Study Regarding the Serum Level of Uric Acid and the Metabolic Syndrome

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The goal of this study is to investigate the relationship between the serum level of uric acid (UA) and metabolic syndrome (MetS) according to age and gender. The study included 395 patients (200 women and 195 men), with a mean age of 53.6±18 years. Hyperucemia (HU) was defined by a serum level UA ≥7mg/ dL in men and ≥ 6mg/dL in women (according to the EULAR guide), and MetS was defined according to the criteria of the International Diabetes Federation (IDF). The prevalence of hyperuricemia in the study lot was 17.21%, and MetS was 35.44%. In women, the prevalence of HU and MetS increases with age: 13.88% of women over 65 years show HU, and 44.44% of them comprise the elements of MetS. In men, HU and MetS do not vary significantly depending on age. MetS has a higher prevalence in HU patients than in HU-free patients. HU prevalence in MetS patients was 32.65% in women versus 46.15% in men. In conclusions, the prevalence of HU and MetS differs significantly according to gender and age. The prevalence of MetS was higher in male subjects of medium age and HU did not vary significantly depending on age. In women, the prevalence of HU and MetS was higher in those over 65 years. Hyperuricemia in middle-aged female patients can predict the MetS development.

Keywords: hyperuricemia, metabolic syndrome, age, gender, prevalence

Hyperuricaemia is a metabolic disorder characterized by increased blood levels of monosodium urate (salt of uric acid) due to the disruption of purine metabolism. Uric acid (UA) is the ultimate product of human purine metabolism and is primarily generated (approximately 2/3) by the enzymatic metabolism of endogenous purines (phosphoribosyl-pyrophosphate-synthase, hypoxanthine-guanine-phosphoribosyl-transferase, xanthineoxidase), and secondary (approximately 1/3) of the purine food intake. Uric acid overproduction can occur in the following situations: excessive catabolism of nucleic acids (gout), mass production and destruction of cells (leukemia) or inability to excrete the final product (renal failure) [1, 2].

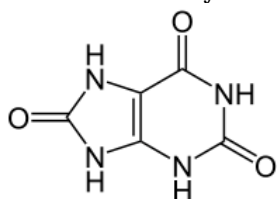Uric acid is a heterocyclic compound: $C_5H_4N_4O_3$.(fig. 1).

Fig. 1. Uric acid

For many years, uric acid has been regarded as a metabolically inert substance. However, there is increased evidence that uric acid has several actions that impact cellular metabolism. Thus, uric acid can behave as an endogenous antioxidant and a powerful collector of reactive oxygen species and hydroxyl radicals. Uric acid reacts with peroxynitrite and stabilizes nitric oxide synthase endothelial activity (eNOS) [3].

Its chemical limitations include the fact that uric acid can have antioxidant effect only in the presence of plasma ascorbic acid. In the absence of this, uric acid behaves paradoxically as a pro-oxidant and as an inflammatory factor. Uric acid works differently in the intra-cellular environment over the extracellular environment, where it is present in a soluble form. Although in extracellular fluids uric acid has a strong antioxidant effect, in the intra-cellular environment it exerts nicotinamide-adenine-derived nicotinamide-adductin-mediated nicotinamide-oxidase (NADPH oxidase) mediated prooxidation effects [3].

In recent years, a number of evidence suggests that hyperuricemia may play a role in the development and pathogenesis of an increased number of metabolic diseases, including metabolic syndrome, hypertension, stroke and atherosclerosis. Hyperuricemia is generally a part of the group of metabolic and hemodynamic abnormalities, including abdominal obesity, glucose intolerance, insulin resistance, dyslipidemia and hypertension, all of which are often found under the term *metabolic syndrome* [4].

Although the role of hyperuricemia in cardiovascular and renal disease remains controversial, the results of recent studies show a strong relationship between elevated serum uric acid levels and the presence of metabolic syndrome. Not only associated, but also individually, hypertension, obesity, dyslipidemia, hyperglycemia and insulin resistance are positively correlated with serum levels of uric acid [5-9].

Hyperuricemia and the risk for metabolic syndrome (MetS) may vary depending on age and gender. Although hyperuricemia is generally considered to be a strong and independent predictor of MetS in both genders, a clear correlation has not been established. Despite epidemiological research demonstrating a positive relationship between the UA serum levels and MetS prevalence, prospective serum uric acid levels as a predictor of MetS prevalence are limited.

The purpose of this study is to investigate the relationship between serum uric acid (UA) and metabolic syndrome (MetS), differentiated by age and gender.

Experimental part
Material and method

395 patients with cardiovascular risk factors were selected for cardiology consultations or outpatient internal medicine (Timisoara Circumvalatiunii Polyclinic) during 2016-2017, where waist circumference, body mass index (BMI) and blood pressure (BP) values were determined. It should be noted that the biological parameters (lipid profile, blood glucose levels, serum uric acid level) were noted on the analysis bulletins with which the patients presented at the consultation or were recommended to be performed by the treating physician. Biological parameters were determined in the same lab. Patients with a history of diabetes, dyslipidemia, hypertension, or treatment for these conditions previously diagnosed were included in the study.

Hyperuricemia has been defined as serum uric acid (UA) $\geq$ 7mg/dL in men and $\geq$ 6mg/dL in women according to the European League Against Rheumatism Guide (EULAR) [10].

Metabolic Syndrome (MetS) was defined according to the International Diabetes Federation (IDF) criteria [11]:

-abdominal circumference > 94cm in men and > 80cm in women, or BMI $\geq$ 25 kg/m^2;

-TG $\geq$ 150 mg/dL or specific treatment for this type of dyslipidemia;

-HDL- cholesterol < 40mg/dL in men and < 50mg / dL in women or specific treatment for this type of dyslipidemia;

-Hasting plasma glucose $\geq$ 100 mg/dL or type 2 diabetes mellitus diagnosed previously;

-BP $\geq$ 130/85mmHg or previously diagnosed hypertension under treatment.

Exclusion criteria:

-patients under 18 years of age;

-patients without determined waist circumference or BMI;

-patients without determined the levels of serum uric acid, fasting plasma glucose and lipid profile;

-alcoholic patients;

-the presence of other chronic conditions (invasive or non-invasive established 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 enrolled in the study.

395 patients with a mean age of 53.6 $\pm$18 years were enrolled in the study.

The included patients were divided into two groups: those who did not meet the criteria for MetS and those who met the IDF criteria for defining MetS.

Statistical processing

Data analysis was performed using the SPSS program. Descriptive data has been described as mean $\pm$ SD. The statistics were conducted separately for men and women and for each age group. The normal variables were evaluated using the Chi-square test for the presence or absence of MetS and hyperuricemia. Differential analysis was used to test the correlation between MetS and UA. $p < 0.05$ values were considered statistically significant.

Results and discussions

The general characteristics of the 395 patients included in the study are presented in table 1.

Of the 395 patients enrolled in the study, 200 (50.63%) were women and 195 (49.36%) men.

The 395 enrolled patients were randomized by age group (table 2), considering that the main objectives of this study was to determine the prevalence of metabolic syndrome

Table 1
CHARACTERISTICS OF PATIENTS

Parameters	Mean ± DS/Procent (395 patients)
Age (years)	53.6±18 years
Gender M/F (%)	49.36/50.63
BMI (kg/m²)	31.2±5
Waist circumference (cm)	98.5±15
Triglycerides (mg%)	168.4±45.62
HDLc (mg%)	42.72±10
Blood sugar levels (mg%)	95.2±22.78
TAS (mmHg)	136.08 ± 18.5
TAD (mmHg)	85.5± 10.9
Uric acid (mg%)	5.85±1.8

Table 2
DISTRIBUTION OF PATIENTS BY AGE GROUP

Age	≤ 44 years	45 - 64 years	≥ 65 years
No. patients (%)	76p (19.24%)	236p (59.74%)	83p (21.01%)

and hyperuricemia by age and gender groups. The mean age of the enrolled patients was 53.6 $\pm$ 18 years; patients under the age of 18 were excluded from the study.

Middle-aged patients (45-64 years) are the majority: 59.74%. In approximately equal proportions are represented the patients $\geq$ 65 years (21.01%) and those aged $\leq$ 44 years (19.24%).

The data are consistent with those found in Chiou et al., where both middle-aged female and male patients were predominated [12].

Another aspect in the paper was the determination of *MetS prevalence* in the entire batch as well as its prevalence according to gender and age (by age group).

Of the 395 enrolled patients, 140 patients (35.44%) met the IDF criteria for defining the metabolic syndrome, a percentage comparable to literature data where the MetS prevalence was 30.1% and 39.3% [13, 14]. The data is shown in figure 2.
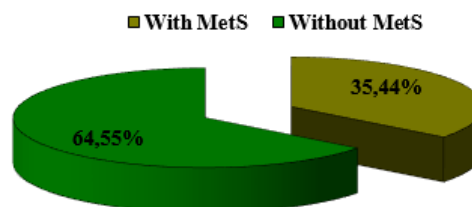

Fig. 2. MetS prelevance

It is established that MetS affects over 25% of the general population, and about two-thirds of MetS patients are predisposed to a cardiovascular event. Worldwide, IDF estimates that approximately 20-25% of the adult population can be classified as MetS subjects (www.idf.org), causing an increase in the frequency and severity of cardiovascular disease [15].

Although the MetS prevalence of the studied group was 35.44%, higher than that reported by IDF, data from a recently published study (conducted on a population in Serbia, the Vojvodina region, a population similar to that in our region, Banat) indicates a much higher prevalence of MetS, of 50.64% [16].

Hyperuricemia, per se, is prooved to be an independent predictor for atherosclerosis in patients with hypertension. Recent clinical studies have shown that serum uric acid levels are associated with subclinical atherosclerosis, especially in men with type 2 diabetes [3].

In this paper the *prevalence of hyperuricemia* was also studied, as well as its prevalence in patients with and without MetS.

The prevalence of hyperuricemia among the patients enrolled in the study was 17.21%, as shown in figure 3.
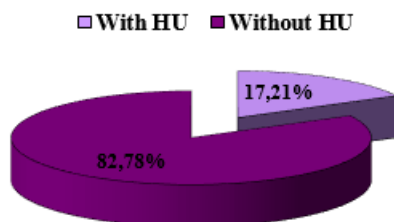
Fig. 3. Prelevance of hyperuricemia

The prevalence of hyperuricemia increases with age, as demonstrated by the study of Liu et al.: the prevalence of hyperuricemia in the study population (age > 60 years) was 16.7% [14].

Another aspect of the paper was the *gender and age group analysis of MetS distribution and hyperuricemia.*

In *women*, MetS prevalence increases with age, 44.44% for the age group over 65 years compared to 22.48% for the 45-64 years age group and 11.42% for those aged ≤ 44 years (fig. 4).
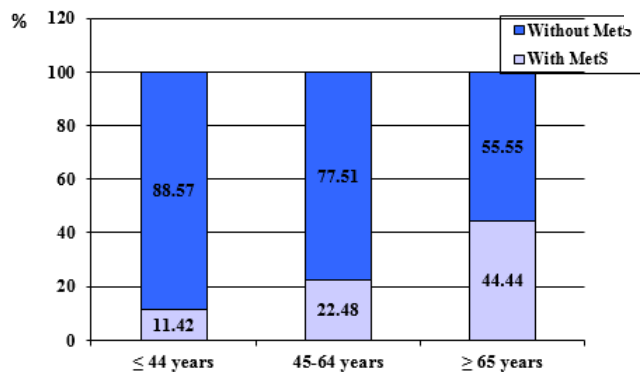
Fig. 4. MetS prelevance on age groups at women

Data from literature also shows that the prevalence of MetS in women increases with age, this increase being more significant after 50 years [17]. Also in the study conducted by You and collaborators, MetS's prevalence increased progressively, with age, in women: those younger than 35 years rarely met MetS criteria, while in women over 60, the MetS prevalence was higher than that observed in males [18].

In *male patients,* MetS prevalence was higher in the age group of 45-64 years (49.53%), followed by the age group ≥ 65 years (44.68%) and that d" 44 years (41.46%) (fig. 5).

Chiou et al. showed the percentage of male subjects with MetS increased with the age increase until the age of 55 years; at this age 35.4% of men developed MetS. After the age of 55 years, the percentage of men with MetS decreased slightly with age, but continued to increase with increasing age in women [12].
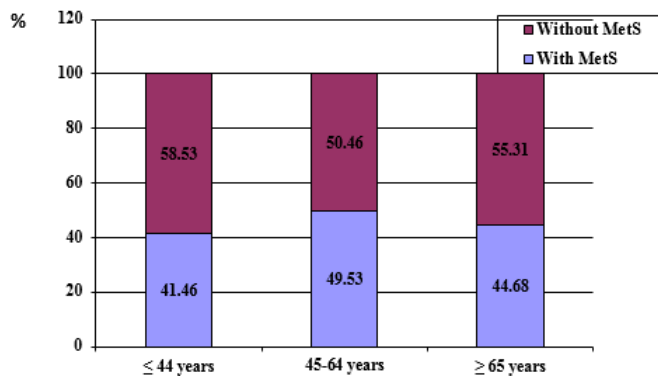
Another clinical trial shows that MetS prevalence

Fig. 5. MetS prelevance on age groups at men

increases gradually by age up to 60 years, after that it has the tendency to decrease [17].

The *prevalence of hyperuricemia in women* also increases with aging: 13.88% of women aged 65 years were hyperuricemic, while in women between 45-64 years, hyperuricemia was present in 9.30% of subjects, compared to 5.71% in women ≤ 44 years (fig. 6).
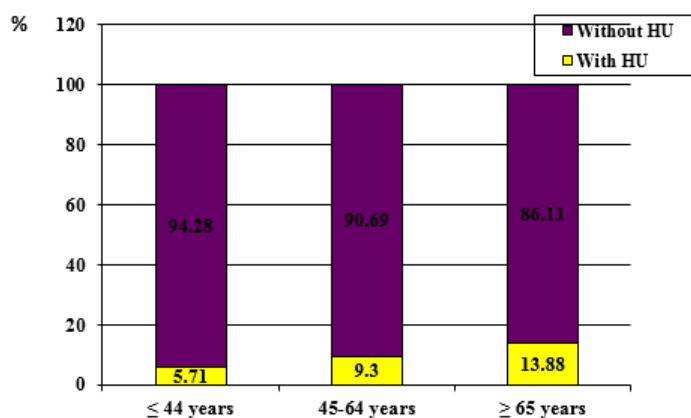
Fig. 6. Prelevance of HU by age group at women

As a particular aspect in women, the uric acid level remains constant until the menopause, and then it begins to rise to the level found in men of comparable age. This is explained by the fact that estrogen favors the excretion of uric acid during the reproductive period.

Older age influences the occurrence of hyperuricemia through several mechanisms: impairment - reduction of renal function, use of diuretics and other drugs that alter uric acid clearance, connective tissue changes and degenerative osteoarticular lesions favoring the formation of monosodic urate crystals.

Wu et al. Found that the prevalence of hyperuricemia in women was 4.8% in those aged 40-44 years, and it increased to 25.3% in those women over 80 years [17].

In *men, the prevalence of hyperuricemia* varies insignificantly by age groups. Thus, it was 21.95% for the age group under 44 years compared to 26.16% for men between 45-64 years, and 25.53% in those over 65 years (fig. 7).

In the study of Wu et al., although the overall prevalence of hyperuricemia was higher in men (15.7%) than in women (12.3%), the prevalence of hyperuricemia according to age group was different in the two genders: in men, the prevalence of hyperuricemia remained stable with age [17].

Actual literature data shows that although the prevalence of hyperuricemia and that of MetS is different according to age and gender, it is higher in male subjects compared to females, especially in young and middle-aged subjects [17, 19- 22].
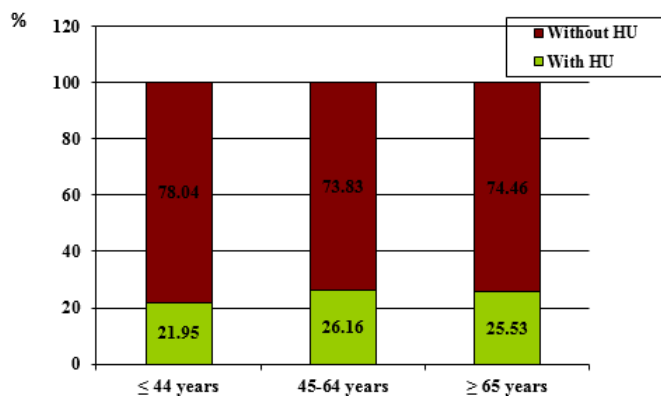
Fig. 7. Prelevance of HU by age group at males

Hyperuricemia should be considered as a component of MetS and as a risk factor for cardiovascular diseases. According to the latest blood pressure management guideline of the European Society of Cardiology, the serum level of uric acid is listed as cardiovascular risk factor next to traditional cardiovascular risk factors [23].

Hyperuricemia is metabolic disorder that can be considered as a possible defining marker in those with metabolic syndrome. An elevated serum uric acid level was associated with an increased risk of MetS. There is a positive association between serum uric acid and metabolic syndrome and a positive correlation between the individual components of metabolic syndrome with uric acid [24].

Hyperuricemia should be considered as a component of the metabolic syndrome and a risk factor for cardiovascular disease. Hyperuricemia has a higher prevalence in MetS patients than in non-MetS patients [24]. The link between MetS and hyperuricemia is insulin resistance and consecutive hyperinsulinism.

Another objective of the paper was to determine the *prevalence of hyperuricemia in patients with MetS.*

Of the 140 patients who met MetS criteria, 58 patients were also HU and 82 had normal uric acid values, so HU prevalence in MetS patients in the study group was 41.42%.

Table 3
HU PRELEVANCE AT METS PATIENTS, DIFFERENTIATED BY GENDER

Gender	Women with MetS number=49	Men with MetS number=91
Cu HU	16 (32.65%)	42 (46.15%)
Fără HU	33 (67.34%)	49 (53.84%)

The gender-differentiated analysis of HU prevalence in patients with MetS is shown in table 3.

The prevalence of hyperuricaemia in patients with MetS was 41.42%. According to gender, in the batch included in the study, the prevalence of hyperuricemia was higher in male patients (46.15%) versus the prevalence in women (32.65%). Both the prevalence of hyperuricemia and MetS was higher in male subjects.

MetS's prevalence increases with elevated serum uric acid levels. The higher the serum acid uric levels are, the higher is the prevalence of MetS.

Chiou and colleagues showed that although the prevalence of hyperuricemia was similar in elderly men and women, women with hyperuricemia had a higher prevalence of MetS than men with hyperuricemia. In the same study, the prevalence of subjects with MetS and hyperuricemia increased significantly in women aged 45-64 years and over 65 years, but not in men, most likely because MetS and its components developed more frequently after menopause, due to the decrease in uricosuric effect of estrogen [12].

Literature data showed that serum uric acid levels had been closely associated with the presence of MetS, more pronounced in women than in men, and it has been observed that the highest risk for MetS is for middle-aged women with hyperuricemia [12].

Epidemiological studies over the last five decades have confirmed an association of elevated uric acid levels with cardiovascular diseases, although not all agree that this correlation is independent of other risk factors. Among all the factors that influence the activity of uric acid in its relation to cardiovascular diseases (coronary, cerebral, peripheral arterial), vascular nitric oxide plays a cardinal role [25, 26].

Based on several studies, both epidemiological and clinical, there have been findings that suggest that hyperuricemia is a risk factor for cardiovascular disease by inducing endothelial dysfunction, proliferation of smooth muscle cells in the blood vessels, the stimulation of inflammation and atherosclerosis, leading finally to clinical manifestation of coronary ischaemia.

Conclusions

Uric acid is a potential marker of the metabolic syndrome. Metabolic syndrome and hyperuricemia are considered to be important risk factors for cardiovascular disease through inflammatory processes that can lead to more rapid development of atherosclerosis.

The prevalence of hyperuricemia and MetS differs according to gender and age. Serum uric acid levels correlate positively with MetS and are more closely associated with its presence in males than at women. The prevalence of MetS and hyperuricemia was higher in male patients compared to their prevalence in women.

In middle-aged male subjects, the prevalence of MetS was higher, whereas the prevalence of hyperuricaemia did not vary significantly with age. In contrast, in women, the prevalence of hyperuricemia and MetS increases with age, estrogen favoring the excretion of uric acid during the reproductive period. Hyperuricemia among middle-aged women can predict the development of MetS.

Despite epidemiological research demonstrating a positive relationship between serum uric acid and MetS prevalence, prospective studies regarding serum uric acid levels as a predictor of MetS incidence are limited, this motivating the present study.

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