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RESEARCH ARTICLE

Metabolic syndrome in patients with gout

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ABSTRACT

Introduction. The definition of metabolic syndrome is not yet consistent. However, many studies have been conducted in the latest decades about the effect of increased uric acid on metabolic syndrome development. Large epidemiological studies on the association between hyperuricemia and MS showed that increased concentration of serum urea is often observed in subjects with metabolic syndrome. The aim of the study was to characterize specific dysmetabolic changes and features of extraarticular evolution in patients with gout.

Materials and methods. A descriptive study was conducted that included 501 patients with gout. The mean age of gout (423 men and 78 women) was 49.2 (36.9; 59.9). The diagnosis of gout was established according to the classification criteria for gout ACR/EULAR 2015. The raw data was processed in SPSS version 26.0.

Results. According to our data, the highest severity of obesity and LDL-cholesterol was detected in those with tophaceous gout, which also caused an increase in the frequency of high blood pressure and type 2 diabetes, with age differences in the frequency of detection of metabolic syndrome and insulin resistance. Our data have noted that serum levels of uric acid correlated with the risk of developing both metabolic syndrome as well as its components - obesity, hypertension, and dyslipidemia, but inversely correlated with hyperglycemia.

Conclusions. Gout is associated with a severe lipid metabolism dysfunction, significantly increasing the rate of metabolic syndrome especially among patients with chronic tophaceous gout, than in the group of patients with gout under the age of 59 years. On the other hand, in patients with the onset of gout who are ≤59 years lipid metabolism disorders occur significantly earlier than in patients with the onset of gout at the age of ≥60 years.

Keywords: gout, metabolic syndrome, dyslipidemia.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Gout is classified in the group of metabolic diseases, but to this day, the interrelationships between blood lipid values and indicators of the evolution of gout remains unclear.

The research hypothesis

Studying the most important indicators of dyslipidemia and lipid metabolism disorder in gout will discern new possibilities in the correct management of these patients.

The novelty added by manuscript to the already published scientific literature

Knowledge of changes in blood lipids and disorders of carbohydrate metabolism in various forms of gout (tophus and non-tophus) will allow a correct management of patients that will help prevent complications and the development of comorbidities.

Introduction

While it's not clear why there has been a rise in complications related to gout, many experts believe that this may be due to a growing prevalence of factors that contribute to gout, such as higher rates of obesity and metabolic syndrome [1, 2]. Lifestyle factors have an important effect on the incidence of gout. This was confirmed by researchers, authors of a 12-year cohort study conducted on 47150 cases of gout. The risk of gout was more frequent among individuals who were either obese or had a greater consumption of alcohol overall, or in situations where both factors were present [3-5].

Tophus is a cardinal feature of gout; it is a complex mass consisting of monosodium urate crystals, a variety of immune and inflammatory cells, and a fibrous capsule [6, 7]. Tissue deposition of uric acid crystals initiates the formation of tophus with a local inflammatory response of fibrotic tissue. Clinically, it is difficult to separate the different components of a tophus, and these can vary between different anatomical sites in different patients. Stimulation of immune/inflammatory system cells through MUS crystals can lead to chronic inflammation, pain, and tissue remodeling, including bone erosions [8].

In 1998, the World Health Organization (WHO) described „metabolic syndrome" for the first time. The classification criteria for metabolic syndrome (MS) have been proposed by WHO, the National Adult Cholesterol Education Program Treatment Panel III (NCEP ATP III) and the International Diabetes Federation. However, the definition of MS is not yet consistent. Multiple studies have been conducted in recent decades about the effect of increased UA on MS development. Large epidemiological studies on the association between HU and MS showed that increased concentration of serum urea is often observed in subjects with MS. Scientists evaluated data from 8 669 participants in the third National Health and Nutrition Review Study (NHANES-III) (1988-1994) and demonstrated that MS prevalence increased with increasing serum UA levels [9-11].

In another study, out of a total of 2 374 subjects who received a health exam, subjects with HU had a 1.63 times higher risk of MS compared to those without HU based on MS criteria defined by the American Heart Association/National Institute of Heart, Lungs and Blood. In two other studies, the average level of serum UA in patients with MS was approximately 0.5-1.0 mg/dL higher than controls. In addition, another study showed that serum UA levels increased with the number of components of MS after adjusting for age, sex, creatinine clearance, and the use of alcohol/diuretic. Recently, HU is recognized as a distinct feature and/or major associated factor of MS [12-15].

The aim of this study was to characterize of specific dysmetabolic changes and features of extraarticular evolution in patients with gout.

Material and methods

A descriptive study was conducted, and 501 patients with gout were included. There were 423 males and 78 females in the study. The mean age of gout debut was 49.2 (36.9; 59.9). The study was carried out in accordance with the requirements of the Ministry of Health for „Clinical and financial-economic research" within the postdoctoral scientific program at the *Nicolae Testemițanu* State University of Medicine and Pharmacy of the Republic of Moldova, Department of Internal Medicine, Discipline of rheumatology and nephrology. The patients were separated into two groups, depending on their age when gout debuted: ≤59 years (group I, 233 subjects) and the age of onset ≥60 years (group II, 268 subjects).

From the electronic medical records of the Departments of Arthrology, Rheumatology and Nephrology of the Republican Clinical Hospital „Timofei Moșneaga" were extracted the clinical, laboratory and treatment data points on 693 patients with gout hospitalized between 2015-2022. Of the 693 patients, 501 met the including criteria and were selected for the statistical processing. The diagnosis of gout in the database was carried out in accordance with the classification criteria for gout according to ACR/EULAR 2015 [12]. The raw data was processed in SPSS version 26.0.

Results

Metabolic syndrome - a complex of metabolic, hormonal, and clinical disorders associated with atherosclerosis, is detected in most of our patients with gout, but in a higher frequency among those with chronic tophaceous gout. Thus, our study showed that the frequency of MS in patients with tophaceous gout is 1.6 – 2.8 times higher than in the population, reaching 65% in people over 60 years of age. The main components of MS currently include abdominal obesity, impaired lipid (Table 1, Figures 1-5) and carbohydrates metabolism (Figure 6), hypertension and insulin resistance. The frequency of detection of individual components of MS in patients with gout is also quite high and made it possible to diagnose MS in 68% of cases, insulin resistance in – 67%, diabetes mellitus type 2 – in 18% and hypertension – in almost 80%.

The analysis of our study included results from 268 patients who were >60 years, had a chronic course of gouty arthritis and poor drug control. Tophi, a classical characteristic of chronic gout, was present in 27.6% cases (74 patients), and absent in 72.4% cases (194 patients).

Thus, according to our data, in patients with tophaceous gout, the severity of obesity and LDL-cholesterol (including cholesterol) was higher, while HDL-cholesterol was lower, causing an increase in the frequency of high blood pressure and type 2 diabetes, with age differences in the frequency of detection of MS and insulin resistance. The independent association between insulin resistance and MS prevalence is confirmed by many studies [16]. Therefore, the data from the literature, have noted that serum levels of UA correlated with the risk of developing both MS and its components – obesity, hypertension, and dyslipidemia, but inversely correlated with hyperglycemia (Figure 1) [17, 18].

The prevalence of MS in patients with gouty chronic arthritis was 30%-42% according to NCEP ATP III guidelines and 50%-59% according to WHO obesity criteria, both of

which were significantly higher than normal control groups. These findings showed a concomitant increase of prevalence of MS and gout and suggested that the two diseases are related [19-22].

Table 1. Values of the basic components of metabolic syndrome

		Tophus	
		Not present	Present
Total cholesterol	*Minimum, Maximum*	2.10; 72.60	3.10; 8.00
	Mean	5.42	5.21
	Standard Deviation	3.71	0.89
	Median	5.20	5.20
	Percentile 25	4.60	4.70
	Percentile 75	5.80	5.80
HDL-cholesterol	*Minimum, Maximum*	0.26; 1.60	0.42; 1.45
	Mean	1.00	0.91
	Standard Deviation	0.25	0.20
	Median	0.98	0.85
	Percentile 25	0.81	0.79
	Percentile 75	1.20	1.02
LDL-cholesterol	*Minimum, Maximum*	1.99; 6.90	2.18; 6.90
	Mean	4.60	4.91
	Standard Deviation	0.87	.86
	Median	4.70	4.90
	Percentile 25	3.90	4.50
	Percentile 75	5.20	5.40
Triglycerides	*Minimum, Maximum*	0.47; 5.90	0.80; 12.40
	Mean	2.48	2.52
	Standard Deviation	0.99	1.22
	Median	2.10	2.20
	Percentile 25	1.80	1.90
	Percentile 75	3.30	2.70
Uric acid in serum	*Minimum, Maximum*	81.00; 747.00	160.00; 797.00
	Mean	432.70	480.02
	Standard Deviation	119.96	117.64
	Median	437.00	480.00
	Percentile 25	345.00	418.30
	Percentile 75	506.50	559.00
Hemoglobin A1C	*Minimum, Maximum*	0.90; 58.30	0.40; 10.50
	Mean	6.29	5.99
	Standard Deviation	3.83	1.18
	Median	5.90	6.00
	Percentile 25	5.20	5.30
	Percentile 75	6.80	6.40

Note: HDL-cholesterol – high-density lipoprotein; LDL-cholesterol – low-density lipoprotein.

The values of the main clinical and laboratory indicators of blood (glucose, UA, creatinine) exceeded the normal and showed significant differences in groups with predominance in those with chronic tophaceous gout. Indicators of lipid metabolism also had significant differences in groups: cholesterol, TG, LDL-C levels were higher, and HDL-cholesterol was below the optimal values in those with tophi. Hyperuricemia was detected in 2/3 of the patients in both groups (65% and 66%).

It was found that five metabolic risk factors have significant or moderately significant correlations with the UA levels in the general group, as demonstrated in Figures 1-6.

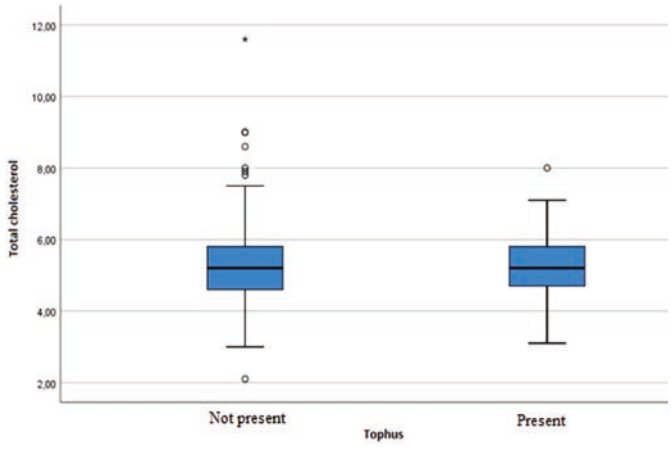

Fig. 1 Interdependence of the values of total cholesterol (mmol/L) and the presence of tophus

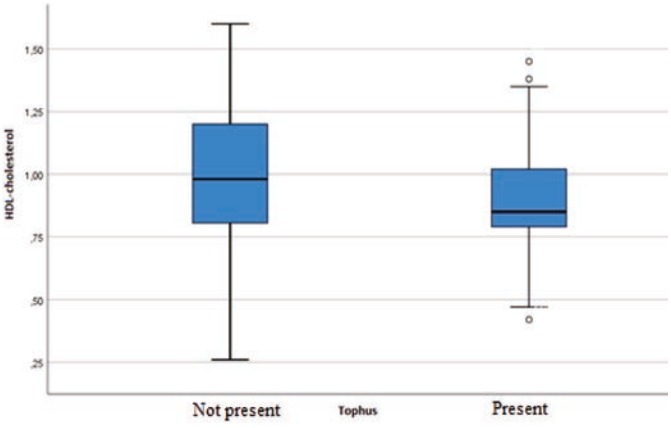

Fig. 2 Interdependence of HDL-cholesterol (mmol/L) values and the presence of tophus

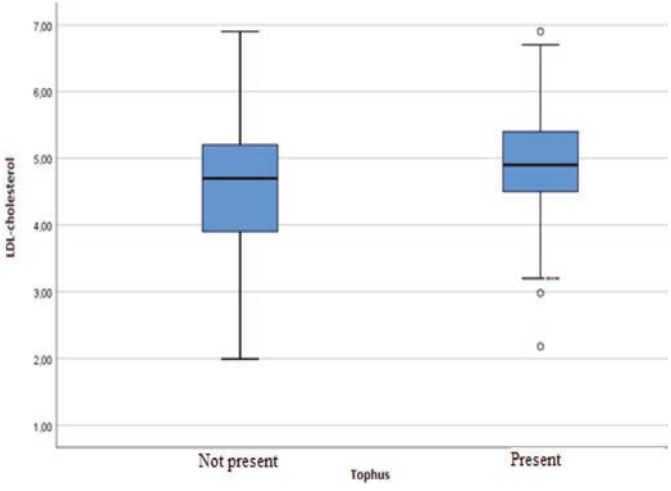

Fig. 3 Interdependence of LDL-cholesterol (mmol/L) values and the presence of tophus

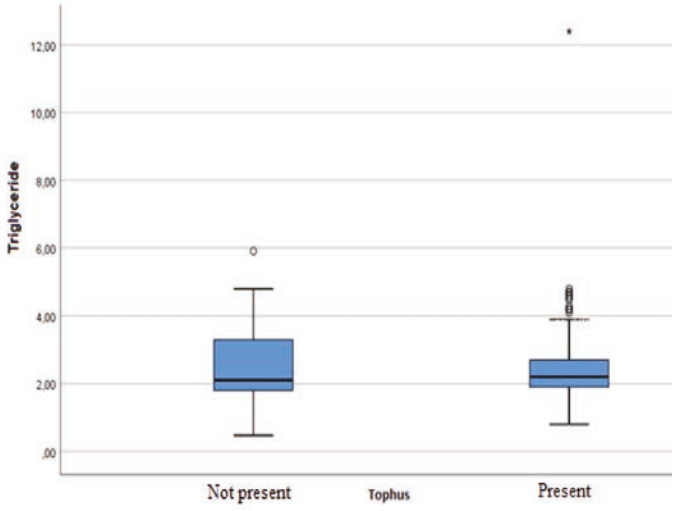

Fig. 4 Interdependence of triglyceride (mmol/L) values and the presence of tophus

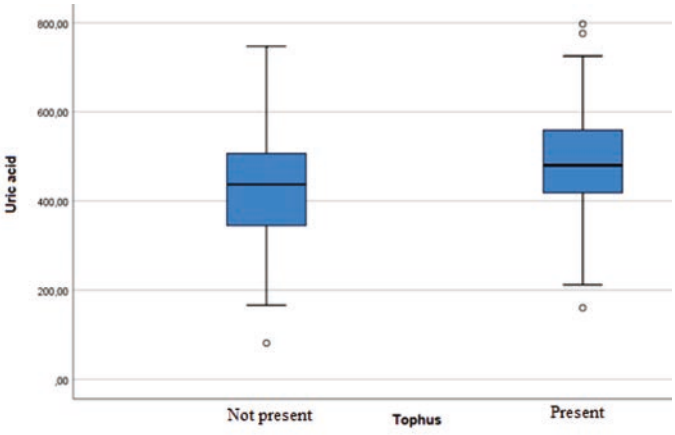

Fig. 5. Interdependence of uric acid values (mmol/L) and the presence of tophus

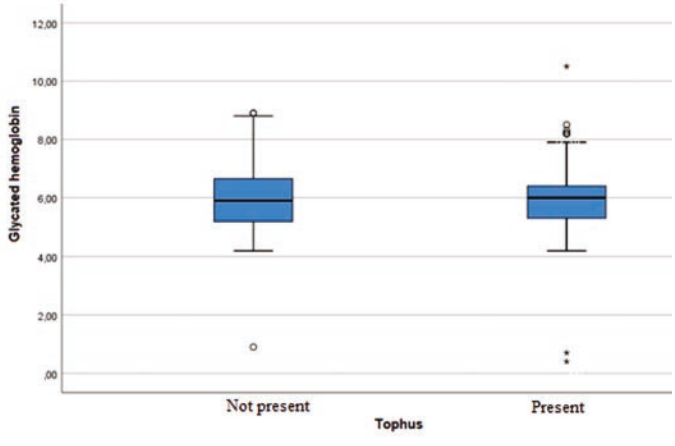

Fig. 6 Interdependence of glycated hemoglobin (%) values and the presence of tophus

In people without metabolic syndrome, uric acid levels did not exceed the upper reference value, except for fasting blood glucose (p = 0.146). In people with metabolic syndrome, it was found that the levels of glucose, triglycerides, HDL and waist circumference have a slight or moderate correlation, while blood pressure did not give such a correlation with uric acid [21]. The effectiveness of non-pharmacological measures to reduce the level of hyperlipidemia is confirmed by reducing the values of total cholesterol and LDL-cholesterol, but it does not have a significant rate.

Discussions

The prevalence of MS and hyperuricemia/gout has steadily increased. There are data on the epidemiology of gout and hyperuricemia in US adults in NHANES-III (1988-1994) and NHANES 2007-2008 that show that the prevalence of these conditions is substantial and has increased over the past two decades. In addition, the prevalence of MS has been shown to steadily increase according to the data from NHANES-III and NHANES 1999-2006 in the US population. Similarly, in the Korean population over the age of 20, scientists have demonstrated that MS's prevalence has gradually increased from 24.9% in 1998 to 31.3% in 2007. Several clinical studies showed a higher prevalence of MS in patients with gout compared to the general population [22].

In 2022, a few researchers studied the relationship of metabolic syndrome and gout, for an average of 7.4±1.2 years. 88 058 men with gout were examined. The incidence of gout was 3.36 per 1000 people. It has been found that gout in people with MS develops 2 times more often. Of all the components of MS, abdominal obesity came out on the first place; increased TG was in second place [23]. In a large cross-sectional study conducted in NHANES-III, the prevalence of MS in people with gout was 62.8% vs. 25.4% among people without gout according to age and gender [24]807 participants age >or=20 years in the Third National Health and Nutrition Examination Survey (1988-1994.

An analysis carried out in the ARIC study provides similar data for women. A total of 6263 women between the ages of 45 and 64, with no history of gout before inclusion in the study, were tracked for 9 years, identifying 106 cases of incident gout. Compared to women with a BMI <25 kg/m^2 at the baseline, the adjusted relative risk of gout was 1.63. In women with BMI 25–29.9 kg/m^2 and BMI ≥30 kg/m^2 at age 25 years, multivariate relative risks for gout were 3.36 and 2.84, respectively, compared to those with BMI <25 kg/m^2 at age 25 years. Women with the highest weight gain indicator (≥16.3 kg) from the age of 25 to the initial age had a 2 times higher risk of gout compared to people in the lowest indicator [25].

In the case study of the THIN database, persons with a BMI between 25-29 kg/m^2 had relative risk of 1.62 for gout and those with BMI of ≥30 kg/m^2, a relative risk of 2.34. With a BMI of 21-22.9 kg/m^2, the relative risk of gout in men was RR 0.85 in those with BMI <21 kg/m^2, increasing to a relative risk of 1.40 in those with BMI 23-24.9 kg/m^2, RR 1.95 with BMI 25-29.9 kg/m^2, RR 2.33 with BMI 30-34.9 kg/

m^2 and RR 2.97 with BMI ≥ 35 kg/m^2 [25]. In addition, the risk of the incidence of gout was increased in men who added 20-29 kg and ≥30 kg in weight from the age of 21, compared to those whose weight was stable. In contrast, weight loss of 10 kg or more reduced the risk of gout by 39% [26].

Although hyperglycemia and IR are recognized components of MS, the role of DM type 2 as a risk factor for the development of gout has received relatively little attention. Interestingly, in the case study THIN *database-control*, people with DM type 2 had a 33% lower risk of developing gout than those without DM type 2 (RR 0.67) [5, 19, 27]. This finding was more marked in men than in women. The risk of developing gout reduced with increased duration DM type 2: duration 0-3 years RR 0.81, 4-9 years RR 0.67, and 10 years or more RR 0.52. The risk was also lower for DM type 1 than for DM type2. Although these findings may seem counter-intuitive, the predisposition to HU and gout induced by hyperinsulinemia and IR in the pre-diabetic state is considered to be reversed by the uricosuric effects of glycosuria once DM type 2 complications develop [2, 17, 28].

Thus, the incidence of metabolic syndrome is 2 times higher in people with tophaceous gout compared without it (33.6% and 15.9%, respectively, after adjusting according to age, $p < 0.001$). This indicator increases with age, and after 60 years, MS occurs in 47.6% of those suffering from gout, which is 2 times more common than in people who do not suffer from gout of the same age (23.8%). Since MS increases the risk of atherosclerotic cardiovascular disease and DM type 2, its presence significantly aggravates the comorbid background, complicates treatment and worsens the prognosis for gout [23, 28].

Conclusions

Gout is associated with a severe lipid metabolism dysfunction, significantly increasing the rate of metabolic syndrome especially among patients with chronic tophaceous gout, than in the group of patients with gout under the age of 59 years. On the other hand, in patients with the onset of gout who are ≤59 years lipid metabolism disorders occur significantly earlier than in patients with the onset of gout at the age of ≥60 years ($p < 0.05$).

Abbreviations

BMI – body mass index, DM – diabetes mellitus, HU – hyperuricemia, IR – insulin resistance, RR – relative risk; MS – metabolic syndrome, MUS – mono-urate of sodium, NCEP ATP III – National Adult Cholesterol Education Program Treatment Panel III, NHANES – National Health and Nutrition Review Study, UA – uric acid.

Declaration of conflict of interest

Nothing to declare.

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