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Insulin resistance is an independent predictor of erectile dysfunction in patients with gout

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Background/Aims: Gout is associated with metabolic disorders that are important risk factors for cardiovascular disease and erectile dysfunction (ED). We aimed to identify independent predictors of ED in patients with gout.

Methods: From August 2014 to August 2015, male outpatients who were being treated for gout in our rheumatology clinic and healthy males without any history of inflammatory disease (control group) were studied. ED was assessed in participants using the five-item version of the International Index of Erectile Function questionnaire. Insulin resistance (IR) was estimated using the homeostatic model assessment (HOMA-IR). Logistic regression analysis was performed to determine the effect of variables on ED risk in all of the study subjects and in patients with gout.

Results: We analyzed 80 patients with gout and 70 healthy controls. The median age of patients with gout was 52 years and median disease duration was 120 months. Gout patients were more likely to have ED than controls (55.3% vs. 41.4%, $p < 0.047$). After adjustment for confounding factors, only HOMA-IR was significantly associated with ED (odds ratio [OR], 1.82; 95% confidence interval [CI], 1.05 to 3.15). Gout patients with ED were more likely to be older ($p < 0.001$), have higher HOMA-IR ($p = 0.048$), and have lower glomerular filtration rate ($p = 0.038$) than those without ED. Multivariate logistic regression analysis showed that HOMA-IR was an independent predictor for ED (OR, 1.62; 95% CI, 1.03 to 2.82) in gout patients.

Conclusions: IR is an independent predictor of ED in patients with gout.

Keywords: Arthritis, gouty; Erectile dysfunction; Insulin resistance

INTRODUCTION

Gout is the most common type of inflammatory arthritis in men and is characterized by deposition of monosodium urate crystals in joints and adjacent tissues, alongside chronic hyperuricemia [1,2]. However, gout is not just a joint disease but occurs in association with a number of metabolic disorders, including hypertension (HTN), obesity, diabetes mellitus (DM), dyslipidemia, chronic kidney disease, and metabolic syndrome [3-6]. Metabolic abnormalities are important risk factors for cardiovascular disease (CVD), which contributes to the increased mortality observed in patients with gout, as well as to the hyperuricemia and arthritic disease itself [7,8]. Consequently, previous guidelines have suggested that gout patients be assessed for comorbidities, including components of the metabolic syndrome, which should be treated as part of the management of gout [9,10].

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Erectile dysfunction (ED) refers to a persistent inability to achieve and maintain an erection sufficient to complete sexual intercourse [11] and is common in the general population. ED reflects an early stage of vascular pathology, specifically relating to endothelial dysfunction [12]. Many pathophysiologic mechanisms have been identified that contribute to the development of ED, many of which are also comorbidities of gout. These overlap not only with conventional risk factors for CVD, such as aging, HTN, DM, chronic kidney disease, and dyslipidemia, but also with obesity-induced hypogonadism, insulin resistance (IR), and low grade inflammation [13-16]. Although previous studies have already reported an increased risk of ED in gout patients [17-19], most of these studies were designed to identify the prevalence and association between gout and ED compared to a control group, and not to evaluate clinical and laboratory features of metabolic disorders in gout patients.

In this study, we have investigated the association between the metabolic disorders of gout and ED. In addition, we have sought to identify which metabolic variables could represent independent risk factors for the presence of ED in gouty arthritis.

METHODS

Patients and controls

We enrolled 102 male outpatients who were being treated for gout at a tertiary care hospital between August 2014 and August 2015. The diagnosis of gout was based on a history of the identification of monosodium urate crystals in affected joint fluid or fulfillment of the clinical criteria of the American Rheumatism Association for primary gout, as determined by rheumatologists [20]. We only included patients who had not suffered an attack of gout in the 6 months preceding enrollment. Eighty-seven healthy males without any history of inflammatory disease were also recruited as a control group. For the analysis of data, we selected individuals aged between 35 and 70 years and excluded subjects with histories of coronary artery disease, cerebrovascular events, peripheral arterial disease, DM, or benign prostatic hyperplasia (BPH). The study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (KC14QISI0626). All subjects gave their informed consent.

Baseline characteristics and laboratory findings

Age, height, weight, and waist circumference were measured in all subjects. Body mass index (BMI) was calculated in kg/m^2. The subjects' history of alcohol consumption, smoking, and the average number of hours of exercise undertaken per week were recorded. The details of comorbidities in subjects with HTN or dyslipidemia who had been prescribed treatment were also recorded, along with disease duration and the type of gout medication being used (colchicine, allopurinol, benzbromarone, or febuxostat) by gout patients. Subjects were required to complete the Hospital Anxiety and Depression Scale (HADS) questionnaire, which is designed to assess anxiety and depression as an evaluation of mood status. This incorporates seven measures on each subscale that are independent of somatic symptoms [21].

Overnight fasting blood samples were obtained for the determination of hemoglobin, platelet count, creatinine, uric acid, glucose, insulin, testosterone, 25(OH)-vitamin D, total cholesterol, triglyceride (TG), high density lipoprotein cholesterol, and low density lipoprotein cholesterol. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were determined only in gout patients. Glomerular filtration rate (GFR) was calculated using the modification of diet in renal disease (MDRD) formula (MDRD-GFR = 186 × serum creatinine [mg/dL]$^{-1.154}$ × age$^{-0.203}$). IR was evaluated using the homeostatic model assessment (HOMA-IR): HOMA-IR = insulin (μIU/mL) × glucose (mmol/L)/22.5.

Assessment of erectile function

ED was assessed using the five-item version of the International Index of Erectile Function (IIEF-5) and this was validated using a self-administered questionnaire [22]. Each question is scored from 1 to 5, with a maximum score of 25 denoting perfect erectile function. The severity of ED is generally classified into five categories: severe (1 to 7), moderate (8 to 11), mild to moderate (12 to 16), mild (17 to 21), and normal (22 to 25). The presence of ED was defined by an IIEF-5 score of below the normal range.

Statistical analysis

Continuous variables are expressed as median (interquartile range [IQR]) and categorical variables as absolute numbers (%). We compared the variables between

patients with gout and the control group, as well as between the groups of gout patients with and without ED, using the Mann-Whitney *U* test for continuous variables, and the chi-square or Fisher exact tests for categorical variables. Logistic regression analysis was performed to identify which variables were independent risk factors for the development of ED, involving adjustment for important confounders. A $p < 0.05$ was considered to be statistically significant. All data were analyzed using the SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographics and clinical characteristics of subjects

Eighty gout patients and 70 control subjects were included, and 22 patients with gout and 11 control subjects were excluded. Of these excluded subjects, seven were aged less than 35 or over 70 among the gout patients and eight among the controls. The subjects excluded because of a history of comorbid disease comprised 15 patients with gout (six CVD, five DM, and BPH) and nine in the control group (three DM and six BPH). Baseline demographic and clinical characteristics are presented in Table 1. The median age of patients with gout was slightly greater than the controls, but this difference did not reach statistical significance (52 years [IQR, 44 to 59] vs. 50 years [IQR, 42 to 55], $p = 0.090$). Weight, BMI, and waist circumference were significantly higher in gout patient than in controls ($p = 0.019$, $p < 0.001$, and $p < 0.001$, respectively). There were no differences between the groups with regard to history of smoking, alcohol consumption, or exercise. Gout patients had a median systolic blood pressure of 124 mmHg (IQR, 119 to 130) and diastolic blood pressure of 83 mmHg (IQR, 78 to 87). The HADS questionnaires showed that both anxiety and depression scores were similar between the two groups.

There was no difference in fasting glucose between gout patients and controls. By contrast, the median plasma insulin and HOMA-IR were significantly higher in gout patients than controls (insulin: 8.02 μIU/mL [IQR, 6.01 to 11.38] vs. 5.48 μIU/mL [IQR, 3.19 to 7.73] in controls, $p < 0.001$; HOMA-IR: 1.86 mL/min/1.73 m^2 [IQR, 1.55 to 2.70] vs. 1.29 mL/min/1.73 m^2 [IQR, 0.82 to 1.77] in con trols, $p < 0.001$), as expected. Patients with gout had similar median serum uric acid to controls (5.9 mg/dL [IQR, 5.0 to 6.7] vs. 5.9 mg/dL [IQR, 5.0 to 6.4] in controls, $p = 0.393$). The gout patients had significantly higher serum creatinine and lower GFR than controls. There were no significant differences in lipid profiles between groups, except that plasma TG was higher in the gout patients ($p = 0.005$). Plasma testosterone was significantly lower in gout patients than controls ($p < 0.001$), as was 25(OH)-vitamin D ($p = 0.045$). In gout patients, the median ESR was 9 (IQR, 4.5 to 16) and CRP was 0.11 (IQR, 0.04 to 0.20). Gout patients had higher prevalences of the comorbidities HTN and dyslipidemia than control subjects (34.2% vs. 8.6% in controls, $p < 0.001$; 77.6% vs. 2.9% in controls, $p < 0.001$).

The median IIEF-5 score was lower in the patient group than the control group, but this did not reach statistical significance (21 [IQR, 17 to 24] vs. 22 [IQR, 18 to 24] in controls, $p = 0.443$). However, the incidence of ED was significantly higher in the patient group than in the control group (55.3% vs. 41.4% in control, $p = 0.047$). In gout patients, the median disease duration was 120 months (IQR, 59 to 207). Of gout patients, 97.5% were currently using urate-lowering medication. Allopurinol was most frequently used (61.3%), followed by febuxostat (27.5%), and benzbromarone (8.8%).

Associations between clinical variables and ED in study subjects

We performed univariate and multivariate analysis of ED risk using variables that showed statistically significant differences between the groups (Table 2). Univariate analyses did not demonstrate a significant association of gout with ED (OR, 1.69; 95% CI, 0.88 to 3.23). Older age, higher waist circumference, higher HOMA-IR, and lower MDRD-GFR and testosterone level were significant predictors of ED in unadjusted analyses. Comorbidities such as HTN and dyslipidemia were not significantly associated with ED in gout patients. Multivariate logistic regression analysis revealed that only HOMA-IR was significantly associated with ED (adjusted OR, 1.82; 95% CI, 1.05 to 3.15).

Differences in clinical variables between gout patients with and without ED

To determine whether there were differences in clinical variables between gout patients with and without ED, patients were divided into two groups (44 patients with ED and 36 without). Variables that were significantly

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Table 1. Demographics and clinical characteristics of the study participants

Characteristic	Patients with gout (n = 80)	Controls (n = 70)	*p* value
Age, yr	52 (44–59)	50 (42–55)	0.090
Height, cm	172 (167–176)	172 (168–176)	0.813
Weight, kg	74 (68–81)	71 (65–75)	0.019
Body mass index, kg/m^2	25.3 (23.6–27.1)	24.0 (22.3–25.0)	< 0.001
Waist circumference, cm	86.8 (83.8–92.4)	83.0 (79.0–86.3)	< 0.001
History of smoking	57 (75.0)	45 (64.3)	0.091
Current smoking	29 (38.2)	35 (50.0)	0.116
Smoking, pack/year	17 (10–30)	16 (10–23)	0.412
Alcohol drinking, no./wk	1 (0–3)	2 (1–3)	0.126
Exercise, no./wk	3 (1–5)	2 (1–4)	0.595
HASD score			
Anxiety score	4 (2–6)	5 (2–7)	0.153
Depression score	4 (2–7)	5 (3–6)	0.542
Hemoglobin, g/dL	15.3 (14.5–16.0)	15.6 (14.7–16.5)	0.277
Platelet, 10^9/L	218 (192–260)	233 (212–265)	0.050
Fasting glucose, mg/dL	99 (94–105)	95 (89–102)	0.117
Insulin, μIU/mL	8.02 (6.01–11.38)	5.48 (3.19–7.73)	< 0.001
HOMA-IR	1.86 (1.55–2.70)	1.29 (0.82–1.77)	< 0.001
Uric acid, mg/dL	5.9 (5.0–6.7)	5.9 (5.0–6.4)	0.393
BUN, mg/dL	15.2 (12.7–17.2)	14.1 (12.2–18.2)	0.630
Creatinine, mg/dL	1.07 (0.96–1.22)	0.95 (0.89–1.03)	< 0.001
MDRD-GFR, mL/min/1.73 m^2	83.3 (66.8–102.2)	96.1 (88.1–111.7)	0.006
Total cholesterol, mg/dL	180 (162–206)	176 (165–200)	0.629
Triglyceride, mg/dL	184 (113–238)	138 (84–160)	0.005
LDL, mg/dL	105 (84–125)	109 (92–122)	0.703
HDL, mg/dL	47 (41–52)	46 (42–57)	0.564
Testosterone, ng/mL	3.92 (3.34–5.10)	5.32 (4.66–6.39)	< 0.001
25(OH) vitamin D, ng/mL	23.37 (17.93–27.96)	26 (22.09–29.13)	0.045
Comorbidities			
Hypertension	26 (34.2)	6 (8.6)	< 0.001
Dyslipidemia	59 (77.6)	2 (2.9)	< 0.001
Erectile function			
Total IIEF-5 score	21 (17–24)	22 (18–24)	0.443
Erectile dysfunction	42 (55.3)	29 (41.4)	0.047
Gout disease duration, mon	120 (59–207)		
Medication of gout			
Colchicine	22 (27.5)		
Allopurinol	49 (61.3)		
Febuxostat	22 (27.5)		
Benzbromarone	7 (8.8)		

Values are presented as median (interquartile range) or number (%).
HADS, hospital anxiety and depression scale; HOMA-IR, homeostatic model assessment of insulin resistance; BUN, blood urea nitrogen; MDRD-GFR, modification of diet in renal disease-glomerular filtration rate; LDL, low density lipoprotein; HDL, high density lipoprotein; IIEF-5, 5-item version of the International Index of Erectile Function.

different between groups and important confounders are presented in Table 3. Gout patients with ED were significantly older and had higher HOMA-IR and lower MDRD-GFR than patients without ED ($p < 0.001$, $p = 0.048$, and $p = 0.038$, respectively). Subgroup analysis of gout patients with data from 6 months check-ups for 2 years prior to the study showed no significant differences of ED between those who had ever changed in serum uric acid over 6 mg/dL and had not (data not shown).

Independent predictors of ED in gout patients

Age (OR, 1.12; 95% CI, 1.05 to 1.19) and HOMA-IR (OR, 1.57; 95% CI, 1.14 to 2.60) were identified as risk factors for ED in gout patients using univariate analyses (Table 4). To identify independent predictors of ED in gout patients, multivariate logistic regression was performed. Age, waist circumference, HOMA-IR, MDRD-GFR, testosterone level, and history of HTN or dyslipidemia were entered into a logistic regression model as independent confounders of ED risk. After adjustment for covariates, HOMA-IR (adjusted OR, 1.62; 95% CI, 1.03 to 2.82) was shown to be an independent predictor of ED in gout patients.

Table 2. Unadjusted and adjusted ORs for erectile dysfunction

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Gout	1.69 (0.88–3.23)	0.62 (0.11–3.53)
Age	1.11 (1.06–1.17)	1.09 (0.99–1.20)
Waist circumference	1.07 (1.01–1.13)	1.04 (0.92–1.17)
HOMA-IR	1.71 (1.11–2.64)	1.82 (1.05–3.15)
MDRD-GFR	0.98 (0.96–0.99)	0.99 (0.96–1.03)
Testosterone	0.72 (0.53–0.97)	0.99 (0.68–1.46)
HTN	1.61 (0.74–3.53)	1.48 (0.36–5.65)
Dyslipidemia	1.37 (0.71–2.64)	0.54 (0.17–1.75)

OR, odds ratio; CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; MDRD-GFR, modification of diet in renal disease-glomerular filtration rate; HTN, hypertension.
[a]Adjusted ORs for the participants were adjusted for gout, age, waist circumference, HOMA-IR, MDRD-GFR, testosterone, HTN, and dyslipidemia.

DISCUSSION

In this study, we have observed a significantly increased prevalence of ED in patients with gout vs. healthy controls. We have also shown that gout patients were significantly more likely to have metabolic abnormalities, such as obesity, increased HOMA-IR, reduced renal function, HTN, and dyslipidemia. However, only HOMA-IR showed a strong significant association with ED after multivariate analysis. In addition, HOMA-IR was an independent risk factor for ED in gout patients after adjustment for confounding variables.

Recently, Chen et al. [17] showed that there is a higher incidence of ED in gout patients than in subjects without gout (12.36 per 10,000 person-years vs. 9.07 per 10,000 person-years, $p < 0.001$), and a 1.21-fold adjusted hazard ratio for ED in gout versus the control group in their cohort study. Our results have also shown that there is an approximately 1.3-fold higher prevalence of ED in gout patients compared to controls. Schlesinger et al. [19] reported that a significantly higher proportion

Table 3. Comparison of gout patients with and without ED

Characteristics	With ED (n = 44)	Without ED (n = 36)	*p* value
Age, yr	55 (50–60)	48 (41–55)	< 0.001
Waist circumference, cm	87.0 (83.9–93.9)	86.0 (81.3–90.4)	0.316
Insulin, μIU/mL	8.82 (6.89–12.65)	7.28 (4.86–9.28)	0.061
HOMA-IR	2.05 (1.72–3.05)	1.75 (1.06–2.35)	0.048
Creatinine, mg/dL	1.09 (0.99–1.22)	1.05 (0.91–1.22)	0.484
MDRD-GFR, mL/min/1.73 m^2	77.0 (64.8–96.4)	94.9 (69.9–108.9)	0.038
Testosterone, ng/mL	3.82 (3.25–4.78)	4.10 (3.76–5.23)	0.100

ED, erectile dysfunction; HOMA-IR, homeostatic model assessment of insulin resistance; MDRD-GFR, modification of diet in renal disease-glomerular filtration rate.

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Table 4. Unadjusted and adjusted OR for erectile dysfunction in gout

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Age	1.12 (1.05–1.19)	1.08 (0.97–1.21)
HOMA-IR	1.57 (1.14–2.60)	1.62 (1.03–2.82)
MDRD-GFR	0.99 (0.97–1.01)	0.99 (0.96–1.04)

OR, odds ratio; CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; MDRD-GFR, modification of diet in renal disease-glomerular filtration rate.

[a]Adjusted ORs for the patients were adjusted for the covariates age, waist circumference, HOMA-IR, MDRD-GFR, testosterone, hypertension, and dyslipidemia.

of gout patients also had ED, when compared to subjects without gout but with other rheumatic diseases, including rheumatoid arthritis, osteoarthritis, and psoriatic arthritis (76% vs. 51%, $p = 0.0003$). The prevalence of ED in gout patients in this study was approximately 20% higher than in our study, which may be explained by the exclusion from our analysis of participants with CVD, DM, or BPH, and those aged less than 35 or over 70.

Mounting evidence suggests that both hyperuricemia and inflammation can increase the risk of ED, especially in patients with gout. Salem et al. [23] reported that serum uric acid level was predictive of ED and several studies have shown an association between hyperuricemia and endothelial dysfunction, which causes ED by decreasing nitric oxide production and increasing production of reactive oxygen species [24]. Low grade inflammation, represented by increased levels of plasma markers, such as CRP, tumor necrosis factor-α, and interleukin-6, is also positively associated with ED [15,25].

The prevalence of IR in patients with gout has also been previously investigated. Yoo et al. [26] reported that gouty arthritis patients had significantly higher IR than healthy controls (HOMA-IR, 2.63 ± 1.36 vs. 1.91 ± 1.01, respectively). Another report estimated that hyperinsulinemia and IR occur in 95% and 76% of gout patients, respectively [27]. Furthermore, increased plasma insulin in gout patients was independently correlated with hyperuricemia, which is also associated with coronary artery disease [28,29]. Insulin can increase renal reabsorption of urate through stimulation of the tubular ion exchange and elevate concentration of systemic adenosine, which leads to renal retention of urate [30]. Given that IR plays an important role in the pathogenesis of endothelial dysfunction and atherosclerosis by promoting a direct proatherogenic effect in the arterial wall, which can subsequently progress to plaque formation and coronary artery disease [31,32], we hypothesized that increased IR has an important role in the development of ED in gout patients. This hypothesis was supported by a previous study showing that endothelial dysfunction and atherosclerosis induced by IR and inflammation resulted in dysregulation of both the penile and coronary artery circulations [33]. Consistent with the hypothesis, we found that IR was a significant independent risk factor for ED in gout, after adjustment for confounding factors.

There are several limitations to our study. First, IIEF-5 is a validated tool for the assessment of ED but may not accurately differentiate between organic and psychogenic ED [34,35]. Second, although anti-hypertensive drugs such as β-blockers, thiazides, and calcium channel blockers can affect both ED and IR [36,37], we did not make a detailed assessment of patient prescriptions. Third, all of the subjects had presented to our tertiary medical institution; therefore, there could have been a selection bias and extrapolation of the conclusions of the present study to all gout patients should be undertaken with caution. Despite the limitations, however, we believe that our study has important implications. This is the first study to reveal which metabolic parameter represents an independent risk factor for ED in patients with gout. Furthermore, to minimize the effects of organic risk factors for ED and gout itself, we excluded subjects with several comorbidities and histories of attacks of gout within the 6 months preceding their participation. The interesting finding of no difference in uric acid level between patients and controls and the low levels of ESR and CRP in gout patients might reflect these exclusion criteria. Thus, the present study is especially relevant to patients with clinically stable gout and without significant active inflammation.

In conclusion, we have confirmed that IR is an independent predictor of the presence of ED in patients with gout. Our finding implies that insulin sensitivity should be assessed to assist in the prevention of ED in patients with gout, even when disease activity and serum uric acid are well controlled.

KEY MESSAGE

1. Patients with gout had a higher prevalence of erectile dysfunction (ED) than controls.
2. Risk factors of ED were older age, higher homeostatic model assessment of insulin resistance, and lower glomerular filtration rate in gout.
3. In our study, insulin resistance was an independent predictor of ED in patients with gout.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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