ORIGINAL ARTICLE

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THE PRESENCE OF MONOSODIUM URATE DEPOSITS IN THE JOINTS OF PATIENTS WITH ASYMPTOMATIC HYPERURICEMIA IS ASSOCIATED WITH A HIGHER CARDIOVASCULAR RISK, BUT NOT WITH MORE ADVANCED KIDNEY DAMAGE

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Abstract: Aim: *To evaluate the association between asymptomatic hyperuricemia, renal damage and cardiovascular events and to investigate whether the presence of monosodium urate (MSU) deposits in the joints is related to more advanced renal changes and increased cardiovascular risk.* ***Methods:*** *This was a study on 73 consecutive patients divided into 34 patients with osteoarthritis, 25 subjects with asymptomatic hyperuricemia and no ultrasound (US) evidence of MSU crystals in the joints and 14 individuals with asymptomatic hyperuricemia and MSU deposits in the joints. Patients underwent bilateral US examination of the joints of the hands, elbows, knees, ankles, feet and the kidneys. Routine abdominal ultrasound with evaluation of kidney and parenchymal size and echogenicity and renal vascular indices was performed. The presence of cardiovascular complications in the past was evaluated from the patients' history. The study protocol was a continuation of another project from 2013 (14-D-2013, approved by the ethics committee of the Medical University – Sofia). Informed consent was obtained from all patients prior to the inclusion in the study. The study was conducted in accordance with the Declaration of Helsinki.* ***Results:*** *The highest proportion of patients with cardiovascular events was detected in the group of asymptomatic hyperuricemia with MSU deposits in the joints. The patients with osteoarthritis had the lowest prevalence of eGFR < 90 ml/min. Renal parenchymal echogenicity and the prevalence of nephrolithiasis were compatible for all groups. Patients with hyperuricemia and MSU deposits in the joints had higher BMI (p = 0.018) and smaller kidney size (p = 0.015) compared to those with osteoarthritis. The comparison of hyperuricemia without MSU deposits in the joints to osteoarthritis group demonstrated a significant difference only in the age (p = 0.001). Finally, the comparison of the two groups with hyperuricemia showed that subjects with MSU deposits in the joints had higher BMI (p = 0.041) with no difference in the age, kidney size, RRI, eGFR and thickness of renal parenchyma.* ***Conclusions:*** *Hyperuricemia, independent of the presence of articular crystals, is associated with compatible kidney damage. Cardiovascular risk is higher when MSU crystals are detected in the joints using US.*

Key words: *articular MSU deposits; asymptomatic hyperuricemia; kidney damage*

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INTRODUCTION

Several epidemiological studies conducted in the general population and in patients with chronic renal failure have shown that uric acid (UA) is a major independent risk factor for the development and progression of kidney disease [1-4]. This relationship has also been confirmed in studies with individuals suffering from diabetes mellitus [1, 5-7]. In a meta-analysis including more than 190.000 subjects with normal renal function, the presence of hyperuricemia was an independent predictor for the development of chronic kidney disease (CKD). On the other hand, in CKD the risk of developing hyperuricemia is twice as high, as this effect is being comparable in patients without and with diabetes mellitus [1].

UA damages the kidneys by causing systemic and glomerular hypertension [8, 9, 10, 11]. Elevated serum UA levels are associated with arteriolosclerosis characterized by arterial wall thickening and hyalinosis [9, 10, 11] and increases cardiovascular risk [10, 11].

AIM

The aim of our study was to evaluate the association between asymptomatic hyperuricemia, renal damage and cardiovascular events and to investigate whether the presence of monosodium urate (MSU) deposits in the joints is related to more advanced renal changes and increased cardiovascular risk, using clinical, laboratory and ultrasound methods.

PATIENTS AND METHODS

This was a study on 73 consecutive patients divided in three groups: 34 patients with osteoarthritis (OA), 25 subjects with asymptomatic hyperuricemia and no US data of MSU crystals in the joints, and 14 individuals with asymptomatic hyperuricemia and MSU crystal deposits in the joints (the demographic, clinical, laboratory and US characteristics of the kidneys in the three groups are summarized in Table 1).

At enrollment, all patients were physically examined by a rheumatologist from the Rheumatology Clinics at the University Hospitals “Sv. Iv. Rilski” and “Sofiamed”, Sofia. The study protocol was a continuation of another project from 2013 (14-D-2013, approved by the ethics committee of the Medical University – Sofia). Informed consent was obtained from all patients prior to the inclusion in the study. The study was conducted in accordance with the Declaration of Helsinki.

Clinical-laboratory assessments included: collecting detailed information related to current smoking habits, arterial hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or use of antihypertensive medication); diabetes mellitus (based on medical history, investigations or treatment for diabetes); dyslipidemia (elevated fasting lipid levels or low HDL and/or documented use of lipid-lowering agents); reduced glomerular filtration rate (GFR, eGFR < 90 ml/min, using Cockroft-Gault formula). The laboratory investigations included: serum UA, creatinine, blood urea nitrogen (BUN), tested with the use of standard methods. Hyperuricemia was defined as serum level of UA more than 360 μmol/l for women and more than 400 μmol/l for men [12]. The patients were defined as having suffered a cardiovascular event, if they had past history of myocardial infarction, stroke and/or occlusion of a peripheral artery (peripheral vascular disease). Exclusion criteria were: exacerbated cardiac or renal failure, and history of malignancy as well as arterial blood pressure > 140/90 mm Hg and heart rate < 50 bpm or > 90 bpm during the US measurements of the kidneys.

All patients underwent bilateral US 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 zones were evaluated in standard positions [13] covering all parts of the joints and tendons by sweeping the regions. The presence of double contour sign, intra-tendinous MSU aggregates, “snow storm”, tophi, tophi with erosions, or a combination of these US features was assessed. In each of the examined joint regions of each patient the presence of the particular US MSU finding or the absence of MSU crystal deposits was registered.

Furthermore, all subjects underwent US of the kidneys using Sonoscape medical corp. S22, by another certified operator, who was blinded to the cases clinical and laboratory data. Kidneys were examined using 3.5 MHz probe, working with pulse Doppler frequency of 2.5 MHz. Renal length, parenchymal thickness and echogenicity were determined for both kidneys. The presence or absence of nephrolithiasis was reported. By means of the value of renal resistive index (RRI) we measured for intrarenal blood flow [14] – for both kidneys at the level of interlobar

arteries. The Doppler probe volume was 2 mm with pulse repetition frequency from 1.5 to 2 kHz and angle of orientation < 60°.

Patients with OA had only degenerative joint changes, normal serum UA and no US data of MSU deposits in the joints. Asymptomatic hyperuricemia subjects had serum uric acid above the normal range and no history of gout attack. These individuals were divided into two groups according to the presence/absence of US MSU crystals in the joints. The investigated patients were evaluated both in out-patient settings and during hospital stay.

STATISTICAL ANALYSIS

Statistical analysis were performed using statistical software SPSS for Windows® version 20.0. The distribution of the quantitative variables was tested using One-Sample Kolmogorov-Smirnov test. Normally distributed data were presented as Mean ± SD. Categorical variables were presented as number (n) or percentage (%). Comparisons of two independent groups were conducted by t-test. The relationship between two categorical variables was evaluated by Chi-square test or Fisher`s exact test. A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

In this study, we included 15 males and 19 females with OA and without ultrasound evidence of crystal deposits in the joints; 14 males and 11 females with asymptomatic hyperuricemia and no MSU deposits in the joints and 5 males and 9 females with asymptomatic hyperuricemia and ultrasound evidence of MSU crystals in the joints. The distribution of males and females (p = 0.441), smokers and non-smokers (p = 0.147), patients with arterial hypertension and normotensive individuals (p = 0.298) as well as subjects with diabetes and without diabetes (p = 0.775) and patients with dyslipidemia and normal lipid levels (p = 1.000) was similar among the groups. The proportion of patients who had suffered a cardiovascular event was the highest in the group of asymptomatic hyperuricemia with MSU deposits in the joints (21.4%) compared to the group of osteoarthritis (14%) and hyperuricemia without MSU crystals in the joints (0%), (p = 0.048). In the group of osteoarthritis the share of individuals with eGFR < 90 ml/min was the lowest (5.9%) in comparison to the group of hyperuricemia without MSU deposits in the joints (29.2%) and hyperuricemia with crystals in the joints (46.2%), (p = 0.005). The percentage of obese subjects was the highest in hyperuricemia with MSU crystals in the joints (57.1%), but without reaching a significant difference with hyperuricemia without crystals in the joints (40%) and the group of osteoarthritis (29.4%), (p = 0.195). The echogenicity of the kidneys (p = 0.630) and the distribution of nephrolithiasis (p = 0.596) was compatible among the groups, (Table 1 presents the general characteristics of the subjects).

Patients with hyperuricemia and MSU deposits in the joints compared to those with osteoarthritis had higher BMI (mean±SD; 31.79 ± 5.92 kg/m2 vs 28.06 ± 4.27 kg/m^2, p = 0.018) and smaller kidney size (mean ± SD; 55.36±5.58 mm vs 59.58 ± 5.12 mm, p = 0.015), (fig. 1A and 1B). The comparison of hyperuricemia without MSU deposits in the joints to osteoarthritis group demonstrated a significant difference only in the age (mean±SD; 49.7 ± 16.4 years vs 61.5 ± 9.4 years, p = 0.001), (fig. 1A). Finally, the comparison of the two groups with hyperuricemia showed that subjects with MSU deposits in the joints had higher BMI (mean ± SD; 31.79 ± 5.92 kg/m^2 vs 28.26 ± 4.41 kg/m^2, p = 0.041) with no difference in the age (p = 0.072), kidney size (p = 0.141), RRI (p = 0.296), eGFR (p = 0.528) and thickness of renal parenchyma (p = 0.232), (fig. 1A, 1B, 1C and fig. 2A, 2B and 2C).

DISCUSSION

In the present study, we found that asymptomatic hyperuricemia patients with MSU deposits in the joints had higher cardiovascular risk in comparison to asymptomatic hyperuricemia subjects and individuals with osteoarthritis who had no MSU deposits in the joints. Our results demonstrated the highest prevalence of cardiovascular events among patients with MSU deposits in the joints. The comparison of the two groups with hyperuricemia showed higher BMI in individuals with articular crystals with no difference in the age, kidney size, glomerular filtration rate, renal blood flow and thickness of renal parenchyma.

The co-existence of hyperuricemia with other comorbidities (diabetes, obesity, dyslipidemia, arterial hypertension), associated with increased cardiovascular risk, makes it difficult to evaluate the role of high UA as independent cardiovascular risk factor. The first steps in this direction are the observations on the predictive value of serum UA in patients who have survived a cardiovascular event and in subjects with heart failure. Hyperuricemia and gout have been shown to alter myocardial morphology and contribute to the development of congestive heart failure. The persistent pro-inflammatory state in the body, the connection with insulin resistance, the stimulation of the proliferation of smooth muscle and endothelial cells and the influence on the metabolism of nitric

Table 1. General characteristics of the investigated patients.

Characteristic		Patients with osteoarthritis	Patients with asymptomatic hyperuricemia and no MSU deposits in the joints	Patients with asymptomatic hyperuricemia and MSU deposits in the joints	Total	p
Sex	Male	15 (44,1)	14 (56,0)	5 (35,7)	34 (46,6)	0,441
	Female	19 (55,9)	11 (44,0)	9 (64,3)	39 (53,4)	
Smoking	No	22 (64,7)	20 (80,0)	7 (50)	49 (67,1)	0,147
	Yes	12 (35,3)	5 (20,0)	7 (50)	24 (32,9)	
Arterial hypertension	No	10 (29,4)	11 (44,0)	3 (21,4)	24 (32,9)	0,298
	Yes	24 (70,6)	14 (56,0)	11 (78,6)	49 (67,1)	
Patients suffered with cardiovascular event	No	29a (85,3)	25b (100)	11a (78,6)	65 (89)	0,048
	Yes	5a (14,7)	0b (0,0)	3a (21,4)	8 (11)	
Diabetes mellitus	No	27 (79,4)	21 (87,5)	12 (85,7)	60 (83,3)	0,775
	Yes	7 (20,6)	3 (12,5)	2 (14,3)	12 (16,7)	
Dyslipidemia	No	3 (10,0)	1 (5,3)	0 (0,0)	4 (7,4)	1,000
	Yes	27 (90,0)	18 (94,7)	5 (100)	50 (92,6)	
Patients with chronic renal failure	No	32a (94,1)	17b (70,8)	7b (53,8)	56 (78,9)	0,005
	Yes	2a (5,9)	7b (29,2)	6b (46,2)	15 (21,1)	
Patients with obesity	No	24 (70,6)	15 (60)	6 (42,9)	45 (61,6)	0,195
	Yes	10 (29,4)	10 (40)	8 (57,1)	28 (38,4)	
Patients with nephrolithiasis	No	27 (79,4)	21 (84)	13 (92,9)	61 (83,6)	0,596
	Yes	7 (20,6)	4 (16)	1 (7,1)	12 (16,4)	
Renal echogenicity	No	25 (73,5)	21 (84)	11 (78,6)	57 (78,1)	0,630
	Yes	9 (26,5)	4 (16)	3 (21,4)	16 (21,9)	

Legend: The presence of identical superscript between different groups demonstrates the lack of significant difference in the mean values of the examined parameter ($p > 0.05$). Different superscripts indicate a significant difference in the mean values of the examined parameter ($p < 0.05$). The absence of superscripts in the intergroup comparisons means no significant differences in the mean values.

oxide and the renin-angiotensin-aldosterone system are considered to be the cause of the increased general and in-hospital mortality. In hyperuricemia, a pro-inflammatory state is maintained in the body [15]. Serum uric acid induces proliferative and inflammatory changes in cultured vascular smooth muscle and endothelial cells [15, 16]. There is in vivo evidence that uric acid affects nitric oxide metabolism and the renin-angiotensin-aldosterone system [17-20]. M. McAdams used data from the longitudinal study Campaign Against Cancer and Heart Disease (CLUEII), involving 15.553 individuals, of whom 517 developed gout. The prevalence of obesity at the start of the study in 1989 was 16.2%, and the mean age at onset was 59.3 years. Patients were followed for 18 years [21]. Gout developed 3.1 years earlier in the obese and 11 years earlier in the 21-year-old obese. The authors conclude that obesity is not the only risk factor for gout, but is associated with its earlier onset. Among John Hopkins medical students in 1991, a one-unit increase in BMI was found to raise the risk of gout by 1.12, and a 1.88 kg/m² increase before age 35 doubled the risk [22]. In a study from Thailand on participants divided into three age groups between 19-44 years, 45-64 years, and over 65 years of age, the risk of gout in obese participants was 1.70, 1.17, and 1.36 higher, respectively [23].

In a previous study [24], we examined 201 patients, divided into three groups: asymptomatic hyperuricemia, gouty arthritis without tophi, and gout with tophi. Individuals in each group were subdivided according to BMI > 30 kg/m² and BMI < 30 kg/m². We assessed

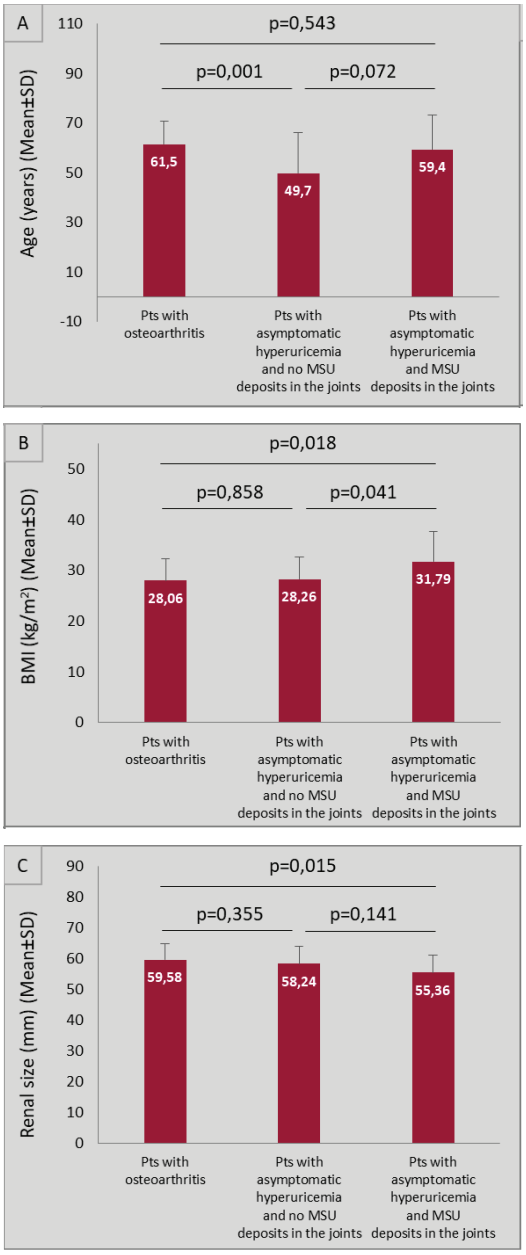

Fig. 1. Summary statistics and t-test results for the variables: age, body mass index (BMI) and renal size

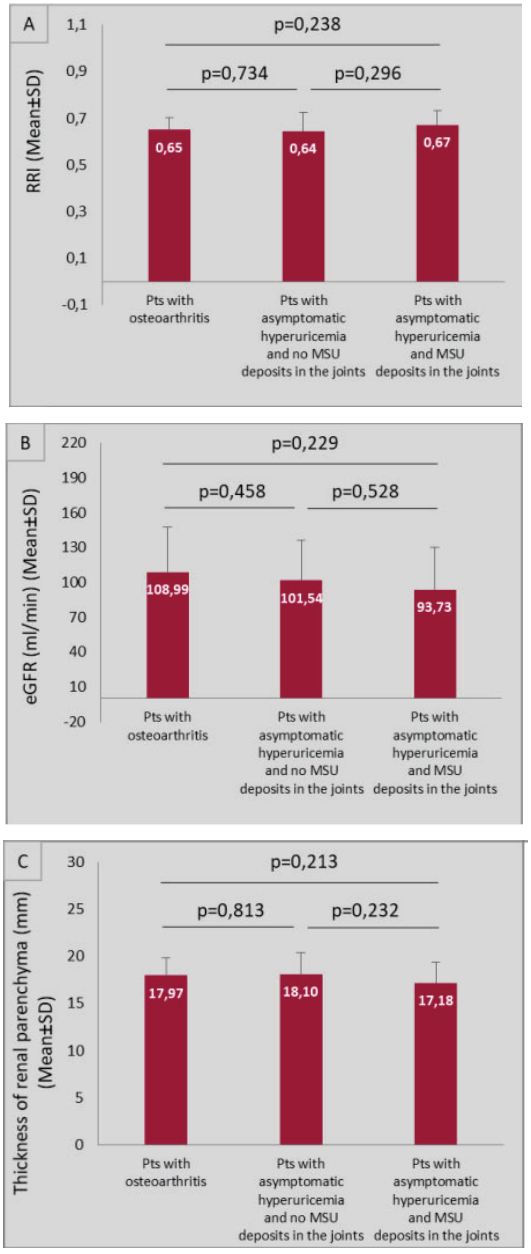

Fig. 2. Summary statistics and t-test results for the variables: renal resistive index (RRI), estimated glomerular filtration rate (eGFR) and thickness of renal parenchyma

cardiovascular risk using the Framingham Risk Score (FRS) and transthoracic echocardiography. We found no significant difference between obese and non-obese patients in the groups in FRS and in functional echocardiographic indicators reflecting systolic and diastolic function. Obese patients in the three groups have a thicker interventricular septum and posterior wall of the left ventricle. Through multiple linear regression analysis, we demonstrated that obesity in gout with tophi less affected left ventricular posterior wall thickening compared to earlier stages of the disease. These results led us to hypothesize that in gout with tophi, additional factors such as chronic inflammation, greater urate load, and a higher level of oxidative stress contribute to left ventricular posterior wall thickening [24]. Obesity is a modifiable risk factor for hyperuricemia. Weight reduction of more than 10 kg quadruples the chance of reaching a serum uric acid concentration ≤ 360 μmol/l. A 1 kg reduction in body weight was associated with an 11% higher chance of reaching the therapeutic goal. These connections are independent of age, diuretic use, arterial hypertension, presence of congestive heart failure, renal function, alcohol intake, and dietary habits [25]. Weight loss increases renal excretion of urate and partially decreases its formation [26]. In 27 obese patients, the fractional excretion of uric acid was significantly reduced. The amount of uric acid excreted

in the urine is lower in obese subjects than in healthy controls. The authors prove that lowering body weight normalizes the fractional excretion of uric acid [27]. A possible explanation is that this could be due to a decrease in insulin resistance and insulin levels, since insulin resistance correlates directly with serum uric acid and inversely with renal urate clearance [28]. Of the components of the metabolic syndrome, obesity is the strongest risk factor for hyperuricemia [29].

CONCLUSION

We performed a single-center cross-sectional study on 73 consecutive patients divided in three groups: 34 patients with OA, 25 subjects with asymptomatic hyperuricemia and no US evidence of MSU crystals in the joints, and 14 individuals with asymptomatic hyperuricemia and MSU crystal deposits in the joints. Our results showed that obesity is more common in asymptomatic patients with intra-articular monosodium urate deposits compared to those without. Moreover, their cardiovascular risk is higher even in the absence of changes in renal morphology and function.

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