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Associations between anemia and insomnia or excessive daytime sleepiness in older adults

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ABSTRACT

Objective: Sleep disorders including excessive daytime sleepiness (EDS), insomnia and anemia are both common. The aim of this study is to investigate associations between anemia and insomnia/EDS in the elderly.

Methods: A total of 744 older outpatients were included in this cross-sectional study. Anemia was defined as a hemoglobin concentration below 12 g/dL in females and <13 g/dl in males. Patients were divided into two groups as anemic and non-anemic. The Epworth Sleepiness Scale score of ≥11 points indicates EDS. Insomnia Severity Index with scores of ≥8 indicates insomnia.

Results: The mean age was 79.8±7.7 years. The prevalence of insomnia, EDS and anemia was 62.1%, 23.8%, and 47.2%, respectively. Insomnia (66.3% vs 58.5%) and EDS (29.6% vs 18.6%) were more common in patients with anemia compared to those without anemia ($p<0.05$). In univariate analysis, there were significant associations between anemia and insomnia [odds ratio (OR):1.4, 95% confidence interval (CI):1.0–1.9], and EDS (OR:1.8,95% CI:1.3–2.6). In multivariate analysis, the relationship between insomnia and nocturia, chronic obstructive pulmonary disease (COPD), and number of drugs used persisted, whereas being male, of an older age, coronary arterial disease, COPD, Parkinson's disease, dementia, and urinary incontinence were associated with EDS ($p<0.05$), but there was no significant relationships between anemia and insomnia/EDS ($p>0.05$).

Conclusion: The present data suggests that an elderly who has anemia is 1.4 times more likely to experience insomnia and 1.8 times more likely to experience EDS than those without anemia.

KEYWORDS
Anemia; excessive daytime sleepiness; insomnia; older adults

Introduction

Anemia is defined by The World Health Organization (WHO) as a hemoglobin concentration of <12 g/dl in women and <13 g/dl in men. While it is observed with a rate of 15.5% in the elderly who apply to the geriatric clinic, the frequency may increase up to 65.7% depending on the presence of multimorbidity and frailty [1,2]. Anemia in the elderly results mainly from nutritional deficiencies and chronic diseases, but sometimes it may not be possible to identify the underlying pathology [3]. As the level of anemia increases, clinical symptoms become more pronounced. These symptoms include, for example, weakness, fatigue, lack of attention, palpitation, dizziness and dyspnea, as well as reductions in quality of life. These symptoms subsequently worsen the course of other comorbid outcomes such as falls, cognitive impairment, heart failure, frailty, poor nutritional status, decreased muscle strength and increased mortality [2,4,5]. The presence of anemia can be considered as an indicator of generally impaired health in the elderly.

Anemia has also been identified as an important risk factor for the occurrence of sleep disorders such as obstructive sleep apnea syndrome and restless leg syndromes (RLS) [6,7]. Importantly, literature suggests that there is an improvement in these sleep disorders with the treatment of anemia [6,7]. For example, RLS is a chronic sensorimotor neurological and sleep disorder that iron deficiency in the brain plays a fundamental role in RLS pathogenesis. As the improvement in anemia with increments in ferritin levels is important for managing RLS in patients with iron deficiency anemia [6]. However, the most common sleep disorders in the elderly are insomnia and excessive daytime sleepiness (EDS) [8], but the relationship between these two conditions and anemia is unknown. By reducing cerebral blood flow, anemia may cause a decrease in cortical thickness in the frontotemporal regions, which has been shown to be associated with sleep duration, and thus insomnia [9,10]. Moreover, since optimum hemoglobin level is necessary for the transport of sufficient oxygen for the maintenance of cellular

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functions in all organs, especially in the brain and skeletal muscles, it is possible that anemia increases the risk of EDS by causing fatigue, weakness and deterioration in physical activity [11]. If associations exist between anemia and insomnia or EDS in the elderly, anemia may be deemed as a modifiable factor for the management of sleep disorders or vice versa.

Therefore, the aim of this study is to investigate associations between anemia and insomnia or EDS in the elderly.

Methods

A total of 1076 outpatients admitted to a single geriatric center in Turkey were included in this study. Informed consent was provided by each participant or a legal guardian before participating in the study. The local Ethics in Research Committees of the institutes approved this study.

Patients with acute bleeding, such as massive hematuria, hematochezia, melena, hematemesis and intra-abdominal bleeding, as well as patients with moderate and severe dementia, those who cannot walk with an assistive device, those with localized muscle strength reduction due to stroke, those with severe visual and hearing impairments that prevent communication and understanding of commands during examination, those who refuse to participate, those with terminal disease (e.g. cancer), and those who were hospitalized for a life-threatening illness or major surgery in the last 6 months were not included in the present study. Patients with sleep disorders such as sleep apnea syndrome, or central disorders of hypersomnolence such as narcolepsy, or RLS were also excluded. As a result, 744 patients were included in the present analysis.

Comorbid diseases (hypertension, diabetes mellitus, renal failure, Chronic Obstructive Pulmonary Disease (COPD), Cerebrovascular Disease, Congestive Heart Failure, Coronary Arterial Disease), Parkinson's Disease, Benign Prostatic Hyperplasia, dementia, urinary incontinence, and nocturia were recorded [12].

Laboratory findings

Laboratory tests including, CRP, biochemical, metabolic and nutritional status of patients, complete blood count (CBC), kidney and liver function, thyroid stimulating hormone, HbA1c, iron levels, iron-binding capacity (IBC), ferritin, cobalamin, folate and vitamin D (25- hydroxia D3) tests were performed. Creatinine clearance was estimated using the glomerular filtration rate (GFR) and calculated using the chronic Renal Disease Epidemiology Collaborative (CKD-EPI) equation. Chronic Kidney Disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) below 60 mL/ min/1.73 m2 and/or albuminuria (>30 mg/ day) for more than 3 months.

Detection of anemia

Anemia was defined as hemoglobin concentrations below 12 g/dL in women and 13 g/dl in men. Following this criteria, patients were divided into two groups as anemic and non-anemic [13].

Assessment of insomnia

The Insomnia Severity Index (ISI) consists of 7 questionnaire items that capture self-reported symptoms and daytime consequences of insomnia, according to criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. ISI scores range from 0 to 28, with higher scores indicating more severe insomnia. ISI scores of 8 or higher indicated insomnia, with severity further stratified according to ISI score as subthreshold (herein termed mild) (8–14), moderate (15–21), and severe (22–28) [14].

Assessment of Excessive daytime sleepiness (EDS)

EDS was assessed using the Epworth Sleepiness Scale (ESS). The ESS is a 4-point Likert-style questionnaire composed of eight items, in which the patient marks the possibility of napping while watching television, lying down to rest, and traveling in a vehicle. The scoring for each item varies from 0 (no chance of napping) to 3 (great probability of napping). The total score is based on a scale of 0 to 24. A score of ≥ 11 indicates EDS [15].

Statistical analyses

Descriptive statistics, frequency, and percentages were used to summarize characteristics of the study population. Kolmogorov-Smirnov or Z test was performed to show the normal distribution of groups. Group comparisons were carried out using the student t-test and chi-square test. Binary logistic regression analysis was performed. The effect of variables (age, gender, anemia, chronic hypertension, CKD, congestive heart failure, coronary arterial disease, cerebrovascular disease, Parkinson's disease, BPH, dementia, nocturia, incontinence, drugs affecting sleeping and number of drugs used daily) on sleeping and daytime sleepiness were investigated using binary logistic regression. All variables were first analyzed individually. Multivariate regression analysis was performed with all significant covariates. IBM SPSS Version 25 was used for statistical analysis.

Results

A total of 1076 patients who visited one geriatrics outpatient clinic in Turkey were screened. Two hundred seventy patients without hemogram and 62 patients without sleeping scores were excluded from the study; as a result, 744 patients, with a mean age of 79.79 ± 7.75 and 60–99 years, were included in the study and the women to men ratio was 2.3 (Table 1).

The patients were divided into 2 groups; those with and without anemia. Demographic data of patients in both groups and accompanying comorbidities are shown in Table 1. The median ISI and Epworth scores of all the patients were 12 (quartiles 4–22, range 0–28) and 4 (quartiles 1–10, range 0–28), respectively. The prevalence of insomnia was 62.1% and was moderate/severe in 45.7% of cases. The prevalence of EDS was 23.8%.

The median ISI scores of patients with and without anemia were 13 (5, 24.5) and 11 (4, 21), respectively (p:0.020). The Median Epworth scores of patients with and without anemia were 6 (1, 11.5) and 4 (0, 9), respectively ($p < 0.001$). The prevalence of insomnia in patients with and without anemia were 66.3% and 58.5%, respectively (p:0.031). The prevalence of excessive daytime sleepiness in patients with and without anemia were 29.6% and 18.6%, respectively ($p < 0.001$).

Binomial logistic regression was performed to ascertain the effects of demographic features, comorbidities, and drugs that may be associated with sleep, on patients' probability of insomnia. In univariate analysis, patients with anemia had 1.4 times higher odds of insomnia than patients without anemia. In multivariate analysis, three variables were statistically significant: nocturia, COPD, and the number of drugs used daily (Table 2).

Another logistic regression was performed to determine the same parameters on patients' probability of EDS. Patients with anemia had 1.8 times higher odds of EDS than patients without anemia. In multivariate analysis, eight parameters were associated with EDS: being a male, age, coronary arterial disease, COPD, Parkinson's disease, dementia, and urinary incontinence (Table 3).

In patients with anemia, regression analysis was performed to show whether anemia due to nutritional deficiencies (iron, folate, or vitamin B12) affected insomnia or EDS. No statistically significant presumption was found with a nutritional deficiency ($p > 0.05$). CRP levels were higher, while GFR was lower in patients with anemia than those without anemia ($p < 0.05$). There was no significant difference between the two groups in terms of laboratory parameters including CBC, liver functions, thyroid stimulating hormone, HbA1c, IBC, ferritin and vitamin D (25- hydroxia D3) ($p > 0.05$).

Discussion

In the present sample of older adults residing in Turkey the frequency of anemia was 47.2%, insomnia 62.1%, and EDS 23.8%. Anemia in the elderly increases the risk of insomnia by 1.4 times and the risk of EDS by 1.8

Table 1. General characteristics of the study sample and patients with and without anemia.

	All Patients n:744	Patients with Anemia n:351	Patients without Anemia n:393	P value
Demographics				
Age, mean ± SD	79.79 ± 7.75	81.88 ± 7.47	77.94 ± 7.53	**0.001**
Sex, female, n (%)	525 (70.5)	230 (65.5)	295 (75.1)	**0.004**
Marital Status, n(%)				
Single	73 (9.9)	31 (9)	42 (10.7)	**0.011**
Married	351 (47.6)	149 (43.1)	202 (51.5)	
Widow	308 (41.7)	165 (47.7)	143 (36.5)	
Divorced	6 (0.8)	1 (0.3)	5 (1.3)	
Living Situation, n (%)				
Single	91 (12.3)	37 (10.7)	54 (13.7)	**0.031**
With husband/wife	343 (46.4)	145 (41.9)	198 (50.4)	
With children	264 (35.7)	141 (40.8)	123 (31.3)	
With caregiver	37 (5)	22 (6.4)	15 (3.8)	
Other	4 (0.5)	1 (0.3)	3 (0.8)	
Total Time Spent in Education, mean ± SD	5 (0, 7)	4.81 ± 4.62	4.88 ± 4.4	0.840
Drugs, mean ± SD	6 (4, 8)	7.07 ± 3.55	5.26 ± 2.92	**0.001**
Comorbidities & Drugs				
Hypertension, n (%)	506 (68.4)	249 (71.8)	257 (65.4)	0.063
Diabetes Mellitus, n (%)	278 (37.6)	149 (42.8)	129 (32.9)	**0.005**
Chronic Renal Failure, n(%)	165 (23.4)	119 (36.2)	46 (12.2)	**0.001**
Chronic Obstructive Pulmonary Disease, n (%)	65 (8.8)	31 (9)	34 (8.7)	0.883
Cerebrovascular Disease, n (%)	82 (11.1)	40 (11.5)	42 (10.7)	0.725
Congestive Heart Failure, n (%)	81 (10.9)	55 (15.8)	26 (6.6)	0.001
Coronary Arterial Disease, n (%)	149 (20.2)	79 (22.9)	70 (17.9)	0.089
Parkinson's Disease, n (%)	59 (8)	41 (11.8)	18 (4.6)	0.001
Benign Prostatic Hyperplasia, n (%)	54 (7.3)	30 (8.6)	24 (6.1)	0.188
Dementia, n (%)	186 (25.3)	98 (28.6)	88 (22.4)	0.054
Nocturia, n (%)	604 (84.9)	284 (85.5)	320 (84.4)	0.589
Incontinence, n (%)	397 (54.5)	197 (57.8)	200 (51.7)	0.100
Psychotropic drug use, n (%)	187 (25.1)	101 (28.8)	86 (21.9)	**0.031**

Table 2. Regression analysis for insomnia.

	Univariate Analysis				Multivariate Analysis			
			95% CI				95% CI	
	Sig.	OR	Lower	Upper	Sig.	OR	Lower	Upper
Anemia	**0.031**	**1.396**	**1.031**	**1.89**				
Male gender	0.052	1.383	0.988	1.916				
Age	**0.036**	**1.021**	**1.001**	**1.042**				
Hypertension	0.209	1.228	0.891	1.693				
DM	**0.016**	**1.476**	**1.076**	**2.026**				
CKD	**0.009**	**1.67**	**1.137**	**2.452**				
CAD	0.984	1.004	0.69	1.461				
COPD	**0.028**	**1.932**	**1.074**	**3.476**	**0.025**	**2.071**	**1.095**	**3.918**
Cerebrovascular Disease	0.884	1.036	0.642	1.672				
CHF	0.549	1.163	0.71	1.903				
Parkinson's Disease	0.873	1.047	0.598	1.834				
BPH	0.204	1.497	0.804	2.789				
Dementia	0.135	0.781	0.565	1.08				
Nocturia	**0.001**	**2.144**	**1.403**	**3.278**	**0.002**	**2.049**	**1.289**	**3.259**
Incontinence	**0.025**	**1.416**	1.045	1.919				
Number of drugs used daily	**0.001**	**1.105**	**1.053**	**1.159**	**0.035**	**1.065**	**1.004**	**1.13**
Psychotropic drug use	**0.041**	**1.455**	**1.015**	**2.084**				

BPH, Benign Prostatic Hyperplasia; CAD, Coronary Arterial Disease; CHF, Congestive Heart Failure; COPD, Chronic Obstructive Pulmonary Disease; CKD, Chronic Kidney Disease; DM, diabetes mellitus

Table 3. Regression analysis for excessive daytime sleepiness.

	Univariate Analysis				Multivariate Analysis			
			95% CI				95% CI	
	Sig.	OR	Lower	Upper	Sig.	OR	Lower	Upper
Anemia	**0.001**	**1.846**	**1.311**	**2.599**				
Male Gender	**0.001**	**2.160**	**1.517**	**3.074**	**0.004**	**0.517**	**0.331**	**0.807**
Age	**0.001**	**1.038**	**1.015**	**1.062**	**0.033**	**1.031**	**1.002**	**1.060**
Hypertension	0.420	1.165	0.804	1.687				
DM	**0.014**	**1.540**	**1.093**	**2.172**				
CRF	0.211	1.286	0.867	1.909				
COPD	**0.024**	**1.865**	**1.087**	**3.198**	**0.024**	**2.060**	**1.099**	**3.859**
Cerebrovascular Disease	**0.005**	**2.019**	**1.243**	**3.281**				
CHF	0.192	1.404	0.843	2.339				
CAD	**0.001**	**2.171**	**1.472**	**3.204**	**0.012**	**1.827**	**1.143**	**2.919**
Parkinson's Disease	**0.001**	**4.403**	**2.555**	**7.588**	**0.001**	**3.197**	**1.684**	**6.068**
BPH	**0.044**	**1.826**	**1.016**	**3.281**				
Dementia	0.001	2.310	1.626	3.284	0,001	2.100	1.389	3.177
Nocturia	0.360	1.276	0.757	2.151				
Incontinence	**0.001**	**1.997**	**1.390**	**2.869**	**0.011**	**1.698**	**1.127**	**2.557**
Number of drugs used daily	**0.001**	**1.111**	**1.056**	**1.169**				
Psychotropic drug use	**0.038**	**1.486**	**1.023**	**2.158**				

BPH, Benign Prostatic Hyperplasia; CAD, Coronary Arterial Disease; CHF, Congestive Heart Failure; COPD, Chronic Obstructive Pulmonary Disease; CKD, Chronic Kidney Disease; DM, diabetes mellitus

times. However, many factors including age, gender, diabetes mellitus, CKD, number of drugs used and psychotropic drug use may affect the development of all three. When the effects of these factors are controlled for, anemia in the elderly is not associated with neither insomnia nor EDS.

Sleep duration and quality are important for regulating physical health. Insomnia is one of the most common sleep disorders in the elderly. In our study, the prevalence of both insomnia and moderate and severe insomnia was found to be similar to one previous study carried out in Turkey [14]. However, levels of insomnia have have been found to be lower in other settings. In general, the higher prevalence of sleep disorders in those with lower socioeconomic and lower education levels may explain the reason for the higher prevalence that have been identified in Turkey [16]. Another reason may be that the mean age of patients in the studies carried out in Turkey were higher than in other studies (80 years) [17]. Along with age, gender and educational status, the high number of comorbidities is also closely related to sleep and complaints [16]. Therefore, when investigating the relationship of insomnia with any condition in the elderly with multiple comorbid diseases, the effect of the comorbidities should also be reviewed. This also applies to the insomnia-anemia relationship. So far, few studies have examined the relationship [18]. For example, Kim et al aimed to identify factors affecting insomnia in the elderly, they showed that history of head trauma, hyperlipidemia, heart disease, anemia, and depression were significantly related to insomnia [18]. In another study, which included all adults, not just the elderly population, it was observed that insomnia was 1.32 times higher in those with anemia than in

those without anemia, after adjustment for multiple confounding factors, except COPD, nocturia and the number of daily medications, which were found to have multivariate significance in the present study [19]. Finally, in a study including 1,053 older adults, the number of comorbid diseases was examined, and adjustment was made according to +2 comorbid disease status, anemia and insomnia were found to be associated [20]. However, rather than the number of comorbid disease, what the comorbid disease is, may be more important. In the present study, insomnia was indeed associated with anemia in univariate analysis (1.4 fold), but multivariate analysis revealed COPD, nocturia, and polypharmacy were associated with insomnia in the elderly.

EDS, which was detected in almost every 4–5 patients in our study, is the second most common sleep disorder in the elderly. The prevalence of EDS and multiple factors including age, male gender, Parkinson's Disease, dementia, diabetes mellitus, COPD, cerebrovascular disease, coronary artery disease, BPH, incontinence, psychotropic drugs and number of drugs are consistent with previous study results [21,22]. However, the association of anemia with EDS in the elderly has not been investigated so far. The optimum hemoglobin level is a very important factor for cellular functions in all organs, especially the brain and skeletal muscles. Hypoxia due to anemia may cause fatigue, weakness and deterioration in physical activity and increase the risk of EDS. There were three studies in the literature investigating the relationship between anemia and EDS that included adults, not the elderly. In a study of chronic heart failure patients, it was shown that correction of anemia with erythropoietin and intravenous iron can improve daytime sleepiness [7], however, this study was conducted in those with central sleep apnea or obstructive sleep apnea. It was concluded that the improvement in Hb also correlated significantly with the improvement in minimal oxygen saturation seen during sleep and with the improvement in daytime sleepiness. In two studies conducted in chronic hemodialysis patients, anemia was found to be a risk factor in sleep apnea patients, and daytime sleepiness was shown to be decreased as anemia improves with erythropoietin treatment [23,24]. In the last two studies, patients with sleep problems, such as periodic limb movements in sleep, or obstructive sleep apnea, which are known to be associated with anemia, were all included [6,25]. In the present study, we investigated whether anemia has a direct effect on EDS, independent of the other sleep disorders. Just as in insomnia the anemia-EDS relationship was significant in univariate analysis (1.8 times), and it was attenuated to the null when the effect of other factors was controlled for. However, being a male, age, COPD, CAD, Parkinson's disease, dementia, and incontinence were shown to increase the risk of EDS.

The strengths of the present study include the large sample size and the simultaneous evaluation of many parameters. However, findings must be interpreted in light of the studies limitations. First, the study is of a cross-sectional design and thus it is not possible to determine the direction of the association. Second, only the ESS and Insomnia severity index were used for EDS and insomnia; hence, future studies should consider using objective measures of sleep to diagnose daytime sleepiness, such as actigraphy. Third, analysis was not performed according to the severity or cause of the anemia.

Conclusion

Considering that anemia is an indicator of impaired health in the elderly, it is important to know that an elderly person who has anemia is 1.4 times more likely to have insomnia and 1.8 times more likely to have EDS than those without anemia; however, they seem to occur with other factors that may cause anemia rather than anemia itself. Longitudinal studies are needed to understand whether there is improvement in insomnia and EDS by treating anemia alone. Confounding factors such as age, sex, diabetes mellitus, number of drugs used daily, and psychotropic drug use should be taken into account in these future studies.

Author contributions

Concept – OK, PS; Design – OK, PS; Supervision – LS; Data collection and/or processing – OK, TE; Analysis and/or interpretation – OK, PS; Literature review – OK, PS, SKO; Writing – OK, PS, SKO; Critical review – LS and approval of final version: OK, TE, SKO, LS, PS.

Disclosure statement

The authors report no declarations of interest.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Ethical approval

The local Ethics in Research Committees of the institutes approved this study. Informed consent was provided by each participant or a legal guardian before participating in the study. We declare that all methods of this study were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

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