# Effects of secukinumab and adalimumab on serum uric acid level in patients with plaque psoriasis

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### **Abstract**

**Background:** Psoriasis is a chronic systemic inflammatory disease, and hyperuricemia is a common comorbidity in patients with psoriasis. However, there are limited reports on the relationship between serum uric acid levels and biological treatment efficacy. The purposes of this study were to compare the differences in serum uric acid levels between patients with psoriasis and healthy controls and analyze the risk of hyperuricemia.

Methods: A total of 196 patients with psoriasis and 191 age- and sex-matched healthy controls were enrolled in this retrospective cohort study. One hundred and twenty-seven patients with severe psoriasis were treated with biologics. Sixty-eight patients received adalimumab, and 59 patients received secukinumab. Serum uric acid levels were measured at baseline, week 24, and week 48 of treatment

Results: Patients with psoriasis had higher serum uric acid levels than healthy controls  $(6.4 \pm 1.7 \text{ mg/dL} \ vs. 5.7 \pm 1.5 \text{ mg/dL}, P < 0.001)$ . Hyperuricemia was found in 33.7% (66/196) of patients with psoriasis, which was significantly higher than that in healthy controls (13.1% [25/191], P < 0.001). Serum uric acid levels and hyperuricemia were not related to the severity of psoriasis (P > 0.05). No significant changes in serum uric acid levels and hyperuricemia were observed following adalimumab treatment (P > 0.05). The serum uric acid level in patients treated with secukinumab was  $6.7 \pm 1.6 \text{ mg/dL}$  at week 24, which was not statistically different from that at baseline  $(6.6 \pm 1.4 \text{ mg/dL}, P = 0.885)$ . Serum uric acid levels were significantly decreased at week  $48 (6.3 \pm 1.5 \text{ mg/dL} \ vs. 6.6 \pm 1.4 \text{ mg/dL}, P = 0.007)$  in patients treated with secukinumab. Secukinumab had no significant effect on hyperuricemia either (P > 0.05).

Conclusions: The serum uric acid levels and prevalence of hyperuricemia in patients with psoriasis were significantly higher than those in healthy controls. Secukinumab treatment for 48 weeks successfully decreased serum uric acid levels in patients with psoriasis, whereas adalimumab had no significant effect on serum uric acid levels.

Keywords: Psoriasis; Serum uric acid; Adalimumab; Secukinumab; Hyperuricemia

# Introduction

Psoriasis is a chronic inflammatory disease. [1] In addition, patients with psoriasis have various comorbidities, such as arthritis, cardiovascular disease, metabolic syndrome, obesity, and diabetes mellitus. [2-5] In particular, psoriasis is associated with an increased risk of developing hyperuricemia. [6]

Uric acid is the end product of purine metabolism in humans, and it scavenges oxygen free radicals and prevents red blood cell membrane lipid oxidation. Urate deposits in joints, tendons, and other tissues in patients with hyperuricemia and induces gout. Hyperuricemia was found in 13.0% to 40.7% of patients with psoriasis, [7] and psoriasis was identified as an

independent risk factor for gouty arthritis.<sup>[8]</sup> However, it was also reported that hyperuricemia and gout were not significantly associated with psoriasis.<sup>[9]</sup> Moreover, there have been few studies on the relationship between uric acid and psoriasis in Chinese patients.

The clinical symptoms of patients with psoriatic arthritis often appear 5 to 12 years after the initial skin manifestations. The quality of life of patients with joint deformities is significantly decreased. The use of biologics in patients with psoriasis can reduce the risk of developing psoriatic arthritis, and multinational guidelines recommend biologics as first-line treatment options for psoriasis and psoriatic arthritis. However, whether long-term treatment with biological agents affects

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serum uric acid levels in patients with psoriasis, especially Chinese psoriasis patients, remains unreported.

In summary, the purposes of our study were to compare the differences in serum uric acid levels between patients with psoriasis and healthy controls and analyze the risk of hyperuricemia. Furthermore, a 48-week follow-up was conducted to analyze the effects of adalimumab or secukinumab on uric acid levels in patients with psoriasis.

# Methods

# Ethical approval

The study protocol was approved by the Ethics Committee of Peking University People's Hospital (No. 2020PHB303-01). Given the retrospective nature of the study, the requirement of written informed consent was waived.

# Study population

The study population consisted of adult patients with plaque psoriasis in the Peking University People's Hospital from January 2019 to December 2020. All patients were diagnosed with plaque psoriasis clinically or histopathologically. The control group consisted of non-psoriatic healthy individuals who underwent regular health checkups in our hospital during the same period. The severity of psoriasis was stratified according to body surface area (BSA) as follows:  $\geq 10\%$  indicated severe psoriasis, and BSA <10% indicated mild to moderate psoriasis. Patients with severe plaque psoriasis who failed to respond, had a contraindication or were intolerant to other systemic therapies were divided into two groups and received adalimumab or secukinumab.

Excessive drinkers, subjects with advanced chronic kidney disease, or those taking drugs that affect serum uric acid levels (including allopurinol, diuretics, salicylate, ketoconazole, theophylline, pyrazinamide, and ethambutol) were excluded from the study. Other exclusion criteria for patients with biological treatment were previous exposure to active inflammatory or infectious diseases, hematologic or solid cancers, systemic treatments (including methotrexate, acitretin, and cyclosporine A) in the previous 1 month, and biological agents in the previous 3 months.

The sample size was calculated using PASS software (version 15.0.5, NCSS, Kaysville, UT, USA). Based on data from previous studies, we used the random meta-analysis model to estimate the mean difference in serum uric acid levels between patients with psoriasis and controls. [16-18] According to the results, the estimated mean difference in serum uric acid levels was 0.6 mg/dL. We assumed that the standard deviations of serum uric acid levels in patients with psoriasis and controls were 1.6 and 1.4 mg/dL, respectively, which were the largest values reported by previous studies. [16-18] With a two-sided significance level (alpha) of 0.05, a 1:1 group allocation ratio, and an estimated 20% non-response rate, we calculated that a total of 326 participants (163 for patients and 163 for controls) would be needed to obtain a 90% power to reject the null hypothesis using a two-sample unequal-variance *t* test.

# Study design

This was a retrospective cohort study. The baseline demographic and disease characteristics were collected. Physical examination and blood biochemistry analysis were performed at the first visit. Patients treated with biologics were followed up for 48 weeks after the first injection. Serum uric acid levels were measured at baseline, week 24, and week 48.

# Primary outcomes and related parameters

The primary outcomes of this study were the differences in mean serum uric acid levels between patients with psoriasis and healthy controls, the relationship between psoriasis and hyperuricemia, and the effects of biologics on serum uric levels. A patient was defined as developing hyperuricemia if their diagnosis was confirmed by a physician and/or fulfilled hyperuricemia criteria. Generally, hyperuricemia was defined as an increased serum uric acid level >7 mg/dL in men and >6 mg/dL in women at two different visits. [19,20]

# Statistical analysis

All statistical analyses were performed with SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Continuous variables were expressed as the mean ± standard deviation or median (interquartile range). Categorical data were expressed as a frequency (percentage). Quantitative indicators were compared using the Student t test or Mann-Whitney *U* test according to the data distribution. Categorical indicators were compared by the chi-square test and Fisher exact test. A generalized linear model was built to determine the correlative factors for hyperuricemia. The covariates included in the generalized linear model were sex, age, and body mass index (BMI). The serum uric acid levels and the prevalence of hyperuricemia in patients using biologics at baseline, week 24, and week 48 were analyzed by the paired t test and McNemar test. The missing values in this study were filled using the last observation carried forward (LOCF) method. Sensitivity analyses of the LOCF method were performed to further analyze the effects of biologics on serum uric acid levels and hyperuricemia. Statistical significance was defined as a P value < 0.05.

# **Results**

# Study population characteristics

The patients' demographic characteristics at baseline are shown in [Table 1]. Based on the enrolment procedure, 196 patients (134 males, 62 females) with plaque psoriasis were included in this study. The average age was  $40.4 \pm 12.0$  years, and the average BMI was  $25.9 \pm 4.4$  kg/m<sup>2</sup>. The control group consisted of 191 adults (128 males, 63 females), and the average BMI was  $24.4 \pm 3.5$  kg/m<sup>2</sup>.

# Serum uric acid levels in patients with psoriasis and healthy controls

Patients with psoriasis had higher serum uric acid levels compared with healthy controls  $(6.4 \pm 1.7 \text{ mg/dL } vs.$ 

Table 1: Demographic and clinical characteristics of the study population at baseline.

	Ps	oriasis patients			
Characteristics	Mild/moderate (N=69)	Severe (N=127)	Total <i>(N=196)</i>	Healthy controls (N=191)	P values
Sex (M/F) n	43/26	91/36	134/62	128/63	0.750
Age (years)	$41.0 \pm 13.1$	$40.1 \pm 11.4$	$40.4 \pm 12.0$	$40.8 \pm 10.1$	0.728
BMI (kg/m <sup>2</sup> )	$25.2 \pm 3.3$	$26.2 \pm 4.8$	$25.9 \pm 4.4$	$24.4 \pm 3.5$	< 0.001
Psoriasis duration (months)	$15.2 \pm 9.1$	$16.6 \pm 8.8$	$16.7 \pm 8.7$	_	_
BSA (%)	$5.6 \pm 2.7$	$33.9 \pm 19.6$	$23.8 \pm 20.0$	_	_
Uric acid (mg/dL)	$6.4 \pm 1.6$	$6.4 \pm 1.6$	$6.4 \pm 1.7$	$5.7 \pm 1.5$	< 0.001
Normal weight	$6.2 \pm 1.7$	$5.8 \pm 1.6$	$6.0 \pm 1.6$	$5.3 \pm 1.2$	0.002
Overweight and obesity	$6.5 \pm 1.6$	$6.9 \pm 1.5$	$6.8 \pm 1.5$	$6.2 \pm 1.5$	0.011
Male	$7.0 \pm 1.6$	$6.9 \pm 1.4$	$6.9 \pm 1.4$	$6.3 \pm 1.2$	< 0.001
Female	$5.4 \pm 1.3$	$5.0 \pm 1.3$	$5.2 \pm 1.3$	$4.5 \pm 0.8$	< 0.001
Hyperuricemia	25 (36.2)	41 (32.3)	66 (33.7)	25 (13.1)	< 0.001
Normal weight	12 (35.3)	9 (15.0)	21 (22.3)	8 (7.0)	0.002
Overweight and obesity	13 (37.1)	32 (47.8)	45 (44.1)	17 (22.1)	0.002
Male	20 (46.5)	37 (40.7)	57 (42.5)	22 (17.2)	< 0.001
Female	5 (19.2)	4 (11.1)	9 (14.5)	3 (4.8)	0.064

Overweight and obesity were defined as BMI  $\geq$ 25.0 and 30.0 kg/m<sup>2</sup>, respectively. [42] Data are presented as the mean  $\pm$  standard deviation or n (%). Statistical significance was defined as a P value <0.05. BMI: Body mass index; BSA: Body surface area.

Table 2: Effects of adalimumab on serum uric acid levels in patients with psoriasis.							
Items	Baseline	Week 24	Week 48	<i>P</i> 1	<i>P</i> 2		
Serum uric acid level (mg/dL) Hyperuricemia	$6.2 \pm 1.9$ 22 (32.4)	$6.2 \pm 2.0$ 20 (29.4)	$6.1 \pm 1.9$ $19 (27.9)$	0.762 0.480	0.235 0.257		

Data are presented as the mean  $\pm$  standard deviation or n (%). The missing values in this study were filled using the LOCF method. P1: the P value of week 24 compared with the baseline. LOCF: Last observation carried forward.

 $5.7 \pm 1.5$  mg/dL, P < 0.001). Hyperuricemia was found in 33.7% (66/196) of patients with psoriasis, which was significantly higher than that in healthy controls (13.1% [25/191], P < 0.001). No significant difference was found between patients with mild to moderate psoriasis and severe psoriasis (P > 0.05). Of note, the above results showed statistical significance after the calibration of BMI [Table 1].

# Risk factors of hyperuricemia

# Male sex was associated with an increased risk of hyperuricemia

Hyperuricemia was found in 42.5% of male patients, which was significantly higher than that in female patients (14.5%, P = 0.001). Hyperuricemia was more frequent in male controls than in female controls (17.2% vs. 4.8%, P = 0.017).

# Hyperuricemia was related to higher BMI

Hyperuricemia was found in 44.1% of overweight and obese patients with psoriasis and 22.3% of normal-weight patients. Similarly, the prevalence of hyperuricemia in overweight and obese patients with psoriasis was higher than that in normal-weight patients (P = 0.002). In healthy controls, hyperuricemia was more frequent in overweight and obese subjects than in normal-weight subjects (22.1% vs. 7.0%, P = 0.004).

# Effects of biologics on serum uric acid levels

# Effects of adalimumab

At baseline, 68 patients were treated with adalimumab. During follow-up, 12 patients (17.6%) and 26 patients (38.2%) were lost to follow-up at week 24 and week 48, respectively, because of the epidemic, poor responses, and infectious diseases. The serum uric acid levels in patients with psoriasis were  $6.2 \pm 1.9$ ,  $6.2 \pm 2.0$ , and  $6.1 \pm 1.9$  mg/dL at baseline, week 24, and week 48, respectively. No significant difference was found in serum uric acid levels before and after adalimumab treatment (P = 0.762and P = 0.235, respectively). The prevalence of hyperuricemia was 32.4%, 29.4%, and 27.9% at baseline, week 24, and week 48, respectively. There was no statistical difference at week 24 and week 48 compared with the baseline (P = 0.480 and P = 0.257, respectively) [Table 2]. Through the sensitivity analysis, the results after interpolation were consistent with those before interpolation [Supplementary Table 1, http://links.lww.com/CM9/B31].

# Effects of secukinumab

Fifty-nine patients were treated with secukinumab at baseline. The proportion of loss to follow-up was 5.0% (3 patients) and 6.8% (4 patients) at week 24 and week 48, respectively. These patients dropped out because of the epidemic and poor responses. The mean serum uric

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Table 3: Effects of	secukinumah	on serum	uric acid	levels in	natients v	with nsoriasis.

Items	Baseline	Week 24	Week 48	<i>P</i> 1	P2
Serum uric acid level (mg/dL)	$6.6 \pm 1.4$	$6.7 \pm 1.6$	$6.3 \pm 1.5$	0.885	0.007
Hyperuricemia	19 (32.2)	19 (32.2)	20 (33.9)	1.000	0.706

Data are presented as the mean  $\pm$  standard deviation or n (%). The missing values in this study were filled using the LOCF method. P1: the P value of week 24 compared with the baseline. P2: the P value of week 48 compared with the baseline. LOCF: Last observation carried forward.

acid levels were  $6.6 \pm 1.4$  mg/dL at baseline and  $6.7 \pm 1.6$  mg/dL at week 24 (P = 0.885). The serum uric acid level was  $6.3 \pm 1.5$  mg/dL at week 48, which was significantly lower than that at baseline (P = 0.007). Treatment with secukinumab for 48 weeks significantly decreased serum uric acid levels. However, secukinumab had no effects on the prevalence of hyperuricemia [Table 3]. The results after interpolation were consistent with those before interpolation [Supplementary Table 2, http://links.lww.com/CM9/B31].

# **Discussion**

Psoriasis was previously reported to be associated with elevated serum uric acid levels. [6,8] Goldman<sup>[21]</sup> proposed that serum uric acid was involved in the pathogenesis of psoriasis. Tsuruta *et al*<sup>[22]</sup> also suggested that uric acid mediates inflammation.

Hyperuricemia is related to multiple factors, including gender, age, race, lifestyle, and environmental conditions. The United States Health and Nutrition Examination Survey showed that the prevalence of hyperuricemia in men and women was 20.2% and 20.0%, respectively. In addition, a Chinese study reported that the prevalence of hyperuricemia was 18.5% in males and 8.0% in females. According to a meta-analysis, the prevalence of hyperuricemia in Mainland China was 13.3%. In this study, we found that the prevalence of hyperuricemia was 17.2% in males and 4.8% in females, consistent with previous reports.

The relationship between psoriasis and hyperuricemia remains controversial. Gisondi  $et~al^{[16]}$  reported that hyperuricemia was frequently observed in patients with psoriasis. However, Kwon  $et~al^{[27]}$  reported that there was no significant difference in serum uric acid levels between patients with psoriasis and healthy controls. In this study, we found that the prevalence of hyperuricemia was significantly higher in patients with psoriasis than that in healthy controls.

Similarly, whether serum uric acid is related to the severity of psoriasis is controversial. Gisondi *et al*<sup>[16]</sup> found that serum uric acid levels in patients with Psoriasis Area and Severity Index (PASI) scores  $\geq$ 10 were significantly higher than those in participants with PASI scores <10. Yilmaz *et al*<sup>[17]</sup> also found that the PASI score was positively correlated with serum uric acid levels. However, Gui *et al*<sup>[18]</sup> reported no significant correlation between serum uric acid levels and PASI scores in patients with psoriasis. Our study showed that the serum uric acid levels and prevalence of

hyperuricemia were unrelated to the severity of psoriasis. Therefore, serum uric acid levels should be carefully considered, regardless of the severity of skin lesions.

The mechanism by which patients with psoriasis are prone to hyperuricemia remains unclear. Goldman<sup>[21]</sup> proposed that the replacement rate of keratinocytes in psoriasis patients was accelerated, and the increase in purine decomposition caused excessive uric acid production, subsequently increasing serum uric acid levels. Furthermore, urate crystals, a type of alarmin, activate innate immunity through NALP inflammasomes and increase cytokine production, including interleukin (IL)-1 and IL-8. [28] Uratsuji *et al* [29] confirmed that epidermal keratinocytes cultured in the presence of uric acid crystals formed NALP inflammasomes and produced large amounts of tumor necrosis factor (TNF)-α, IL-1a, IL-8/ chemokine (CXC motif) ligand 8, and IL-6. These cytokines play an important role in the pathogenesis of psoriasis. In summary, psoriasis increases serum uric acid levels, and urate crystals may further promote the development of psoriasis.

Other factors that may affect serum uric acid levels and hyperuricemia in patients with psoriasis include age, gender, and BMI. Gui et al<sup>[18]</sup> found that serum uric acid levels were significantly positively correlated with BMI (P < 0.001). Similarly, Lai et  $al^{[30]}$  proposed that serum uric acid levels were positively correlated with BMI (P < 0.001), and overweight status showed the strongest correlation with hyperuricemia in patients with psoriatic arthritis (P < 0.001). Kwon *et al*<sup>[27]</sup> found that serum uric acid levels in patients with psoriasis had no significant correlation with age, age at psoriasis onset, or family history of psoriasis. Here, we also analyzed the correlation between serum uric acid levels and BMI. The results showed that serum uric acid levels in overweight and obese patients with psoriasis were significantly higher than those in normal-weight patients. Therefore, to reduce the risk of hyperuricemia, patients with psoriasis should be instructed to strictly control their diet and weight, especially male patients.

Long-term dietary exposure to alcohol, red meat, seafood, and sugar-sweetened beverages can increase the risk of hyperuricemia. Alcohol and fructose increase the production of urate, and alcohol consumption inhibits renal urate excretion. Conversely, the intake of dairy products and coffee reduces the risk of hyperuricemia. Is a Dietary management has been reported to lower serum uric acid levels by approximately 1.0 mg/dL. Therefore, health education regarding a low-purine diet in patients with psoriasis is necessary.

TNF- $\alpha$  is a key cytokine in the pathogenesis of psoriasis and associated comorbidities. TNF- $\alpha$  inhibitors are commonly used in the treatment of moderate to severe plaque psoriasis with good effectiveness and safety. Montaudié *et al*<sup>[37]</sup> found no significant change in serum uric acid levels at the 3rd and 6th month of follow-up in patients with psoriasis treated with biological agents (etanercept, infliximab, adalimumab, and ustekinumab). However, Hasikova *et al*<sup>[38]</sup> reported increased serum uric acid levels in 128 patients with systemic autoimmune rheumatic diseases treated with TNF- $\alpha$  inhibitors for 3 months. Our study revealed no significant change in the serum uric acid levels or prevalence of hyperuricemia in patients with psoriasis after adalimumab treatment for 48 weeks.

Secukinumab, a fully human monoclonal anti-IL-17a antibody, has shown good efficacy and safety in Chinese patients with moderate to severe plaque psoriasis. [39] Gerdes *et al* [40] reported that uric acid levels tended to decrease over 52 weeks of treatment with secukinumab in plaque psoriasis patients. However, Karataş *et al* [41] found that serum uric acid levels were not significantly different from baseline in 30 patients with ankylosing spondylitis and six patients with psoriatic arthritis treated with secukinumab for 6 months. Our study revealed slightly lower serum uric acid levels in patients treated with secukinumab for 48 weeks compared with baseline values, but the prevalence of hyperuricemia was not significantly different. The mechanism underlying the decrease in serum uric acid levels associated with secukinumab treatment remains elusive.

In conclusion, as a comorbid condition related to metabolism in psoriasis, hyperuricemia should attract our attention. Our study revealed that the serum uric acid levels and prevalence of hyperuricemia in patients with psoriasis were higher than those in healthy controls. Moreover, the serum uric acid levels and prevalence of hyperuricemia were related to obesity and gender rather than the severity of psoriasis. The above results suggested that patients with psoriasis should limit their diet and maintain a healthy weight regardless of disease severity, especially male patients. Compared with baseline values, adalimumab and secukinumab had no significant effect on the prevalence of hyperuricemia in patients with psoriasis after 48 weeks of treatment. Both biologics can be applied to psoriasis patients with hyperuricemia.

The limitations of our study include its retrospective nature, single-center design, and short-term observation period. In our hospital, there are more patients with severe psoriasis than patients with mild to moderate psoriasis. Therefore, selection bias cannot be avoided. Because this was a retrospective cohort study, the effects of biologics on patients lost to follow-up could not be determined. Therefore, a large sample, multi-center, long-term prospective study should be performed to demonstrate the correlation between psoriasis and serum uric acid levels. Although our study excluded patients with excessive alcohol consumption, the effects of dietary habits on serum uric acid should be considered. However, this study provides a theoretical basis for the prevention of

hyperuricemia in patients with psoriasis and the development of biological treatment strategies.

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# Conflicts of interest

Lin Cai has participated in advisory boards as an investigator and/or speaker and received grants and/or honoraria from Novartis, AbbVie, Sanofi, and Eli Lilly Inc. Jianzhong Zhang has participated in advisory boards as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, AbbVie, Bayer, Janssen-Cilag, Henlius, Kyowa Kirin, and Pfizer Inc.

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