

Characteristic and Outcome of Psoriatic Arthritis Patients with Hyperuricemia

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ABSTRACT. Objective. To determine the characteristics of patients with psoriatic arthritis (PsA) who have hyperuricemia (HUC) and their outcomes, especially cardiovascular (CVD) and kidney diseases.

Methods. Patients have been followed prospectively at the PsA clinic according to a standard protocol at 6- to 12-month intervals. We defined HUC in men $> 450 \mu\text{mol/l}$ or women $> 360 \mu\text{mol/l}$. We matched patients with HUC based on sex and age ± 5 years with normal uric acid patients. Demographics information and disease characteristics were reviewed. Outcomes of patients with HUC, especially CVD and kidney diseases, were recorded. Conditional logistic regression was performed to determine factors independently associated with HUC in patients with PsA.

Results. There were 325 (31.9%) out of 1019 patients with PsA who had HUC. Of these, 318 cases were matched to 318 controls. There were 11 (3.4%) out of 325 patients with HUC who had gout. Patients with HUC had longer disease duration and a higher Psoriasis Area and Severity Index. They had more concurrent comorbidities, including CVD and metabolic diseases, as well as higher prevalence of kidney stones and higher creatinine. Only 1 patient with HUC was treated with allopurinol at first evaluation visit and 7 patients during followup. Over the followup, 163 of the 318 patients had persistent HUC (pHUC) for more than 2 visits. Patients with pHUC developed more myocardial infarction, heart failure, and renal impairment. Multivariate analysis showed an association between pHUC, PsA disease duration, and obesity.

Conclusion. HUC is common in patients with PsA, especially in those with longer disease duration and obesity. Proper control of HUC and metabolic diseases may play a preventive role in improving PsA outcomes. (J Rheumatol First Release December 1 2017; doi:10.3899/jrheum.170384)

Key Indexing Terms:

PSORIATIC ARTHRITIS HYPERURICEMIA CARDIOVASCULAR DISEASE OUTCOMES

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis and affects 20–30% of patients with psoriasis^{1,2}. Although PsA was initially considered a benign

disease, it is now recognized that PsA can lead to severe joint damage and deformities and significantly affect function, quality of life, and work productivity^{3,4}. Further, most of the patients with PsA have associated comorbidities (which significantly lower quality of life^{5,6}), as well as increased risk of morbidity and mortality⁷.

A comorbidity associated with PsA is hyperuricemia (HUC). The prevalence of asymptomatic HUC in the general population is estimated at 2–13%, while in psoriatic patients, it is 3 times greater⁸. The higher prevalence in psoriatic patients may be related to increased cell turnover, as well as the known systemic inflammation associated with the disease⁹.

Although several studies have shown a correlation between HUC and psoriasis, results were conflicting^{10,11,12}. It is not clear whether HUC is correlated with the extent of skin involvement, or whether it results from the effects of coexisting features of the metabolic syndrome. In 2000, Bruce, *et al*¹³ found HUC in 20.7% of patients with PsA, and it reflected mainly metabolic changes. On the other hand, a Korean study showed a correlation between the severity of skin involvement and high uric acid level¹⁴.

HUC not only causes gout but also stimulates systemic inflammation that contributes to the development and patho-

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genesis of cardiovascular (CVD) and renal diseases¹⁵. Moreover, previous studies confirmed that elevated uric acid level is predictive of severe subclinical atherosclerosis in patients with PsA^{16,17}.

The aim of our study was to determine the prevalence and characteristics of psoriatic patients with HUC and to determine the adverse effect of HUC on outcomes, particularly CVD and renal diseases.

MATERIALS AND METHODS

Setting. The University of Toronto Psoriatic Arthritis Clinic was established in 1978. The clinic serves as a referral center and follows patients in a prospective manner according to standard protocol¹⁵. Patients are included in the cohort if they have psoriasis and inflammatory arthritis; other types of arthritis have been excluded¹⁸. There are 98% of patients in the clinic who fulfill the Classification of Psoriatic Arthritis criteria (CASPAR) for the classification of PsA¹⁹. Each patient is assessed at 6- to 12-month intervals. At each visit, a complete history, physical examination, and laboratory assessment are performed. All data are stored in a Web-based database. Written consent from all subjects was obtained according to the Declaration of Helsinki. The study was approved by the research ethics board of the University Health Network (REB 08-0630-AE).

Patient selection. Only patients followed from 2006 were included because data on body mass index (BMI) were not recorded before 2006. We defined HUC as male > 450 $\mu\text{mol/l}$ or women > 360 $\mu\text{mol/l}$. Patients with PsA and HUC at any clinic visit were selected as cases, while patients with PsA who have had normal uric acid level at all assessments and were matched for age (± 5 yrs) and sex served as controls.

Measures. Demographic data were collected, including age, sex, race, ethnicity, duration of PsA and psoriasis, employment and education level, smoking status, alcohol consumption, and postmenopausal status. Comorbidities were also recorded, including hypertension (HTN; systolic > 140 and/or diastolic > 90), diabetes mellitus, hypercholesterolemia (> 5.2 mmol/l), hypertriglyceridemia (> 3.2 mmol/l), ischemic heart disease, kidney stones, and cancer. Clinical assessments including BMI, psoriatic area severity index (PASI), tender and swollen joint counts, and spine metrology were collected. Laboratory results included levels of uric acid, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatinine, aspartate transaminase (AST), and alanine transaminase (ALT). Medication history, including usage of urate-lowering therapy, was recorded.

Outcomes. We identified patients with persistent HUC (pHUC, high uric acid level for more than 2 visits) and determined new development of CVD and kidney disease. CVD were defined as the following: (1) myocardial infarction (MI), characterized by definite electrocardiographic abnormalities, typical symptoms with probable electrocardiographic abnormalities and abnormal enzymes, or typical symptoms and abnormal enzymes; (2) angina pectoris, characterized by chest discomfort that was aggravated by physical activity, relieved by rest or by the use of nitroglycerine, and confirmed by a cardiologist or abnormal findings on myocardial perfusion study or angiography; (3) congestive heart failure, identified from typical symptoms and signs on physical examination, abnormal chest radiograph, or abnormal finding on echocardiogram; and (4) cardiomyopathy, including restrictive, dilated, or hypertrophic heart muscles. Kidney disease was defined as raised serum creatinine > 120 $\mu\text{mol/l}$ or the presence of kidney stones as determined by patient report.

Statistical analysis. The demographic variables and baseline characteristics were reported with descriptive statistics to describe the prevalence of HUC. In the descriptive analysis, continuous variables were compared using 1-way ANOVA; categorical variables were compared using chi-square test. All continuous variables were plotted into a quantile-quantile plot for normality check. All non-normal variables were reported as median and used Kruskal-Wallis rank sum test for comparison.

Control patients with normal uric acid level (NUC) were selected from the same PsA cohort and matched 1:1 with case group (HUC) by sex and baseline age (± 5 yrs). A multivariate conditional logistic regression was used to analyze the difference between HUC versus NUC, with the following covariates in the full model: PsA duration, psoriasis duration, smoking status, elevated ESR (> 20 mm/h for women, > 15 mm/h for men), HTN, kidney stone, diabetes, PASI score, elevated creatinine, elevated AST, elevated ALT, and BMI. A backward stepwise elimination method was then performed to find significant predictors for a reduced model.

Further, patients with > 2 consecutive visits with high uric acid level were selected from the HUC cohort (pHUC). A descriptive summary was performed between the pHUC group versus the NUC group for the following variables: elevated creatinine, angina, cardiomyopathy, MI, congestive heart failure, and kidney stones. To keep consistency with previous multivariable regression analysis, the same matched control patients were selected for full and reduced models.

The threshold for a statistically significance difference was set at $p < 0.05$. SAS (version 9.3, SAS Institute) was used for all statistical analyses.

RESULTS

Among 1019 patients with PsA who had a followup in our clinic from 2006, 318 patients (31.2%) with high serum uric acid (HUC) and 318 control patients with normal uric acid (NUC) were included. They were matched 1:1 [based on sex and age (± 5 yrs)]. Their baseline characteristics are shown in Table 1. There was no significant difference in baseline characteristics including age, sex, ethnicity, education, and employment between patients with HUC and NUC. There were 11 (3.5%) out of 318 patients with HUC who had gout. Smoking was higher in patients with HUC ($p = 0.021$), but alcohol consumption was similar between the 2 groups. Patients with HUC appeared to have longer disease duration of PsA ($p < 0.001$) and psoriasis ($p = 0.0016$) compared to patients with NUC. PASI was significantly higher in patients with HUC ($p = 0.006$). No statistical difference in swollen or tender joint counts was found between the 2 groups. Inflammatory markers including ESR and CRP were higher in the HUC group. Compared to patients with NUC, patients with HUC had more associated comorbidities, more CVD including HTN ($p < 0.001$) and angina ($p = 0.037$). Also, the prevalence of diabetes mellitus ($p = 0.0042$), obesity ($p < 0.001$), and elevated liver function tests ($p = 0.01$) were higher in the HUC group. There was no statistically significant difference in hypercholesterolemia and hypertriglyceridemia. Kidney diseases including high serum creatinine, and kidney stones were also higher in the HUC group compared to patients with NUC. No significant difference in cancer between the 2 groups was identified (data not shown). Also, there was no statistically significant difference between the 2 groups in the treatment modalities including use of nonsteroidal antiinflammatory drugs, disease-modifying antirheumatic drugs, and biologics.

Over the followup, 163 of the 318 patients had pHUC on more than 2 consecutive visits. Patients with pHUC developed more MI ($p = 0.008$) and congestive heart failure ($p < 0.001$). No statistically significant difference was found in angina and cardiomyopathy between the 2 groups. Also,

Table 1. Characteristics of the study population at clinic entry. Values are n (%) or mean ± SD, unless otherwise specified.

Covariate	NUC, n = 318	HUC, n = 318	p
Sex			1
Female	126 (40)	126 (40)	
Male	192 (60)	192 (60)	
Age	51.4 ± 13.3	53.4 ± 13.7	0.059
Median (min, max)	52 (18.2, 88.2)	54.2 (17.5, 85.2)	
Race			0.67
White	268 (84)	262 (82)	
Others	50 (16)	54 (17)	
PsA duration	8.4 ± 8.6	13.9 ± 11.9	< 0.001
Psoriasis duration	20 ± 14.5	23.7 ± 14.1	0.0016
Duration of followup	3.6 ± 2.9	6.1 ± 3.1	
Median	3.02	6.5	
Employment			0.57
Employed	188 (59)	196 (62)	
None	130 (41)	122 (38)	
Smoking	132 (42)	162 (51)	0.021
Alcohol intake			0.61
Daily	27 (9)	32 (10)	
Social	152 (48)	140 (44)	
Hypertension	77 (24)	141 (44)	< 0.001
Angina	2 (1)	10 (3)	0.037
Cardiomyopathy	1 (0)	1 (0)	1
Myocardial infarction	1 (0)	4 (1)	0.37
Congestive heart failure	0 (0)	4 (1)	0.12
High creatinine	6 (2)	26 (8)	< 0.001
Kidney stones	9 (3)	28 (9)	0.0019
Diabetes mellitus	25 (8)	48 (15)	0.0042
Swollen joints count	0.4 ± 1.4	0.6 ± 1.9	0.21
Tender joints count	2.8 ± 6.8	3 ± 6.3	0.76
PASI	3.3 ± 5.4	4.7 ± 7.3	0.0062
ESR, > 20 mm/h for men, > 15 mm/h for women	76 (24)	130 (41)	< 0.001
CRP, mg/l	57 ± 29	89 ± 49	< 0.001
Hypercholesterolemia	54 (17)	60 (19)	1
Hypertriglyceridemia	14 (4)	13 (4)	0.7
BMI	28.5 ± 6.5	31.7 ± 5.7	< 0.001

BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HUC: hyperuricemia; NUC: normal uric acid; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis.

kidney diseases, including high serum creatinine, developed more often in patients with pHUC (Table 2). Regarding use of urate-lowering therapy, only 1 patient with HUC was taking allopurinol at first visit, and 7 patients were treated with allopurinol over the followup.

Multivariable analysis. Multivariable analysis revealed these variables to be independent predictors for HUC in patients with PsA: kidney stones (OR 4.430, 95% CI 0.50–29.24) and BMI (OR 1.085, 95% CI 1.027–1.146, Table 3). On multivariable analysis for patients with pHUC, PsA disease duration (OR 1.073, 95% CI 1.028–1.113) and BMI (OR 1.176, 95% CI 1.062–1.303) were predictors for pHUC (Table 4).

Table 2. Outcomes of PsA patients with persistent HUC. Values are n (%).

Variables	NUC, n = 318	Persistent HUC, n = 163	p
Serum creatinine, > 120 µmol/l	14 (4)	30 (18)	< 0.001
Angina	4 (1)	7 (4)	0.07
Cardiomyopathy	1 (0)	3 (2)	0.12
Myocardial infarction	1 (0)	3 (2)	0.008
Congestive heart failure	0 (0)	8 (5)	< 0.001
Kidney stones	23 (7)	20 (12)	0.19

Data in bold face are statistically significant. HUC: hyperuricemia; NUC: normal uric acid; PsA: psoriatic arthritis.

DISCUSSION

Literature highlights the significant association between high serum uric acid level and psoriasis. In our study, we initially investigated the prevalence and characteristics of PsA patients with HUC. We found the prevalence of HUC in patients with PsA is 32%, higher than previously reported^{8,20,21}.

Additionally, we showed that patients with HUC had a higher PASI score and more associated metabolic diseases. An earlier report from our cohort had shown that the extent of skin involvement was not associated with HUC but was mainly associated with metabolic changes¹³. The extent of skin involvement, as measured by the PASI score, was not associated with HUC in the current study. Previous literature has provided some conflicting results as to whether HUC is related to the severity of psoriasis^{8,10,11} or metabolic dysregulation^{21,22}. It was reported that the serum uric acid is 1 of the determinants of the metabolic syndrome in nonpsoriatic patients; with 1 unit increase of serum uric acid, the odds of developing metabolic syndrome roughly doubled²². Most of the literature is in favor of metabolic dysregulation as a reflecting factor for HUC.

Importantly, we found that PsA disease duration, obesity, and kidney stones were independent predictors for HUC in patients with PsA. Prolonged disease duration in PsA patients with chronic inflammatory diseases may promote the release of proinflammatory cytokines and tumor necrosis factor, which are positively associated with high uric acid level^{23,24}. A recent large Korean cohort study showed that an increased serum uric acid was modestly and independently associated with increased risk of development of nephrolithiasis, after adjustment for hemostasis model assessment of insulin resistance and high-sensitivity CRP²⁵. Additionally, a previous study confirmed the association between obesity (1 of the metabolic syndrome components) and HUC in psoriatic patients, which is in agreement with our results⁸. In our study, we did not identify psoriasis severity as a predictor for developing HUC. A study by Scarpa, *et al*²⁶ identified PsA patients without psoriasis but unfortunately did not document whether the patients had HUC.

Treatment of HUC is a potential target for preventing the

Table 3. Conditional logistic regression for matched pairs of 318 patients with at least 1 visit of HUC: a multivariable analysis.

Effect	OR (95% CI)	p	Multivariate Reduced, OR (95% CI)	p
PsA duration	1.059 (1.022–1.098)	0.001	1.066 (1.03–1.1)	< 0.0001
Psoriasis duration	1.017 (0.991–1.043)	0.198		
Smoking	1.078 (0.563–2.062)	0.821		
High ESR	1.492 (0.728–3.057)	0.274		
HTN	1.071 (0.495–2.314)	0.862		
Kidney stones	4.430 (0.50–39.24)	0.181		
Diabetes	1.321 (0.368–4.740)	0.669		
PASI	1.007 (0.952–1.065)	0.815		
High creatinine	2.328 (0.196–27.724)	0.503		
High AST	1.423 (0.553–3.664)	0.464		
High ALT	1.754 (0.588–5.232)	0.313	2.59 (1.06–6.32)	0.036
BMI	1.085 (1.027–1.146)	0.003	1.095 (1.04–1.15)	0.0005

AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: body mass index; ESR: erythrocyte sedimentation rate; HTN: hypertension; HUC: hyperuricemia; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis.

Table 4. Conditional logistic regression for matched pairs of 163 patients with persistent HUC: a multivariable analysis.

Effect	OR (95% CI)	p	Multivariate Reduced, OR (95% CI)	p
PsA duration	1.073 (1.02–1.13)	0.007	1.06 (1.017–1.107)	0.006
Psoriasis duration	0.99 (0.957–1.042)	0.947		
Smoking	0.728 (0.247–2.149)	0.565		
High ESR	0.806 (0.208–3.123)	0.754		
PASI	1.082 (0.974–1.203)	0.14		
High creatinine	5.349 (0.164–174.139)	0.345		
High AST	0.467 (0.091–2.396)	0.345		
High ALT	3.943 (0.630–24.6)	0.142		
BMI	1.176 (1.062–1.303)	0.0018	1.160 (1.066–1.263)	0.0006

AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: body mass index; ESR: erythrocyte sedimentation rate; HUC: hyperuricemia; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis.

incidence of CVD and kidney diseases. Previous studies have shown a correlation between CVD and kidney diseases in PsA patients with HUC^{13,27,28}. However, it remains to be determined whether the relationship between HUC, cardiovascular, and kidney events is related only to the elevated level of uric acid or whether it is a combination of metabolic syndrome and HUC.

Several studies showed that the risk of developing cardiovascular events in patients with PsA is higher than in the general population and may be higher than in people with psoriasis alone^{29,30,31}. Importantly, Gonzalez-Gay, *et al* showed in their study that in patients with PsA, there was a significant association between high uric acid level and subclinical atherosclerosis in patients without CVD risk factors¹⁷. We found in our study increased prevalence of CVD in PsA patients with pHUC, especially MI and congestive heart failure.

Moreover, a previous metaanalysis has found an elevated

serum uric acid was positively associated with new-onset kidney disease in populations with normal baseline renal function³¹. Similarly, we found an increased serum creatinine in PsA patients with pHUC.

Whether we should treat asymptomatic HUC in patients with PsA is not clear. An interesting study by Wei, *et al*³², which included a large number of nonpsoriatic patients taking allopurinol for HUC, found that higher doses of allopurinol were associated with better control of urate and lower risks of both cardiovascular events and mortality in all patients taking allopurinol treatment. In our study, only a small number of patients were treated with allopurinol (2.5%); thus, we cannot comment on whether treatment with urate-lowering therapy improves CVD and kidney diseases. However, we showed in our study higher prevalence of CVD and kidney impairments in patients with pHUC. Thus, controlling metabolic diseases and HUC in psoriatic patients may play a preventive role in improving PsA outcomes.

Our study demonstrates that almost one-third of the patients with PsA have HUC and half of those have pHUC, but only a few develop clinical gout. These patients are at risk for developing metabolic syndrome. It is therefore important to screen patients with PsA for HUC and it may be necessary to treat it to improve the outcomes in these patients.

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