the lower esophageal sphincter. It is visible a mild hyperemia of the esophagus lining

Given a diagnosis of LPR and GERD we prescribed 2x20mg PPIs for 3 months and the patient has already felt subjective better after 4 weeks, without symptoms of upper respiratory tract. Control RFS was 5 (Table 2).

Table 2. RFS after 4 weeks of PPI therapy ("bold" refers to our patient)

subglotic edema	2-yes; **0 – no**
ventricular obliteration	**0 – no;** 2 – partial; 4 - complete
erythema/ hyperemia	**2 - only the arytenoid cartilage**, 4 diffuse
edema of the vocal cords	1- slight, **2-moderate**, 3-serious, 4-polypoid
diffuse laryngeal edema	1- slight, 2-moderate**,** **3-serious**, 4-obstructive
hypertrophy of the posterior commissure	**1- mild**, 2-moderate**,** 3-serious, 4-obstructive
granulomas / granulations	2-yes; **0 - no**
dense laryngeal mucus	2-yes; **0 - no**

Discussion

Laryngopharyngeal reflux is the return of gastric contents from the stomach through the esophagus into the first laryngopharinx.

The predominant symptom of LPR is hoarseness (92% -100%) with chronic cough, snoring,

burning throat, otitis media, irrigative drip and dental caries, which does not exist in patients with GERD. On the other hand, a burning sensation in the chest is present in only 6% of patients with LPR and 89% in those with GERD. The majority of these patients will not have typical GERD symptoms like heartburn, and endoscopic oesophagitis. Therefore, the symptoms of patients with LPR are symptoms of the throat - laryngopharinx, and those with GERD are gastrointestinal. [3,4,5,6,12]

Typical changes are caused by reflux into the larynx and reflect upon the indirect laryngoscopy and / or endoscopy. There are eight specific changes contained in larynx, and may occur as a result of reflux. They were quantified in the so-called. RFS (reflux finding score).These are pseudosulcus vocalis, ventricular obliteration, erythema / hyperemia, edema of the vocal cords, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma / granulation and dense endolaringeal mucus (Table 1). Each of these findings are quantified according to the instructions in Table 1 and the sum of "points"> 11 points to secure diagnosis of LPR-a.[7]

LPR is a risk factor for abnormal breathing during sleep (snoring and obstructive sleep apnea). Increased acidity in the upper esophageal sphincter is proven and measured (pH-metry) in patients with breathing disorders during sleeping.[8]

According to a research-Erb et al. 4% of patients with ankylosing spondylitis have abnormal breathing during sleep. The same study confirmed a Solak et al. [9]

In addition patients with ankylosing spondylitis are often on long-term NSAID therapy and because of underlying disease they have impaired function of the upper and lower esophageal sphincter so it is expected the appearance of symptoms of upper respiratory tract and in that sense should be directed the diagnostic process.

In our patient is confirmed the LPR and GERD by objective 24-hour ph-metry and it is included therapy with proton pump inhibitors (PPIs), 2x20 mg (pantoprazole) according by the American Academy of Otolaryngology and Head and Neck Surgery. In life threatening forms of LPR and it is necessary to give 80 mg daily for at least six months. When improvement occurs, therapy should be gradually reduced and then completely disrupt.[1,3,4]

PPIs act directly on the H +-K + ATPase, which is a key enzyme in the final stage of the mechanism of acid formation. Medication works by reducing the exposure of tissue to acid and reduces pepsin activity that requires a certain acidity to its activation. Furthermore, there are studies that suggest that PPI increases the tone of the sphincter, which additionally contributes to reducing reflux.[10]

Giving the drug once daily PPI is not sufficient because of the possible occurrence of reflux at any time during the 24 hours (more frequently during the day, less often at night), a half-life of these drugs in plasma is a maximum of 15 hours. It is therefore necessary to provide treatment that works 24 hours.[11]

Improving the RFS and reducing symptoms of upper respiratory therapy after one month confirms earlier mentioned research.

Conclusion

The appearance of symptoms of upper airway (hoarseness, cough, foreign body sensation in the throat, burning throat, and snoring) in patients with ankylosing spondylitis may involve the presence laryngopharyngeal reflux and in this sense should be directed treatment and therapy (ENT examination and 24-hour pH -metry, and ev. gastroenterologist review).

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Advanced Langerhans Cell Histiocytosis- a case report of a rare disease

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Abstract

Adult Langerhans Cell Histiocytosis (LCH) is a quite rare and tobacco smoking related disease. We report on a case of pulmonary LCH, diagnosed at the Teaching Hospital of Lung Disease, Clinical Centre of Serbia in Belgrade. On admission, a 45-year-old mechanician, smoker (30 pack/years) had severe dyspnea, fatigue and massive pretibial/ankle oedema due to right-heart failure. Since the age of 19 years, he suffered from recurrent pneumothorax, and the first radiographic changes (bilateral micronodular shadows) were present at the age of 39 together with obstructive disturbance of ventilation and respiratory failure. At the patient's age of 40 years, open lung biopsy led to diagnosis of LCH. Investigation was completed with computed tomography scans, hemodynamic investigation (heart catheterization and pneumoangiography), echocardiography, skeletal scintigraphy, and additional lung function testing. Treatment included methylprednisolon, sildenafil, and diuretics. The patient is being followed up and severe pulmonary arterial hypertension is usually considered a poor prognosis.

Key words: Langerhans cell histiocytosis, pneumothorax, tobacco smoking, pulmonary arterial hypertension, case report

Introduction

Langerhans cell histiocytosis (LCH), named histiocytosis X by Lichenstein in 1953, is a disorder of unknown etiology characterized by proliferation of $CD1a^+$ dendritic cells [1]. Adult LCH is a quite rare disease with an incidence of 1–2 cases per million [1]. LCH may present as a single organ system disease or multi-organ system disease. In the single organ system disease, skin, lung and bone involvement are common. Unlike LCH in children and adolescents, who are predominantly affected, disease is often monosystemic in adults with relatively better prognosis [2]. Skin involvement is the most common type of presentation and lung involvement is the most severe form of the disease [3]. The most striking epidemiological characteristic of adult pulmonary LCH, which occurs sporadically, is that 90-100% of patients are smokers (often smoking >20 cigarettes $a \cdot day^{-1}$) [4]. However, the low incidence of pulmonary LCH compared with the high prevalence of smoking in the population at large strongly supports the existence of host-related factors that predispose to the development of this disease.

Many questions related to LCH etiopathogenesis and treatment still remain unanswered [3,5]. Owing to available advanced imaging and molecular genetic techniques, LCH is in focus of current research [6,7]. Genetic alterations at the cellular level may disrupt mechanisms controlling the proliferation and apoptosis of Langerhans cells (LC). Previous studies have examined the expression and functional significance of LC-specific genes. However, only a few studies have examined the genes involved in the cell cycle of LC, such as *p53*, MDM2, *p16*, *p21*, *ki-67*, and *Bcl-2[3]*. Much remains unclear regarding the expression of these genes and their clinical significance in LCH. Recently, Zhang X, et al. reported on the first case that hints at an association between LCH and X-linked lymphoproliferative disease [5].

Because of its rarity and the broad clinical spectrum, the diagnosis of LHC is often delayed or missed [5]. We report on a case of the disease diagnosed at the Teaching Hospital of Lung Diseases of the Clincal Centre of Serbia in Belgrade after a long-term episodes of reccurrent pneumothorax on one or the other side with normal both lung function tests and chest x-ray findings for years.

Case description

A 45-year-old mechanician, a smoker (30 pack/years), was admitted with chief complains of severe dyspnea (New York Heart Association [NYHA] functional class III or IV), fatigue and massive pretibial and ankle oedema as evidence of right-heart failure.

Patient's history - History taking and review of previous medical files showed that the patient has been suffering from epilepsy since the age of 7 years when 100mg a.day^{-1}.phenobarbital therapy started. At the age of 19 years, he had the first spontaneous pneumothorax on the left side, and since then, several hospitalizations due to pneumothorax at one or the other side - five times in total over the period of 26 years. Microbiological investigation of sputum samples for *Mycobacteria* was negative all the time. At the age of 39 years, after prolonged period without functional or radiographic changes, the first micronodular shaddows were detected together with obstructive disturbance of ventilation. Performed bronchoscopy has not been effective with regard to diagnosis and performed open lung biopsy led to diagnosis of LCH and bullous emphysema. Skeletal scintigraphy was normal. Hemodynamic investigation included heart catheterization, which confirmed a moderate precapilary pulmonary hypertension, while pneumoangiography has not showed segmental defects. Coronary arteries were found to be without significant stenoses; left ventricle was of normal size and contactility with ejection fraction about 65%. Therapy composed of methylprednisolon 30mg a.day^{-1}, sildenafil 12.5mg 3 times a.day^{-1}, and diuretics, has led to clinical improvement and the patient was discharged. At the age of 41 years, spontaneous pneumothorax occured on the right side again and thoracic drainage was effectively performed. A medical notification showed that between the two hospitalizations, medication therapy was interrupted by patient's decision. Thus, sildenafil and diuretics were reintroduced.

Two years prior to current addmission, lung function testing showed severe obstructive disturbance of ventilation, marked hyperinflation, reduced diffusing capacity, and consequently, partial respiratory failure. Resistance in pulmonary pathwys was normal. Bronhodilation test was markedly positive.

Physical examination - On addmission, the patient was dyspnoic, with signs of central and peripheral cyanosis, afebrile, with mass bilateral pretibial and ankle oedema, without jaundice, peripheral lympadenopathy or left cardiac failure. Lung auscultation showed distant sound, and rare inspiratory rales over both bases. Heart rate: 120/bpm; BP: 120/80 mmHg; respiratory rate: 24/min; the rest of the findings was normal.

Routine peripheral blood laboratory findings showed leukocytosis (WBC:12.9xl0^{9}/L (normal range: (3.4-9.7xl0^{9}/L) and the rest was within normal limits including erithrocyte sedimentation rate. Arterial blood gas analysis showed hypoxaemia - PaO_2:7.2kPa (normal: 11.05kPa).

Imaging studies - Standard chest x-ray showed bilateral micronodular shadows and widening of the hilus region (Figure 1).

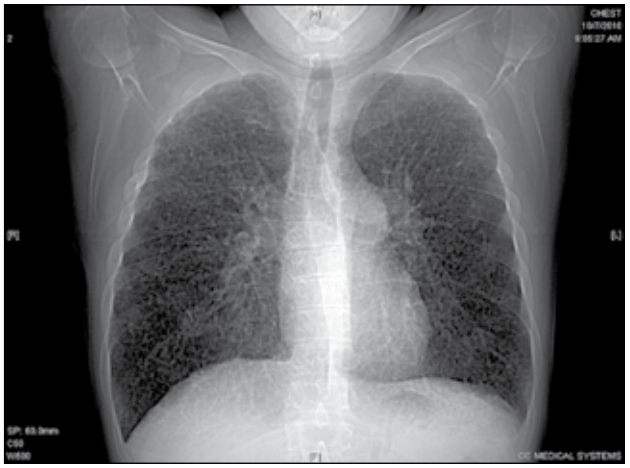

Figure 1. Standard chest radiograph in patient with Langerhans Cell Histiocytosis

Multislice chest computed tomography (MSCT), showed bilateral diffuse microcystic changes of pulmonary parenchyma with multiple numerous bullous formation the largest being 19x20x32mm, localized in the apical segment of the left lower lobe. The majority of the others were up to 10mm in diametre. In the middle and right lower lobe, several micro- and nodular opacities were seen subpleurally and along great incisure up to 10mm in diametre. Marked interstitial fibrosis was also seen (Figure 2).

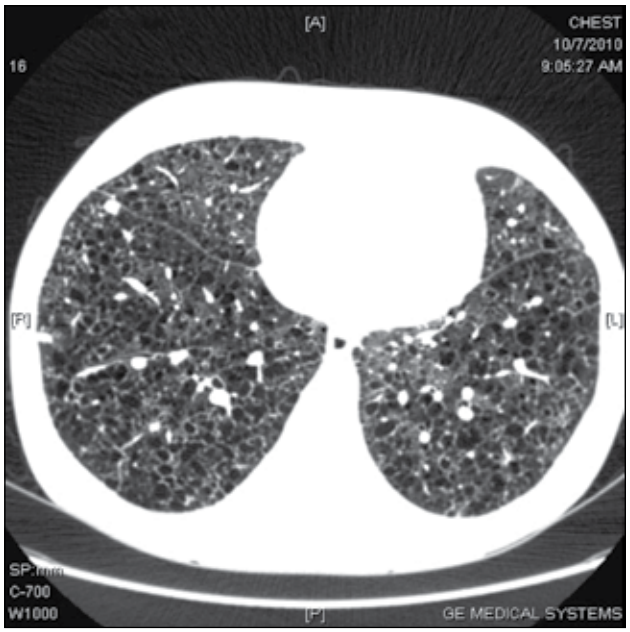

Figure 2. High-resolution computed tomography scan of the chest in a patient with advanced pulmonary Langerhans Cell Histiocytosis shows numerous variably sized pulmonary cysts and nodules that are confluent at some places

Pulmonary artery diametres were as folllowes: truncus: 39x49mm, right main branch: 29mm, left main branch 26mm; the lobar branches are dilated bilaterally, while peripheral vascular structures were reduced (Figure 3).

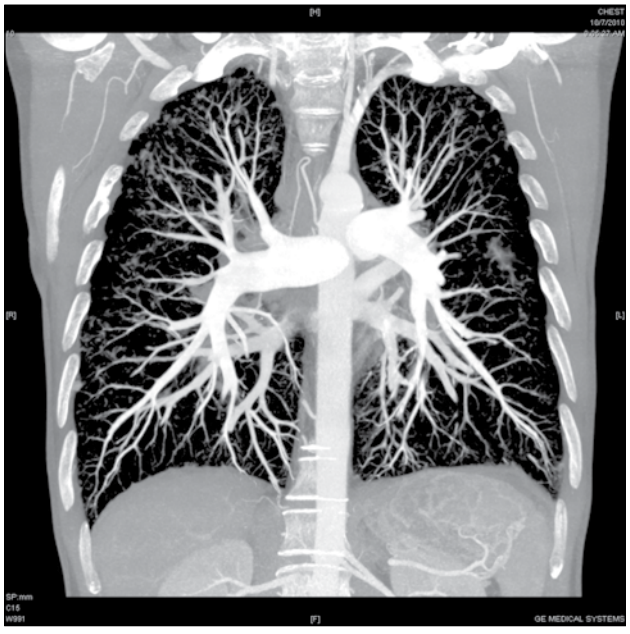

Figure 3. High-resolution computed tomography scan shows markedly dilated pulmonary artery branches

Lung function testing showed FVC: 65%, FEV_1: 33%, FEV_1%FVC: 42.09, hyperinflation, and markedly dicreased gas transfer (transfer factor and carbon monoxide transfer coefficient).

Echocardiography: normal findings of thoracis aorta and left ventricle; right ventricle is markedly enlarged (RV:40mm) and pulmonary artery is dilated (3.lcm), right main branch being 2.5cm. Important tricuspidal regurgitation (+3) was found and indirectly estimated sistolic pressure in the right ventricle was 80 mmHg. Pulmonary regurgitation was found to be 1+ and diastolic gradient 30 mmHg. Pericardial layers were only slightly separated for 2-3 mm in diastole near anterior part of the right ventricle while adhaesions were seen near posterior and lateral wall of the left ventricle. Mitral valve and left atrium were normal in terms of diametres and kynetics.

The patient's condition improved under therapy (sildenafil 50mg 3 times $a.day^{-1}$, and diuretics) and continual oxygene therapy, which was recommended to be continued at patient's home. Professional help in smoking cessation was also recommended.

Discussion

We have presented a case of rare disease – advanced pulmonary LHC in a 45-year-old male smoker that caused severe pulmonary hypertension, and was diagnosed at the patient's age of 40 years. This heavy smoker initiated smoking at the age of 15 years. For pulmonary LCH in adults, which occurs almost exclusively in smokers, accurate epidemiological data are not available. It predominantly affects young adults, with a frequency peak at 20-40 yrs of age [4]. A marked male predominance was initially reported for pulmonary LHC [8], but, in more recent studies, a similar proportion of males and females, or even a slight predominance of females, was observed, particularly in series from the USA [9,10]. It is possible that these differences reflect smoking prevalence changes over time with shift towards women [11].

It is considered that the prevalence of pulmonary LCH is probably underestimated because some patients exhibit no symptoms or experience spontaneous remission, and histological findings are nonspecific in the advanced forms. Our patient had recurrent pneumothorax and experienced no respiratory

symptoms between the episodes. Both his chest x-ray and lung function tests were normal for years.

Chest high-resolution computed tomography (HRCT) has proved a major breakthrough in the diagnosis of pulmonary LCH, and is now mandatory when this condition is suspected [10,12]. The wide use of HRCT in the evaluation of patients may lead to an increase in the number of patients in whom pulmonary LCH is diagnosed in the future. In our patient, HRCT provided additional details about the parenchymal elementary lesions, such as cavitations of nodules, which were not visible on standard radiograph. Diagnosis was confirmed on lung biopsy. However, in patients with suggestive clinical manifestations, HRCT findings are often sufficient to establish the diagnosis, such that the need for surgical biopsy should be discussed on a case-by-case basis by an experienced pulmonologist [4].

Standard laboratory tests are uninformative in LCH [10]. A mild increase in peripheral neutrophil counts as found in our patient may be related to smoking. Evidence of a systemic inflammatory reaction like increased sedimentation rate was also typically absent.

Pulmonary LCH can be associated with severe pulmonary arterial hypertension, and symptoms and hemodynamic features similar to those seen in primary pulmonary hypertension can dominate in the clinical presentation [13]. This actually has occurred in our patient, who also had an evidence of pulmonary artery enlargement.

Differential diagnosis includes Mycobacteria and other infections, sarcoidosis, Wegener's granulomatosis, cavitated pulmonary metastases, bronchiolar alveolar carcinoma, septic emboli or cavitated P. Jiroveci pneumonia [14]. In females, pure cystic pulmonary LCH may be difficult to differentiate from lymphangioleiomyomatosis [15].

Our patient belongs to those approximately 10-20% of patients that have early severe manifestations, consisting of recurrent pneumothorax or progressive respiratory failure with chronic cor pulmonale. Long-term follow-up is mandatory and may detect exacerbation of respiratory dysfunction after many years, or, rarely, a relapse with recurrent nodule formation. Although a resolution of the disease after smoking cessation has been reported, in general, severe pulmonary arterial hypertension indicates a poor prognosis [16].

Acknowledgement

Supported by the Ministry of Science, Technology and Development of the Republic of Serbia through contract No. 175095, 2011-2014.

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Pregnancy and delivery after conservative management of the uterine rhabdomyosarcomatous adenosarcoma in adolescence – Case report

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Abstract

Introduction. The occasional case of leiomyosarcoma is diagnosed upon histologic examination of the specimen after a patient has undergone a myomectomy. In some young and nulliparous women with a low risk of disease recurrence, conservative treatment protocol should be considered for the sake of possible fertility.

Case report. A 15 year-old girl had an urgent operation because of severe bleeding from the uterus. Wide excision of the uterine tumor was performed. She was referred to a medical center with extensive experience in treating cancers that occur during childhood and adolescence. Subsequent treatment (chemotherapy and surgical restaging of the disease) with routine control examinations enabled the patient to conceive and delivery at 35/36 gestational weeks by cesarean section, 13 years after surgery.

Conclusion. The management of uterine sarcomas is always controversial. In some cases it is possible to cure the patient and preserve fertility with wide surgical excision and subsequent chemotherapy.

Key words: uterine sarcoma, conservative treatment, pregnancy

Introduction

Uterine sarcomas are rare malignant tumors. Their microscopic appearances and often unpredictable biological behavior pose problems of classification and management. Hysterectomy and bilateral adnexectomy is the treatment of choice when the diagnosis is made preoperatively. The occasional case of leiomyosarcoma is diagnosed upon histologic examination of the specimen after a patient has undergone a myomectomy. The treatment of choice in these patients is a subsequent hysterectomy and adequate surgical staging, with or without adjuvant therapy. Psychological rehabilitation could be problem in such patients (1). However, well informed young and nulliparous women, in the presence of good prognostic factors, may choose to accept a low risk of recurrence for the sake of possible fertility.

Fortunately, cancer in children and adolescents is rare, although the overall incidence of childhood cancer has been slowly increasing since 1975 (2). Rhabdomyosarcoma is the most common form of soft-tissue sarcoma in the first two decades of life. Children and adolescents with cancer should be referred to medical centers that have a multidisciplinary team of cancer specialists with experience treating the cancers that occur during childhood and adolescence.

Case report

In April 1997 a 15 year-old girl M.Z. experienced severe bleeding from the vagina and was taken to the operating room. Examination revealed a large polyp coming through the cervical canal. It was tried to twist it off without success and the bleeding did not stop. At the necessary laparotomy a tumor was seen in the left corneal region of the uterus involving the serosa. Excision of that part of the uterus was performed. The histopathological diagnosis was mixed Mullerian tumor. A second opinion was sought, and the diagnosis of endometrial stromal sarcoma (high grade) was established.

The patient was referred to MD Anderson Cancer Center, Houston, Texas. The slides from the uterus were reviewed and showed that tumor was a rhabdomyosarcomatous adenosarcoma, a tumor with histological features of both embryonal rhabdomyosarcoma and adenosarcoma (Picture 1). Afterwards, an initial investigation of patient was per-

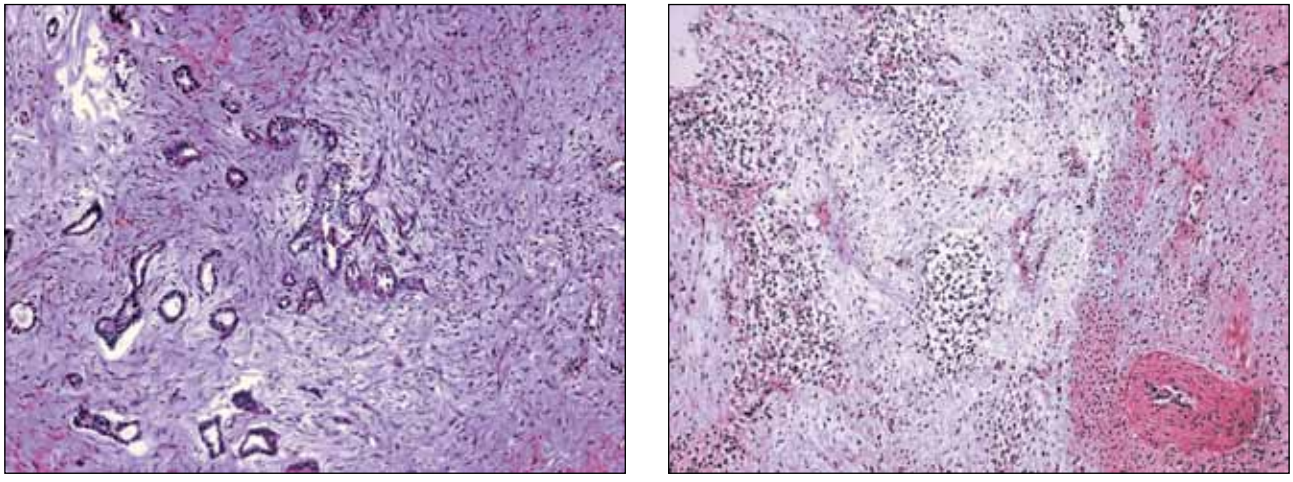
formed and her history was presented at two expert conferences. The consensus from these presentations was that the patient should receive 3 cycles of chemotherapy with vincristine, actinomycin D and cyclophosphamide (VAC protocol), have magnetic resonance imaging and surgical restaging procedure.The chemotherapy started in August 1997, consisting of vincristine 1.5 mg/m^2 to be given weekly, actinomycin D 1.5 mg/m^2 to be given every three weeks and cyclophosphamide 2.2 mg/m^2 to be given every three weeks with mesna. Mesna (sodium 2-mercaptoethane sulfonate) was the only protective agent for prevention of hemorrhagic cystitis connected with cyclophosphamide application. Sugical restaging consisted of hysteroscopy, endocervical and uterine cavity curettage followed by laparoscopy. There was no sign of residual disease and a normal left tube and ovary were noted, but the right ovary was not seen. Lymphadenectomy was not performed, so lymphnode status was not known. Chemotherapy was continued in Serbia where another 6 cycles were applied. The total number of VAC courses was 9, with regular menstruation commencing eight weeks after the last one in 1998. Routine control examinations (physical examination, laboratory analyses, pelvic and abdominal ultrasound, chest X ray, CT of thorax and pelvic MRI) were performed every 6 months until 2001. The patient has remained in good health with no evidence of recurrence.

In 2010, the patient conceived naturally and had a normal pregnancy. She was admitted in preterm labor at 35 gestational weeks, delivered by cesarean section and got a healthy boy (2450 g, 49 cm). During the operation only some adhesions around the uterus were seen, without macroscopic suspected changes in the abdominal cavity. Peritoneal washings were negative for malignant cells.

Discussion

Rhabdomyosarcoma is a highly malignant tumor characterized by muscle differentiation. With modern treatment, more than 70% of children and adolescents with this disease are cured. Adequate specimen of tissue for accurate diagnosis is critical. Patient must be assessed for tumor extent. Local control relies on complete surgical excision when possible. Those whose tumors are not completely excised and those with alveolar histology tumors require local irradiation to maximize local control. Rhabdomyosarcoma is sensitive to chemotherapy (3). A combined surgical approach and chemotherapy is most appropriate treatment for the most of patients, but the extent of the surgery that should be performed is still a question.

Few authors have published cases of successful pregnancy after fertility-preserving surgery for uterine sarcomas (4,5). In our case, suspicion on malignancy was made during the urgent operation by an experienced surgeon who decided to perform a wide excision of suspicious uterine tumor and suture the uterus because of the patients adolescent state. Three different groups of pathologists arrived at three different histopathological diagnosis. A discussion of histology of rare tumors is always interesting and of the greatest importance for further treatment steps. It is necessary for the tumor tissue to be reviewed by pathologists



Picture 1. Histopathologic features of the uterine tumor

with experience in the evaluation and diagnosis of tumors in children. Another problem in this case was whether or not there were clear margins in the uterus after resection of the tumor. When a lesion has been excised without knowledge of its malignancy, wide re-excision is indicated in order to obtain tumor-free margins (2). There was also the concern that some malignant cells may have entered the peritoneal cavity at the time of the prior surgery, and for that reason chemotherapy was necessary. Should any evidence of tumor persistence have been found in the uterus at the time of follow-up examinations a hysterectomy would have been performed.

Conclusion

Wide excision of a malignant uterine tumor in a 15 year-old patient and subsequent treatment (chemotherapy and surgical restaging of disease) with routine control examinations enabled the patient to conceive and deliver a healthy newborn by caesarean section, 13 years after surgery.

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Research on Knowledge, Attitude and Practice among Roma and Displaced Population on the Topic of Tuberculosis

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Abstract

Introduction: Some population groups are under an increased risk of tuberculosis disease due to insufficient awareness of this risk, insufficient knowledge on how to protect themselves, possibilities of treatment, stigma associated with TB, etc. Therefore an important part of every tuberculosis control programme is a health-education strategy aimed not only at those carrying the disease, but also the general population, especially vulnerable populations such as Roma and the displaced.

The aim of this paper is to show results of research about knowledge, awareness and behaviour, instances of experience of stigma and discrimination associated with tuberculosis among the Roma and internally displaced populations as especially vulnerable populations, aiming to measure changes in knowledge and awareness of TB after educational promo activities conducted between the two phases of research.

Methodology: This paper analyses and presents results of research conducted in Bosnia and Herzegovina (B&H) in two phases at the end of 2008, beginning of 2009, on a sample of 420 Roma and displaced people.

Conclusion: Results of the research show a need for raising the level of knowledge about TB, ways of transmission, early recognition of symptoms, possibilities of treatment, as well as advancement of attitudes and behaviour of population towards the carriers of the disease especially among the population more exposed to the risks of TB.

Key words: Tuberculosis, Roma, internally displaced, B&H

Introduction

Tuberculosis (TB) is an infectious disease, source of it being a pulmonary tuberculosis sufferer. Tuberculosis germs are present in sufferer's sputum, and are spread via air droplets: coughing, sneezing and speech. Tuberculosis is a disease that can be cured and must be cured undoubtedly not only for the reasons of curing the patient, but also to prevent recurrence of the disease**, prevention of occurrence of resistant breeds and protection of other persons from the disease[1]. Bosnia and Herzegovina counts among the countries with a higher incidence of tuberculosis** (41,32/100,000pop.)[2]. Prevention of TB, its early detection and treatment, require programmes targeted at raising the level of knowledge, awareness about the problem of TB, and the need for change in behaviour, especially among the vulnerable populatin[3]. We used the KAP study to collect base information about what the target population knows, believes and does in connection with tuberculosis, as well as information needed for planning and application of prevention-promoting activities and their evaluation[4].

Majority of KAP studies collect information via interview questionnaires, using a structured, standardised questionnaire. That way needs, problems, barriers and factors that affect prevention, detection and control of TB infection are identified.[5,6]

As part of the GFTAM Project „Further Strengthening of the DOTS Strategy in B&H“ implemented by UNDP B&H, this KAP study was conducted with the aim of evaluating the effect of conducted IEC (Information, Education, Communication) activities. The study was run in two phases - before and after IEC activities conducted in the interval of 6 months.

Data from the KAPB study are used in creation of lobbying, communication and social mobilisation especially needed among the vulnerable population that usually displays lack of knowledge of TB symptoms, awareness of TB prevention, possibility of treatment and the stigma that is associated with TB.[7]

AIM

Aim of this paper is to show results of research about knowledge, awareness and behaviour of Roma population and the displaced as especially vulnerable groups in the case of tuberculosis, to research their awareness, the experience of stigma and discrimination associated with tuberculosis, measure changes in knowledge and awareness in connection with TB after the conducted educational promo activities, i.e. campaign run between the two phases of research, as well as acceptance of communication channels and key messages about TB.

Research of this kind aids the detection of insufficiencies in knowledge about TB symptoms, awareness about TB prevention, possibilities of treatment, the stigma that accompanies TB, but also defines primary sources of information about TB for those target populations, telling us what communication channels, key messages and educational materials are most acceptable to this population.[8]

With this aim in mind, standardised indicators were selected as being: % of respondents who correctly identify main ways of TB transmission, % respondents who correctly identify main symptoms of TB, and % of respondents who consider it is embarrassing to carry TB.

Methodology and respondents

Research was conducted in 2008/2009 in two phases, as a cross-sectional study among internally displaced and Roma population groups, via a field research on a sample of 397 displaced persons (number of respondents in first phase, whilst the second phase covered 436 people), and 387 Roma, (number of respondents in first phase, second covering 351). Standardised questionnaire with 34 questions was used to cover respondents in pre-selected localities. Participation in this research was anonymous (coded questionnaire) and voluntary, conducted after an informed consent of participants.

Prior to this research, a mapping and estimation of the size of displaced and Roma populations was conducted, determining a list of localities with highest concentration of estates/inhabitants that fall within the frame of the groups targeted by this research.

Sample design

Sub-sample of displaced persons and Roma is three-staged and stratified.

At first stage, estates were selected by probability method proportional to their size.

In the second stage, households/communes were selected – the number being proportional to the number of households in every chosen estate.

In the third phase, interviewers randomly selected one member of a household/commune (the respondent that is subject of research) among all suitable subjects.

Criteria for inclusion into the sub-sample of the Roma group and the displaced were age above 18, also ensuring they do not have a medical background (health workers, pupils, students).

Processing, data entry and statistical analysis

After logical processing, data from the questionnaire of surveyed respondents was entered in the database using Access software and then statistically processed using SPSS computer software.

Data for three selected indicators is presented after logical and technical processing of secondary data gathered in a separate study by agreed methodology in selected areas of Federation of Bosnia and Herzegovina (FB&H) and Republika Srpska (RS). After processing data gathered in this way, descriptive statistical analysis was used to show unified results for Bosnia and Herzegovina (B&H) with parallel indicators for FB&H and RS.

Results

Socio-demographic data

Number of respondents belonging to the displaced persons group was 397 in the first phase (436 in the second), whilst Roma sample consisted of 387 respondents in the first, and 351 in the second phase.

Average age of respondents: displaced persons at 45 years of age, Roma at 42 y.o.a. Women were more represented in the displaced persons sample (67,1:32,951,3), men in the Roma sample (60,1:39,9).

Over 50% of Roma respondents have none, or incomplete elementary school education.

Over 30% of displaced persons respondents have none, or incomplete elementary school education.

One third of the latter have secondary education (27%), and 4% have completed two years of university or fully completed university education.

Data was processed for three selected standardised indicators:

1. % respondents who correctly identify main symptoms of TB
2. % of respondents who correctly identify main ways of TB transmission
3. % of respondents who consider it is embarrassing to carry TB

And are shown for each of the four sub-samples for B&H and parallel for FB&H and RS:

First indicator: % respondents who correctly identify main symptoms of TB

Rate of correct answers to the question „What are the signs and symptoms of TB?“ was the most significant criteria on the topic of knowledge about TB. „Cough and weight loss“ were taken as acceptable answers.

To calculate the correct percentage of those who are familiar with TB symptoms, analysis included only those respondents who positively answered to the question *„Have you heard of a disease called tuberculosis (phthisis)?“:*

Out of 387 respondents from the Roma subsample in the first phase of research, largest number (66,9%) correctly indicated cough among signs and symptoms of TB with a statistically significant increase (X^2 : 16,253; p<0,001) in the second phase of research (80,3%), whilst weight loss was pointed out by 19,6% (first phase), and this percentage increases in phase two to 27,3% (statistical significance X^2: 5,701; p<0,05).

Percentage of respondents who correctly cited a symptom of TB is slightly higher in FB&H. Out of respondents, 76,2% cite cough in the first, and

Table 1. Respondents' answers to question "What are signs and symptoms of TB?" – Roma group

Roma group																					
Symptoms of TB	Bosnia and Herzegovina						Federation of B&H						Republika Srpska								
	First phase N=387		Second phase N=351		Statistical significance		First phase N=151		Second phase N=170		Statistical significance		First phase N=236		Second phase N=181		Statistical significance				
	Rank	%	Rank	%	χ^2	P	Rank	%	Rank	%	χ^2	P	Rank	%	Rank	%	χ^2	P			
Cough	1	66,9	1	80,3	16,253	<0,001	1	76,2	1	87,1	6,418	0,011	1	61,0	1	74,0	7,235	0,007			
Coughing-up blood	2	48,3	2	56,4	4,509	0,034	2	55,6	2	55,9	0,002	0,964	2	43,6	2	56,9	6,687	0,010			
T>7 days	3	27,6	3	43,9	20,496	<0,001	3	31,1	3	39,4	2,397	0,122	4	25,4	3	48,1	22,028	<0,001			
Weight loss	4	19,6	4	27,3	5,701	0,017	5	22,5	4	28,2	1,375	0,241	6	17,8	6	26,5	4,104	0,043			
Chest pain	5	19,1	5	25,1	3,464	0,063	7	8,6	5	20,0	8,302	0,004	3	25,8	4	29,8	0,628	0,428			
Fatigue/ weakness	6	18,6	6	21,4	0,716	0,031	6	15,9	7	14,7	0,087	0,768	5	20,3	5	27,6	2,633	0,105			
Night sweats	7	17,3	7	16,5	0,035	0,852	4	27,2	6	16,5	5,407	0,020	7	11,0	7	16,6	2,264	0,132			

N= number of respondents who answered to this question

Table 2. Respondents' answers to question „What are signs and symptoms of TB?"-Displaced group

Symptoms of TB	Displaced persons group																	
	Bosnia and Herzegovina						Federation of B&H						Republika Srpska					
	First phase N=397		Second phase N=436		Statistical significance		First phase N=188		Second phase N=191		Statistical significance		First phase N=209		Second phase N=245		Statistical significance	
	Rang	%	Rang	%	$\chi 2$	P	Rang	%	Rang	%	$\chi 2$	P	Rang	%	Rang	%	$\chi 2$	P
Cough	1	64,0	1	84,2	43,606	<0,001	1	66,0	1	85,9	20,577	<0,001	1	62,2	1	82,9	24,617	<0,001
Coughing-up blood	2	45,6	2	58,7	13,829	<0,001	2	55,9	2	51,3	0,786	0,375	3	36,4	2	64,5	35,723	<0,001
T>7 days	3	39,8	3	44,5	1,691	0,193	3	36,2	3	50,8	8,233	0,004	2	43,1	4	39,6	0,561	0,454
Night sweats	4	25,4	5	31,4	3,355	0,067	4	25,0	5	33,0	2,932	0,087	5	25,8	6	30,2	1,062	0,303
Weight loss	5	24,4	6	31,2	4,383	0,036	6	21,8	6	24,6	0,416	0,519	4	26,8	5	36,3	4,714	0,030
Chest pain	6	20,4	4	40,1	37,094	<0,001	5	23,9	4	35,1	5,560	0,017	6	17,2	3	44,1	37,562	<0,001
Fatigue/ weakness	7	16,9	7	20,6	1,688	0,194	7	18,1	7	23,0	1,421	0,233	7	15,8	7	18,8	1,382	0,056

N= number of respondents

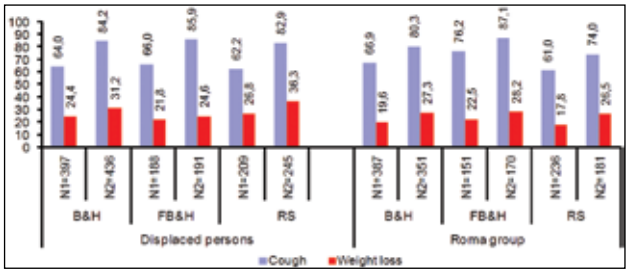
87,1% in the second phase of research, with a statistical significance (X^2: 6,418; p<0,05). Weight loss is cited by 22,5% of them (first phase), and 28,2% in the second phase without statistical significance (X^2:1,375; p>0,05).

Respondents belonging to the internally displaced group quoted cough as a symptom of TB in a large percentage (64% in the first, and 84,2% in the second phase, with statistical significance X^2: 43,606; p<0,001), while weight loss is quoted by 20,4% in the first, and 31,2% in the second phase (with statistical significance present X^2:4, 383; p<0,05).

Weight loss as a sign/symptom of TB was quoted by 26% of respondents (first phase) with a rise in this percentage in the second phase (37,8%) with statistical significance present also (X^2:16,246; p<0,001).

A slightly lower rate of correct answers was demonstrated by respondents in FB&H, showing an increase in the second phase (without statistical significance for weight loss: X^2:2,748; p>0,05)

Comparison of percentages of respondents that quote TB symptoms correctly (cough, weight loss) among certain targeted sub-populations shows there is generally a certain knowledge of TB symptoms, slightly higher among the displaced group (total sample for B&H) with an increase in this percentage in the second phase of research. Comparing results in FB&H, respondents from the displaced persons sub-sample shows a slightly lower rate of correct answers for both selected symptoms in comparison with the Roma sub-sample.



Graph 1. Signs and symptoms of TB – rate of correct answers of the displaced and Roma groups
Second indicator: % of respondents who correctly identify main ways of TB transmission (through air)

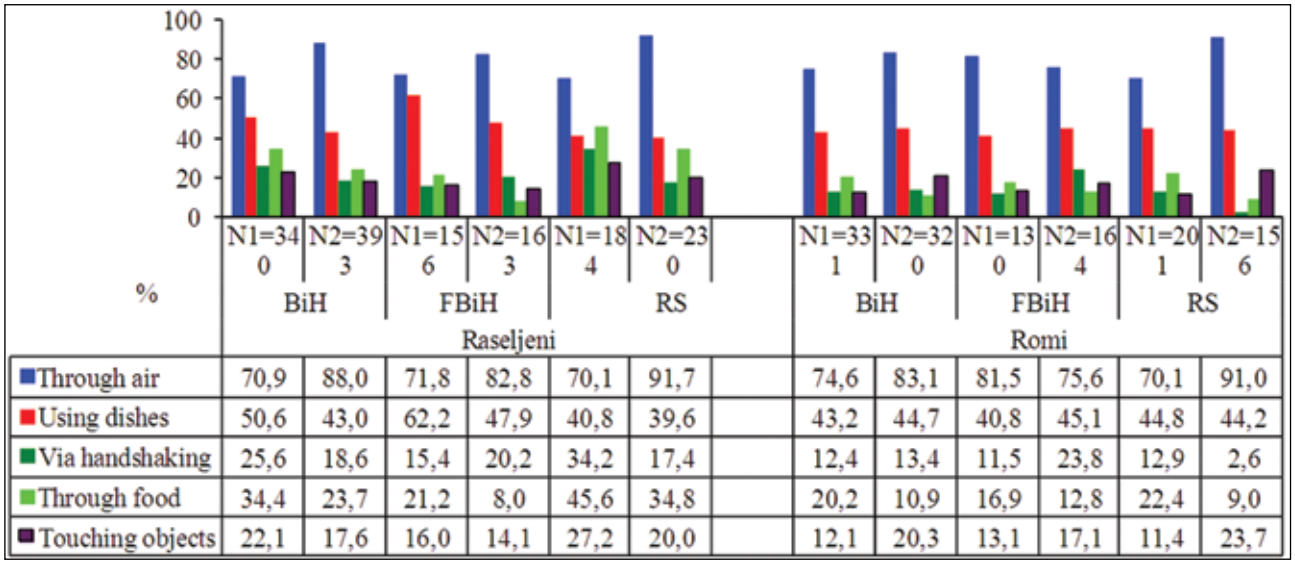
Next criteria on knowledge about TB is percentage of respondents who correctly identified main ways of transmission of TB infection. Criteria was

counted in every instance of respondent answering TB can be transmitted/acquired through „air when a person with TB coughs or sneezes".

Respondents in both sub-samples showed a relatively good knowledge about ways of transmission of TB even in the first phase of research, with the percentage increasing in the second phase (except among respondents from the Roma population sub-sample in FB&H where a decline occurred in the percentage of respondents answering correctly that TB is transmitted through air.

Percentage of correct answers increases in the second phase of research at a statistically significant rate: displaced pop. 88,0% (statistical significance X^2: 32,579; p<0,001); Roma pop. 83,1% (X^2: 6,542; p<0,05).

For all other answers offered citing ways of transmission/acquiring of TB (with possibility to choose multiple answers), all respondents in the first phase of research – apart from transmission by air – highly rated the option „using dishes", followed by „through food" and „via handshaking".



	Raseljeni						Romi					
	BiH		FBiH		RS		BiH		FBiH		RS	
Through air	70,9	88,0	71,8	82,8	70,1	91,7	74,6	83,1	81,5	75,6	70,1	91,0
Using dishes	50,6	43,0	62,2	47,9	40,8	39,6	43,2	44,7	40,8	45,1	44,8	44,2
Via handshaking	25,6	18,6	15,4	20,2	34,2	17,4	12,4	13,4	11,5	23,8	12,9	2,6
Through food	34,4	23,7	21,2	8,0	45,6	34,8	20,2	10,9	16,9	12,8	22,4	9,0
Touching objects	22,1	17,6	16,0	14,1	27,2	20,0	12,1	20,3	13,1	17,1	11,4	23,7

Graph 2. How can TB be transmitted/acquired / - displaced pop, Roma pop

Table 3. Comparison of respondents who correctly identify ways of transmission of TB (through air)

	Bosnia and Herzegovina				Federation of B&H				Republika Srpska			
	%		Stat. significance		%		Stat. significance		%		Stat. significance	
	1st phase	2nd phase	x^2	P	1st phase	2nd phase	x^2	P	1st phase	2nd phase	x^2	P
Roma pop.	74,6	83,1	6,542	0,010	81,5	75,6	1,497	0,221	70,1	91,0	23,296	<0,001
Displaced pop.	70,9	88,0	32,579	<0,001	71,8	82,8	5,546	0,019	70,1	91,7	32,581	<0,001

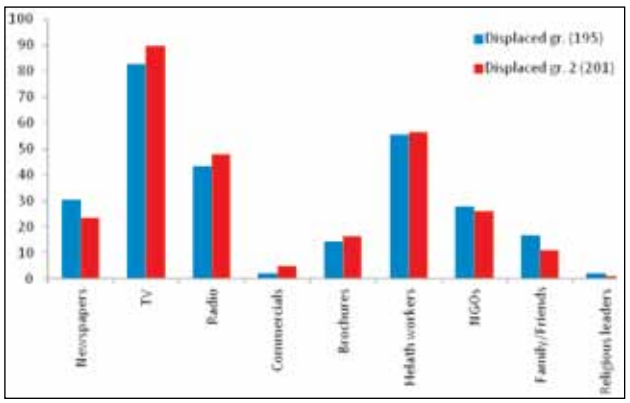
Table 4. Question on "If you discovered you have TB, what would be your first reaction?"

Stigma associated with TB	Displaced persons group						Roma group					
	B&H		FB&H		RS		B&H		FB&H		RS	
	Phase		Phase		Phase		Phase		Phase		Phase	
	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Sorrow	5,5	6,6	5,4	3,2	5,6	9,6	7,5	8,4	12,1	15,0	8,9	6,2
Worry	33,8	31,2	33,0	40,0	34,5	34,7	23,5	25,9	21,5	21,0	24,9	30,9
Fear	45,0	40,3	46,5	44,7	43,6	36,5	40,9	43,7	41,6	41,9	40,4	45,4
Surprise	11,3	13,0	10,3	8,4	12,2	16,9	12,3	11,7	14,8	9,0	10,7	14,2
Shame/ Embarrassment	2,4	2,2	1,1	2,1	3,5	2,3	8,3	2,3	4,7	2,4	10,7	2,3

In the second phase of research, answers on other forms of transmission decreased (apart from air), but the percentage of answers quoting handshaking remained pretty high (Graph 2).

Third indicator: % of respondents who consider it is embarrassing to carry TB

Feeling of shame/embarrassment from stigma against persons carrying TBs was quoted by a small number of respondents, while largest number quote feelings of fear and worry. Respondents' answers suggest that TB does not represent such a great stigma. Much larger is the number of respondents who would react with a feeling of fear upon finding out they carry TB (40-45%, grown-ups) with an increase in this percentage in the second phase (Roma population).



Graph 3. What is your best source of information on TB?

Largest number of respondents during both phases of research quoted TV as the best source of information on TB, followed by health workers and radio as a source, but less the printed materials, something that should be taken into account during planning phase of activities on health education and awareness-building in the local community.

Discussion

This study was conducted among two different sub-population groups in Bosnia and Herzegovina – displaced persons and Roma population, both in their own way vulnerable to TB. Considering the different socio-economic, cultural and community profile, they represent different segments of population that vary in terms of conditions and way of life, behaviours, experience of stigma associated with TB, accessibility to health services and awareness of risks from TB - and are therefore differently susceptible for IES (Information, Education, Communication).[9] Most important sources of information about tuberculosis and health in general, by respondents' opinion, are television and health workers, with less respondents choosing printed materials. This should be taken into account during planning of promotional/preventative activities in the local community.[10]

This research has shown that majority of subjects display certain knowledge about symptoms of tuberculosis, but misconceptions are also present to a significant percentage. Although stigma associated with TB is not perceived in a larger percentage through respondents' answers, responses to other questions in the questionnaire point out that experience of stigma and discrimination is present in the community (intent to avoid persons with TB; significant number of respondents would not tell friends they carry TB; majority would not like to come in contact with an infected person; a misconception that TB can be transmitted via handshaking, etc.) Such attitudes can represent a serious barrier for early detection, timely treatment and prevention of a tuberculosis infection. [11,12]

Results of this research help define priority objectives for future education on tuberculosis - raising the level of knowledge about TB, ways of its transmission, timely detection of symptoms, when to contact the health services, as well as improvement of attitudes and behaviour of people towards those infected with tuberculosis. Besides being educated about ways of protection from tuberculosis, TB patients and their families should also be informed to raise awareness about the importance of regular tuberculosis therapy administration and patient's co-operation during treatment. However, data shows that knowledge is not the only determining factor in terms of attitude and behaviour because stigma can represent a significant barrier to an adequate and timely treatment, and can be the main cause of social stigmatisation.

Results of the study show a need for continuation and intensification of IEC campaigns, because knowledge and behaviour of the patient and his surroundings represents a key component of the TB control programme. As part of these IEC activities supported by the Global Fund (GFATM)

plans are in place to continue monitoring and evaluating results of the education strategy in B&H (next study in B&H is planned in 2011/2012).

Conclusion

Awareness of symptoms and ways of transmission of TB, the possibility of prevention and treatment and awareness of existence of stigma associated with TB are all preconditions for planning of health education activities in the local community with the correct choice of communication channels, target messages and educational materials adapted to a certain population exposed to a higher risk of tuberculosis.

Acknowledgments

Authors of this paper would like to acknowledge the contributions in conducting the survey to Marija Zeljko, Radovan Bratic, Jelena Niskanovic. Our sincere thanks go to all those respondents who agreed to participate in this study. Implementation of this research would not be possible without the contribution of our partners in NGO sector (Red Cross) and we would like to thank them for the efficient conduct of the field work. This survey was made as a part of GFTAM Project "Further strengthening of the DOTS strategy in Bosnia and Herzegovina" implemented by UNDP B&H.

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Combination of depression and cardiovascular risk factors in pit miners

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Abstract

Cardiovascular disseases and metabilocal szndrome have shown connection with depression, which is often health problem (1). The aim of research is to determine depression prevalence in Banovići coal mine pit miners and depression influence on total cardiovascular risk.

Materials and methods: epidemiologial study performed included 492 employees in pit mine department of coal mine Banovići. According to Becks' scale a depression score was determined, the blood preasure value was taken along with height and weight, BMI, weist, total cholesterol concentration, HDL and LDL cholesterol, triglicerids, sugar in blood and smoking status. According to NCEP ATP III criteria, metabolical syndrome was defined. **Results:** out of 492 testers 34,34 % were with depression, all measured risk factors excluding the weist values were more evident in pit miners with depression. Significant statistical difference was evident in age, smoking status and blood preasure values in pit miners with depression. Metabolical syndrome was evident in 44,97% of pit miners wtih depression along with increased total cardiovascular risk (4 (0-20), p=0,0001.

Conclusion: the high risk prevalence of depression diagnosing is evident with expressed tendency of risk factor grouping, higher metabolical sndrome presence and higher total cardiovascular risk among tested pit miners.

Key words: depression, pit miners, cardiovascular risk, metabolical syndrome

Introduction

Cardiovascular disseases and gloucosis metabolism disturbance appeared to be connected with depression which is ussual health problem (1). Reasons for depression and cardiovascular dissease connection can be unhealthy life stile of those with depression and/or permamanent disregulation of adrenocortical and autonomous nerv system what can result with increasment of body mass, viscellar fatness and insulin resistence (2).

It is known that depresive individuals have tendency to follow unhealthy life style such as smoking, sitting life style, unhealthy food and low cooperation with doctors (3). Behavioral changes such as intensing of smoking, decreased physical activity and bad feeding habits can appear as adaptation or response on psychological stress what activates other important risk factors for deseasse development (4).

Dperession is related to physiological disturbances which can result in metabolical concequences, includung activation of system hypothalamus – glandula pituitaris – glandula adrenalis system and disfunction of autonomous neural system (5).

Activating hypothalamus – glandula pituitaris – glandula adrenalis system and sympatic neural system, psychosocial stress activates patophysiological mechanisms that include inflamatory processes, processes of homeostasys and changed metabolical and cardiac autonomuos controle (6).

These identical abnormalities are connected to several, even all, components of metabolical synrome (2), what explains influence of psychosocial factors on diagnosing of metabolical syndrome (2). Adrenergic stimulation during stress can increase demands and needs of miocard for oxigen, also can cause vasocontriction and relate it to trombocit and endotel disfunction (7) and metabolic syndrome (8). Increased reactivity of trombocites is connected to higher level of depression in healthy and (9) and patients with Cardiovascular disseases (10). The role of seratonin in both cases,

reactivity of trombocites (11) and depression (12), also provides suggestive proof which relate trombocite activity and depression.

Connection between psychosocial stress and cardiovascular dissease is identified as important public health problem (6). Although, despite numeruous and convicing datas of different studies depression can not be treated as cause, consequence or marker of metabolical syndrome. For example, physical limitations or social stigmas caused with body mass increasment can cause depression, while emotional problems in those wit increased body mass can cause additional producement of cikotine which can contribute to depression ethiology (13).

Depression is often evident in general poulation (14) as well as in those with cardial problems (15), esspecialy among women (16). According to 10 th international clasification of disseases, depression is characterised by following symptoms+ mood changes, lack of interes and pleasure,energy decreasment, lack of selfconfidence, selfaccusations or feelnig of guilt, repeeting thoughts of death or suicide, thinking process diturbance and lack of concentration, agitation or retardation, sleeping and apetite disturbance. In those with evident diagnosis cognitive functions are disturbed as well as speech, vegetative functions (sleeping, apetite, sexual activity) along with changes in look, behaviour, thinking, feeling about oneself and surrounding enviroment which results eventualy in significant social functions damadges.

Observational studies have given solid proofs of depression connection with cardiovascular disseases and general mortality rate among patients without cardiovascular disseases at first (17) and those with cardiovascular complications later (18). The mechanisms of this effect are still in discussion (19). Thesis verification on connection between mental disturbances and patients with cardiovascular diagnosis is not random and has provided several factors: fast progression of diagnostic and epidemiologic procedures, new findings on autonomous neural system and other physiological stress consequences influence and recognition of cardiovascular influence of psychotropic medicines (20). There are three possible scenarios which can be enroled in comorbidity of mental and cardiac disturbances such as: pathological mechanisms of neural system are triggers for neural system disfunction, pathological mechanisms of neural system are triggers of cardiovascular system disfunction or these two systems share common patobilogical mechanisms which always don't cause each other (21). In comorbidity basis of psychological disturbances different mechanisms can occur:

1. mutual gene predisposition for cardiovascukar and psychological disturbances;
2. exposure to stress and psychotrauma has important role in initialing of cardiovascular and osychological disturbances, and in their patogenesys metabolical syndrome caused by stress take important role, endocrine disfunction, immunological process disturbances.
3. toxine exposure which cause psychological and cardiovascular disseases (ex. Bisfenol A);
4. increased frequencz of unhealthy habits and life styles such as smoking, alcoholism etc;
5. psychological disturbances are often reactive conditions on cardiovascular disseases and limitations which are included (22,23).

Cumalative frequency of clinical depression in mediacal students in 40 years of observing was 12 % but men with clinical depression have had signifficantly increased risk for later development of coronary dissease and heart attack (24). Clinical depression was related to increased risk for heart attack 10 years after first deprresive episode. Therefore, it seems that depression is independent risk factor for coronar arteries dissease and heart attack several decades after initiation of clinical depression (24).

It is proven that older people with stroke have bigger possibility for existence of depression disturbance and that depression is related to later development of ischemic coronary disease as well as existence of strong relation between expressed coronary aorta calcifications and depressive disturbances what leads to conclusion that atherosclerosis and depressions are related in older people (25).

It is proven that older people with stroke have larger probability for depressive disturbances and that depression is related to later development of ischemic cardiac disorder along with existence of relation of expressed coronary calcifications and

depressive disturbances what leads to conclusion that atherosclerosis and depressions are related in older people (25).

Many of earlier research describes how are negative emotions evident before heart attack (26). Even larger number of epidemiologic research show that depression is a risk factor for coronary dissease development (27). Diagnosing of cardiovascular dissease can increase symptoms, while patients with depression have worse outcome with coronary dissease (28).

Diabetes melitus is often related to depression what means double burden for individual and society (29). Depression is related to bad glikemia control whereas depression prevalence is larger among patients with diabetes melitus diagnosed (30).comorbidity of these disseases can mean that those with diabetes melitus type 2 have increased risk of appeareance of deppressive episodes and vice versa (31). Researches ahave shown that approximately one third of patients with diabetes melitus have extrem depression symptoms evident urging for medical treatment (32). On the other hand, other patients with depression have 37% increased risk for development of diabetes melitus type 2 (33). Becouse of depression symptoms that lead to behavioral changes and lack of interes for just about everything including health, patients with depression diagnose ussualy have unhealthy life styles (34). Observation of patients with diabetes melitus in past five years gave conclusion that patients with diabetes comorbidity and large depression have had 36% larger risk for development of microvascular complications in progression such as terminal phase of kidney insufficiency or blindeness in comparing to patients with diabetes but without depression diagnosed.

The same research have shown that microvascular complications such as heart attack or stroke were 24% more frequent in patients with diabetes and large depression than in those only with diabetes melitus but without depression diagnosed (35).

Despite certain importance on deoression and diabetes melitus and theit mutual influence on each other and on health system of organism, it os estimated that only one third of people with both of these diagnosis is treated properly in medical sense (36).

There are many researches which document unproportional high frequency of depression in cardiovascular patients in comparing to general population. It is estimated that depression prevalence for general population is in range from 4% to 7% (37). For comparing purposes, depression prevalence in patients with cardiovascular illnes are in range from 14% to 47% with higher prevalence ussually evident in patients with unstabile angina pectoris or patients who wait for bypass operation (38).

Prospective study for Pannix and co. In 2001 have shown that testers with large depression disturbance were in 3,9 times larger probability for heart attack lethal outcome in comparing to those without depression at the beggining of research, even after control and other risk factors treatment (39). Research results have shown that that patients with medium or large depression form were in 69% larger risk for development of soronary death and 78% larger risk for all thers causes of death.

According to meta-analasys (40) it is cocncluded that depression leads patient with different health problems to double size risk for avoiding of proper theraphy, including patients with cardiovascular disseases (41).

Only avoiding of recomended life style changes and ways of medicine taking is related to decreased survivings for cardiovascular patients (42), and points to fact of egzistence of possible mechanism which connects depression with unwanted outcome of cardiovascular disseases. Smoking and physical inactivity are relevant risk factors for development and outcome of cardiovascular dissease and often are target for prevention and treatment (43).

It is important to remind that cardiovascullar disseases and psychiatric disturbances are leading illneses of today, i.e. leading causes of morbidity, mortality and decreased life and working capablity (44). Depression and anxiety are important prefactors in initiation and and important recovery factors from cardiovacular disseases and highly-prevalent comorbid conditions in cardiovascular patients and psychiatric disturbances positively corelate with younger age of life, female sex, lower education and socioeconomic status i.e. life quality (45).

Depresion is strongly involved into prediction of cardiovascular dissease predistion (46). Depression influence on comorbidity and outcome of other diseases may be decreased or eliminated with more intensive treatment approach to depression (47).

In primary prevention of cardiovascular dissease patients with anxiety or depresion should be considered as patients with high risk of ateroscleric vascualr disseases, metabolic syndrome and diabetes and diabetes melitus type 2. Patients with diagnosed depression being significantly more often diagnosed of cardiovascular disseases in comparing to general population and it is believed that cardiovascular disseases are more frequent approximately one decade after first depressive episode (48).

Treatment of these illneses as secondary prevention in patients with anxiety and depression must be more invasive and intensive in comparing to patients without psychiatric disturbances. Research that took 13 years and covered 1551 of testers have shown that probibility of cardiac arrest diagnosing was 4,5 times larger than in patients with large depressive episode (49). Study performed on 138 male testers with blood preasure values taken during working hours and during brake time, estimated cardiovascular risk and determined anxiety and depression value by Hamiltons' scale, have shown that healthy individuals with increased blood preasure on work place have the same cardiovascular risk as those individuals with hypertensive diagnose, while patients with arterial hypertension were with more accented anxiety-depressive changes in comparing to healthy individuals (50).

Aims of the work

Determination of depression prevalence in pit miners of Banovici coal mine;

Determination of relation of depression with other cardiovascular risk factors;

Investigation of tendency of cardiovascular risk factors grouping in miners with depression;

Investigation of grouping of depression and metabolic syndrome;

Investigation of depression dependance and general cardiovascular risk in pit miners of Banovici coal mine.

Materials and methods

Epidemiological research was conducted in Banovici coal mine department „Pit Omazici". This research included 500 miners of this department out of which 492 miners completed this research untill its end. All testers completed Becks' scale for determination of anxiety and depression. This questionaire consisted of groups reflecting different conditions.testers were warned on carefull reading of given options and selection of one condition in each given group that best describes their subjective feelings inpast week including feeling they have in moment of questionaire fullfillment and to circle the number next to chosen condition given in questionaire. If there were several suitable conditions in one group, than testers were chosing them as their answers. Adding of circled numbers estimated the degree of testers depression according to following criteria: 0-9 normal condition, 10-15 low depression condition, 16-19 low to controled depression condition, 20-29 controled to serious depression condition, 30-36 serious depression condition. Based on final score according to Becks' scale depression frequency among testers is estimated and testers were divided into two groups: a group with depression and grout without depression.

All testers were taken blood preasure values, hight and body mass values, weist values and BMI. Blood preasure values were taken in medical department of banovici coal mine with expected microclimatic conditions, noise isolated and in comfortable sitting position.

Measurement were conducted according to Korotkovs' method, on both upperarms in five minutes time distance and by the same person. Calibrated blood preasure instrument were used with dimensions of uperarm strap *13 x 45 cm and 16 x 70 cm.*

All testers were taken laboratory values of sugar in blood concentration values, concentration of cholesterol and triglicerids in blood, HDL and LDL cholesterol concentration. Laboratory analasys were taken in laboratory of medical fascility in Lukavac. According to results of blood preasure values, weist values, HDL cholesterol and triglicerids values, sugar in blood values, certain frequency of metabolical syndrome was determined in both tetsed groups.

Criteria, according to National educational cholesterol programe, were used for diagnosing of metabolical syndrome - National Cholesterol Education Program, Third Adult Tretman Panel, NCEP-ATP III. This program understands metabolical syndrome as egzistence of tree or more of

the following criteria: weist value >102 cm in men and >88 cm in women, serum triglicerids ≥1,7 mmol/l, HDL cholesterol <1,03 mmol/l in men or 1,29 mmol/l in women, sugar in blood values ≥6,1 mmol/l and blood preasure values ≥130/85 mm/Hg.As ideal aimed value of LDL cholesterol we have taken values from 2,0 to 2,6 mmol / l, and wanted cholesterol value 5,0 mmol/l (51).

Described epidemiological study estimated frequency of metabolical syndrome and other factors in pit mniners with diagnosed depression. Based on these results, egzistence of relation between depression and grouping of other cardiovascular risk factors in pit miners factors is determined. Testers provided anamnestic datas on smiking ststuas and according to Sistematic Coronary Risk Evaluation (SCORE) grading system their 10 years cardiovascular risk is determined. Collected datas were imputed in speccialy created data basis in PC. Statistiical scientific metod was performed by computer programme Package for Social Sciences for Windows, version 18.0 PASW-SPSS Inc., Chicago, IL, USA. Statistical scientific methods applied in this research include descriptive statistics with central values showing and adequate data dispersion measures along with inferential statistics. Numeric data were shown by central tendency of measures and appropriate disperssion measures. For hypothesis testing between groups concept of independent samples used T- test and Mann-Whitney-test if distribution discrepancy is noticed. For testing of difference in repetitive measurement concept of dependent sample is used in paired T-test or Wilcoxon test depending on distribution normality. For frequency analasys Hi-square test was used. Results were shown transparently in tabels and graphicons. Usual level of signifficance ”p < 0,05” for statistical ”p” value was chosen.

Results

According to score results by Becks' scale for depression, out of 492 testers 169 (34,34%) of them were with depression in comparing to 323 (65,65%) testers without depression. There is statisticaly signifficant difference in average value of Becks' scale score in testers with depression, 16 (10-47), in comparing to tetsers without depression (table 1). Average age in testers with depression is 43 (38-49) and without depression it is 41 (36-45) (p=0,003).

Researching of cardiovascular risk factors in testers with and without depression lead us to conclussion that apart from blood preasure values there is no statistical difference in average values of other factors among tested groups (table 1), although signifficatly statistiocal values in general sardiovascular risk is evident.

On the other hand, it is noticed that grouping of risk factors in pit miners is more expressed in comparing to testers without depression (table 2).

Table 1. Values of cardiovascular risk factors in comparing to depression

	Without depression (n=323)	With depression (n=169)	p-value
SBP mm*Hg.*	134 (125-145)	155 (125-200)	0,0001
DBP mm*Hg.*	85 (75-95)	95 (75-105)	0,0001
BMI kg/m²	27.43 ± 3.61	27.53 ± 3.76	0,77
WV cm	98.21±9.57	99.27±11.12	0,27
SIB (mmol/l)	4.50 (4.12-4.80)	4.30 (3.80-4.70)	0,01
TGL (mmol/l)	1.84 (1.21-2.79)	2.0 (1.36-2.93)	0,06
Uk.Hol (mmol/l)	5.70 (4.90-6.70)	5.70 (4.90-6.52)	0,99
HDL (mmol/l)	1.09 (0.91-1.25)	1.04 (0.86-1.22)	0,06
LDL (mmol/l)	3.75±1.11	3.66±1.08	0,40
Becks' score	3.0 (0-8)	16 (9-47)	0,001
KV risk	1 (0-14)	4 (0-20)	0,0001

Legend: SBP- systole blood preasure. DBP-diastolic blood preasure. WV- weist values> BMI- body mass index. LDL-low density lipoprotein. HDL-high density lipoprotein. TGL-triglicerdis. SIB-sugar in blood. CV-cardiovascular. Parameters expressed as medianawith 25-75 percentige as values. SBPMann-Whitney U Test statistic Z = -3.01, p=0.003; DBP Mann-Whitney U Test statistic Z = -3.70, p<0.0001; SIB Mann-Whitney U Test statistic Z = -2.59, p=0.01; Mann-Whitney U Test statistic Z = -3.70, p<0.0001; CV risk:Mann-Whitney U Test statistic Z = -3.59, p<0.0001; Beck-score:Mann-Whitney U Test statistic Z = -18.16, p<0.0001.

Table 2. Grouping of risk factors in comparing to depression in pit miners

No of CV RF	Bez RF	One RF	Two RF	Three RF	Four RF	Five RF	Six RF	Seven FR	Eight RF
Total (492)	7	20	49	75	83	88	80	53	29
Total %	1,42	4,06	9,95	15,24	16,86	**17,88**	16,26	10,77	5,89
With depression N 169	1	8	8	21	27	37	36	20	11
With depression %	0,59	4,73	4,73	12,42	16,97	**21,89**	21,3	11,83	6,5
Without depression N 323	6	20	42	47	57	70	48	20	13
Without depression N 323%	1,8	6,19	13,0	14,55	17,64	**21,67**	14,86	6,19	4,02

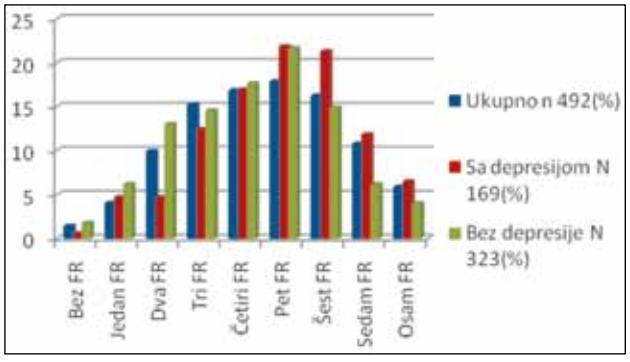
Legend: RF / Risk factors; N-Number.

Table 3. Frequency of certain risk factors in comparing to depression in pit miners

Risk factors	Total number		Without depression		With depression	
	N	%	N	%	N	%
Smoking	294	(59,75%)	181	(56,3%)	113	(66,86%)
WV	185	(37,60%)	122	(37,77%)	63	(37,27%)
BMI	349	(70,93%)	224	(69,34%)	125	(73,96%)
Blood preasure	216	(43,90%)	120	(37,15%)	96	(56,8%)
Cholesterol	332	(67,47%)	207	(64,08%)	125	(73,96%)
Triglicerids	274	(55,69%)	164	(50,77%)	110	(65,08%)
HDL-hol	194	(39,43%)	118	(36,53%)	76	(44,97%)
LDL-hol	327	(66,46%)	209	(64,70%)	118	(69,82%)
SIB	13	(2,64%)	6	(1,85%)	7	(4,14%)

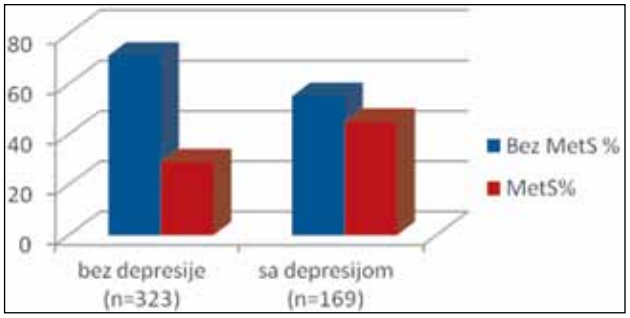
Legend: WV-Weist va;ues BMI-Body mass index, LDL-hol density lipoprotein, HDL-hol-high density lipoprotein, SIB- sugar in blood

Research on grouping of depression with other cardiovascular risks have shown that both groups of testers with and without depression, most of them have 5 risk factors grouped together (tabke 2) but in group with depression, most of them have 6 or more factors grouped together (picture 1) in comparing to healthy group in which most of testers are with 3 or 4 risk factors.



Picture 1. Risk factor joining in comparing to depression in pit miners
Legend: RF- risk factors; N-Number.

Such grouping of risk factors in depressive testers explains larger frequency of metabolical syndrome in that group. In group of depressive testers (n=169) 76 of them (44,97%) were with metabolical syndrome, while the group with depression 28,79% of testers were with metabolical syndrome (picture 2).

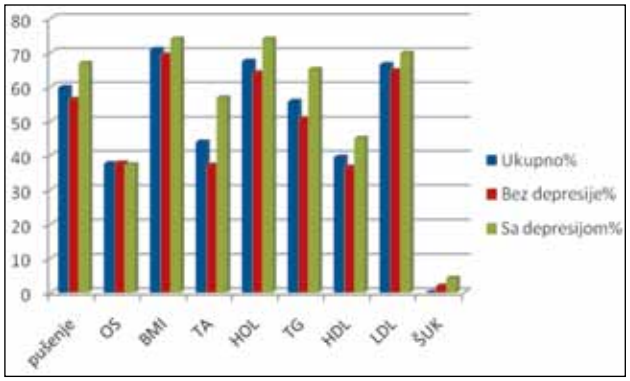


Picture 2. Frequency of metabolical syndrom (MetS) in tested groups

When we speak of certain risk factors frequency, larger frequency of all risk factors in tetsers with depression was evident, excluding weist values (table 3).

The largest difference in certain factors frequency was evident in level of blood preasure, triglicerdis concentration in blood and smoking, and

the smallest difference in BMI, while difference in weist values isn't proven (Picture 3).



Picture 3. The presence of certain risk factors in testers with and without depression
Legend: OS-weist values, BMI-body mass index, TA- blood preasure, HOL-choletserol, TG- triglicerids, LDL-low density lipoprotein, HDL-high density lipoprotein, ŠUK-sugar in blood

Discussion

Depression is evident in 18% of women and 6% men in general population and that percentage goes up to 40% in those with diagnosed bnodily disseases (52). A research that lasted 31 years have shown that prevalence of depression was 13,55% (10,4% in men and 16,5% in women). Our research conducted in mine pit of Banovici coal mine have shown that 33,94% of testers (every third tetser) were in criteria for depression according to Becks' scale.

In comparing of metabolical syndrome and cardiovascular risk parameters in testers with depression with those without depression sugnifficantly lower value of blood preasure, BMI, triglicerids level and HDLCholesterol was evident in group with depression but signifficant statistical difference of insulin in serum in values of insulin sensitivity and resistence index, gloucosys concentration and LDL choletserol in tetsed groups was not determined (54).

Second research confirmed that depression of women was connected with increased blood preasure and high level of triglicerids in blood and that women with history of large depressive episode were in double risk of diagnosing of metabolical syndrome in comparing to those without depression (55). Our research results prove that triglicerids are more evident among depressive pit miners, even in 65,08% of them. Some earlier studies that followed testers 6-9 years have shown positive correlation between depression and later hypertension (56). A certain research have proven that testers with bad quality of sllep, which is a symptome of depression, measured as shorter time of sleeoing and more often awakening with more hard apneas during slleping time and decreased SWS were with more expressed risk factor for development of arterial hypertension (57).

The same research have proven that bad sleep quality influence on hypertension development is not dependent on increasment of body mass and that testers were with average BMI values 26,4 kg/m². Our research confirms relation between depression and hypertension, becouse even 56,8% of testers with depression were with diagnosys of hypertension and average BMI valeu is 27.53 kg/m². Depression is related with levels of smoking in CV patients (58) and can decrease success of quitting programme of smoking (59). Among workers in pit mine department there is signifficant number of smokers but smoking as risk factor is more evident among pit miners with depression, 66,86% in comparing to 56,3% smokers among pit miners without depression.

Depression is related with metabolic syndrome (60,55) and is leading problem in USA as well as important risk factor for cardiovascular disseases and their lethal oucomes (61,62). This only proves longitudinal research of women which confirmed that women with depression, tension and anxiety at the beggining could overlook development of metabolical syndrome during observation, but in those with metabolical syndrome at the beggining could also be speculated the development of depression in following years (63). PILS III (Pilsen Longitudinal Study III) has proven egzistence of relation between depressive behavioral disturbance and metabolical syndrome meaning that depressive disturbances are twice more often in those with metabolical syndrome than in those without such diagnose. However, Such researching of relations between depression and anxiety with metabolical syndrome in cross study of 9571 tetsers between 20-89 zears of life, so called Nord-Trondelag Health Study (HUNT 2), didn't prove any relation between anxiety and depression with metabolical syndrome (64). Research in Finland also didn't show relation between metabolical

syndrome and psychological stress in 31 year of obseravtion of patients, even though all testers were young and adult with 31 years of life i.e. in lifeage when cardiovascular dissease pravalence is low (53). Our research have proven that more evident appearance of grouping of cardiovacular risk factors among pit miners with depression, which have 6 and 7 grouped factors, in comparing to those without depression. Such result is also a proff that metabolical syndrome is signifficantly evident testers with depression (44,97%) in comparing to those without depression (28,79%). Only avoiding of recomended life styles and medicine taking (42) which result in smoking and physical inactivity explain the fact that the most dominant risk factors in pit miners is BMI and increased value of blood cholesterol.

Psychosocial factors are included in ethiology and progression of cardiovascular disseases for a long time (66). Certain study have pointed out importance of depression and metabolical syndrome as independent risk factors for CV disseases in women, suggesting that depression and metabolical syndrome increase risk for CV disseases mostly through independent ways (67). Depression is strongly invovled in predictment of CV disseases development (46). Adrenergic stimulation during stress can increase demand and need of miocard for oxigen, can cause vasoconstriction and is related to trombocite and endotell disfunction (7) and metabolical syndrome (8). Even though depression is related to increasment of CV morbidity and mortality, there are very few information on weather such risk egzists in younger population. Certain research have proven that in adults of 40 years of age depression and suicide attempts are signifficant and independent predictors of premature cardiovascular illness and mortality caused by ishemic cardiovascular dissease in both sexes (68). Depression also increases stroke risk but this increasment is probably not depending on other risk factors including hypertension and diabetes melitus (69). Our research confirmed that miners with depression are older and there are more smokers among them, also with increased blood preasure values and more evident frequency of other CV risk factors, except for weist values and larger possibility for grouping of these factors in comparing to miners without depression.

All this points points to proven fact that there is statistically signifficant difference in CV risk in testers with and without depression.

Conclusions

1. 34.34 % of pit miners in Banovici coal mine have depression;
2. all risk factors, excluding weist values, are more evident among depressive pit miners in comparing to those without depression.
3. larger number of pit miners with depression have 6 or 7 grouped cardiovascular risk factors in comparing to those without depression;
4. 44,97% of miners with depression have metabolical syndrome;
5. depressive pit miners have statisticaly signifficant larger cardiovascular risk in comparing to those without depression.

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Calculation of body mass norm using the mathematics of harmony

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The development of man in harmony with nature leads to health,
and the violation of natural law leads to disease.
Hippocrates

Abstract

Standardization of physical quantities that determine the structure and function of the human organism under the laws of physics and the language of mathematics is important for medicine, because it bring it closer to the exact sciences. In this paper we standardize body mass by using mathematics of harmony. The boundaries are naturally determined by law according to which is built and by which the human body function. The basis of the structure of man (and all living beings) is a mathematical law of the golden ratio, which expresses the relationship between the whole and its parts in proportion 1.618 : 1 : 0.618 : 0.382. Numerous measurements have shown that the deviations from the golden ratio in healthy people are up to 5%, and only in exceptional cases reaching up to 10%.

Key words: Body mass index, golden ratio, golden mass

Introduction

Health Assessment in Medicine

Quantitative determination of health is only possible when we determine the standards of physical quantities. The standard defines the structure and function of a healthy organism. To determine the standard of physical size means to determine the numbers between which changes the value of that physical size, and that there is no change in body nor in the neither morphological nor physiological sense. This standard provides the physical size for the separation of healthy and ill individuals, as well as their ability to work and function. Because of that in the medicine is very important to determine the standard of physical size, but due to a complex mathematical apparatus is quite unpopular job. If we use, however, the approach of symmetry and harmony of mathematics, the problem becomes simpler.

Golden section and the human body

Since Euclid's Elements, along with classical mathematics, was developing a separate, less-known branch of mathematics, the mathematics of harmony (1). In today's interpretation, mathematics of harmony starts from a task about dividing segment AB by point C into two parts, so that longer part CB toward shorter AC refers in order that the whole segment AB is related to its greater part:

$$\frac{AB}{CB} = \frac{CB}{AC}$$

The task is reduced to solving the algebraic equation

$$x^2 - x - 1 = 0$$

which positive root is an irrational number

$$\Phi = \frac{1+\sqrt{5}}{2} = 1.618...$$

If we write this equation in the form

$$x^2 = x + 1$$

Then its right side equals

$$x + 1 = \frac{1+\sqrt{5}}{2} + 1 = \frac{3+\sqrt{5}}{2}$$

and the left

$$x^2 = \left(\frac{1+\sqrt{5}}{2}\right)^2 = \frac{1+2\sqrt{5}+5}{4} = \frac{6+2\sqrt{5}}{4} = \frac{3+\sqrt{5}}{2}$$

which is obvious proof of equality. It is therefore possible to write the following relation for the number Φ:

$$\Phi^2 = \Phi + 1 = 1.618\ldots + 1 = 2.168\ldots$$
$$\Phi = 1 + \frac{1}{\Phi}$$

From these equations, by simple substitutions, we get amazing relations characteristic only for the number Φ (1):

$$\Phi = 1 + \cfrac{1}{1 + \cfrac{1}{1 + \cfrac{1}{1 + \cfrac{1}{1 + \cfrac{1}{1 + \ldots}}}}}$$

$$\Phi = \sqrt{1 + \sqrt{1 + \sqrt{1 + \sqrt{1 + \sqrt{1 + \ldots}}}}}$$

$$\Phi^n = \Phi^{n-1} + \Phi^{n-2}\ ,\ n = 0, \pm 1, \pm 2, \pm 3, \ldots$$

Due to its characteristics and unique properties it was named the *golden number, golden section, divine proportion*. No other number has any such qualities of beauty, simplicity and naturalness:

The number Φ occurs as the foundation of many sequences that are related to the structure and functions of living organisms, in Fibonacci $F(n)$ and Lucas $L(n)$ series that are defined by the following recursive formulas (1):

$$F(n) = F(n-1) + F(n-2)$$
$$L(n) = L(n-1) + L(n-2)$$

The application of mathematics to the study of harmony and structure functions of the human body shows that parts of the body as a whole are in the golden ratio between themselves and the organism as a whole, they are in mutual agreement and are harmonized with the environment. The measure of harmony, conformity, harmony is the number Φ and today it is accepted as the *basic morphological law of nature*.

Slices are in the golden ratio are presented by irrational numbers $\Phi = 1.618\ldots$, $\Phi^{-1} = 0.618\ldots$ $\Phi^{-2} = 0.382\ldots$ and represents coefficients of the Fibonacci series of numbers. Rule of golden symmetry appears in the energy transitions of elementary particles, the structure of chemical compounds, the planetary, galactic and cosmic systems, the genetic structure of living things, the structure of certain organs of man and man's body as a whole, the vertical proportions of the human body, time characteristics of ECG , the structure of the arterial system, the parameters of blood pressure ... Although we encounter golden ratio everywhere, it seems to be most common in living systems: plants, animals and humans.

In this paper we start from the fact that health is presented as balance of the organism, and it is reflected in the harmony of internal structure and balance with the environment. Every living organism, including man, is built to meet the basic mathematical laws of symmetry and the golden ratio. In language of mathematics of harmony, symmetry is the ratio of individual body parts and their functions that they combine into one unit. Harmonious organism state corresponds to the numbers (*physical size*) that satisfy the golden ratio, i.e., stand in the ratio $\Phi = 1.618\ldots$

The harmony of numbers is determined by the relationship of the whole (an organ or its function) and its parts among themselves (2). If we divide the whole number 1 (which does not diminish the generality of the conclusions), parts of the whole will have a value of 0.618 and 0.382, and their quotient is the number $\Phi = 1.618\ldots$ These numbers

Table 1. The first 10 members of the Fibonacci and Lucas series of numbers

N	1	2	3	4	5	6	7	8	9	10
F(n)	1	1	2	3	5	8	13	21	34	55
L(n)	1	3	4	7	11	18	29	47	76	123

are invariants of the living structure and define a norm in which the value of an physical size are oscillating. Due to the size of such a relationship we can write the relation that connects the parts of a whole (the body or organs) that characterizes the structure and function of living systems

$$0.382 + 0.618 = 1$$

The symmetry of the living organism manifests itself in an adequate reaction to the constant fluctuation of environmental factors as a function of the uniform deviation from the mean value of the organism. Therefore, the mean (or, the point around which oscillate given physical size) is the number and these numbers represent a human health standard. Statistical analysis of a large number of samples eventually leads to a high standard and overall physical size and so it becomes a health standard that is used in assessing the health and diagnosing illness (pulse, blood pressure, organs proportions...).

Studying the structure and function of human body based on mathematics of harmony allows creating mathematical scale of certain norms, standardization of given physical size in the typical limits for healthy people. Standard of healthy body is a realistic, objective and individual (individuality is the result of age, sex and physical condition of the body). It has been shown that in children, due to the growth, the ratio of the whole and parts deviates from the ideal relationship between a given number $\Phi = 1.618...$ to higher values, and in the elderly there is a deviation towards smaller values.

It is recommended to set a standard of measurement by data obtained in people aged 20-30 years. This standard is very close to ideal, and is the starting point of standardization (2).

The accumulation of a large number of standards, exact numbers which fluctuate between the physical quantities that reflect the structure and function of organisms and the use of mathematical and physical laws apparatus for determining the health of man, bringing medicine closer to exact sciences.

One of the physical sizes which at the start of the diagnostic procedure is necessary to know is the body mass. The medicine commonly use BMI (Body Mass Index), which is only approximate indicator used to assess overweight and obesity. BMI is determined by artificially index and may not be the standard measure of weight, but serves as a convenient size for the statistical evaluation of nutritional status of the population, particularly due to the fact that body weight and height of a man are routinely recorded in all medical examinations.

Patients and methods

Estimates of the mass according to the formulas:

$$m = H - (100 \pm 5) \text{ i } m = H - (100 \pm 10)$$

One of the easiest ways to quickly reach the standards of the mass is to determine the mass by the height of a man. From the height in meters is deducted the number of K and thus gain the appropriate amount of weight.

$$m = \alpha H - \beta K$$

Number K is estimated, and in assessment are involved various factors: aesthetic, health, gender, race, and has the value $K = 90, 95, 100, 105; 110...$ Depending on the choice of number K we have the following formula for ideal weight:

$$m = \alpha H - 110\beta$$
$$m = \alpha H - 105\beta$$
$$m = \alpha H - 100\beta$$
$$m = \alpha H - 95\beta$$
$$m = \alpha H - 90\beta$$

m – body weight in kg,
H – height in cm,
α i β – coefficients, whose numerical value equals 1, and their SI units are kg cm^{-1}, or kg.

By this method we can only be rough, especially statistically, determine the mass of a larger group of people (some regions, states or of an entire nation). Here you can get information about the relative masses of adipose tissue and muscle and bone mass, which is important to assess the ideal weight norm. Also this method does not distinguish between male and female body, which is

structurally quite different, with different percent of muscle and bone mass representation by the mass of adipose tissue. Its main feature and the reason lie in the application of a simple calculation with no formulas and calculators.

Standardization of body weight by applying mathematics of harmony

By accepting the mathematics of harmony as the basis of the human body structure (3,4,5), it seems natural to standardize the body mass under the laws of symmetry and the golden ratio. Morphology and function of the human body indicate that its basis is the number Φ, but there are differences in the structure of men and women: the golden ratio is the basis of body structure both for men and women but for men is characteristic Fibonacci and for women Lucas series of numbers. Starting from these facts we will determine the standard weight for men and women. This method of body mass standardization has at least two advantages over the standard BMI:

- Weight are standardized according to mathematical laws by which the human body is built and by which it works (and not some bogus numbers)
- It is made immediately at the start the difference in the standard weight for a man and a woman (which does not exist in standard BMI)

Given that members of the Fibonacci and Lucas series of numbers and a *fixed* and determined by number Φ, the standard weight must be in the interval between two members of the series. In this way, quite naturally, by the same law that was built and by which function human body, is determined the standards of mass, or, setting the boundaries in which they should be oscillating, and determines the weight that is ideal for a given organism (so called *golden weight*).

Due to the specific structure of the male and female body we must make a difference in body mass standardization. For the male there is a typical Fibonacci series of numbers, so we will limit the mass of a man determined by the members of the Fibonacci sequence. The lower limit is determined by the standard mass relation

$$m_{\min}^{M} = \alpha H F_6 \Phi^3$$

and the upper

$$m_{\max=}^{M} \alpha H F_7 \Phi^3$$

H is the height of the man in meters, α is a constant whose numerical value equals 1, and its SI unit is kgm^{-1}, $\Phi = 1.618...$

Golden mass, the mass of the body that is most appropriate, closest to the ideal value, is determined by adding to the standard weight lower limit 61.8% of the total standard mass interval

$$m_z^M = m_{\min}^M + 0.618\left(m_{\max}^M - m_{\min}^M\right)$$

The structure of the female body is characterized by a Lucas series and the standard weight of a woman to be determined by the members of this series. The lower limit is determined by the standard relation

$$m_{\min}^F = \alpha H L_6 \Phi$$

and the upper

$$m_{\max}^F = \alpha H L_7 \Phi$$

Gold weight for women, according to the same rule as for men is given by the expression

$$m_z^F = m_{\min}^F + 0.618\left(m_{\max}^F - m_{\min}^F\right)$$

Sample

This survey included 1000 respondents from which data were taken about gender, age, weight and height. Also, each respondent was, at its sole discretion, by use of his/hers life experience gave assess their ideal weight, weight at which he felt would be best.

A survey example

Respondent	**Gender**	**Age**	**Height** $H(cm)$	**Body mass** m (kg)	**Desired body mass** m_i (kg)
M. Bosnian	M	33	182	90	85
F. Bosnian	F	27	167	72	60

From these data we calculated MBI, a standard assessment of mass in different ways and compared with a personal assessment of weight for each participant.

Then we use mathematics of harmony to determine the lower and upper limit of the standard weight of each subject, and its golden body mass. Standard weight and golden mass is compared with the respondent's personal assessment of ideal weight and the weight given by standard methods. The results of measurements and calculations are shown in tables and figures.

Results

Standard of body weight, as a factor that characterizes the structure and function of the human organism, we determined by the different methods used in the processes of health assessment of the human organism. First we used the simplest methods, those that require less data and requiring a simple calculation. These methods are related to the formula $m = \alpha H - \beta K$. By varying the different values of constant *K*, which until now are used in medicine, we get the values for the body mass which represents a rough estimate of ideal weight. Disadvantages of this method of determining body mass standards are evident: there is no difference in sex, which is a major drawback, the constant *K* is artificially determined, depending on race, age. Different authors choose different constants *K* (from 90 to 110), which significantly affects the results (Figure 1).

To obtain these values, we need only the height of the subjects, we took our respondents from 1000 and included in the formula.

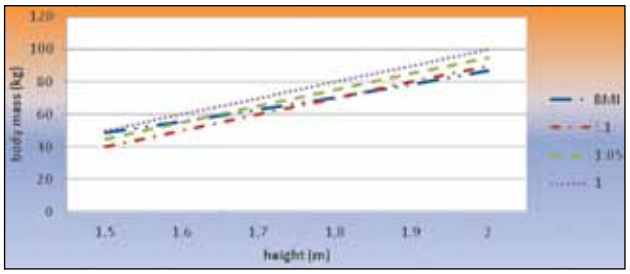

Figure 1. Standard indicators of body mass: K=100; 105; 110 and BMI

Tables 3 and 4 show the comparative assessment of different methods of weight. For example, we took one man and one woman of equal height, and we determined their standard mass by different methods. As you can see, all these standard methods are blind to the distinction between male and female bodies. For example: using "H - 90" both man and woman with height of 1.86m for a standard weight 96 kg. It is evident that this is not a good standard for the female body, and that really deviates from the desired level values of the mass of our subjects (as much as 22 kg!). Similarly, with as with other standard methods. However, calculation of standard mathematics of harmony gives weight limit standards in a natural way, by members of the Fibonacci and Lucas series are based on the golden ratio, and so a certain standard, and gold weight from the norm, it is very close to the coveted weight of both men and women which are very different (Tables 3 and 4).

Desired body mass of men and women are very different to the standard methods for estimating the body mass that do not distinguish male and female body, leading to large discrepancies. Mathematics of harmony respects the difference between the structure of the male and female body, this difference is reflected in application two

Table 3. Comparison of BMI standard methods for estimating the mass of our method and the personal assessment of ideal weight of subjects

Gender	Height (cm)	Body mass (kg)	MBI	Wanted ideal body mass (kg)	Golden body mass (kg)
M	180	92	28.4	85	83.87
F	180	92	28.4	70	71.78

Table 4. Comparison of different methods of assessment of weight and mass of the respondents wished

Height H (cm)	Actual body mass m (kg)	H-90 (kg)	H-95 (kg)	H-100 (kg)	H-105 (kg)	H-110 (kg)	Golden body mass m_z (kg)	Desired body mass (kg)
186 (M)	95	96	91	86	81	76	87.36	**88**
186 (F)	95	96	91	86	81	76	75	**74**

sets of numbers, Fibonacci which is characteristic of a man and a Lucas that characterizes a woman's body. But both series are based on the golden ratio, number PHI, so in that sense we speak of a unique human organism.

If we compare these estimates with our results (Figure 2 and 3) we can conclude that the slope of the line represents our results less than the slope of standard methods, which leads to less variation in weight the amount of patients and closer to the actual and desired results.

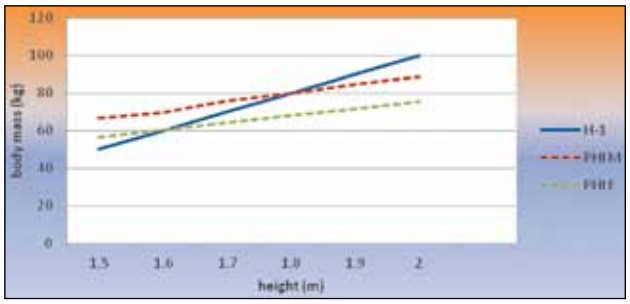

Figure 2. Comparison of indicators of mass PHI and H-100

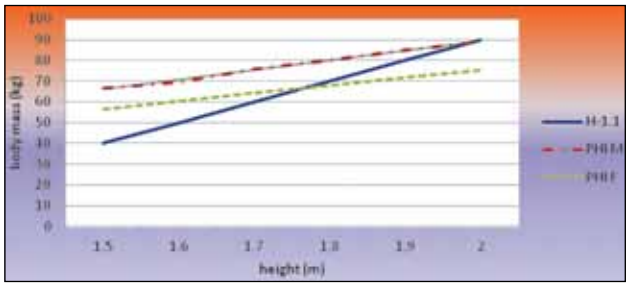

Figure 3. Comparison of indicators of mass PHI and H-110

Figure 4 shows the estimate of the mass by standard method H-105, and gold weight of a man and a woman using mathematics of harmony. There is an advantage of our method: the slope of lines that show the results obtained by our method are smaller, it means that the variation of the mass on the height is smaller, more natural and closer to the actual (and desired) values. Another important advantage of our method is the existence of two graphics: one for men organism and the other for the female organism. The standard method does not recognize these differences and because of that the deviations from the actual value is much higher, especially in cases of low and high people.

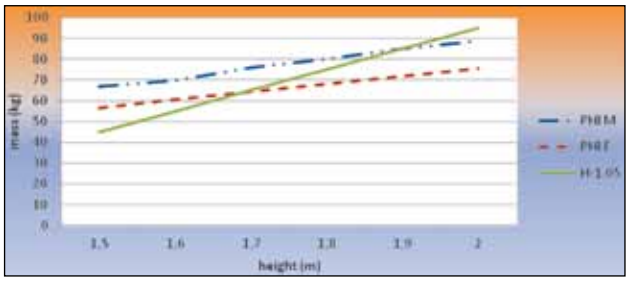

Figure 4. Comparison of body mass indices by H-105 with PHI method

Figure 5 shows the results of the assessment of weight by standard BMI and by using our PHI method. Although this method is the most common standard method, within the chart we see that there are disadvantages as well as other standard methods: it is blind to the differences in structure of male and female body, and there are large variations in the mass function of the height of the body, which is particularly evident at very short and extrapolations very tall people.

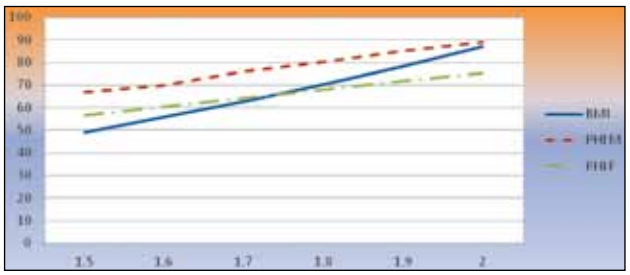

Figure 5. Comparison of indicators of body mass obtained by BMI standard method and our method

In figure 6 we joined all the standard method and our method of evaluation and display standards of the body mass in function of the height of the body.

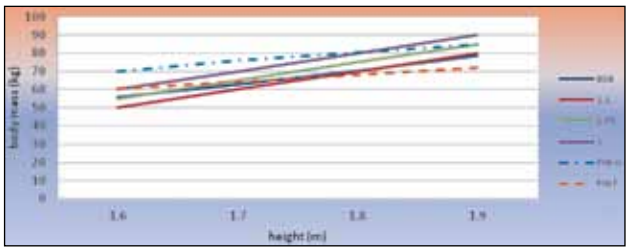

Figure 6. Standard methods for estimating the body masses and our method

Discussion

Body Mass Index - BMI is a simple index of weight and height ratio that is most often used to classify overweight adults. It is obtained by dividing the weight in kilograms by the person height squared in meters (kg/m^2).

According to World Health Organization, those with a BMI equal to or greater than 25 are defined as overweight, and when BMI over 30 is considered obese. BMI is the most useful method for the determination of people with excessive weight and obesity in specific population for both sexes and for adults of different ages. Excess body weight and obesity are the fifth leading cause of death. At least 2.8 million adults die as a result of excess body weight. 44% of cases of diabetes, 23% of ischemic heart disease, and between 7 and 41% of cancers attributed to excessive body weight. According to the World Health Organization (Report of 2008), 1.5 billion people age 20 years or older are overweight. Among these 1.5 billion, 200 million of men and nearly 300 million of women are considered obese (one of ten people in the world in 2010 - were considered obese). About 43 million children under age of 5 years are overweight.

Basic cause of overweight and obesity is energy imbalance between calories consumed and used. Globally, it is the excessive intake of food that has a high percentage of fat, salt and sugar and low vitamins, minerals and other micronutritients, with low levels of physical activity, sedentary work for many jobs, the increasing tendency of less walking. Elevated BMI is a major risk factor for cardiovascular disease, diabetes, musculoskeletal diseases and some types of cancers such as endometrial, breast, bowel.

However BMI index is imperfect for obesity because of the great individual differences between BMI and body fat, cardiovascular risk factors and long-term health of the patient (6). The prevalence of excessive body weight and obesity is high and still rising in industrialized countries. The Body Mass Index-BMI is an internationally recognized index for weight estimate. The lowest prevalence in Europe is found in France (7-14%), while Eastern European countries showed a high prevalence which ranges up to 40%. Results of DHP studies suggest that 50% of adult Germans are overweight, while 20% is obese. Data from Monica studies show a lower prevalence in Switzerland, where 34% of the adult population is overweight, while 11% is obese (7).

Obesity can be defined as excessive accumulation of fat in adipose tissue, to a level when it can endanger the health of individuals. Obesity is now world health problem with 315 million people who have BMI of 30 or more (8).

BMI allows simple numerical expression for evaluation of person's weight, allowing medical professionals to objectively discuss the problems of excessive or low body weight. The main causes of obesity epidemic are the use of nutritional foods with high sugar, salt and fat in combination with reduced physical activity, and obesity increased three times since 1980 in some regions of North America, UK, Eastern Europe and the Middle East. The epidemic of obesity is not just limited to industrialized countries, so the faster increase of obese people in developing countries.

BMI over 25 kg/m^2 is defined as excessive body mass, while a BMI over 30 kg/m^2 indicates obesity. The mean BMI in Africa and Asia is 22-23 kg/m^2, while in North America and Europe is 25-27 kg/m^2. Excess body weight and obesity have a number of negative consequences including metabolic, cardiovascular, and mechanical complications, and psychosocial repercussions (9).

Table 5. WHO classification of BMI ranges

BMI	Category
<20	Underweight
20-25	Ideal body mass
25- 0	Overweight
>30	Obesity

Excessive risk for chronic diseases and mortality is clear when BMI exceeds 30 kg/m^2. Probably much more important factor in assessing risk is the distribution of fat in the body. Accumulation of fat in abdominal cavity (mesenteric and omentum fat) leads to significant metabolic aberrations and increased incidence of diabetes, cardiovascular disease and stroke. What is important is that the increased risk associated with abdominal obesity is seen in obese people with normal weight as well as in person, or persons with normal BMI (10).

Very obese people with BMI over 40 have very high risk for the diseases, so that they are the pri-

mary group for consideration of surgery (Bariatric Medicine). Pathophysiological consequences of excessive body weight in large part are result from increased uptake and/or reduced physical activity. Individuals with a BMI over 40 and have additional problems related to obesity, including cardiomyopathy, Pickwick/sleep apnea syndrome, gonadal dysfunction, acanthosis nigricans and significant osteoarthritis (11).

Maintaining proper body weight is important for athletes and sportsmen. BMI in the case of sportsmen and athletes, who may have a high body mass for greater total body mass at the expense of hypertrophic muscular, BMI may result in these cases with wrongly marking these persons as individuals with excessive weight and obese individuals (12).

In Canada during the period since 1970 to 1992 the prevalence of obesity for people at age 20-69 years increased from 8% to 13.5% in men and from 13% to 15% in women. Particularly vulnerable groups are children and immigrants (13).

Overweight and obesity are conditions that are preventable. At the individual level people should limit intake of fats and sugars and in the diet use more fresh fruits and vegetables, and increase physical activity. The prevalence of extreme obesity (BMI over 40) is increasing in recent years so that now affects the one of twenty Americans. The prevalence of extreme obesity was higher among women than men and higher among African Americans than Caucasians and Hispanics. The effect of extreme obesity on total mortality is higher among young people than among older, higher in women than men. Number of bariatric procedures applied in these patients is relatively small (14).

Over 60% of people older than 20 years have the wrong perception of their body weight (15). Wrong perception is more pronounced in men, people over 64 years, people living in rural areas and in poverty.

Defining the standard weight in different ways, we showed that this approach which uses mathematics of harmony and golden ratio as a tool gives the best results. In order to confirm these results, we made a survey with the respondents that contained the necessary data on body weight, height, gender, age, and information on the body mass with which the respondent would best feel, the weight they wants (m_i). Some studies (16) show that one third of subjects with reduced body mass think to have normal weight. More interesting is the fact that even 56% of women and 70% of men who are overweight considered themselves normal (16). The results of our survey show that the estimate of the standard weight, based on the mathematics of harmony and the golden ratio, and from certain golden masses supposedly are closest to weight of subjects. Therefore we consider that determining weight standards is a natural limit in which the healthy weight ranges of human body, and that the interval from the standard golden weight is determined weight to suit ideal weight of the human organism. A special feature of this method is the possibility of determining the ideal weight separately for men and women, which standard method does not allow.

Conclusions

Using the symmetry and the mathematics of harmony we have defined a standard body weight and showed that the body weight of men and women is standardized in various ways. For certain standard mass limits we determine the golden mass of man and woman. By comparing the values obtained with standard methods of mass estimation, we conclude that the standardization of mass by mathematics of harmony and the golden ratio is a more natural and closer to the desired mass of subjects.

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Analysis of noise affect in production processes at open pit mines to level of hearing impairment of employees

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Abstract

Aim Determining the hazardous noise level, that is the noise level that may be a cause to hearing impairment of employees working in surface mines.

Methods Reaserches conducted in period from 2004 to 2011, based on periodical medical examinations of employees as well as continouous noise measurments in working environment.

Results There's been a mild increase of employees with hearing impairment from 20 to 40 (dBA), or with diagnostic evaluation of light hearing loss at employees that had been expossed to the noise up to level of LAE= 83 (dBA). Above considered range of noise exposure it's been recorded a significant increase of number of employees with listed hearing impairments. In order to preserve the health of employees, humanize work and improve ergonomic conditions, the employers are recomended to change the legal uper margin for noise exposure of LAE=85 (dBA) and to apply the lower one of LAE=83 (dBA).

Conclusion The determined hazardous levels of noise exposure to the employees of LAE=83 (dBA) is a sugestion to relevant, competent institutions with A role in creating and legal bill passing regarding the norms in domain of noise protetction.

Key words: Mining, noise, ergonomy, health, hearing.

Introduction

Noise sensitivity depends on noise characteristics (strength, rhythm, content), on individual characteristics of an exposed person (ears condition, age, individual sensitivity to noise), as well as on duration, type and exposure regime (person's position to the noise source, presence or non presence of the noise during the break taken in working hours, and in free time).

Consequences of noise presence to the human health are:

- Auditory (out of hearing and deafness based on understanding and communication disorder)
- Extra-auditory, that may be the cause for an occurrence of health problems or deterioration of the existing health.

Reactions to the noise is individual, and depending on the level and frequency of noise and the exposure time, they may vary from mild and transitory to permanent damages.

The consequences of excessive noise to the hearing condition result in motion of hearing threshold, and these are divided as: *[1]:*

- Temporary movement of hearing threshold
- Permanent movement of hearing threshold

Methods

Research of noise affect of open pit's working machines to the heath of employees

The noise affect research for working machines and equipment of open pits at Coal Mine „Banovici“ to the employees' health, had been done on the basis of conducted periodical medical examination of employees *[2]*.

Analysis of diagnostic findings of employees' health in 2004, 2007 and 2009, with registered health damage on which, the noise with its excessive influence may directly or indirectly affect are *(hearing impairment, posttraumatic stress disor-*

der-PTSD, Neurosis, Insomnia, Hypertension art., Bradycardia, Tachycardia, Obesities/Adiposities, Angina pectoris, Hyperlipoproteinemia, St.post. inf.myocardi). This is presented in table 1.

From the table above, it is evident that for significant number of employees, an excessive noise represents a danger for occurrence or deterioration of the existing diseases.

The determined risk group of employees of 40, 9 (%) for 2004, with tendency to increase up to 52,3 (%) for 2009, represents an alarming data that assigns the necessity for application of noise level optimization, and to take protection measures for the excessive noise.

The noise influence of open pits work machines to the risk of auditory health violation

The noise effect to the human hearing may lead to professional out of hearing and deafness condition. First, there is a loss of hearing sensitivity in frequency range of 4000 (Hz) (so called starting or primary acoustic trauma). Since this involves the frequency area above speech zone (1000-3000 Hz), at the beginning of impairment, an employee doesn't have any subjective disorders and without an audiology testing is not aware of hearing impairment.

Later, the primary acoustic trauma deepens and extends, catching wider area of frequencies with higher level of hearing sensitivity. At this point, a person start to notice his/her out of hearing condition and he/she can not follow conversation.

Acoustic trauma (auditory effect) depends on *[3,4]*:

- Intensity, spectrum and character of noise
- Exposure duration
- Individual sensitivity and life age
- Work conditions and presence of other harms
- Use of otic toxic medications and remedies, alcohol, tobacco
- Prior hearing impairments, condition of cardiovascular and neurrovegetative systems.

Professional hearing impairment has a progressive course. The hearing loss and deafness of professional etiology are usually mutual processes (as opposed to many unprofessional ear diseases that typically catching one ear).

People individually differentiate in noise sensitivity. There are persons in which the hearing loss will occur fast while in others, even after years of excessive noise exposure, their hearing will be damaged relatively little. Previous ear diseases may affect development and level of professional hearing impairment. Therefore, prior to hiring new employees in conditions of excessive noise exposure, it's necessary to conduct a hearing test with an objective determination of hearing stage (audiometric). By this, the doctor in charge at the same time ensures him/herself from mistaking to declare an employee with previous unprofessional hearing impairment in to professionally diseased.

Hearing loss evaluation in guiding-diagnostic purposes is categorized by following criteria *[5]*:

- Slightly hearing loss – person doesn't hear sound of level of 20 (dBA)
- Light hearing loss – person doesn't hear sound of level of 20-40 (dBA)
- Medium hearing loss– person doesn't hear sound of level of 40-60 (dBA) (which enters the speach register)
- Heavy hearing loss – person doesn't hear sound of level of 60-90 (dBA) (according to some authors the margin is 93 (dBA)

Hearing impairment of 93 (dBA) is referred as deafness.

Table 1. Analysis of diagnostic findings of employees' health in 2004, 2007 and 2009, with registered health damage on which, the noise with its excessive influence may directly or indirectly affect are

Periodic medical examinations of employees (year)	Total of exanimate employees	Number of employees with health issues that may be the consequence of noise	Percentage of employees with health problems that may be the consequence of noise (%)
2004	589	241	**40,92**
2007	798	323	**40,48**
2009	880	504	**52,27**

Determining methods for noise influence of production processes in open pit to the hearing impairment level

In order to evaluate the noise dangers at production processes of work machines and equipment in open pit, we performed an estimation of employees' hearing impairment by following methods:

- computational (mathematical); based on age, noise exposure years, noise exposure level, and source (emission) of noise *[6]*
- Experimental; based on periodical medical examinations of employees at sample open pits

Listed methods for evaluated dangers of noise to the employees hearing impairment level are presented in table 2.

From table presented above, it can be noted that listed mathematical methodology of analysis for employees' hearing impairment in open pits, significantly deviate from more referent experimental analysis, so to these purposes can be applied in "rough" estimations.

Based on recorded periodical tests of employees with hearing impairment, we had conducted researches of influence of work years that is the time period of noise exposure and level of noise exposure to the level of hearing impairment. The researches are presented in table 3.

Under the table above, there are employees with registered unprofessional hearing impairments, with diagnostic estimation of medium and heavy hearing loss (access to employees' medical charts). Concerning the high level of listed hearing impairments of employees, the presented analysis can be used for "rough" estimations, and during conducted researches we performed an analysis of production processes noise influence to the diagnostic evaluation of employees' hearing loss.

Experimental analysis of diagnostic evaluation o employees' hearing loss at sample open pits, was based on periodical medical examinations of the employees for 2007 and is shown in table 4.

From the table for we can notice that arithmetic mean of employees' hearing loss was based on diagnostic evaluation of light hearing loss, that is hearing impairment from 20 to 40 (dBA).

Table 2. Noise danger evaluation to the level of employees' hearing impairment

Hearing impairment estimation	Arithmetic mean of analysed employees (a_{sr})			Hearing loss estimation (mathematical)			Determined level of hearing loss (a_{sr})- medical examinations (dBA)
	Age	Job years	Noise exposure level (dBA)	Due to noise level exposure H (dBA)	Age influence P (dBA)	Total hearing loss HL (dBA)	
Maintenace workers of work machines and equipment (mechanical and electrical maintenance)	47	25	84,6	9	9	**18**	**33,4**
Employees of secondary works	50	29	84	9	11	**20**	**32,3**
Handlers of secondary work machines and equipment	47	26	83,6	8	9	**17**	**31,1**
Handlers of shovels	46	24	82,5	6	8	**14**	**31**
Supervision and technical staff	53	31	80,3	5	13	**18**	**30,1**
Truck drivers	47	27	77,4	0	9	**9**	**31,6**
Conveying transport handlers	49	22	73,6	0	10	**10**	**38,5**

Table 3. Influence of working years and noise exposure level to the employees' hearing impairment level.

Influence of noise exposure to employees' hearing impairment	Working service			Level of noise exposure (dBA)	Level of hearing impairment (dBA)
	Work years	Number of employees	Working service average		
Maintenace workers of work machines and equipment (mechanical and electrical maintenance)	1-20	15	12	84,6	**33,9**
	21-40	63	29		**33,3**
	Σ	78	26		**33,4**
Employees of secondary works	1-20	5	13	84	**38,3**
	21-40	28	31		**31,2**
	Σ	33	29		**32,3**
Handlers of secondary work machines and equipment	1-20	2	13	83,6	**29,7**
	21-40	18	28		**31,2**
	Σ	20	26		**31,1**
Handlers of shovels	1-20	5	14	82,5	**30**
	21-40	10	29		**31,6**
	Σ	15	24		**31**
Supervision and technical staff	1-20	1	20	80,3	**27,8**
	21-40	9	32		**30,4**
	Σ	10	31		**30,1**
Truck drivers	1-20	2	19	77,4	**27,7**
	21-40	9	30		**32,4**
	Σ	11	28		**31,6**
Conveying transport handlers	1-20	1	3	72,5	**27,3**
	21-40	8	31		**40**
	Σ	9	24		**38,5**

Table 4. Experimental analysis of diagnostic evaluation o employees' hearing loss at sample open pits

Employees' hearing loss estimation	Number of analyzed employees	Light hearing loss/ 20-40 (dBA)		Medium hearing loss/ 40-60 (dBA)		Heavy hearing loss/ 60-80,93 (dBA)	
		number	Percentage (%)	number	Percentage (%)	number	Percentage (%)
Maintenace workers of work machines and equipment (mechanical and electrical maintenance)	265	66	**24,9**	7	2,6	5	1,9
Employees of secondary works	128	29	**22,7**	3	2,3	1	0,8
Handlers of secondary work machines and equipment	103	19	**18,4**	1	0,97		
Handlers of shovels	100	15	**15**				
Supervision and technical staff	77	10	**13**				
Truck drivers	79	10	**12,7**			1	1,3
Conveying transport handlers	46	4	**8,7**	5	10,9		

Table 5. Comparison of the noise affect to diagnostic assessment of light hearing loss of employees

Employees' hearing loss estimation	Number of analyzed employees	Level of noise exposure to employees (dBA)	Number of employees with hearing impairment from 20 to 40 dBA	Percentage of employees with hearing impairment from 20 to 40 dBA (%)
Maintenace workers of work machines and equipment (mechanical and electrical maintenance)	265	**84,6**	66	**24,9**
Employees of secondary works	128	**84**	29	**22,7**
Handlers of secondary work machines and equipment	103	**83,6**	19	**18,4**
Handlers of shovels	100	**82,5**	15	**15**
Supervision and technical staff	77	**80,3**	10	**13**
Truck drivers	79	**77,4**	10	**12,7**
Conveying transport handlers	46	**72,5**	4	**8,7**

By direct research (access to employees' findings at ENT specialist) of employees that have medium and heavy hearing loss, it's been determined as unprofessional hearing impairment which points to conclusion that for their overall level of hearing impairment the noise of production processes was not crucial but it could affect the deterioration of existing state. Based on above, in order to compare the influence of noise listed to the employees' hearing impairment; we have analyzed the light hearing loss that is the hearing loss from 20 to 40 (dBA), as presented in table 5.

It is evident that the noise of production processes of working machines and equipment at the sample open pit significantly affects the hearing impairment (table 5).

The noise level influence of certain job positions to the percentage of employees with hearing impairment from 20 to 40 (dBA), or diagnostic evaluation of light hearing loss was presented in diagram 1.

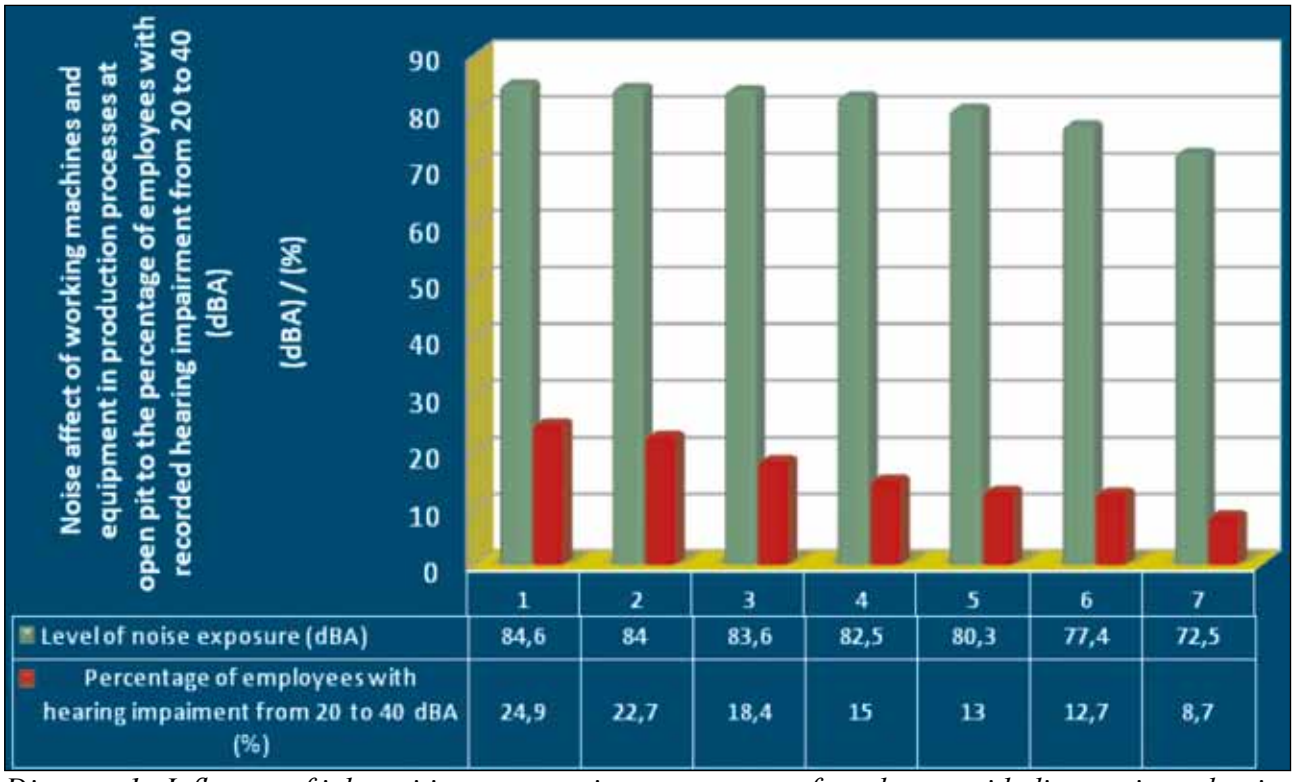

Diagram 1. Influence of job position at open pit to percentage of employees with diagnostic evaluation of light hearing loss

1. Maintenance workers of work machines and equipment -mechanical and electrical maintenance
2. Employees of secondary works
3. Handlers of secondary work machines and equipment
4. Handlers of shovels
5. Supervision and technical staff
6. Truck drivers
7. Conveying transport handlers

Results

Definition of noise influence of production processes at open pit to the level of hearing impairment

By frequent analysis and conducted researches, it's been determined that emitted noise of all production processes of working machines and equipment at open pit is proximately the same origin with nearly the same dominant frequencies *[7,8,9]*. The noise influence to the percentage of employees with hearing impairment from 20 to 40 (dBA), or diagnostic evaluation of light hearing loss was given in diagram 2.

Towards more objective display of noise influence of production processes of working machines and equipment in open pit to the percentage of employees with hearing impairment from 20 to 40 (dBA), we have presented two dependences y_1, y_2 (diagram2).

At the first functional dependence,

$$y_1 = 0{,}658 \cdot x_1 - 39{,}3 \text{ (dBA)} \quad \ldots\ldots\ldots\ldots\ldots \quad (1)$$

Where:

y_1, y_2- percentage of employees with hearing impairment from 20 to 40 (dBA)

x_1, x_2- level of noise exposure for employees

It shows the noise influence of 73, 6 to 82, 5 (dBA) to the percentage of employees with hearing impairment from 20 to 40 (dBA).

At the second functional dependence,

$$Y_2 = 5{,}449 \cdot x_2 - 435{,}3 \text{ (dBA)} \quad \ldots\ldots\ldots\ldots\ldots \quad (2)$$

It shows the noise influence of 82, 5 to 84, 6 (dBA) to the percentage of employees with hearing impairment from 20 to 40 (dBA).

By analysis of listed diagram, and based on table 5, we have determined the following indicators:

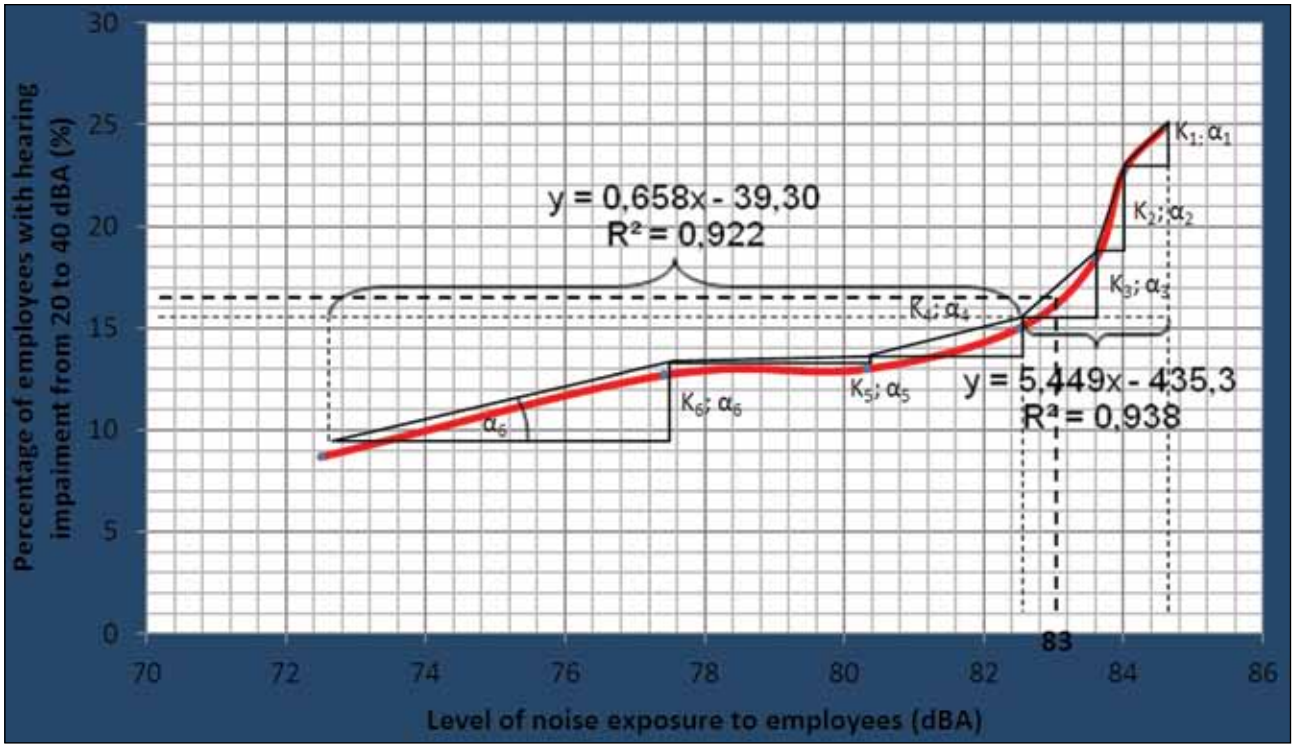

Diagram 2. Influence of noise of production processes of work machines at open pit to the percentage of employees with diagnostic evaluation of light hearing loss

- Indicators of dependence of percentage of employees with hearing impairment from 20 to 40 (dBA) and level of noise exposure to the employees:

$$K = \frac{M}{N}\left(\frac{\%}{dBA}\right) \quad K = \frac{M}{N}\left(\frac{\%}{dBA}\right) \quad \text{..... (3)}$$

Where:

M- Percentage indicator of employees' with hearing impairment from 20 to 40 dBA (%)

$$M = P_n - P_{n-1}\ (\%) M = P_n - P_{n-1}\ (\%) \text{ .... (4)}$$

N- Indicator of the noise exposure level to employees (dBA)

$$N = LAE_n - LAE_{n-1}\ (dBA) \quad \text{..... (5)}$$
$$N = LAE_n - LAE_{n-1}\ (dBA)$$

- Indicators of percentage increase of employees with hearing impairment from 20 to 40 (dBA) depending to the level of noise exposure:

$$\alpha = arctg\left(\frac{M}{N}\right) = arctg(K)\ (^\circ) \quad \text{..... (6)}$$
$$\alpha = arctg\left(\frac{M}{N}\right) = arctg(K)\ (^\circ)$$

Results of conducted researches acquired by diagram 2 analysis are shown in table 6.

By analyzing the listed influential indicators, we had determined a latent increase of percentage of employees with hearing impairment from 20 to 40 (dBA), or diagnostic evaluation of light hearing loss to the area of noise exposure of employees LAE= 82,5-83,6 (dBA),and significant percentage increase of employees with hearing impairment above the listed range of noise exposure.

Thus, it is evident that in working area of noise exposure level of LAE= 82,5-83,6 (dBA), or from equivalent level of listed noise area of LAE≥ 83,1 (dBA) percentage of employees with hearing impairment "extremely" grow, which can clearly be noted by indicators of percentage increase of employees with hearing impairment from 20 to 40 (dBA) in relation to the level of noise exposure „α".

Based on conducted researches and in order to preserve the health of employees, humanization of work and improvement of ergonomic conditions, the employers are recommended to change the legal measures for noise protection from LAE=85 (dBA) and apply them at LAE=83 (dBA), in other words, the normative upper value of exposure in the design documentation for noise protection is LAE=83 (dBA).

Table 6. Results of conducted researches for noise influence to the level of hearing mpairment

Influence of noise exposure level to the percentage of employees with hearing impairment	Noise exposure level LAE (dBA)	Percentage of employees with hearing impairment from 20 to 40 dBA P (%)	Indicator of noise exposure level to the employees N (dBA)	Percentage indicator of employees with hearing impairment from 20 to 40 dBA M (%)	Indicators of percentage dependence of employees with hearing impairment from 20 to 40 dBA and noise exposure level K (%/dBA)	Indicators of percentage increase of employees with hearing impairment from 20 to 40 dBA related to the noise exposure level α (°)
n_1	84,6	24,9	0,6	2,2	3,7	**74,9**
n_2	84	22,7	0,4	4,3	10,7	**84,7**
n_3	83,6	18,4	1,1	3,4	3,1	**72,1**
n_4	82,5	15	2,2	2	0,9	**42**
n_5	80,3	13	2,9	0,3	0,1	**5,7**
n_6	77,4	12,7	4,9	4	0,8	**38,7**
n_7	72,5	8,7				

Discussion

The production processes of exploitation of mineral ore in open mine emits significant levels of noise that auditory and extra auditory affect the health of employees.

The results of conducted researches show a percentage of employees with hearing impairment, degree of impairment, and present data of production processes which are possible cause to such impairments.

By analysis of research within influence of noise to health, or to level of hearing impairment of employees, we had determined the level of noise exposure of LAE=83 (dBA) above which the percentage of employees with hearing impairment significantly increases.

Based on listed analysis, and in order to preserve the health of employees, humanization of work and improvement of ergonomic conditions, the employers are recommended to change the legal measures for noise protection from LAE=85 (dBA) and apply them at LAE=83 (dBA), in other words, the normative upper value of exposure in the design documentation for noise protection is LAE=83 (dBA).

Therefore, scientific novelty of conducted researches with determined risky level of noise exposure of LAE=83 (dBA) is a suggestion to relevant authorized institutions that may have role in creating and nominating, or adoption of legal measures and regulations in domain of noise protection in Mining.

Based on presented estimation of noise danger due to operation of production processes on open pit, it is evident that in the future, we will have to play more significant role in order to decrease the noise to acceptable ergonomic levels, and to increase more humane conditions for employees and improve the life quality in direct surrounding.

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Copying letters, syllables, words and sentence skills of a deafblind child (case study)

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Abstract

The aim of this paper is to examine the quality of written expression in a child with concurrent damage to hearing and sight. As the test material we used the "Diagnostic kit for testing the ability of speech, language, reading, and writing in children" and the "Diagnostic material for detection of specific difficulties in reading and writing of students in regular schools- field of testing the writing. The general purpose of this part of the study is to determine the degree of mastering the writing, finding out the difficulties in writing, specifying the mechanisms, the form and the extent of those difficulties. We believe that the errors made in copying were caused by the deprivation of senses of sight and hearing, due to which the child cannot fully perceive the presented material. When it comes to writing, the writing technique alone is not a big problem, however due to the inadequate development of speech as a result of deafblindness, some agratisams have been noticed, inadequate linking of the words, and not perceiving the relation of the letters in a word, and words in the sentence. Inability of a complete visual perception and orientation manifests itself in mixing and deforming of the letters.

Key words: deafblindness, coping, skills

Introduction

The deafblindness is a specifically double sensory damage. With the term deafblindness we consider those people that at the same time have damaged hearing and sight to that extent that he/she has difficulties in their daily functioning. Deafblindness does not necessarily mean total loss of sight or hearing. Completely deafblind people make only 1% of the deafblind(1) population, while 83% of them have remaining sight, and 61% of them have residual hearing(2). Bearing in mind the fact that people with damaged hearing, in an attempt to overcome the impairment primarily rely on sight, and opposite as well: persons with damaged sight mainly rely on their hearing, the existence of both sensory modalities at the same time involves a completely different approach of work and support. Considering the fact that "blindness separates people from things, and deafness from people"[1], we can conclude that one of the main problems of deafblind people is the access to information and communication. Good communication with deafblind children is necessary in order to prevent the child from being isolated and neglected throughout life. In that case it is necessary to give the opportunity to the child and to enable him/her to communicate and bond with the environment. The ultimate goal of the support is the independent functioning of the child in the greatest extent possible. In today's age of technological development and progress, receiving and exchanging of information, ideas and knowledge is easily accessible by the use of conventional orthography. To talk about literacy, without knowing the techniques of reading and writing, is simply not possible. Both forms of expression are very closely related. Practicing of oral skills in great deal improves the written expression and vice versa (3). Literacy in its broadest sense includes listening, speaking, reading and writing. Thus it includes the use of language. Reading and writing allows a transfer of information and increases the scope of knowledge. It allows us to acquire and share information and stimulate the mental activity. Precisely because of this, reading and writing are of the utter most importance for the deafblind, bearing in mind, that the ways of knowing and gaining the experiences are reduced due to the damage of the vision and hearing. This allows us to develop abstract concepts, improve our commu-

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nication, independence and social interaction and improve the quality of life.

In this regard, deafblind children face the following challenges:

1. Reduced incidental opportunities to develop language through watching and listening to the people around them
2. Reduced amount of materials presented in the appropriate modality
3. Inability to learn through the visually presented material, and also auditively presented materials
4. The difficulties caused by the lack of appropriate educational media (Braille, and enlarged black print)
5. Reduced experiences because of the additional damage- deafblindness combined with the intellectual deficit, cerebral paralysis, and so on, demands extra attention and engagement, concerning the specific disorders in reading and writing
6. Lack of timely and appropriate treatment- deafblind children are often not covered with an early and adequate treatment which results in initial delay in obtaining literacy.

Regarding all that, a deafblind child must be given timely information and also in the appropriate modality(4).

Objective

The aim of this paper is to examine the quality of written expression in a child with concurrent damage to hearing and sight.

Methodology

Sample of variables

- Variables related to the copying of the letters
- the child is correctly copying all the letters
- the child is correctly copying most of the letters, some less significant errors were made caused by the insufficient development of graphomotoric skills
- the child is copying the letters with some optical errors
- the child is copying the letters with some kineticall errors
- the child is not able to copy most of the letters
- the child mixes printed and cursive letters

Variables related to the transcribing of syllables

- the child is correctly transcribing all the syllables
- the child is copying syllables with optical errors
- the child is copying syllables with kinetic errors
- the child is making errors on the level of syllabic analysis and synthesis
- the child mixes printed and cursive letters

Variables related to the transcribing of the letters

- the child is correctly transcribing all the words and the sentence
- the child is making optical errors
- the child is making kinetic errors
- the child is making phonological-phonematic errors
- the child is making errors on the level of letters and syllables
- the child is making errors on the level of words
- the child is making errors on the level of sentence

Instruments

As the test material we used the "Diagnostic kit for testing the ability of speech, language, reading, and writing in children" and the "Diagnostic material for detection of specific difficulties in reading and writing of students in regular schools- field of testing the writing(5). The general purpose of this part of the study is to determine the degree of mastering the writing, finding out the difficulties in writing, specifying the mechanisms, the form and the extent of those difficulties. Examining the adopting of the writing, we evaluate the tasks qualitatively.

Data collecting

In the first task the examiner asks the participants to according to the sample transcribe a letter, and with that, large printed letters and small prin-

ted letters on large printed letters, and also small printed letters on small cursive letters. The purpose of the second task is to examine the ability to transcribe successive letters and link them into syllables. The examiner asks the child to transcribe the syllables in large printed letters, and also from small printed onto small cursive letters. The purpose of the third task is to examine the ability of successive copying of words and of the sentence. The examiner asks the child to transcribe the given words and the sentence.

Results and discussion

From the Table 1. it is clear that when transcribing the large letters, of the total of 22 letters, the child correctly copied 17 of them. Not one letter was incorrectly copied, but with 5 of them the child made specific errors (optical-with the letter "r", kinetic-with the letters "t", "b","d" and "n"). When copying the small letters, errors of kinetic type were noticed with the letters "m" and "n", and also substitutes of the letters "h", "i", "e" (small and large), not differentiated writing of the letters "b", and "d" and also "g" and "d". When transcribing small printed letters on small cursive letters, kinetic errors were noticed with the letters "n", "h", "z", "s", "t", and "i". In case of transcribing the syllables, we noticed the errors syllabic analysis and synthesis, mainly substituting of the places in the syllables "mra" (mar), "co" (oc), "pla" (pal), "um" (mu), writing of the letters "m", "j", substituting printed and cursive letters"g", small "a", small "s", connecting of the letters "z" and "s", with all other letters, and connecting of the letters in syllables "tv", "ta", "je" and "id".

From the Table 2 it can be seen that from the total of 14 words, the child correctly transcribed 9 of them. When transcribing 5 words the rule is of a specific error and kinetic at that- on the letters "k", "c"; phonological-phonematic -on the letters "n"-"m", "d"-"b", "c"- "c", "c", and large "n". Also, the child confuses small and large letters- "i", "r", "a"- writes large instead of small, "e"-small instead of large. Errors have been noticed on the words level of morphological disgramatisam - "marz", "satblo", "zaspat" and leaving out of the letters- "cvao", "vrhje". When copying the sentence leaving out of the letter "i" was noticed serving as the link in a sentence, and he also makes mistakes on the level

Table 1. Copying of letters and syllables

		Correctly transcribed	Makes specific errors	Incorrectly transcribed	Total
Letters	VSS - VSS	17	5	-	22
	MSS - VSS	11	9	-	22
	MSS - MPS	16	6	-	22
Syllables	VSS - VSS	16	2	-	18
	MSS - VPS	17	4	-	21
	MSS - MPS	15	6	-	21

Legend: VSS – large printed letters
MSS – small printed letters
MPS – small cursive letters
VPS –large cursive letters

Table 2. Coping of words and sentences

		Correctly transcribed	Makes specific errors	Makes mistakes at the level of letters and syllables	Makes mistakes at the level of words	Makes mistakes at the sentence	Total
Words	VSS - VSS	9	5	-	-	-	14
	VSS - MSS	9	5	-	-	-	14
Sentences	VSS - VSS	1	-	-	-	-	2
	VSS - MSS	-	-	3	1	-	2

Legend: VSS – large printed letters
MSS – small printed letters

of letters- incorrect writing of the letters "j" and "g", and he also makes mistakes on the word level- "varta", (vatra). We believe that the errors made in copying were caused by the deprivation of senses of sight and hearing, due to which the child cannot fully perceive the presented material. When it comes to writing, the writing technique alone is not a big problem, however due to the inadequate development of speech as a result of deafblindness, some agratisams have been noticed, inadequate linking of the words, and not perceiving the relation of the letters in a word, and words in the sentence. Inability of a complete visual perception and orientation manifests itself in mixing and deforming of the letters. The child mixes the visually similar letters, for example, the letters "n" and, "u", and "b"and "d" differ only with their position in space(3). Due to the underdeveloped visual-motoric coordination we have the mixing of the letters similar in the way of writing, and leaving out of letters or adding elements of letter. In the event of errors on the level of syllables, concerning the replacing of the letters in the syllable, the child has the difficulty of observing the sequence of the letters, as a lack of development of attention and self-control. The child actually perceives every letter, but incorrectly writes down its order. Similar thing happens in the errors on the word level. The errors in incorrect disassembly and assembly of words and unrecognizing their borders indicate difficulties in recognizing some words in the oral speech.

The errors on the word level and sentence level can be caused by the inadequate linguistic experience as a result of damage to the hearing and vision. At the same time, one of the causes is the inability to observe all of the voice components in the composition of the words. When a child with intact hearing and sight reads, it uses special strategies. Thanks to the linguistic experiences and knowledge of the read context, he/she recognizes the words and becomes aware of their significance, even before the word is perceived. This is not the case with deafblind children. They have difficulties at every stage of reading: logographic, alphabetic and orthographic(6).

Conclusions

General objectives for the development of writing skills are: writing in complete sentences, the proper use of spelling and grammar rules in accordance with the age of the child(7) Based on the knowledge gathered during the writing of this paper, and based on the results of the survey itself, following conclusion has been drawn: mastering writing and orthography is one of the problems that children with damaged hearing and sight face. How the deafblind will communicate and which form of written information will be available to them, depends on the degree of their visual and hearing impairment, and also of the age when the impairment occurred.

To improve the communication and to enable access to information it is necessary to:

- create the conditions for positive interaction with others,
- provide support in terms of acceptable communication strategies,
- present the information in such a way so that the child can perceive it correctly,
- use audio-visual aids to take advantage of the remaining sensory abilities,
- provide opportunities for the tactile exploration and direct learning so that the child will be able to understand the effects of his/her own motion,
- help others to understand the child's need to gather information through touch,
- help the child to gain a sense of control,
- encourage communication and thus develop expressive communication skills,
- present the information in a way that fits the unique capabilities of each child,
- Increase the number of hours of support in mastering the grammar in the mother language,
- the materials for the development of literacy must be given in the appropriate formats and modalities, depending to the child's sensory, cognitive and conative abilities.

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