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THE PREVALENCE OF ASYMPTOMATIC HYPERURICEMIA IN PATIENTS WITH OR WITHOUT PSORIATIC ARTHRITIS IS ASSOCIATED WITH A SIMILAR CARDIOVASCULAR RISK

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Abstract. Aim: *To investigate the association between cardiovascular burden and monosodium urate (MSU) deposits in the joints of patients with asymptomatic hyperuricemia and no evidence of arthritis and subjects with psoriatic arthritis and hyperuricemia.* ***Patients and methods:*** *A single-center, cross-sectional study including 52 individuals: 39 with asymptomatic hyperuricemia and 13 with psoriatic arthritis and hyperuricemia. All patients underwent ultrasound of the joints by which the presence or absence of MSU crystal deposits was assessed. Subjects underwent transthoracic echocardiography by which left ventricular mass index (LVMI) was estimated. Intima-media thickness (IMT) of the common carotid arteries was measured and the presence of atherosclerotic plaques was registered.* ***Results:*** *We found no difference in the distribution of cardiovascular risk factors between the two groups. Further, no difference in their distribution was found between those who were not treated and those who were treated with urate-lowering medications. The frequency of articular MSU deposits was similar between non-allopurinol-treated and allopurinol-treated individuals (p = 0.554). There was no difference in the frequency of articular deposits between benzbromarone recipients and non-recipients (p = 0.396). We observed no connection between articular MSU deposits and LVMI (p = 0.625), IMT (p = 0.117) and atherosclerotic plaques (p = 0.102). Among untreated and treated with urate-lowering drugs there was no difference in LVMI (p = 0.063), IMT (p = 0.975) and plaque distribution (p = 1.000).* ***Conclusion:*** *We can assume that in patients with asymptomatic hyperuricemia and no evidence of arthritis and in subjects with psoriatic arthritis and asymptomatic hyperuricemia, only the prescription of urate-lowering medications for reduction of urate load and cardiovascular risk is not sufficient.*

Key words: *psoriatic arthritis, asymptomatic hyperuricemia, intra-articular MSU deposits, cardiovascular burden*

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INTRODUCTION

An increased incidence of myocardial infarction and congestive heart failure has been reported in patients with psoriasis and accompanying hyperuricemia. One third of the patients with psoriatic arthritis have hyperuricemia [1]. The long disease duration may lead to the release of proinflammatory cytokines, which correlate with elevated serum uric acid levels [2, 3].

Gisondi et al. established a link between obesity and hyperuricemia in subjects with psoriatic arthritis [4]. Lai observed that a significant proportion of patients with psoriatic arthritis have asymptomatic hyperuricemia, which is closely related to body mass index but not to the severity of skin lesions, joint inflammation and renal function [5]. Chu et al. found that hyperuricemia in individuals with psoriatic arthritis is associated with metabolic factors and not so much with disease activity [6].

There is also evidence that uric acid can initiate pathological alterations in psoriatic arthritis. The first studies in this direction were conducted in 1981, when Goldman [7] discovered a high frequency of urate crystals in psoriatic plaques. Oliverio et al. established a high frequency of urate crystals in the synovial fluid of patients with psoriatic arthritis. Injection of urate crystals in vivo leads to the formation of Th17 cells and Th17-associated inflammatory cytokines, such as IL-17, which is one of the main mediators in the pathogenesis of psoriatic arthritis [8]. Moreover, urate crystals stimulate human keratinocytes to produce several inflammatory cytokines such as IL-1α and IL1β involved not only in the pathogenesis of gout flares but also in the pathogenesis of psoriatic arthritis [9]. These data suggest that hyperuricemia plays a role in the development of psoriatic arthritis.

In the present study, we aimed to determine the association between cardiovascular burden and monosodium urate (MSU) deposits in the joints of patients with asymptomatic hyperuricemia and no evidence of arthritis and patients with psoriatic arthritis and asymptomatic hyperuricemia without activity of the skin lesions and joint inflammation.

MATERIALS AND METHODS

We performed single center cross-sectional study on 52 consecutive age-matched subjects, divided in two groups: group 1-39 individuals with asymptomatic hyperuricemia, and group 2-13 patients with psoriatic arthritis and asymptomatic hyperuricemia (demographic and clinical characteristics of the patients in the two groups are summarized in Table 1). Asymptomatic hyperuricemia patients had serum uric acid above the normal range, no clinical characteristics of inflammatory arthritis and no history of gout attack. Psoriatic arthritis subjects had hyperuricemia from the laboratory results and no sign of gout. These patients had no activity of the arthritis and psoriatic skin lesions. Some of the patients attended the outpatient clinic, while the others were hospitalized mainly for examinations. At enrollment individuals were physically examined by a rheumatologist from the Rheumatology Clinic of the University Hospital “Sv. Iv. Rilski” in Sofia. The study protocol has been approved by the Ethics committee of the institution. All participants gave informed consent in accordance with the Declaration of Helsinki.

Clinical and laboratory assessments included collecting detailed information related to current smoking habits, presence of arterial hypertension defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mm Hg or use of antihypertensive medication; diabetes mellitus, based on physician diagnosis and/or documented use of insulin and/or oral hypoglycemic agents; dyslipidemia, based on elevated fasting lipid levels or low HDL and/or documented use of lipid-lowering agents; reduced glomerular filtration rate taken at eGFR < 90 ml/min calculated by the Cockroft-Gault formula. The values of CRP and ESR were within normal range. For CRP up to 6 mg/dl and for ESR up to 22 mm/h. Hyperuricemia was defined as serum level more than 360 μmol/l for women and more than 400 μmol/l for men [10]. Laboratory records of men with serum uric acid levels less than 400 μmol/l were reviewed, and if hyperuricemia was present in the previous year, they were also enrolled. Patients were defined as having suffered a cardiovascular event if they had experienced a myocardial infarction, stroke and/or occlusion of a peripheral artery. Exclusion criteria were exacerbated cardiac or renal failure, cardiomyopathy, severe valvulopathy and history of malignancy.

All patients underwent bilateral ultrasound examination of distal interphalangeal, proximal interphalangeal, metacarpophalangeal joints, midcarpal joint, radiocarpal joint together with the six extensor compartments of the wrist; elbow joint and triceps tendon insertion; knee joint together with quadriceps and patellar tendon (both proximal and distal) insertions; tibiotalar joint with peroneous longus and brevis; tibialis posterior and Achilles tendon insertion; talonavicular joint and the five metatarsophalangeal joints. US measurements were conducted on Esaote-Mylab Twice with a high-frequency linear transducer 4-15 MHz, by one trained ultrasonographer, who was aware with clinical and laboratory characteristics of

the patients. All regions were evaluated by standard positions [11] covering all parts of the joints and tendons by sweeping the regions. The existence of double contour sign, intra-tendinous MSU aggregates, "snow storm", tophi, tophi with erosions, or a combination of these ultrasound features was assessed. In each of the examined joint regions of each patient the presence of the particular ultrasound MSU finding or the absence of MSU crystal deposits was registered.

Further, all subjects underwent transthoracic echocardiography and ultrasound of the common carotid arteries performed on Sonoscape medical corp. model S22, by another certified operator, who was blinded to the cases clinical and laboratory data. Cardiac morphology was examined with 2.5 MHz transducer Phased Array. Left ventricular mass (LVM) was measured by the method of Teicholz and LVM index (LVMI in g/m²) was obtained as LVM was related to body surface (The Mosteller formula), defined in square meters. Left ventricular hypertrophy was defined as LVMI > 125 g/m² for males and above 110 g/m² for females. Carotid arteries were examined with 10 MHz linear transducer working with pulse Doppler frequency of 5 MHz. Intima-media thickness (IMT) was bilaterally recorded in the far wall of the common carotid arteries 1-2 cm proximal to the bifurcation. The presence of heterogeneous or homogeneous atherosclerotic plaques was registered.

The specialized statistical package SPSS (Statistical Package for the Social Sciences) version 20.0 was used to process the study data. The Mann-Whitney test was applied in the comparative analyzes of the quantitative variables while the Fisher's exact test was conducted for categorical variables. The accepted level of significance is $\alpha = 0.05$. Statistical significance is considered when the p value is less than α ($p < 0.05$).

RESULTS

No difference was observed in the distribution of sex (p = 0.749), smoking (p = 1.000), diabetes mellitus (p = 0.404), arterial hypertension (p = 0.506), cardiovascular events (p = 0.589), dyslipidemia (p = 1.000), obesity (p = 0.752) and chronic renal failure (p = 1.000) among patients with asymptomatic hyperuricemia and no evidence of arthritis and individuals with psoriatic arthritis and hyperuricemia. In these two groups the mean values of ESR (p = 0.138), CRP (p = 0.305) and serum uric acid (p = 0.711) were similar, (Table 1). Further, when we divided patients into untreated and treated with urate-lowering therapy there was no significant difference between them in the distribution of sex (p = 0.652), smoking (p = 0.308), diabetes mellitus (p = 0.506), arterial hypertension (p = 1.000), cardiovascular events (p = 1.000), dyslipidemia (p = 1.000), obesity (p = 0.662), chronic renal failure (p = 1.000), as well as in the mean serum level of uric acid (p = 0.587), (Table 2). The frequency of MSU crystal deposits in the joints was comparable in those who were not taking and those who were taking urate-lowering drugs (p = 0.286). The distribution of MSU deposits in the metacarpophalangeal joints (p = 0.341), radiocarpal joints (p = 1.000), knee joints (p = 0.530), talonavicular joints (p = 0.410), tarsus (p = 1.000) and the first metatarsophalangeal joints (p = 0.301) in untreated and treated with urate-lowering medicationswas equal.

Table 1. Demographic, laboratory indices and cardiovascular risk factors in patients with asymptomatic hyperuricemia and no evidence of arthritis and subjects with psoriatic arthritis and accompanying asymptomatic hyperuricemia

Index	Patients with asymptomatic hyperuricemia and no evidence of arthritis	Psoriatic arthritis patients with asymptomatic hyperuricemia	p
Sex, n (%)			
Males	19 (48.7)	5 (38.5)	0.749
Females	20 (51.3)	8 (61.5)	
Age (years), Mean (SD)	53 (16)	61 (14)	0.163
Smoking, n (%)	12 (30.8)	4 (30.8)	1.000
Diabetes mellitus, n (%)	5 (13.2)	3 (23.1)	0.404
Arterial hypertension, n (%)	25 (64.1)	10 (76.9)	0.506
Cardiovascular events, n (%)	3 (7.7)	2 (15.4)	0.589
Dyslipidemia, n (%)	23 (95.8)	13 (100.0)	1.000
BMI > 30 kg/m², n (%)	18 (46.2)	7 (53.8)	0.752
eGFR < 90 ml/min, n (%)	13 (35.1)	5 (38.5)	1.000
BMI (kg/m²), Mean (SD)	29.53 (5.22)	30.89 (4.14)	0.398
eGFR (ml/min), Mean (SD)	98.8 (35.3)	92.91 (31.14)	0.500
ESR (mm/h), Mean (SD)	13.59 (5.77)	16.89 (5.78)	0.138
CRP (mg/dl), Mean (SD)	2.39 (1.66)	3.13 (1.55)	0.305
Serum uric acid (μmol/l), Mean (SD)	452.97 (88.08)	444 (86.35)	0.711

Table 2. Demographic, laboratory indices and cardiovascular risk factors in untreated and treated with urate-lowering medications individuals

Index	Patients without urate-lowering therapy	Patients on urate-lowering therapy	p
Sex, n (%)			
Males	21 (44.7)	3 (60.0)	0.652
Females	26 (55.3)	2 (40.0)	
Smoking, n (%)	16 (34.0)	0 (0.0)	0.308
Diabetes mellitus, n (%)	7 (14.9)	1 (25.0)	0.506
Arterial hypertension, n (%)	31 (66.0)	4 (80.0)	1.000
Cardiovascular events, n (%)	5 (10.6)	0 (0.0)	1.000
Dyslipidemia, n (%)	29 (96.7)	2 (100.0)	1.000
BMI > 30 kg/m², n (%)	22 (46.8)	3 (60.0)	0.662
eGFR < 90 ml/min, n (%)	17 (37.0)	1 (25.0)	1.000
ESR mm/h, Mean (SD)	14.68 (5.98)	12.80 (5.45)	0.443
Serum uric acid μmol/l, Mean (SD)	451.23 (87.68)	446.00 (88.43)	0.587

In both groups the distribution of patients treated with allopurinol was similar (p = 0.561). There was no difference in the frequency of intra-articular MSU deposits between allopurinol-naïve and allopurinol-treatedpatients (p = 0.554). When we looked at the distribution of crystal deposits in the individual joint areas between untreated and treated with allopurinol, we observed the following results: in the radiocarpal joint between the non-recipients and recipients of allopurinol, no difference was found in the proportion of patients without MSU deposits, those who had tendon urate deposits and individuals with a snowstorm pattern (p = 1.000). Regarding the knee joint, no difference was registered in the share of patients without MSU deposits, those with double contour and patients with intra-tendinous deposits (p = 0.450). Further, in the talonavicular joint, the distribution of patients without MSU deposits, those with double contour and individuals with a snowstorm was similar (p = 0.341). In the tarsus, the proportion of patients without MSU deposits, those with double contour and patients with intra-tendinous crystals was equal (p = 1.000). In the first metatarsophalangeal joints among untreated and treated with allopurinol there was no difference in the percentage of patients without MSU deposits, those with double contour, subjects with intra-tendinous crystals, individuals with tophi and those with tophi and erosions (p = 0.603).

The prevalence of intra-articular MSU deposits among benzbromarone-naive and benzbromarone-treated individuals was comparable (p = 0.396). No difference in the distribution of MSU deposits was established in the individual joint areas among untreated and treated with benzbromarone patients. In the metacarpophalangeal joints inbenzbromarone recipients and non-recipients, the distribution of subjects without ultrasound MSU deposits, those with a double contour sign and individuals with a snowstorm was equal (p = 0.958). In the radiocarpal joint among untreated and treated with benzbromarone no difference was found in the proportion of subjects without MSU deposits, those who had intra-tendinous deposits and patients with a picture of a snowstorm (p = 1.000). In the knee area among benzbromarone-naive and benzbromarone-treated subjects there was no difference in the distribution of patients without MSU deposits, subjects with double contour and those with intra-tendinous deposits (p = 1.000). In the talonavicular joints, tarsus and first metatarsophalangeal joints, the proportion of individuals without MSU deposits and those with ultrasound evidence of urate load was similar (p = 1.000, p = 0.980, p = 0.200).

No connection was found between intra-articular urate crystals and left ventricular hypertrophy (p = 0.625), (Fig. 1a). In individuals on urate-lowering therapy the mean value of LVMI was lower but without reaching a significance (mean ± SD; 116.80 ± 31.34 g/m² vs 93.07 ± 23.15g/m², p = 0.063), (Fig. 1c). We did not establish an association between intra-articular deposits and the thickness of intima-media (p = 0.117) and the presence of heterogeneous or homogeneous plaques in the carotid arteries (p = 0.102), (Fig. 1b and Fig. 2a). Moreover, among untreated and treated with urate-lowering drugs the IMT (mean ± SD; 0.860 ± 0.082 mm vs 0.870 ± 0.245 mm, p = 0.975) and the distribution of heterogeneous or homogeneous atherosclerotic plaques in the carotid arteries (p = 1.000) were comparable (Fig. 1d, Fig. 2b).

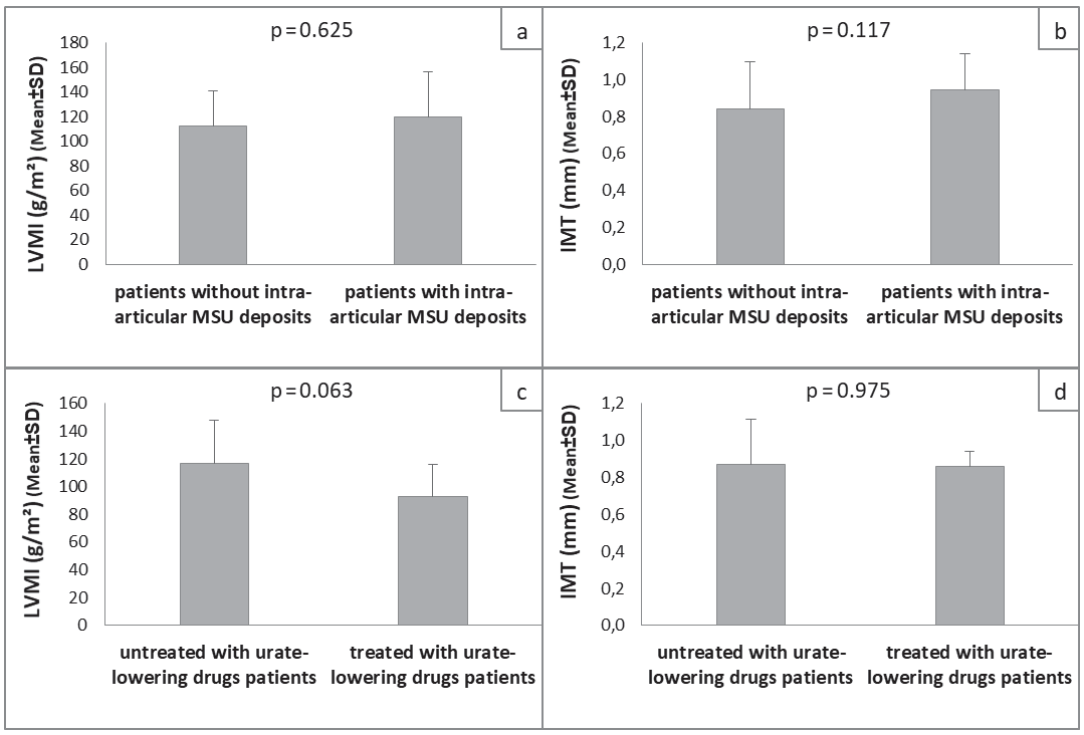


Fig. 1. Mean values and standard deviations of LVMI and IMT in patients without and with intra-articular MSU deposits (part a and b), and in untreated and treated with urate-lowering drugs individuals (part c and d)

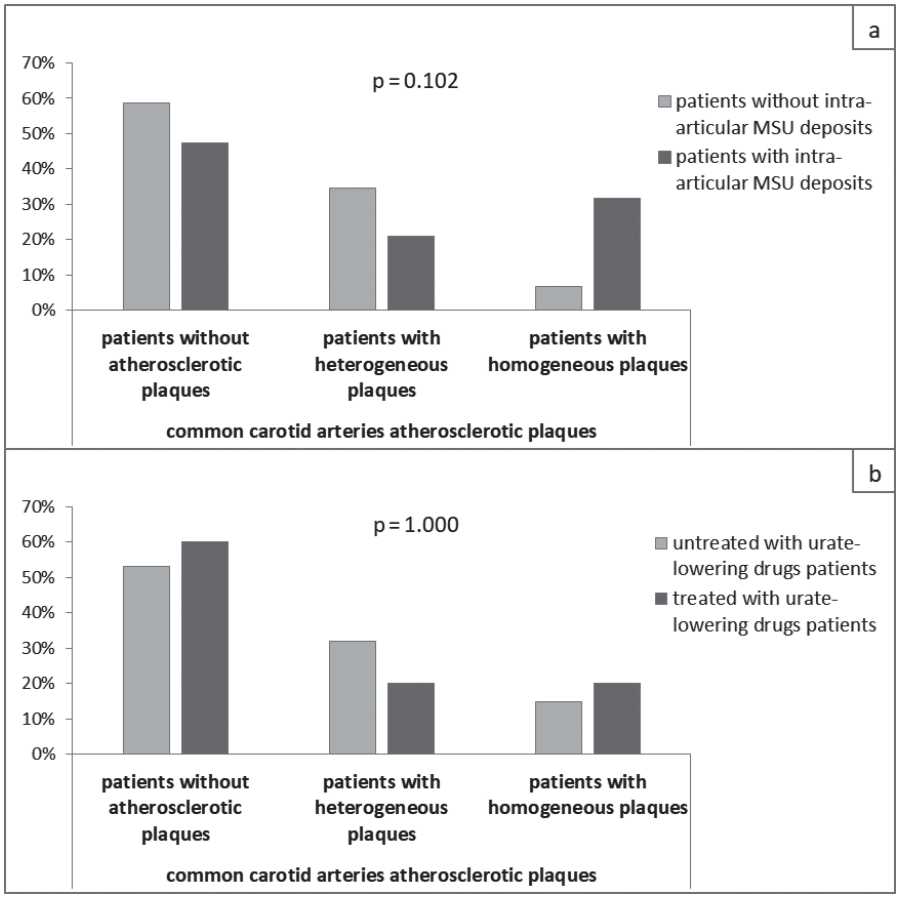


Fig. 2. Distribution of common carotid arteries atherosclerotic plaques in patients without and with intra-articular MSU deposits (part a), and in untreated and treated with urate-lowering drugs subjects (part b)

DISCUSSION

In the present study we found no association between intra-articular MSU deposits and cardiovascular burden in patients with asymptomatic hyperuricemia and subjects with psoriatic arthritis and hyperuricemia. No connection was found between urate-lowering therapy and intra-articular MSU load.

Thirty to fifty percent of psoriasis patients have hyperuricemia [8]. Uric acid is the end product of purine metabolism and the etiological substrate in gout. One of the mechanisms leading to hyperuricemia in psoriatic arthritis is the increased cellular turnover characteristic of this disease. Uric acid synthesis is increased by the proliferation of keratinocytes leading to accelerated nucleic acid catabolism. On the other hand, hyperuricemia may be due to raised production of uric acid in the liver. Increased cytokine synthesis in psoriatic arthritis, especially IL-17, can affect the liver and cause liver complications, such as non-alcoholic liver disease [12]. In hepatic steatosis, the synthesis of adenosine triphosphate is reduced [13, 14], leading to increased uric acid production by hepatocytes [15]. Additional mechanisms are associated with reduced renal and extrarenal uric acid clearance. Although the kidneys play a major role in the excretion of uric acid, other organs such as the gut contribute to its balance. BCRP/ABCG2 is located on the apical membrane of small intestinal epithelial cells and is involved in the secretion of uric acid from the blood into the intestinal lumen [16]. Some patients with psoriatic arthritis have clinical evidence of inflammatory bowel disease, which may decrease levels of these transporters and disrupt uric acid homeostasis [17, 18, 19]. Hyperuricemia may be the result of metabolic disorders connected to psoriatic arthritis: obesity, hypertension, insulin resistance and diabetes [20]. In obese individuals, hyperuricemia results from deteriorated excretion and increased uric acid production [21]. Impaired lipid metabolism plays a role in dyslipidemia. Increased triglyceride production reduces the expression of OAT1 in the kidneys, leading to decreased uric acid excretion [22].

In our study, we did not find an association between intra-articular MSU deposits and left ventricular hypertrophy, intima-media thickness and the presence of atherosclerotic plaques in the common carotid arteries. When we divided patients according to whether they were treated with urate-lowering drugs no difference in IMT and in the distribution of heterogeneous or homogeneous atherosclerotic plaques was registered. However, we noticed a tendency of lower left ventricle mass in individuals receiving urate-lowering medications. Gonzalez-Gay in a small observational study examined the cardiovascular consequences in patients with psoriatic arthritis and hyperuricemia. A total of 52 patients with psoriatic arthritis without previous cardiovascular pathology underwent ultrasound measurement of the intima-media complex of the carotid arteries. Individuals with psoriatic arthritis and hyperuricemia had increased intima-media thickness and a higher incidence of carotid plaques than subjects with normal levels of serum uric acid [23]. Similar results have been reported by Ibrahim et al., who compared patients with psoriatic arthritis and hyperuricemia to patients with psoriatic arthritis and normal serum uric acid. The hyperuricemia group had thicker intima-media complex and present atherosclerotic plaques. The correlation analysis established a relationship between serum uric acid levels and the thickness of intima-media complex, disease activity indices such as DAS28, PASI and disease duration [3]. In the present study, the examined groups of patients had hyperuricemia and concomitant cardiovascular risk factors. There was no difference in the distribution of traditional cardiovascular risk factors between patients with asymptomatic hyperuricemia and no evidence of arthritis and subjects with asymptomatic hyperuricemia in the course of psoriatic arthritis. Furthermore, no difference in the distribution of cardiovascular risk factors was registered between untreated and treated with urate-lowering medications. Interestingly, the frequency of articular crystal deposits was comparable in untreated and treated with allopurinol or benzbromarone, which suggests that other measures are needed to reduce the wholebody urate load. Perhaps such differences could be found in a study with a larger number of patients. It should be noted that the lack of difference in serum uric acid levels among untreated and treated with urate-lowering drugs indicates poor compliance in some patients.

The main limitation of this study is the small number of patients. We also do not have a group treated with febuxostat. However, we are one of the few who have found that in patients with asymptomatic hyperuricemia and no evidence of arthritis and in psoriatic arthritis individuals with hyperuricemia, the cardiovascular burden is similar and that for reduction of intra-articular urate load only the prescription of urate-lowering drugs whether allopurinol or benzbromarone is insufficient. Patients should be regularly monitored. There must be adequate compliance with the urate-lowering therapy. The concomitant cardiovascular risk factors should be managed.

Disclosure Summary: *The authors have nothing to disclose.*

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