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Uric Acid Level and Erectile Dysfunction In Patients With Coronary Artery Disease

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Abstract

Introduction—Erectile dysfunction (ED) is a frequent complaint of elderly subjects, and is closely associated with endothelial dysfunction and cardiovascular disease. Uric acid is also associated with endothelial dysfunction, oxidative stress and cardiovascular disease, raising the hypothesis that an increased serum uric acid might predict erectile dysfunction in patients who are at risk for coronary artery disease.

Aim—To evaluate the association of serum uric acid levels with presence and severity of ED in patients presenting with chest pain of presumed cardiac origin.

Methods—This is a cross-sectional study of 312 adult male patients with suspected coronary artery disease who underwent exercise stress test (EST) for workup of chest pain and completed a sexual health inventory for men (SHIM) survey form to determine the presence and severity of ED. Routine serum biochemistry (and uric acid levels) were measured. Logistic regression analysis was used to assess risk factors for ED.

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Conflict of Interest: Dr R J Johnson is listed as an inventor on a patent for allopurinol to treat essential hypertension, and is also an inventor on patent applications related to lowering uric acid in the prevention or treatment of hypertension, insulin resistance and diabetic nephropathy. He has also served as a consultant for Novartis, Ardea, Danone, and Astellas, and is on the Scientific Board of Amway. All other authors declared no competing interests and all authors had access to the data and played a role in writing this manuscript.

Main Outcome Measures—The short version of the international index of erectile function (IIEF-5) questionnaire diagnosed ED (cutoff score ≤21). Serum Uric acid levels were determined. Patients with chest pain of suspected cardiac origin underwent an exercise stress test.

Results—149 of 312 (47.7%) male subjects had ED by survey criteria. Patients with ED were older and had more frequent CAD, hypertension, diabetes, and impaired renal function, and also had significantly higher levels of uric acid, fibrinogen, glucose, CRP, triglycerides compared with patients without ED. Uric acid levels were associated with ED by univariate analysis (OR = 1.36, p = 0.002); however, this association was not observed in multivariate analysis adjusted for eGFR.

Conclusion—Subjects presenting with chest pain of presumed cardiac origin are more likely to have ED if they have elevated uric acid levels.

Keywords

Uric Acid; Erectile Dysfunction; Coronary Artery Disease; Endothelial Dysfunction

Introduction

Erectile dysfunction (ED) is fairly common, especially among elderly men, and is associated with coronary artery disease (CAD)[1-4]. The association of ED has been attributed to the presence of common risk factors such as obesity, hypertension, diabetes and smoking. Not surprisingly, prospective observational studies have reported that subjects with ED are at risk for future cardiovascular events[5]. A recent meta-analysis also reported that ED significantly increases the risk of cardiovascular disease (CVD), CAD, stroke, and all-cause mortality. Moreover, the increase was independent of conventional cardiovascular risk factors[6].

Erectile dysfunction is strongly associated with the presence of small vessel disease and endothelial dysfunction[7-8]. Subjects with longstanding hypertension, who develop small vessel disease (arteriolosclerosis), are also susceptible to developing ED independent of specific antihypertensive agents[9]. In this regard, uric acid becomes an interesting potential risk factor for ED, as it is strongly linked with endothelial dysfunction[10-12], microvascular disease[13], and hypertension[14-15]. Experimental studies show that uric acid can reduce endothelial nitric oxide bioavailability via multiple mechanisms, including scavenging by uric acid-induced oxidative stress, the stimulation of arginase, and direct scavenging[16-19]. Uric acid can also induce vascular smooth muscle cell proliferation in vitro and induce microvascular disease in vivo, and studies in humans have linked uric acid with microvascular disease[20-24]. An elevated uric acid is also emerging as an independent predictor of hypertension, and pilot clinical studies suggest lowering uric acid can improve endothelial function and lower blood pressure in hypertensive subjects[25-27]. Despite these associations, to date no studies have examined the relationship of uric acid levels to ED.

Uric acid has also been recognized as a novel risk factor for development of CAD, although meta-analyses are mixed on the independence of this relationship[28-30]. Recently we reported that ED is a risk factor for CV disease in subjects presenting with chest pain. Here we used the same cohort study to address a new question—could uric acid be a predictor for ED? We further hypothesized that increased serum uric acid levels may be one of the missing links between CAD and ED. With this background in mind, we evaluated the association of serum uric acid levels with presence and severity of ED in patients presenting with chest pain of presumed cardiac origin.

Materials and Methods

This was a cross-sectional study and the participants were recruited from a prospectively maintained cohort. Previously we reported that reduced eGFR and presence and severity of erectile dysfunction were associated with severity of coronary artery disease in this cohort[31]. We included 312 consecutive adult male patients who for the first time presen**ting** with chest pain to our cardiology outpatient clinic. Only married men with a permanent sexual partner were included. Exclusion criteria were as follows: previous evaluation for CAD by coronary angiography, history of established CAD (previous myocardial infarction, coronary artery bypass grafting surgery, heart failure or percutaneous coronary angioplasty), drug therapy for CAD, drug therapy for known erectile dysfunction, liver cirrhosis, gout, chronic obstructive pulmonary disease, depression, cancer and chronic renal replacement therapy. We also excluded subjects if they were taking allopurinol. After detailed medical history and thorough physical examination, patients with chest pain of suspected cardiac origin underwent an exercise stress test (EST). Patients who were deemed to have noncardiac chest pain or required no further testing were excluded from the study. Final participants were subjects who had chest pain of suspected cardiac origin as determined by the clinical exam and EST.

The study was approved by Local Ethics Committee, and all the participants signed written informed consent forms before recruitment. Patients were examined with good medical and laboratory practice according to the recommendations set forth by the Declaration of Helsinki on biomedical research involving human subjects.

Included patients were instructed to complete the sexual health inventory for men (SHIM) survey form. SHIM, also known as IIEF-5 (International Index of Erectile Function) is an established, valid and reliable questionnaire for determining the presence and severity of ED[32]. Patients with SHIM scores ≤ 21 were diagnosed with ED.

Based on the definitions of the Framingham Heart Study, patients who were smoking > 10 cigarettes/day were accepted as smokers, and patients who ceased smoking more than 2 years ago were accepted as nonsmokers. Hypertension and diabetes mellitus were described according to the Seventh Report of the Joint National Committee[33] and World Health Organization criteria,[34]. Patients with total serum cholesterol values > 200 mg/dl were defined as dyslipidemic.

All patients included in the study underwent exercise stress test (EST) with the multi-stage Bruce protocol. Whenever feasible, beta-blockers and calcium channel blockers were discontinued for 24–48 hours before the treadmill test. The criteria for ending the test involved an ST depression of 2 mm and an ST elevation of 1 mm compared with resting electrocardiogram, a decrease in systolic blood pressure more than 10%, no increase in heart rate or development of bradycardia, a blood pressure reading greater than 250/130 mmHg, presence of class 3–4 angina, significant arrhythmia, reaching target heart rate and fatigue precluding further exercise. Patients with positive EST underwent conventional coronary angiography (CAG). Selective CAG was performed via Judkins technique through femoral artery route with multiprojection. All angiograms were evaluated by two blind observers who were unaware of the results of the ETT. A 50% and more luminal diameter narrowing were accepted as a significant lesion via visual assessment in major epicardial coronary arteries or their major branches. All patients were compared and classified into four groups according to CAG results as follows: normal coronary artery (NCA), single-vessel CAD, two-vessel CAD and three-vessel CAD.

Venous blood samples were collected from all participants to measure serum glucose, blood urea nitrogen, creatinine, sodium, potassium, uric acid, fibrinogen, high sensitive C-reactive protein (hsCRP) and lipid profile. Spot urine sample was collected to measure urinary albumin excretion. eGFR was calculated by using the Cockcroft–Gault equation[35].

Statistical Analyses

Wilcoxon Sign Rank test was used to compare continuous variables between those without erectile dysfunction versus those who do have erectile dysfunction. Chi Square test of independence or Fisher's Exact was used to compare categorical variables between groups. Logistic regression was used to test the unadjusted relationship between uric acid and quartiles of uric acid on ED. Univariate logistic regression was used to test the relationship of several risk factors with ED. A series of multivariate logistic regression models were tested using variables selected from univariate analyses with either uric acid as a continuous variable or quartiles of uric acid. $P < 0.05$ was considered significant. All calculations were performed by using a standard statistical package (SAS 9.2, Cary, NC).

Results

312 male subjects were included in the study, 149 with ED and 163 without ED. Subjects with ED were older and were more likely to have angiographically proven CAD, hypertension, diabetes, worse renal function, and a positive treadmill test (Table 1). In addition, those with ED had higher acetylsalicylic acid use, and higher serum fibrinogen, glucose, CRP, triglycerides, and uric acid levels compared with patients without ED (Table 1). In unadjusted analysis, uric acid, as a continuous variable, was associated with ED for each 1 mg/dl increase in serum uric acid level (OR = 1.361 (1.121-1.652), p = 0.0019). In unadjusted analysis the 4th quartile of uric acid was associated with ED compared with the 1st quartile (OR = 2.638 (1.378℃5.048), p = 0.0034). There was no association of the 2nd or 3rd quartiles of uric acid with ED.

Next we examined risk factors associated with ED in univariate logistic regression analysis. Known CV risk factors and diabetes were significantly associated with ED in univariate logistic regression (Table 2). To determine the independent contribution of uric acid to ED, we constructed a series of multiple regression models based on risk factors impacting ED. All of the parameters that significantly correlated with ED were introduced in standard multivariate regression analysis in a three step procedure. In the first step we evaluated the independent influence of uric acid and age on ED in our population. In this first step uric acid (OR = 1.36; p = 0.0029), and age (OR = 1.08, p < 0.0001) were both statistically significant independent predictors that correlated with ED (Table 3). In the second step we adjusted for age and presence of coronary artery disease. After these adjustment serum uric acid (OR = 1.31, p = 0.01), age (OR= 1.08, p< 0.0001), and coronary artery disease (OR= 3.12, p <0.0001) remained statistically significant predictors of the ED (Table 3). In the third step we adjusted for age, eGFR, and the presence of coronary artery disease. After these adjustments, uric acid lost its significance (OR= 1.21, p=0.088), (Table 3).

Multiple logistic regression was also performed, including the above-selected variables, as well as hypertension and diabetes. As expected, uric acid and quartiles of uric acid were not found to be independent risk factors for ED (Tables 4).

Additional analyses

Serum uric acid had weak correlations with eGFR (r = -0.19, p = 0.0009), DBP (r = 0.17, p = 0.0056), SBP (r = 0.15, p = 0.0129), LDL (r = 0.13, p = 0.0254), CRP (r=0.17, p = 0.0048), cholesterol (r = 0.20, p = 0.0006), and triglycerides (r = 0.22, p = 0.0001). The 4th

quartile of uric acid was associated with increased odds of CAD, OR = 2.30 (1.170-4.521), p = 0.0158. When ED was regressed on CAD and quartiles of uric acid, both coronary artery disease, OR = 2.821 (1.691-4.704), p < 0.0001 and the 4th quartile of uric acid, OR = 2.287 (1.171-4.466), p = 0.0154, were associated with ED.

Discussion

Our primary finding is that an elevated serum uric acid level is associated with the presence of ED in subjects with suspected CAD. For each change in 1 mg/dl uric acid, there was a 31 percent increased risk for having ED. However, when this relation was adjusted for traditional cardiovascular risk factors, the relationship with serum uric acid level was no longer significant.

The importance of epidemiology in generating hypotheses is well established. Ideally, one tries to identify risk factors that are strongly associated with an outcome and which are independent of other risk factors when multivariate analyses are used. For example, coffee drinking may be related to CAD by univariate analysis, yet this association may be accounted for by the finding that coffee drinkers are also more commonly people who smoke tobacco. Hence, coffee drinking may not be independent of smoking as a risk factor for CAD, and coffee is not a true risk factor since it is the smoking that is truly responsible for the association. However, we might also do an analysis that finds that smoking is not independent of hypertension as a risk factor for stroke and we might wrongly conclude that smoking is not a true risk factor, when in fact smoking may cause CAD by causing hypertension. Thus, understanding how a risk factor works may help one to understand the potential assumptions associated with assuming a risk factor is causal[36]. This is particularly important for uric acid, as it is increasingly apparent that it may have multiple biological effects that could have contributory roles in many risk factors for cardiovascular disease[37-38].

Recent studies have shown that soluble uric acid can have marked effects on the microvasculature[39]. Uric acid, while an antioxidant in the extracellular environment[40], causes oxidative stress when it elevated inside the cell, including in vascular smooth muscle cells and vascular endothelial cells[23, 41]. The mechanism may be via the stimulation of NADPH oxidase[42]. In addition, uric acid potently reduces nitric oxide in endothelial cells and vascular smooth muscle cells, via multiple mechanisms[43]. Hyperuricemic rats show evidence for endothelial dysfunction that is reversed by normalizing the serum uric acid[44]. In addition, hyperuricemia is strongly associated with endothelial dysfunction in humans, including in asymptomatic hyperuricemia[11]. We and others have shown that lowering serum uric acid with xanthine oxidase inhibitors can improve endothelial dysfunction[45-48]. Whether this is due to specific blockade of xanthine oxidase or the lowering of intracellular uric acid in vascular cells remains debated. Uric acid can also induce inflammation, and can increase CRP and chemokines via the activation of MAP kinases and NFκB[49-50]. Lowering uric acid has been reported to improve CRP levels in both normal subjects and subjects with CKD[47, 51]. Finally, uric acid can stimulate vascular smooth muscle cell proliferation in vitro and induced renal microvascular disease in vivo[23, 52]. We have also linked serum uric acid with microvascular disease in the heart of patients undergoing myocardial infarction[52].

There are multiple factors involved in the pathogenesis of ED, including endothelial dysfunction, microvascular disease, alterations in testosterone levels, and psychological factors. The observation that uric acid may have a role in driving endothelial dysfunction and microvascular disease provides a potential causal link between uric acid and ED[52,53]. For example, thiazide diuretics are known to be one cause of ED, and may cause ED due to their ability of causing endothelial dysfunction. In our study diuretic use was more common

in subjects with ED (15 vs 6 percent, p <0.01, Table 1). Interestingly, thiazide use also raises uric acid levels, and in animals the thiazide-induced endothelial dysfunction can be reversed by lowering uric acid levels[54]. Thus, these data suggest the complex interplay of CV risk factors and uric acid in the potential etiology of ED. To truly determine if uric acid may have a role in ED, a clinical trial randomizing subjects with ED to uric acid lowering therapy might be useful. The consistent observation that lowering uric acid with allopurinol can improve endothelial dysfunction provides a further argument for performing such a study[55].

The observation that uric acid can induce endothelial dysfunction, oxidative stress, inflammation and microvascular disease could provide a link between uric acid and CV disease and ED, as well as other risk factors for CAD. For example, there is now strong evidence that uric acid can independently predict the development of hypertension and insulin resistance, as reflected by recent meta-analyses[53-54]. Raising uric acid in rats causes hypertension by causing oxidative stress, endothelial dysfunction and microvascular disease[19, 55-56]. Uric acid has also been found to have a causal role in both dietary and nondietary insulin resistance in laboratory animals, again through mechanisms involving oxidative stress and endothelial dysfunction[57-59]. Multiple studies also show that uric acid independently predicts the development of kidney disease, and may accelerate its production by causing endothelial dysfunction[60-61]. Indeed, pilot studies suggest that lowering uric acid may have benefits on blood pressure[26, 47, 62], insulin resistance[63] and chronic kidney disease[51, 64] in humans. Therefore, while our inability to show uric acid as an independent risk factor could be interpreted to mean that uric acid is not a true risk factor, the data is also compatible with the hypothesis that uric acid may have a contributory role to both ED as well as hypertension, insulin resistance and renal function due to its central role in causing endothelial dysfunction, oxidative stress and inflammation.

In conclusion, ED is recognized as a risk factor for CAD. In this study we show that subjects presenting with chest pain of presumed cardiac origin are more likely to have ED if they have elevated uric acid levels. Since lowering uric acid can reverse intracellular oxidative stress, inflammation and endothelial dysfunction in animal models, we might suggest that studies should also be performed to determine the potential benefit of lowering uric acid in subjects with ED, in the presence or absence of CAD.

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Table 1

Comparison of patients without ED versus those with ED

	Patients without Erectile Dysfunction (N = 163)	Patients with Erectile Dysfunction (N = 149)	P-value
Uric Acid (mg/dl)	5.4 ± 1.2	5.8 ± 1.3	**0.0046**
Age (years)	53.8 ± 7.5	58.8 ± 8.5	< **0.0001**
Coronary Artery Disease (n,%)	35 (21.5%)	69 (46.3%)	< **0.0001**
Diabetes mellitus (n,%)	13 (8.0%)	29 (19.5%)	**0.0030**
Hypertension (n,%)	41 (25.2%)	58 (38.9%)	**0.0089**
Smoking (n,%)	71 (43.6%)	68 (45.6%)	0.7120
eGFR	113.4 ± 30.8	93.4 ± 20.9	< **0.0001**
BMI (kg/m^2)	27.7 ± 3.0	27.7 ± 3.1	0.8638
Positive Treadmill Test (n,%)	53 (32.5%)	83 (55.7%)	< **0.0001**
HsCRP	3.8 ± 3.1	5.24 ± 3.83	**0.0005**
Systolic BP (mmHg)	129.9 ± 20.7	133.9 ± 19.1	**0.0498**
Diastolic BP (mmHg)	79.5 ± 14.3	82.0 ± 14.5	0.1393
Total Cholesterol (mg/dl)	191.8 ± 38.4	198.5 ± 46.5	0.2006
LDL cholesterol (mg/dl)	118.6 ± 31.5	118.3 ± 36.3	0.8850
Triglycerides (mg/dl)	162.3 ± 100.5	211.0 ± 159.9	**0.0075**
HDL cholesterol(mg/dl)	40.2 ± 7.6	39.8 ± 8.3	0.4651
SHIM Score	23.0 ± 0.98	16.2 ± 3.54	< **0.0001**
Medications			
ACEi use (n,%)	23 (14.1%)	35 (23.5%)	**0.0334**
ASA use (n,%)	0.20 ± 0.40	0.34 ± 0.47	**0.0053**
Beta Blocker (n,%)	9 (5.52%)	14 (9.46%)	0.1851
Diuretic (n,%)	10 (6.1%)	22 (14.8%)	**0.0121**
Insulin User (n,%)	0 (0%)	6 (4.1%)	**0.0110**
Oral Anti-Diabetic Meds use (n,%)	11 (6.75%)	18 (12.1%)	0.1052
Statin (n,%)	17 (10.4%)	17 (11.4%)	0.7814

Table 2

Univariate logistic regression of risk factor association with erectile dysfunction.

	OR and 95% CI	P value
ACEi	1.869 (1.045–3.342)	**0.0350**
Age (years)	1.082 (1.049–1.115)	< **0.0001**
Beta Blocker	1.788 (0.750–4.262)	0.1900
BMI	0.999 (0.928–1.075)	0.9747
Coronary Artery Disease	3.154 (1.926–5.166)	< **0.0001**
eGFR.	0.960 (0.948–0.972)	< **0.0001**
Diabetes mellitus	2.788 (1.389–5.596)	**0.0039**
Diuretic	2.65 (1.21–5.801)	**0.0148**
Hypertension	1.897 (1.170–3.075)	**0.0095**
hsCRP	1.131 (1.049–1.219)	**0.0013**
Uric acid	1.361 (1.121–1.652)	0.0019
Smoking	1.088 (0.696–1.701)	0.7121
Total Cholesterol	1.004 (0.998–1.009)	0.1642

ACEi, angiotensin converting enzyme inhibitor; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitive C-reactive protein; BMI, body mass index.

Table 3

Erectile Dysfunction and uric acid as a continuous variable.

	OR and 95% CI	P-value
Unadjusted		
Uric Acid	1.361 (1.121–1.652)	0.0019
Adjusted for Age		
Age	1.081 (1.048–1.116)	<.0001
Uric Acid	1.364 (1.112–1.672)	0.0029
Adjusted for Age + Coronary Artery Disease		
Age	1.086 (1.051–1.122)	<.0001
Coronary Artery Disease	3.128 (1.819–5.380)	<.0001
Uric Acid	1.311 (1.060–1.620)	0.0123
Adjusted for Age + Coronary Artery Disease + eGFR		
Age	1.048 (1.009–1.089)	0.0158
Coronary Artery Disease	2.389 (1.347– 4.236)	0.0029
eGFR	0.974 (0.960–0.989)	0.0006
Uric Acid	1.210 (0.972– 1.506)	0.0888

Table 4

Multiple logistic regression with quartiles of uric acid.

Variables	OR (95% CI)	P-value
Age	1.061 (1.014–1.109)	0.0104
Hypertension	1.264 (0.676–2.364)	0.4631
Diabetes mellitus	2.176 (0.953– 4.966)	0.0648
Coronary artery disease	2.771 (1.498–5.126)	0.0012
eGFR	0.970 (0.955–0.986)	0.0003
Triglycerides	1.006 (1.003–1.009)	<.0001
Quartile 2	1.347 (0.652–2.782)	0.4211
Quartile 3	0.899 (0.403–2.007)	0.7958
Quartile 4	1.334 (0.613–2.899)	0.4675