

# Correlations Between Hyperuricemia and Metabolic Syndrome

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*In recent years metabolic syndrome is a major worldwide health problem, affecting the population and the individual, both by increasing prevalence and the cardiovascular risk (CV) it determines. Gout and hypeuricemia may be associated with increased cardiovascular risk. Our study aims to evaluate the association of asymptomatic hyperuricemia and gout with cardiometabolic risk factors. We investigated the medical records of 153 patients hospitalized in the Rheumatology Clinic who fulfilled at least three of the five criteria defining the metabolic syndrome and were diagnosed with gout or asymptomatic hypeuricemia. Individuals were predominantly late middle aged, 50-59 years old. The number of male patients is significantly higher than the number of females. 74 patients have gout (48,4%) and 79 have asimptomatic hypeuricemia (51.6%). The frequency of hypertension was higher in patients with gout compared to those with hyperuricemia. Family history of cardiovascular disease was found in 55 patients, including 23 with gout and 32 with hyperuricemia. Moreover, hypercholesterolemia was present in 33 patients with gout and 44 patients with hyperuricemia. The increase above normal triglyceride values was ascertained in 36 patients with gout and 41 patients with hyperuricemia. Obesity was present in only 27 of the patients (13 with gout and 14 asymptomatic hyperuricemia). elevated ESR was found in 97 patients (47 with gout and hyperuricemia 50 with asymptomatic hyperuricemia), and the CRP increased in 40 patients (15 with gout and 25 asymptomatic hyperuricemia). We confirmed the previously reported sex-specific differences and the strong associations between serum uric acid concentration and age, obesity, hypertension, serum triglycerides levels, serum cholesterol levels, links between increased serum uric acid concentrations and the levels of the individual components of metabolic syndrome.*

**Keywords:** Uric acid, hypertension, triglycerides, cholesterol, glycemia

In recent years metabolic syndrome (MS) is a major worldwide health problem, affecting the population and the individual, both by increasing prevalence and the cardiovascular risk it determines. The MS is defined as a group of risk factors leading to cardiovascular disease, whose pathophysiological foundation is related to insulin resistance [1-5]. Clinical studies have shown that not all patients presenting MS are really insulin resistant, and consequently other cardiovascular risk factors are considered, including essential hypertension, type 2 diabetes mellitus, hyperlipidemia, obesity and others [3-6]. Over the last two decades, the International Health Organization and the National Institutes of Health, together with the American Heart Association have provided several precise definitions of the metabolic syndrome [7-9].

Our study aims to evaluate the association of asymptomatic hyperuricemia and gout with cardiometabolic risk factors. Uric acid is a heterocyclic compound of carbon, nitrogen, oxygen, and hydrogen with the formula  $C_5H_4N_4O_3$ . It forms ions and salts known as urates and acid urates (fig. 1).

Hyperuricemia, defined as a serum urate (SU) concentration above the point of saturation of 6.8 milligrams per deciliter (mg/dL) or more is the most common biochemical abnormality associated with the

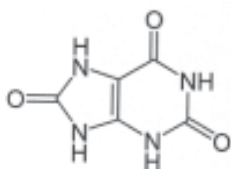


Fig. 1. Acid uric formula

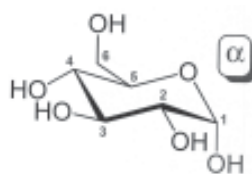


Fig. 2.  $\alpha$ -D-glucopyranose

development of gout, but is not a sufficient causative factor. Individuals that have SU concentrations elevated above saturation levels but have not developed clinical manifestations of gout are considered to have asymptomatic hypeuricemia [10-12]. Gout and hypeuricemia may be associated with increased cardiovascular risk, but analyses in different populations show conflicting results. This study investigates the impact of serum uric acid, inflammation and traditional cardiovascular (CV) risk parameters on CV event risk in patients with MS [13-15]. There are different pathophysiological hypotheses that may explain the observed associations: shared risk factors, direct metabolic actions of uric acid on the vascular wall and/or on renin-angiotensin-aldosterone and insulin resistance pathways, or vascular involvement in systemic inflammatory activation. Even though all of these hypotheses are supported by experimental and/or epidemiologic data, none has been definitely confirmed [16, 17]. Causality in gout associated cardiovascular risk thus remains unclear and pathways are probably complex [18-20].

## Experimental part

### Materials and methods

We investigated the medical records of 153 patients hospitalized in the Rheumatology Clinic within the

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| Clinical criteria                                | Normal values of the parameters                                                                            |
|--------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Obesity                                          | $\geq 30 \text{ kg/m}^2$                                                                                   |
| Serum triglycerides level (TG)                   | $\geq 150 \text{ mg/dL}$ or with treatment for high levels of TG                                           |
| High-density lipoprotein cholesterol level (HDL) | $< 40 \text{ mg/dL}$ in men; $< 50 \text{ mg/dL}$ in women or with treatment for low levels of HDL↓        |
| Blood pressure (BP)                              | $\geq 130 \text{ mmHg}$ BP systolic or $\geq 85 \text{ mmHg}$ BP diastolic with treatment for hypertension |
| Serum glucose level (Glu) (Fig. 2)               | $\geq 100 \text{ mg/dL}$ or with treatment for diabetes                                                    |

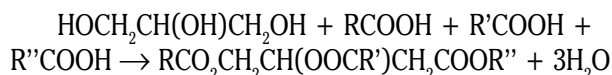
**Table 1**  
DIAGNOSTIC CRITERIA FOR  
METABOLIC SYNDROME  
(ACCORDING TO AHA/NHLBI)

Rehabilitation Hospital Iasi in the period 01 January 2014 – 31 July 2014. We selected the patients who fulfilled at least three of the five criteria defining the metabolic syndrome.

We used the criteria recommended by AHA/NHLBI (American Heart Association). Any three criteria of the five listed establish the MS diagnosis (table 1). Also, patients were diagnosed with gout or asymptomatic hyperuricemia.

The patients were divided according to age groups, gender, gout and the presence of the metabolic syndrome as well as the essential hypertension grade and the number of clinical criteria used in establishing the MS diagnosis (3, 4 or 5 criteria). The frequency of each criterion was then recorded in each sub-group presenting 3, 4 and respectively 5 diagnosis criteria.

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:



The three fatty acids (RCOOH, R'COOH, R''COOH in the above equation) are usually different, but many kinds of triglycerides are known. The chain lengths of the fatty acids in naturally occurring triglycerides vary, but most contain 16, 18 or 20 carbon atoms. The level of triglycerides is very important because high levels stimulate the atherosclerosis process, and, by extension, the risk of cardiovascular diseases and stroke.

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. There are five subfractions of HDL, types 2a, 2b, 3a, 3b, and 3c. HDL inhibits the atherosclerotic process.

Last clinical criteria used to establish the diagnosis of metabolic syndrome is glycemia. Glucose is a monosaccharide with formula  $\text{C}_6\text{H}_{12}\text{O}_6$  or  $\text{H}-(\text{C}=\text{O})-(\text{CHOH})_5-\text{H}$ , whose five hydroxyl (OH) groups are arranged in a specific way along its six-carbon back.

#### Statistical analysis

Differences between groups and associations between CV risk variables and titers of serum uric acid were tested with ANOVA (for continuous CV risk factors), adjusted for differences by age and gender.

#### Results and discussions

From the total number of patients diagnosed with MS, there are 60 female (39.2%) patients and 93 male (60.8%) patients. The average is 60.01. The number of male patients is significantly higher than the number of female patients ( $p < 0.01$ ).

21 female patients came from rural areas and 39 from urban environment. Male patients came from rural areas 52 and 41 were from urban areas. Statistical analysis in terms of backgrounds distribution, it did not reveal significant changes between the rural/urban ( $t = 0.113$ ;  $p = 0.910$ ) (fig. 3). Also, there were no significant differences based on age or sex.

Individuals were predominantly late middle aged, 50-59 years old, average 55.89 (fig. 4).

Another criteria is the value of uricaemia. 74 patients have gout (48.4%) and 79 have asymptomatic hyperuricemia (51.6%).

Another parameter taken in the study was hypertension. Hypertension was present in 93 of the patients studied. Furthermore, the frequency of hypertension was higher in patients with gout compared to those with hyperuricemia (fig. 5). There were no significant differences between the two batches. Most of these patients were diagnosed with essential hypertension grade 3 (55%), while the others presented essential hypertension grade 2 (29%) and grade 1 (16%).

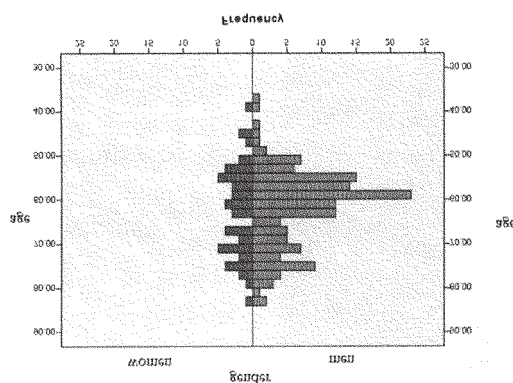


Fig. 3. Age-gender correlation

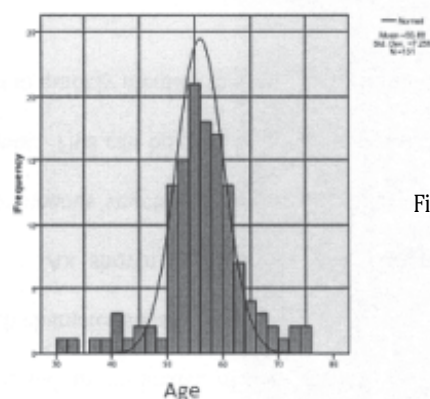


Fig. 4. Age repartition

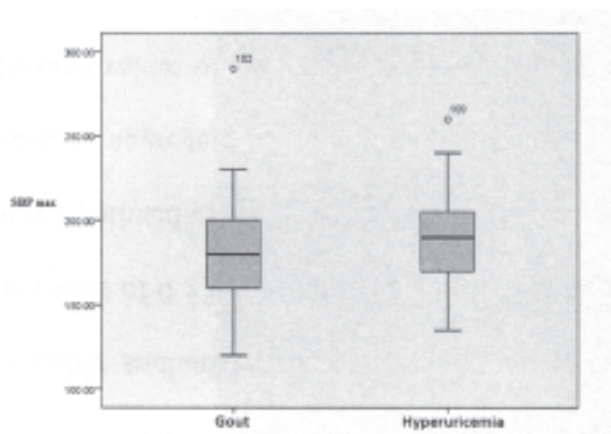


Fig. 5. Relation between SBP and gout, hyperuricemia

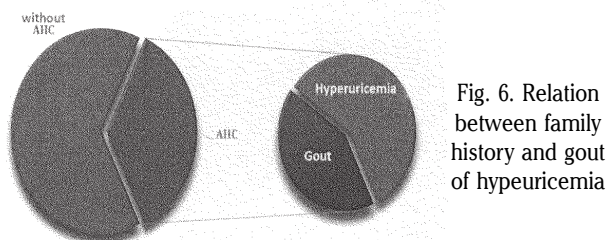


Fig. 6. Relation between family history and gout of hyperuricemia

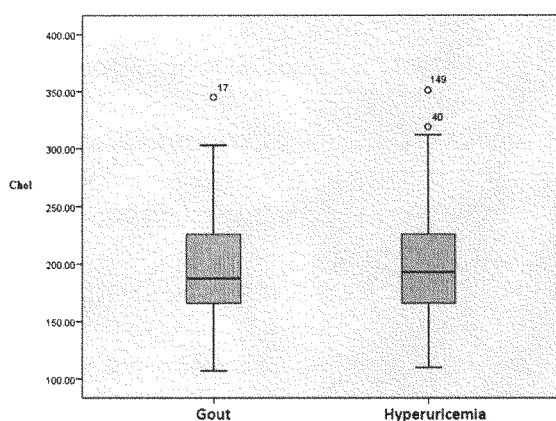


Fig. 7. Relation Chol-gout, hyperuricemia

Family history of cardiovascular disease was found in 55 patients, including 23 with gout and 32 with hyperuricemia. Thereby genetic factors have an influence in the development of elevated uric acid (UA) (fig. 6).

Another parameter considered in the present study was dyslipidaemic syndrome. It was present in 77 patients. Moreover, hypercholesterolemia was present in 33 patients with gout and 44 patients with hyperuricemia. The statistical analysis of the cholesterol (fig. 7) and HDL-cholesterol levels (fig. 8) revealed the following depending on the serum uric acid values:

- normal distribution of cholesterol and HDL-cholesterol levels on gout (107-345 mg/dL, with an average of 187 mg/dL for cholesterol and 19-82 mg/dL, with an average of 40 mg/dL for HDL-cholesterol);

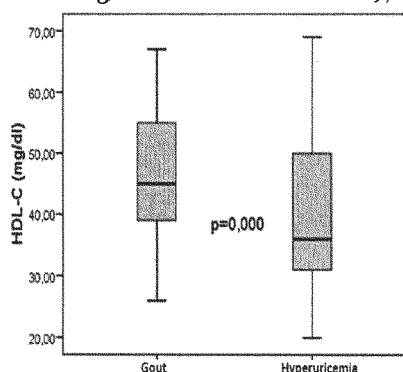


Fig. 8. Relation HDL-gout, hyperuricemia

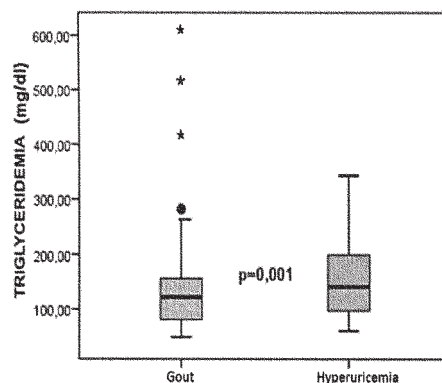


Fig. 9. Relation TG-gout, hyperuricemia

- normal distribution on hyperuricaemia (110-351 mg/dL, with an average of 193 mg/dL, and 27-80 mg/dL, with an average of 41 mg/dL respectively).

Again no significant differences were observed.

In the analysis of MS the value of triglycerides has been studied. The increase above normal triglyceride values was ascertained in 36 patients with gout and 41 patients with hyperuricemia. The difference between the two groups was not statistically significant (fig. 9).

Another parameter studied was obesity. The study batches average body mass index (BMI) was 29 kg/m<sup>2</sup>, with a variation between 18 and 49 kg/m<sup>2</sup>, without a significant difference ( $p = 0.227$ ). It was present in only 27 of the patients (13 with gout and 14 asymptomatic hyperuricemia) (fig. 10).

Inflammatory syndrome has been seen in both the metabolic syndrome and rheumatic disease and has been studied in our group. Thus, elevated ESR was found in 97 patients (47 with gout and hyperuricemia 50 with asymptomatic hyperuricemia) (fig. 11), and the CRP increased in 40 patients (15 with gout and 25 asymptomatic hyperuricemia) (fig. 12). The conclusion is that inflammatory syndrome was more important in patients with gout.

All parameters mentioned above form the MS. The presence of three or more parameters establishes the diagnosis. It was observed in our study that most patients had three criteria (54%), then four criteria (37%) and 9% five criteria. Increased amount of uric acid was directly

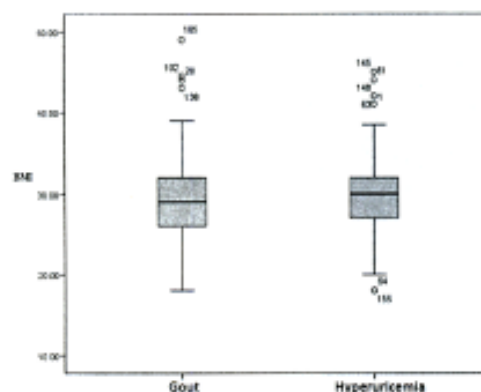


Fig. 10. Relation BMI-gout, hyperuricemia

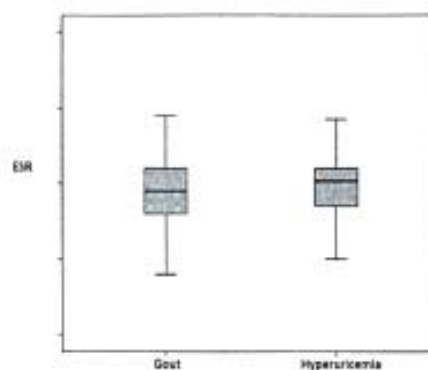


Fig. 11. Relation ESR-gout, hyperuricemia

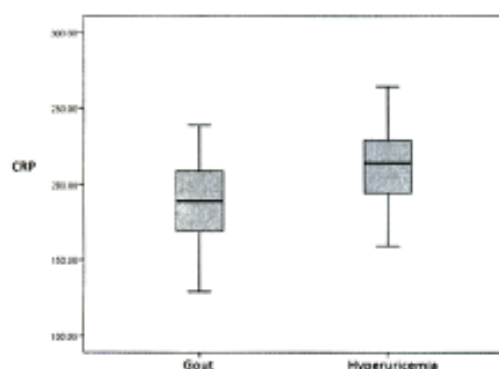


Fig. 12.  
Relation  
CRP-gout,  
hyperuricemia

proportional to the number of criteria, confirming existing data in the literature. All patients with five criteria showed hyperuricemia, 70.4% of those with four criteria and 51.2% of those with three criteria.

In the present study, we confirmed the previously reported sex-specific differences and the strong associations between serum UA concentration and age, obesity, hypertension, serum triglycerides levels, serum cholesterol levels, links between increased serum UA concentrations and the levels of the individual components of metabolic syndrome [21-23]. Many factors, including obesity, body mass index are confirmed to influence serum UA concentrations. Serum uric acid is associated positively with CRP and ESR, so it is a relationship between serum uric acid and markers of systemic inflammation. In clinical practice, hyperuricemia is an indication for investigating MS criteria, and the presence of MS is an indication for investigating the serum UA concentration [24-27]. The results of this study support the association of asymptomatic hyperuricemia and gout with cardiovascular risk factors. Furthermore, gout is an increased risk of cardiovascular disease beyond the potential contributions of hyperuricemia associated with a role due to the inflammation process shown in atherogenesis [28-30] and the development of thrombosis in a manner similar to other inflammatory rheumatic diseases associated with an increased risk of cardiovascular disease (rheumatoid arthritis or lupus) [31-33]. So, the patient suffering an attack of gout is subject to mandatory assessment protocol to determine cardiovascular risk profile [34]. Further studies are necessary to assess the exact role of uric acid in the case of reduction of cardiovascular events.

## Conclusions

In the present study, we demonstrated the following findings: the serum UA concentration was positively correlated with the number of MS criteria (obesity, hypertension, serum triglycerides levels, serum cholesterol levels) that were met, the association between UA and MS components, the relationship between serum uric acid and markers of systemic inflammation (ESR, CRP). The results of this study support the association of asymptomatic hyperuricemia and gout with cardiovascular risk factors.

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