

# Study Upon the Serum Level of Uric Acid and the Metabolic Syndrome Components

MARIA RADA<sup>1#</sup>, DELIA BERCEANU-VADUVA<sup>1\*</sup>, MILAN VELIMIROVICI<sup>2#</sup>, SIMONA DRAGAN<sup>1</sup>, DANIEL DUDA-SEIMAN<sup>1</sup>, MARCEL BERCEANU-VADUVA<sup>1\*</sup>, CORINA DUDA-SEIMAN<sup>3</sup>, MARIANA TUDORAN<sup>1</sup>, DANA VELIMIROVICI<sup>1</sup>

<sup>1</sup> University of Medicine and Pharmacy Victor Babes, Faculty of Medicine, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

<sup>2</sup> Clinical Emergency Children's Hospital Louis Turcanu, 2 Dr. Iosif Nemoianu Str., 300011, Timisoara, Romania

<sup>3</sup> West University of Timisoara, Faculty of Chemistry, Biology, Geography, 16 Pestalozzi Blvd., 300115, Timisoara, Romania

*The serum level of uric acid (UA) appears to be associated with a variety of cardiometabolic risk factors; however, direct association with the metabolic syndrome (MetS) remains controversial. The aim of this study is to investigate the association between serum levels of UA and the components that define MetS, differentiated by gender. 262 patients were enrolled (132 women and 130 men); mean value of the age: 58.7±16 year. Hyperuricemia was considered when the level of serum UA ≥7mg/dL in men, and ≥6mg/dL in women; MetS was defined according to the IDF criteria. The prevalence of MetS in the studied group was 35.11% and the prevalence of hyperuricemia was 16.79%. Men with hyperuricemia had the highest prevalence of abdominal obesity (87.5% vs. 66.32%, p <0.001) and hypertriglyceridemia (65.62% vs. 45.91%, p <0.001) versus men with normal level of serum UA. Women with hyperuricemia also had a significantly higher incidence of abdominal obesity (75% vs. 57.51%, p <0.001), hypertriglyceridemia (58.33% vs. 38.33%, p <0.001), decreased HDL (50% vs. 33.33%, p <0.001) and hyperglycemia (66.66% versus 50%, p <0.001) compared to those with normal levels of serum UA. The majority of men with hyperuricemia have more than 4 of the MetS components. Hyperuricemia had a higher prevalence in patients with MetS, it may be considered as a causal factor of MetS. Elevated levels of serum uric acid were significantly more associated with the increasing number of MetS components. Early detection and treatment of hyperuricemia is essential for preventing the metabolic syndrome and its complications.*

**Keywords:** uric acid, metabolic syndrome, components, cardiovascular disease

Hyperuricemia and metabolic syndrome (MetS) are very common disorders in many countries, being considered risk factors for cardiovascular disease [1]. The prevalence of MetS and hyperuricemia is high among most populations. In the NHANES study (2003-2006), MetS prevalence was approximately 34% in adults over 20 years with elevated serum uric acid [2]. The same NHANES study conducted in 2007-2008 reveals a prevalence of hyperuricemia of 21.6% in women and in men of 21.2% [3].

Uric acid is a final enzyme product of purine metabolism in humans, suggesting that hyperuricemia is associated with MetS, and they may have common pathophysiology [4]. The renal clearance of urate is inversely proportional to the degree of insulin resistance. Thus, reduced kidney excretion in patients with MetS may explain the increased frequency of hyperuricemia. Based on these considerations, hyperuricemia was suggested as a marker of MetS [5].

In addition to classical conditions that lead to elevated serum uric acid levels, local ischemia is the mechanism that could explain the relationship between serum uric acid and cardiovascular pathology. It is possible that free radicals production, due to ischemic transformation of hypoxanthine or of xanthine via the xanthineoxidase (XOD) pathway, is actually responsible for vascular lesions when increased levels of uric acid are registered.

This would also explain the apparent dual effect of uric acid (as antioxidant/prooxidant), defined as *uric acid paradox*: on the one hand experimental studies prove the antioxidant effect of the uric acid molecule, and, on the other side, the high serum uric acid level is related to pro-inflammatory effects: decreased nitric oxide synthesis at vascular level, activation of the renin-angiotensin-aldosterone system, renal microvascular disorder (arteriosclerosis) [6].

MetS is defined by a group of risk factors, including central obesity, dyslipidemia, hypertension and insulin resistance. The aggregation of these factors increases the risk of developing cardiovascular disease and diabetes. Because these risk factors can not entirely explain the cardiovascular events occurring in subjects with MetS, other risk factors such as inflammatory markers, microalbuminuria, hyperuricemia and clotting disorders are considered to be included in the MetS definition [7]. Recently, hyperuricemia has been included as a cardiovascular risk factor in the latest hypertension guideline of the European Society of Cardiology [8].

The global prevalence of MetS varies largely from <10% to 84%, depending on region, gender, age and ethnicity, also underlined in Kaur's study [9].

There is increasing epidemiological evidence suggesting that MetS is associated with an increased risk of cardiovascular disease [10-14], diabetes [15], neoplasia [16] and even osteoporosis [17], MetS thus becoming a public health issue worldwide.

Despite epidemiological research demonstrating a positive relationship between serum uric acid level and MetS prevalence, prospective data on serum uric acid as a predictor of MetS prevalence and correlation of its level with MetS components are limited, motivating this study [18-20]. The primary objective of this study is to evaluate the association between serum uric acid and metabolic syndrome components.

## Experimental part

### Material and method

262 patients (132 women and 130 men), median age 58.7 ± 16 years, selected from patients with cardiovascular risk factors (Timisoara Circumvalatiunii Polyclinic) were included in the study. Patients were divided into two groups:

\* email: deliaberceanu@yahoo.com; berceanumarcel@gmail.com

# Authors with equal contribution

those with non-SMET criteria and, respectively, those meeting the International Diabetes Foundation (IDF) definition criteria for *MetS*: abdominal circumference  $\geq 94$  cm for men and  $\geq 80$  cm for women or BMI  $\geq 25$  kg / m<sup>2</sup>; TG  $\geq 150$  mg / dL or specific treatment for this type of dyslipidemia; HDL-cholesterol  $< 40$  mg / dL in men and  $< 50$  mg / dL in women or specific treatment for this type of dyslipidemia; TA  $\geq 130/85$  mmHg or HTA treatment previously diagnosed; glycemia  $\geq 100$  mg / dL or type 2 diabetes diagnosed previously [21].

*Hyperuricemia* was defined as serum uric acid (AU)  $\geq 7$ mg / dL in men and  $\geq 6$ mg / dL in women according to the European League Against Rheumatism Guide (EULAR) [22].

#### Anthropometric and laboratory measurements

The *waist circumference* was measured at the level of umbilical scarring. Abdominal obesity was defined at  $\geq 94$ cm for men and  $\geq 80$ cm for women respectively. The Body Mass Index (BMI) was calculated and used to classify overweight and obesity in accordance with World Health Organization recommendations. We calculated the BMI as weight (kg) / height (m<sup>2</sup>). Based on BMI values, patients were in normal range (BMI  $< 25$  kg / m<sup>2</sup>), overweight (IMC 25-29.99 kg / m<sup>2</sup>) and obese (BMI  $\geq 30$  kg / m<sup>2</sup>) [23].

*Blood pressure (BP)* was measured by means of a strain gauge, with the patient sitting after at least 5 min and before taking blood samples.

*Biochemical markers* defining the metabolic syndrome were determined in accordance with their standardized protocols.

*Fasting glycemia, serum uric acid, lipid profile* including total serum cholesterol (HD), HDL-c (high-density lipoprotein cholesterol), LDL-c and triglycerides (TG) have been evaluated.

*Glucose* is a monosaccharide with formula C<sub>6</sub>H<sub>12</sub>O<sub>6</sub> or H-(C=O)-(CHOH)<sub>5</sub>-H, whose five hydroxyl (OH) groups are arranged in a specific way along its six-carbon back.

*Uric acid* is a heterocyclic compound of carbon, nitrogen, oxygen, and hydrogen with the formula C<sub>5</sub>H<sub>4</sub>N<sub>4</sub>O<sub>3</sub>.

*Triglycerides* are lipid fractions, formed by combining glycerol with three fatty acid molecules. Alcohols have a *hydroxyl (HO)-group*. Organic acids have a *carboxyl (-COOH) group*. Alcohols and organic acids join to form esters. The glycerol molecule has three hydroxyl (-OH) groups. Each fatty acid has a carboxyl group (-COOH). In triglycerides, the hydroxyl groups of the glycerol join the carboxyl groups of the fatty acid to form ester bonds:



Another lipid fraction who plays an important role in the atherosclerotic process is *HDL -cholesterol*. HDL is one of the five major groups of lipoproteins, the smallest, which transport lipid around the body. Lipoproteins have central core of a hydrophobic lipid, encased in a hydrophilic coat of polar phospholipid, free cholesterol and apolipoprotein [24].

These biological parameters were taken from the analysis bulletins which patients showed at the time of clinical evaluation. Patients with a history of diabetes, dyslipidemia, hypertension or treatment for these conditions previously diagnosed were included in the study.

#### Exclusion criteria:

- patients under the age of 18 years
- patients with not determined waist circumference or BMI

- patients who did not have a determined level of serum uric acid, fasting glucose and lipid levels
- alcoholic and non-cooperative patients
- patients undergoing care therapy could affect the value of the parameters analyzed
- presence of other chronic conditions (inherited or non-invasive atherothrombotic cardiovascular disease, malignant tumors, thyroid disorders, renal or hepatic impairment) that may have an effect on the analyzed parameters
- patients who refused to be included in the study.

#### Statistical processing

All the data was analyzed by the SPSS software and basic parameter was compared using ANOVA test and chi square and p value was calculated; p < 0.05 values were considered statistically significant.

#### Results and discussions

The general characteristics of the 262 patients included in the study are presented in table 1.

**Table 1**  
CHARACTERISTICS OF PATIENTS

Parameters	Mean $\pm$ DS/Procent (262 patients)
Age (years)	58.7 $\pm$ 16 years
Gender M/F (n) (%)	130/132 49.62/50.38
BMI (kg/m <sup>2</sup> )	29.7 $\pm$ 6
Waist circumference (cm)	98.1 $\pm$ 15.70
Triglycerides (mg/dL)	167.2 $\pm$ 43.67
HDLc (mg/dL)	43.68 $\pm$ 10
Fasting plasma glucose (mg/dL)	94.18 $\pm$ 23.81
SBP (mmHg)	134.07 $\pm$ 17.83
DBP (mmHg)	85.39 $\pm$ 11.25
Uric acid level (mg/dL)	5.22 $\pm$ 1.5

Of the 262 patients enrolled in the study, 132 (50.38%) were females, and 130 (49.62%) of the patients were male. The distribution of the batch included in the study by gender is illustrated in figure 1.

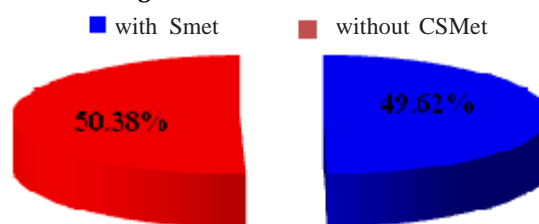


Fig. 1. Batch distribution by gender

The mean age of patients enrolled in the study was 58.7  $\pm$  16 years, with patients under the age of 18 being excluded from the study.

Of the 262 patients enrolled in the study, 92 patients met the IDF criteria for defining the metabolic syndrome, so the *MetS* prevalence was 35.11%, a percentage comparable to the literature data where its prevalence was ranged between 30.1 and 39.3%, [25, 26]. The data is shown in figure 2.

IDF estimates that approximately 20-25% of the adult population can be enrolled in *MetS* (www.idf.org), leading to an increase in the frequency and severity of cardiovascular diseases [27]. *MetS* affects approximately 25% of the general population, and about two-thirds of *MetS* patients are predisposed to cardiovascular events.

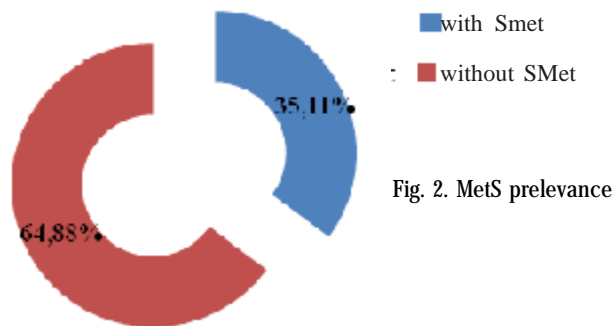


Fig. 2. MetS prevalence

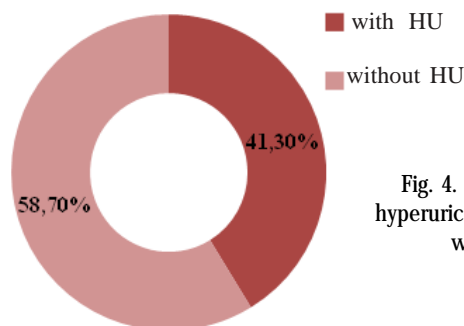


Fig. 4. Prevalence of hyperuricemia in patients with MetS

The MetS prevalence in the studied group was higher than that reported by IDF. Data from recently published studies indicate a higher prevalence of MetS of 50.64% [28] and 35.44% respectively [29].

Clinical studies have shown that serum uric acid levels are commonly associated with subclinical atherosclerosis, especially in men with type 2 diabetes. Hyperuricemia has also been shown to be an independent predictor for atherosclerosis in hypertensive patients [30, 31].

Another objective was to determine the prevalence of hyperuricemia (UA  $\geq 7$  mg/dL in men and  $\geq 6$  mg/dL in women) in the studied group and its prevalence in patients with and without MetS.

The prevalence of hyperuricemia among the patients enrolled in the study was 16.79%, as shown in figure 3.

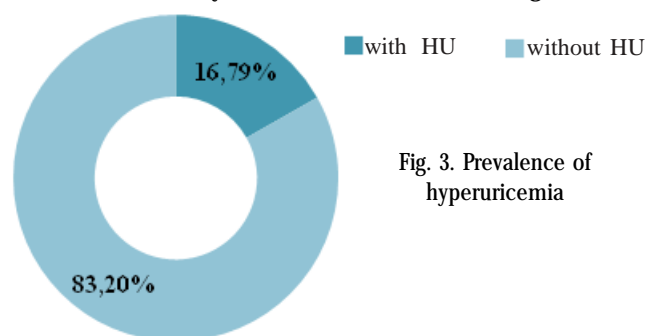


Fig. 3. Prevalence of hyperuricemia

In the study of Wang and colleagues, the prevalence of hyperuricemia (HU) has been shown to increase with age, 16.7% of the population included in the study (age > 60 years) recorded increased UA levels [32].

Of the 92 patients who met MetS criteria, 38 patients also had increased UA levels, and in 54 patients the serum uric acid values were normal, so the hyperuricemia prevalence in MetS patients was 41.30%, as shown in figure 4.

Tables 2 and 3 present the prevalence of MetS and its components in patients with and without hyperuricemia, according to gender.

In men, among the components defining MetS, statistically significant differences were noted in central obesity and hypertriglyceridemia.

Central obesity was commonly associated with hyperuricemia, with a prevalence of 87.5% in HU men, whereas in those with normal uric acid the prevalence was lower, 66.32%, with statistically significant difference,  $p < 0.001$ .

Clinical trials have reported that there are significant associations between HU and visceral or central obesity, increased BMI, triglycerides and vascular endothelial dysfunction [33].

The association between serum triglycerides and uric acid resides in the fact that the synthesis of fatty acids in the liver is associated with de novo purine synthesis and accelerated uric acid production [28].

In the current study, 65.62% of male patients with hyperuricemia also associated hypertriglyceridemia, whereas in those with normal uric acid levels, hypertriglyceridemia was present in 45.91% of patients.

Hyperuricemia and hypertriglyceridemia reflect the patient's lifestyle more than genetic factors, because obesity is also associated with these features.

Considering other MetS components (low HDL, BP  $\geq 130/85$  mmHg or hypertension, fasting plasma glucose  $\geq 100$  mg/dL or type 2 diabetes), there were no significant differences between the patients in the HU group compared to the non-HU group, as shown in table 2.

In women, statistically significant differences were noted for the following components: central obesity, hypertriglyceridemia, low HDL and fasting plasma glucose  $\geq 100$  mg/dL or type 2 diabetes, as shown in table 3.

Central obesity in women, as well as in men, was commonly associated with hyperuricemia, with 75%

	Hyperuricemia n=44	Without hyperuricemia n=218	P value
<b>Men (n=130)</b>	<b>n=32</b>	<b>n=98</b>	
<b>MetS components</b>			
Central obesity	28 (87.5%)	65 (66.32%)	< 0.001
Hypertriglyceridemia	21 (65.62%)	45 (45.91%)	< 0.001
Low HDL	12 (37.5%)	31 (31.63%)	ns
BP $\geq 130/85$ mmHg or hypertension	27 (84.37%)	80 (81.63%)	ns
Fasting plasma glucose $\geq 100$ mg/dL or type 2 diabetes	19 (59.37%)	54 (55.10%)	ns
<b>Number of MetS components</b>			
$\geq 1$	31 (96.87%)	92 (93.87%)	ns
$\geq 2$	28 (87.50%)	73 (74.48%)	ns
$\geq 3$	21 (65.6%)	46 (46.93%)	ns
$\geq 4$	13 (40.62%)	18 (18.36%)	< 0,001
5	6 (18.75%)	9 (9.18%)	ns

Table 2  
PREVALENCE OF MetS COMPONENTS IN MEN WITH AND WITHOUT HU

	Hyperuricemia n=44	Without hyperuricemia n=218	P value
Women (n=132)	n=12	n=120	
<b>MetS components</b>			
Central obesity	9 (75%)	69 (57.5%)	< 0.001
Hypertriglyceridemia	7 (58.33%)	46 (38.33%)	< 0.001
Low HDL	6 (50%)	40 (33.33%)	< 0.001
BP $\geq$ 130/85 mmHg or hypertension	10 (83.33%)	98 (81.66%)	ns
Fasting plasma glucose $\geq$ 100 mg/dL or type 2 diabetes	8 (66.66%)	60 (50%)	< 0.001
<b>Number of MetS components</b>			
$\geq$ 1	12 (100%)	114 (95%)	ns
$\geq$ 2	11 (91.66%)	101 (84.16%)	ns
$\geq$ 3	10 (83.33%)	74 (61.66%)	< 0.001
$\geq$ 4	8 (66.66%)	44 (36.66%)	< 0.001
$\geq$ 5	2 (16.66%)	17 (14.16%)	ns

**Table 3**  
PREVALENCE OF MetS COMPONENTS IN WOMEN WITH AND WITHOUT HU

prevalence in HU, whereas in those with normal values its prevalence was much lower 57.5% ( $p < 0.001$ ).

Literature data shows that, when considering the relation between obesity and uric acid serum level, only the waist circumference remained significantly positive associated with hyperuricemia. Serum uric acid levels are significantly higher in subjects with MetS and obesity compared to overweight and normoponderal patients [28].

In the current study, 58.33% of women with hyperuricemia associated *hypertriglyceridemia*, whereas in those with normal uric acid hypertriglyceridemia was present in only 38.33% of patients, as shown in table 3.

Gender is clearly an important factor in the relationship between hyperuricemia and MetS. Women with hyperuricemia had a higher prevalence of hypertriglyceridemia and HDL decrease, as well as a significant increase in cardiovascular morbidity and mortality compared to men with hyperuricaemia.

The prevalence of women with *low HDL cholesterol* was higher in those who associated increased serum uric acid levels compared to those with a normal value (50% versus 33.33%).

Prevalence of *fasting plasma glucose  $\geq$  100 mg/dL or type 2 diabetes* in women with HU was 66.66% compared to 50% in those with normal uric acid values (statistically significant difference  $p < 0.001$ ). The patients in the present study expressed a change in carbohydrate metabolism, especially those with hyperuricemia. In contrast, no significant statistic difference was found in men, this is probably due to the fact that, especially in diabetics, hyperglycemia may increase uric acid renal excretion, which leads to decreased serum uric acid levels.

*BP  $\geq$  130/85 mmHg or hypertension*, another component of MetS, although it was common ( $> 80\%$  of patients included in the study) in both men and women, the prevalence did not differ significantly in patients with and without hyperuricemia.

The prevalence of MetS and its components was higher in HU patients compared to non-HU in both genders. The number of MetS components increases significantly with the increase of serum uric acid.

As shown in table 2, the number of male patients with hyperuricemia and  $\geq 4$  components was significantly higher (40.62%) compared to those who had a normal serum uric acid value and the same number of components (18.36%).

Female gender shows an increase share of both 3 and 4 components of MetS (table 3). The prevalence of those with  $\geq 3$  components of MetS was 83.33% and the  $\geq 4$  components were 66.66%. It follows that the percentage

of HU patients and 4 components of MetS was significantly lower compared to those with HU and 3 components of MetS.

Data from literature showed that elevated serum uric acid levels were significantly more associated with the increase in the number of MetS components [26, 32, 33].

### Conclusions

The prevalence of hyperuricemia is increasing in recent decades, which is why it should be considered as a component of metabolic syndrome and a risk factor for cardiovascular disease.

Hyperuricemia is frequently associated with metabolic syndrome, which is also a major predictor of cardiovascular disease. The prevalence of hyperuricemia is higher in patients with metabolic syndrome, thus being considered a causal factor.

Increased serum concentrations of uric acid were significantly more associated with the increase in the number of components of the metabolic syndrome. Early detection and treatment of hyperuricemia is essential to prevent the onset of metabolic syndrome and its complications, and it is associated with an increased risk of cardiovascular disease.

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