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The relationship between uric acid and erectile dysfunction in hypertensive subjects

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Abstract

Background. Endothelial dysfunction plays a major role in erectile dysfunction (ED). Uric acid (UA) is a marker of endothelial dysfunction. We hypothesized that increased UA levels may be associated with ED and aimed to investigate whether there is a relationship between, UA and ED in hypertensive patients. *Methods.* A total of 200 hypertensive patients who have a normal treadmill exercise test were divided into two groups based on the Sexual Health Inventory for Men (SHIM) test (<21 defined as ED $n=110$, and ≥ 21 defined as normal erectile function $n=90$). The differences between the ED and normal erectile function groups were compared and determinants of ED were analyzed. *Main results.* The prevalence of ED was found to be 55.0%. Office blood pressure level was comparable between groups. UA levels were significantly increased in the ED group (6.20 ± 1.56 vs 5.44 ± 1.32, $p=0.01$). In a regression model, age [odds ratio (95% confidence interval): 1.08 (1.04–1.14), $p=0.001$], smoking [odds ratio: 2.33 (1.04–5.20), $p=0.04$] and UA [odds ratio: 1.76 (1.28–2.41), $p=0.04$] were independent determinants of ED. An UA level of >5.2 mg/dl had 76.2% sensitivity, 43.7% specificity, 62.9% positive and 59.4% negative predictive value for determining ED. *Conclusion.* UA is an independent determinant of ED irrespective of blood pressure control and questioning erectile function for hypertensive patients with increased UA levels may be recommended.

Key Words: *Endothelial dysfunction, erectile dysfunction, hypertension, uric acid*

Introduction

Erectile dysfunction (ED) is an important public health concern, especially in the hypertensive population, with a reported prevalence of 15–67% in these subjects (1,2). The major pathophysiology of ED is endothelial dysfunction secondary to decreased nitric oxide (NO) bioavailability in hypertension (1,3). In addition to hypertension itself, antihypertensive drugs including beta-blockers, diuretics and centrally acting sympatholytics are also important causes of ED (4). On the other hand, there is insufficient data about the definitive mechanisms of ED among patients with hypertension in the current literature.

Uric acid (UA) is a marker of atherosclerosis and endothelial dysfunction. There are numerous studies that show the association between elevated UA levels and endothelial dysfunction (5–7). Park et al. (6) found that UA attenuated NO production. Also, Matheus et al. (7) reported that UA levels were reversely correlated with the microvascular

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vasodilator response to acetylcholine in Type 1 diabetes. Hypertension is also common disease characterized by endothelial dysfunction. Despite the role of UA in the etiology of essential hypertension being highly speculated by many researchers, it has remained debatable. In addition to many factors affecting UA levels, thiazide-like diuretics cause increased serum UA levels (8,9). It is also known that thiazide-type diuretics might cause endothelial dysfunction via metabolic abnormalities (10). Based on the literature, it seems that there is a possible complex relationship between UA and ED in hypertensive subjects. However, this association has not been studied in the current literature yet. The main hypothesis of the study is that increased UA levels may be related to ED in hypertensive subjects.

Methods

Patient selection

In this cross-sectional study, a total of 448 hypertensive male patients (age range: 30–70 years) using at least one antihypertensive drug for at least 1 year were screened in the cardiology outpatient clinic between January 2012 and April 2013. A total of 200 patients (mean age 56.2 ± 8.9 years), who did not have any exclusion criteria and gave written informed consent, were randomly enrolled. This study was approved by a local ethics committee and adhered to the Declaration of Helsinki. Written informed consent was obtained from all patients participating in the study.

Exclusion criteria included patients with any of the following: history of coronary artery disease (such as myocardial infarction, coronary revascularization), angina pectoris, objective signs of myocardial ischemia on ECG, treadmill exercise test or scintigraphy, cerebrovascular disease, heart failure [ejection fraction (EF) $< 40\%$], severe valvular heart disease, chronic renal [glomerular filtration rate (GFR) < 60 ml/min] or hepatic dysfunction, any systemic disorder, malignancy, hyperlipidemia, gout, known sleep apnea, a score ≥ 8 on the Epworth Sleepiness Scale (ESS), trauma or infection in the last month, hormone replacement therapy for reasons such as thyroid disease or menopause, use of any medications directly affecting UA levels (except diuretics) such as salicylate, allopurinol, probenecid, sulfinpyrazone, known psychiatric disorder and/or psychiatric drug use, alcohol and drug addiction, erectile dysfunctions from organic causes, frequent ventricular extrasystole and atrial fibrillation. Silent myocardial ischemia was excluded using a treadmill stress test for all patients. A positive stress test was defined as horizontal and/or down sloping ST segment depression above 1 mm in two consecutive leads.

A flowchart of the study population is shown in Figure 1.

Study protocol

Demographics and characteristics such as weight, height, resting blood pressure (BP), and medical histories were recorded for all subjects. All patients underwent a treadmill exercise test. After a negative treadmill exercise test, erectile functions of patients were assessed using the Sexual Health Inventory for Men (SHIM) questionnaire. The SHIM questionnaire, also known as the International Index of Erectile Function (IIEF)-5 contains five items and is the short form of the 15-item IIEF questionnaire. Each item is scored either from 0 to 5 or from 1 to 5, yielding a global sexual function score between 1 and 25. Patients with a SHIM score < 21 were defined as having ED and those with a SHIM score ≥ 21 were defined as having normal erectile function (11,12).

Blood pressure

After 10 min resting, office BP was measured twice, separated by 2 min, from the brachial artery using a mercury sphygmomanometer (ERKA D-83646 Bad Tolz, Kallmeyer Medizintechnik GmbP Co. KG, Germany). A mean value of the two BP measurements was obtained. If the two readings differed by more than 5 mmHg, extra readings were obtained.

Blood sample analyses

Patients fasted for 12 h before blood draws for serum UA levels and other laboratory analyses. Fasting blood samples were drawn by antecubital veni puncture. Blood samples were collected directly into serum separator tubes. After coagulation, samples were centrifuged at 1500*g* for 10 min. Sera were separated, stored in aliquots and kept frozen at $-20°C$ until analysis. HbA1c levels were analyzed with high performance lipid chromatography (HPLC) on the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 (Tosoh G8; Tosoh Bioscience, Inc). GFR calculation was performed using the Cockcroft–Gault formula (13).

Statistical analyses

All data were analyzed using SPSS software version 15.0 (SPSS, Chicago, IL, USA). The distribution of the variables was analyzed with the Kolmogorov–Smirnow test. Normally distributed data were presented as mean $\pm$ standard deviation. Data with abnormal distributions were expressed as median [interquartile range (IQR)], and dichotomous data were given as percent. The significance level of the difference between the two groups was tested using

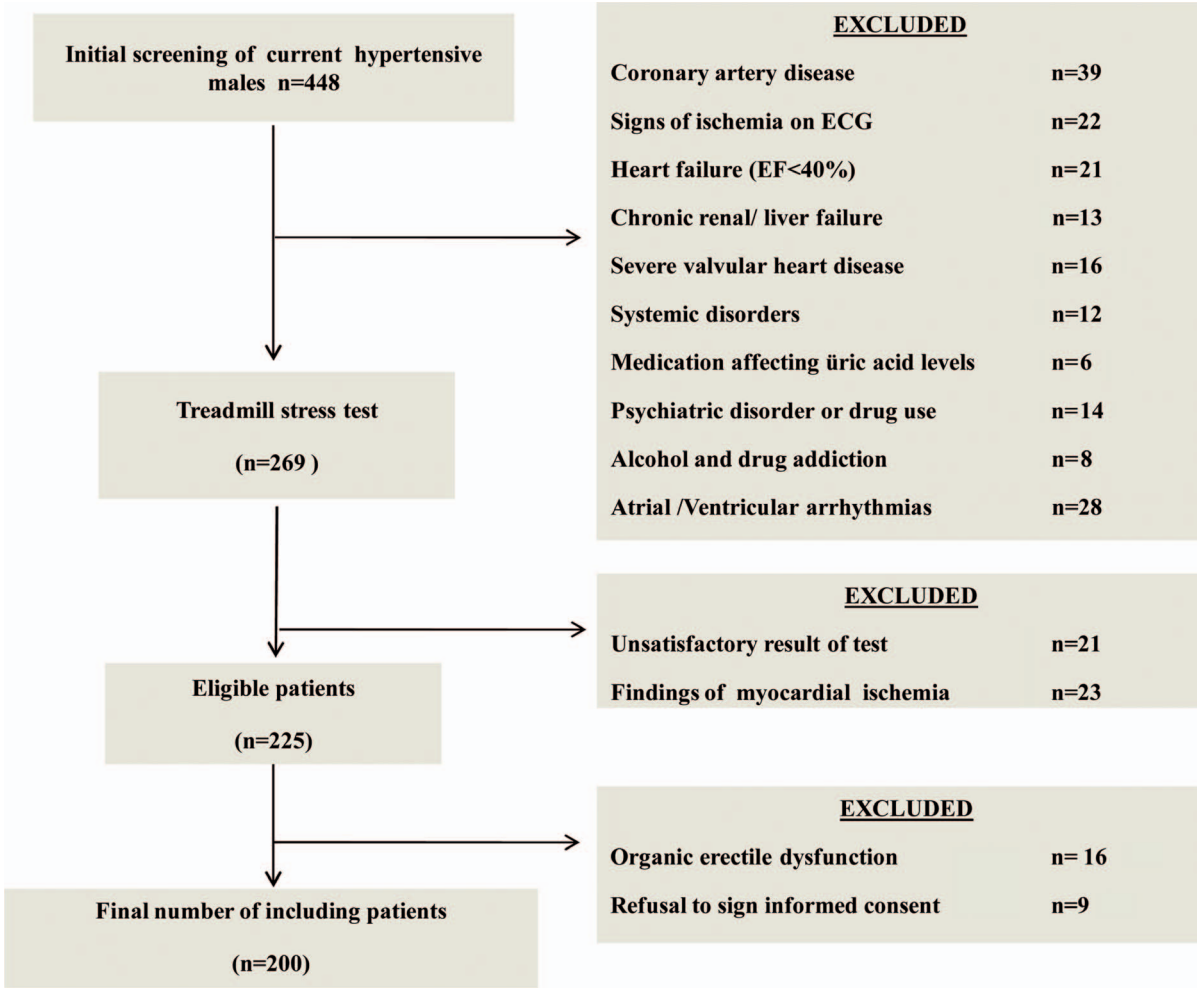

Figure 1. Flowchart of the study population included in the study.

independent Student's *t*-tests for normally distributed variables and with the non-parametric Mann–Whitney *U* test for non-normally distributed variables. The differences between the categorical variables were determined using the χ^2 test. Linear association between parametric variables was evaluated using Pearson's correlation test. Correlation analysis of non-parametric data was performed using the Spearman test. Stepwise multivariate logistic regression was performed to find the determinants of ED (SHIM $<$ 21). Age, systolic BP, smoking, diabetes mellitus, use of beta-blockers, use of diuretics, UA, C-reactive protein, GFR and body mass index (BMI) were entered into a regression model as independent determinants of ED. The backwards elimination method was used and the elimination criterion was defined as $p > 0.10$ for each step. After a five-step elimination, independent determinants of ED were found by the model. The level of statistical significance was accepted as $p < 0.05$ for all tests.

Power analysis was performed using the MedCalc 12.7.0.0 licensed packet program. A sample size of 178 was calculated to determine a difference in UA of about 1.0 mg/dl with 90% power and 95% confidence interval. A MedCalc 12.7.0.0 packet program was used to calculate the receiver operating curve (ROC) and to analyze the specificity, sensitivity, negative and positive predictive values of UA for the ED.

Results

The prevalence of ED was found to be 55.0%. Office BP levels were comparable between the ED and non-ED groups, whereas age, UA (6.20 ± 1.56 vs 5.44 ± 1.32, $p = 0.01$) (Figure 2a), creatinine and fasting glucose levels were significantly greater, and GFR were significantly lower in the ED group. Demographic characteristics and laboratory findings of patients with and without ED are presented in Table I. Beta-blocker users, calcium channel blocker users, smokers and diabetics were more common in the ED group. A total of 72 patients (36%) were using thiazide-like diuretics [25 mg hydrochlorothiazide ($n = 10$), 12.5 mg hydrochlorothiazide ($n = 46$) and 1.25 mg indapamide ($n = 16$)].

The multiple logistic regression model showed that age [odds ratio: 1.08 (1.04–1.14), $p = 0.001$], smoking [odds ratio: 2.33 (1.05–5.20), $p = 0.04$] and

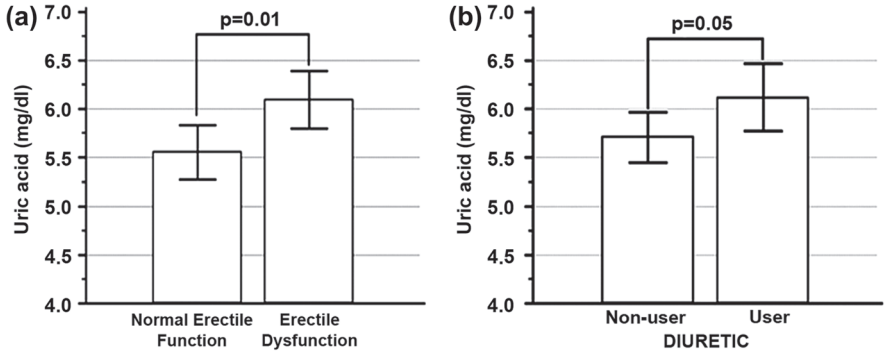

Figure 2. (a) Graph of uric acid levels in patients with and without erectile dysfunction; (b) graph of uric acid levels in patients receiving and not receiving diuretic.

UA [odds ratio: 1.76 (1.28–2.41), $p = 0.04$] were independent determinants of ED (Table II). Beta-blockers and thiazide-like diuretics did not reach statistical significance in the regression model. Also, UA levels were increased in patients using thiazide-like diuretics compared with non-users (6.30 ± 1.5 vs 5.5 ± 1.5 mg/dl, $p = 0.05$) (Figure 2b). A weak negative correlation was observed between SHIM score and UA level ($r = -0.20$, $p = 0.01$) (Table III). To indicate ED in ROC analysis, a cut-off value for a UA level of greater than 5.2 mg/dl had 76.2% sensitivity, 43.7% specificity, 62.9% positive predictive value and 59.4% negative predictive value for prediction of ED. The area under the curve (AUC) was found to be 0.62 (95% CI 0.55–0.69, $p = 0.002$) for this cut-off value (Figure 3).

Table I. Demographic characteristics and laboratory findings of patients with and without erectile dysfunction (ED).

Variables	Patients without ED ($n = 90$), mean ± SD/median (IQR)	Patients with ED ($n = 110$), mean ± SD/median (IQR)	p
Age (years)	53.2 ± 9.4	58.5 ± 8.2	< 0.001
Diabetes mellitus, *n* (%)	8(8.8)	21 (19.1)	0.05
Smoking, *n* (%)	25 (27.8)	42 (38.2)	0.06
Duration of hypertension (years)	4.6 (4.0)	6.1(9.0)	0.18
Body mass index (kg/m$^{2)}$	29.0 ± 3.3	29.4 ± 4.3	0.45
Systolic blood pressure (mm/Hg)	145.5 ± 17.4	145.7 ± 22.2	0.94
Diastolic blood pressure (mm/Hg)	89.8 ± 12.5	87.7 ± 12.4	0.46
Fasting blood glucose (mg/dl)	99.3 ± 20.4	112.4 ± 37.8	0.003
Urea (mg/dl)	28.1 ± 11.7	26.7 ± 12.7	0.46
Creatinine (mg/dl)	0.9 ± 0.1	1.0 ± 0.2	0.001
HbA1c	5.9 (0.90)	6.2(1.03)	0.77
Sodium (mmol/l)	139.6 ± 2.6	138.2 ± 14.0	0.41
Potassium (mmol/l)	4.3 ± 0.4	4.7 ± 3.5	0.33
Uric acid (mg/dl)	5.44 ± 1.32	6.20 ± 1.6	0.01
Glomerular filtration rate (ml/min)	117.3 ± 21.3	103.1 ± 25.7	< 0.001
Diuretics, *n* (%)	38 (42.2)	34 (31.0)	0.74
Beta-blockers, *n* (%)	16 (17.8)	34 (30.9)	0.04
ACE inhibitors, *n* (%)	19 (21.1)	34 (30.9)	0.10
Angiotensin receptor blockers, *n* (%)	18 (20)	23 (20.9)	0.94
ACE/ARB, *n* (%)	37 (41.4)	57 (51.8)	0.19
Statins, *n* (%)	13 (14.4)	24 (21.8)	0.20
CCB, *n* (%)	10 (11.1)	30 (27.3)	0.006
Alpha-blockers, *n* (%)	3 (3.3)	6 (5.5)	0.50
Oral anti-diabetics, *n* (%)	8 (8.9)	19 (17.3)	0.10
ASA, *n* (%)	18 (20)	33 (30)	0.14
Alcohol, *n* (%)	4 (4.4)	8 (7.3)	0.22
Duration of exercise on TET (min)	9.37 (2.64)	8.03 (2.24)	0.06
METs on TET	11.58 (2.89)	10.84 (2.49)	0.16
Heart rate on TET (beats/min)	162.77 (19.06)	149.15 (21.32)	0.03

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid; CCB, calcium channel blockers; METs, metabolic equivalents; TET, treadmill exercise test.

Table II. The independent determinants of erectile dysfunction (ED) in a multiple stepwise logistic regression model.

Variables	Beta	Odds ratio	95% CI of odds ratio	*p*-value
1st step				
Age	0.06	1.06	1.00–1.13	0.05
Systolic blood pressure	−0.02	0.98	0.96–1.01	0.13
Smoking	0.81	2.24	0.97–5.19	0.06
Diabetes mellitus	−0.61	0.54	0.18–1.65	0.28
Usage of beta-blockers	−0.27	0.77	0.28–2.12	0.61
Usage of diuretics	0.16	1.18	0.50–2.76	0.71
Uric acid	0.59	1.80	1.26–2.57	0.001
C-reactive protein	0.07	1.07	0.94–1.21	0.30
Glomerular filtration rate	−0.01	0.99	0.96–1.01	0.33
Body mass index	0.02	1.02	0.90–1.15	0.80
5th step				
Age	0.08	1.08	1.04–1.14	0.001
Smoking	0.85	2.33	1.05–5.20	0.04
Uric acid	0.57	1.76	1.28–2.41	<0.001

$r^2 = 0.32$, model statistic of last step, $p = 0.001$. CI, confidence interval.

Discussion

In the present study, the effect of UA on ED was systematically examined for the first time. The present study demonstrated that age, smoking and UA levels were independent determinants of ED in hypertensive patients without evidence of coronary artery disease.

The prevalence of ED in hypertensive subjects is increased compared with normotensive individuals (1,2,14,15). The prevalence of ED in the present study is 55%, comparable with current literature. It has been shown in various studies that the prevalence of ED is increased in elderly people with or without cardiovascular risk factors (12,16,17). Despite the fact that we excluded patients older than 70 years, age remained a predictor of ED in the present study. It has been demonstrated that smoking is associated with increased ED, especially in young males with or without clinical cardiovascular disease, in various studies (18–21). In the study by Feldman et al. (20), it was shown in a population of 513 subjects that the risk of developing moderate or complete ED doubled due to smoking in men aged 40–70 years without hypertension or diabetes mellitus. Similarly, we found that smoking increased the risk of ED about two-fold in hypertensive patients.

Table III. The correlation of variables with Sexual Health Inventory for Men (SHIM) score and uric acid levels.

	SHIM score		Uric acid	
Variables	*r*	*p*	*r*	*p*
Uric acid	−0.20	**0.01**	–	–
GFR	0.33	**<0.001**	−0.03	0.74
BMI	−0.06	0.43	0.18	**0.01**
sCRP	−0.16	**0.05**	0.02	0.85
Total cholesterol	0.03	0.68	0.12	0.11
LDL-cholesterol	0.07	0.37	0.09	0.24
HDL-cholesterol	0.07	0.37	0.004	0.95
Triglyceride	0.02	0.82	0.06	0.45
HbA1c	−0.20	0.15	−0.11	0.43
METs	0.19	**0.05**	−0.10	0.29
Duration of exercise	0.24	0.11	0.06	0.70
Max. heart rate	0.36	**0.01**	0.13	0.38
Glucose	−0.21	**0.01**	0.18	**0.01**
Duration of HT	−0.21	0.09	−0.07	0.59
Systolic BP	0.05	0.52	−0.03	0.73
Diastolic BP	0.18	**0.01**	0.05	0.53
Age	−0.37	**<0.001**	−0.06	0.45

GFR, glomerular filtration rate; BMI, body mass index; sCRP, serum C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; METs, metabolic equivalents; HT, hypertension; BP, blood pressure.

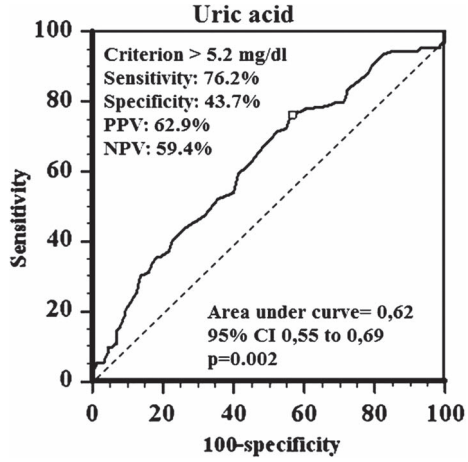

Figure 3. Uric acid receiver operating curve (ROC) curve. AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

The primary aim of the present study was to examine the relationship between ED and UA. UA was not correlated with GFR in the present study. This may be due to the exclusion of patients with a GFR below 60 ml/min. A weak correlation between UA and both BMI and serum glucose was seen in the present study. Although it was previously thought that UA, an end product of purine metabolism, was a major antioxidant and had possible beneficial anti-atherosclerotic effects, it has been demonstrated in the past two decades that it is a risk factor for atherosclerosis and related diseases (22). Hyperuricemia leads to endothelial dysfunction through the generation of reactive oxygen species. There are numerous studies showing the association of increased UA levels with endothelial dysfunction, and that lowering UA was beneficial in improving endothelial function (23). It was demonstrated that UA reduces NO levels in endothelial cell cultures, blocks acetylcholine-induced vasodilation of aortic rings and reduces circulating nitrites in experimental animals (5). Corry et al. (24) reported that UA stimulates vascular smooth muscle cell proliferation, angiotensin II production, and oxidative stress via the vascular renin–angiotensin system. The relaxation of cavernous

smooth musculature and the smooth muscles of the arteriolar and arterial walls has a pivotal role in the erectile process. NO is also one of the key mediators in the relaxation of these smooth muscles (1,25). In addition to increased UA level in the ED group, we observed a weak linear association between UA levels and SHIM scores.

Despite higher prevalence of beta-blocker use in the ED group, beta-blockers failed to predict ED in regression analysis. This may probably relate to the strict exclusion of patients with coronary artery disease and cardiac dysfunction in the present study. Nevertheless, beta-blocker users were more common in the ED group compared with the normal erectile function group. Interestingly, despite no compelling indication for beta-blocker therapy, one third of ED sufferers were continuing beta-blocker treatment. There was no statistical difference on the treadmill test results other than in heart rates between the patients with and without ED. Heart rates were significantly lower in patients with ED. This finding may be related to the higher rates of beta-blocker use among patients with ED compared with normal erectile function group (30.9% vs 17.8%).

Early reports documented that the prevalence of ED is higher among patients taking thiazide group diuretics compared with those taking other antihypertensives, including beta-blockers (26,27). Also, it was shown that the prevalence of impotence and UA levels were higher in patients taking bendrofluazide (the new name of bendroflumethiazide), a thiazide diuretic, compared with those taking different antihypertensive drugs (26). The rate of thiazide use was about 36% in the present study. ED prevalence was comparable between diuretic users and non-users. This may be related to the use of relatively low dosages of diuretics in the present study compared with the literature. In the present study, only 10 patients (13.9%) were receiving 25 mg hydrochlorothiazide daily, 16 patients (22.2%) were receiving 1.25 mg indapamide daily, and the majority of patients (63.9%) were receiving 12.5 mg hydrochlorothiazide daily. It appears that the doses of diuretics are lower in the present study compared with the previously studies in literature (26,28,29); this may be one of the possible reasons why ED prevalence was comparable between diuretic users and non-users. However, UA levels of diuretic users were mildly increased compared with non-users (Figure 2b). These findings suggest that, while alone, thiazide-like diuretics were not determinants of ED, they may contribute to endothelial dysfunction by increasing UA levels. Findings also suggest that low doses of thiazide-like diuretics are not a major risk factor for ED in hypertensive patients.

Contribution to the literature

The present study indicates that UA is increased in hypertensive patients with ED independently from office BP levels and this relationship seems linear. It may be explained by UA related endothelial dysfunction. The present study contributes to the literature as a preliminary report that points to relationship between UA and ED in patients with hypertension.

Limitations

The first limitation of this study is that the assessment of erectile dysfunction was performed using the SHIM questionnaire, a subjective test that may cause to bias in completing the test; however, the SHIM test is the most common questionnaire for the assessment of ED in clinical trials. Second, there are many different causes of ED other than those of vascular origin. Therefore, the results of the study cannot be generalized to all patients suffering from erectile dysfunction. Also, we although excluded organic causes, some patients with erectile dysfunction due to organic or psychogenic causes may be mistakenly included in the study. Third, strict exclusion criteria may limit the ability to generalize the study results to all hypertensive subjects. Elderly subjects especially may be more susceptible to the effects of diuretics on ED. Also, elderly subjects suffer from many health problems, making it difficult to demonstrate the true cause of ED. Therefore, it may be reasonable to perform a study including only elderly people on this issue. We focused on non-complicated arterial hypertension. Despite similar office BP measurements, the lack of ambulatory BP measurements, dipping status and BP variability data is another limitation of the present study. Ambulatory BP monitoring could not be performed due to the cost. Future studies should consider this issue. Another important limitation is the lack of flow-mediated dilatation data. The mechanisms of UA-related ED remained uncertain; we speculate that UA may cause ED via endothelial dysfunction but we did not assess flow-mediated dilation and other markers of endothelial functions. Therefore, future investigations are needed, examining definitive mechanisms of ED in these subjects. Finally, as the study is based on a small sample size, it may not be appropriate to make a solid conclusion.

Conclusion

UA is an independent determinant of ED irrespective of BP control, and questioning of erectile functions for hypertensive patients with increased UA levels may be recommended.

Declaration of interest: The authors report no conflicts of interest.

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