Hyperuricemia and Cardiovascular Risk in The Bulgarian Population

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Received: 14 February, 2020; Accepted Date: 21 February, 2020; Published Date: 27 February, 2020

Abstract

The increase of serum uric acid (sUA) levels over the reference values is defined as hyperuricemia. Sustained hyperuricemia is an important risk factor for cardiovascular diseases.

Aims: To evaluate the prevalence of hyperuricemia by age and sex and main hyperuricemia-related comorbidities in a nationally representative sample of 1242 Bulgarian patient.

To establish whether uric acid levels could be used for evaluation of metabolic status in 200 patients with heart failure (HF) by analyzing its correlations with creatinine levels, glomerular filtration rate, in-hospital diuretic dose, ejection fraction, blood glucose, during follow-up visits after hospital discharge.

Results: The study found that 33.9% of patients had hyperuricemia, which makes it a very common condition in Bulgaria. 27.3% of patients of both sexes had arterial hypertension and every third patient had a high uric acid level. Hyperuricemia was present in 84% of heart failure patients with statistically significant difference depending on the presence and type of diabetes. Patients with HF and insulin-dependent diabetes had relatively highest uric acid levels. A statistically significant considerable positive correlation was established between sUA levels and creatinine, a statistically significant moderate negative correlation between sUA levels and eGFR as well as a modest, but statistically significant positive correlation between sUA levels and in-hospital diuretic dose. The increased levels of sUA are a significant risk factor for atrial fibrillation. This is the first epidemiological study of the prevalence of hyperuricemia in Bulgarian population.

Keywords: Hyperuricemia, Heart failure, Arterial hypertension, Atrial fibrillation, Metabolic syndrome

Introduction

Sustained hyperuricemia, often associated with gout, is an important risk factor for joint damage. In some epidemiological studies, a close association has been reported between hyperuricemia and hypertension, insulin resistance, metabolic syndrome and risk factors for cardiovascular disease [6,10].

Studies in Europe and in the United States have shown that Mean sUA concentrations in male subjects are about 297 to 339 μmol/l, and slightly lower in female patients-220 to 297 μmol/l. Worldwide, the prevalence of hyperuricemia appears to be increasing as it is diagnosed in 5-30% of the general population [5,6]. Serum uric acid levels have been shown to increase with the age and are further increased in postmenopausal women. The growing prevalence of obesity and metabolic syndrome, arterial hypertension and heart failure, and the increasing amount of evidence on the relationship between hyperuricemia and cardiovascular complications call for a reconsideration of the role of hyperuricemia as a risk factor [5,7,9].

The association between sUA levels and heart failure is subject to numerous reports in literature, yet it is still unknown whether sUA levels could be used to diagnose HF or as predictive markers of mortality in HF patients [1,2,12]. The most widely used predictors in HF are hemodynamic parameters such as left ventricular ejection fraction (LVEF), performance status (6-minute walking test) and metabolic factors [1,2,3]. Hyperuricemia in HF (irrespective of renal function and diuretic dose) is a marker of impaired oxidative metabolism and hyperinsulinenemia, pro-inflammatory cytokine activation, and impaired vascular function [2,3,5,23]. Data from several studies have shown that uric acid levels in patients with HF reflect the activity of circulating xanthine oxidase.
The XOR system is an important source of oxygen-derived free radicals, which in turn lead to endothelial dysfunction and oxidative stress with deleterious consequences in heart failure patients. Another probability is a direct deleterious impact of uric acid itself in HF such as pro-inflammatory and proliferative activity. In the same way, UA may be harmful for the kidneys.

Data about the prevalence and epidemiological characteristics of hyperuricemia in Bulgaria are very limited.

**Methods**

**Study groups**

The study was conducted from October 2016 to January 2018. Two patient groups were studied:

- The first group included 1242 patients with concomitant cardiovascular disease or metabolic syndrome referred by their general practitioners for sUA tests, which were all performed in the same laboratory. The database contains information on patients’ demographic and clinical characteristics, such as clinical events and diagnoses.
- The second group included 200 patients with chronic heart failure (CHF) followed-up at the specialized heart failure outpatient office at “St. Marina” Hospital in the city of Varna.
- In our study, hyperuricemia was defined as a serum urate level >421 μmol/l in men, and >321 μmol/l in women. Patients were stratified by sex in three groups depending on uric acid levels. In female individuals, values of up to 141 μmol/l were considered decreased, from 141 μmol/l to 320 μmol/l – normal, and above 321μmol/l – increased. In male subjects, values of up to 200 μmol/l were considered decreased, from 200 μmol/l to 420 μmol/l – normal, and above 421 μmol/l – increased.

**Statistics**

The statistical analysis of the results was performed using the IBM SPSS Statistics, Version 25 software package. The following methods were used:

- Descriptive statistics for quantitative and qualitative variables – mean, standard deviations, standard errors, incidence rates and percentages
- The normality of distribution was tested with Kolmogorov-Smirnov or Shapiro-Wilk tests
- Correlation analysis with Pearson and Spearman’s rank correlation coefficients
- Nonparametric Mann-Whitney test and Student’s t-test
- Analysis of variance (ANOVA) with a Dunnett post-hoc test
- Nonparametric χ² test for hypothesis testing
- Two-tailed P<0.05 was considered significant.

**Results**

The sUA levels for all patients in our study, irrespective of their sex, were from 68 μmol/l to 906.3 μmol/l, Mean=346.62 μmol/l, SEM=3.22, SD=113.38. The normal values in female individuals were: 140-320 μmol/l, and in male individuals – 200-420 μmol/l (figure 1).

![Graph showing uric acid levels in hypertensive patients](https://via.placeholder.com/150)

**Figure 1:** Uric acid levels in hypertensive patients (percentage of presence/absence of hypertension by sex).
We found increased sUA levels in 39.4% (183) of the women and in 30.6% (238) of the man. Using the χ² (chi-square) test we found that sex had a significant impact on uric acid levels (decreased, normal and increased). Differences in normal uric acid levels by sex were statistically significant (P=0.005).

Body mass index (BMI) was calculated for 554 patients (BMI), and their values varied between 17 and 49.22 kg/m², Mean=28.98 kg/m², SEM=0.2, SD=4.77. A weak but statistically significant positive correlation was seen between BMI values and uric acid levels (r=0.173, P<0.0001) (Table 1).

Most patients with obesity had increased sUA levels. Increased adiposity and weight gain are strong risk factors for development of gout as they increase uric acid levels [19]. In our study about 50% of patients with BMI≥25 kg/m² had gout events.

It is generally accepted that prevalence of hyperuricemia is age-dependent [6,9]. In the present study, the incidence rates of hyperuricemia were relatively low in younger subjects (6.2% in the age group up to 44 years), but considerably increasing up to 46.1% in the age group between 45 and 65 years, and up to 47.7% in the group of patients aged over 65 years.

In female patients with increased sUA levels were mainly in the group aged over 65 years (61.5%). In male individuals, those with increased sUA levels were mainly in the age group between 45 and 65 years (54%), while in both sexes urate levels were increased in adult individuals (over 45 years), with prevalence in patients over 65 years of age (47.7%). A positive yet very weak statistically significant relationship was observed between patient age and sUA values (r=0.063, P=0.027). Other studies have also reported a similar increase in the prevalence of hyperuricemia with aging [5,6,23].

We performed a correlation test between BMI and sUA levels which revealed a positive but weak statistically significant correlation (r=0.173, P<0.0001).

### Table 1: BMI values by uric acid levels in percentages.

<table>
<thead>
<tr>
<th>BMI</th>
<th>Uric acid level</th>
<th>Decreased</th>
<th>Normal</th>
<th>Increased</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal-up to 25</td>
<td>Number</td>
<td>10</td>
<td>89</td>
<td>22</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>% by uric acid level</td>
<td>37.0%</td>
<td>25.6%</td>
<td>12.3%</td>
<td>21.8%</td>
</tr>
<tr>
<td>Above normal-25-30</td>
<td>Number</td>
<td>10</td>
<td>153</td>
<td>85</td>
<td>248</td>
</tr>
<tr>
<td></td>
<td>% by uric acid level</td>
<td>37.0%</td>
<td>44.0%</td>
<td>47.5%</td>
<td>44.8%</td>
</tr>
<tr>
<td>First degree obesity-&gt;30</td>
<td>Number</td>
<td>7</td>
<td>106</td>
<td>72</td>
<td>185</td>
</tr>
<tr>
<td></td>
<td>% by uric acid level</td>
<td>25.9%</td>
<td>30.5%</td>
<td>40.2%</td>
<td>33.4%</td>
</tr>
<tr>
<td>Total</td>
<td>Number</td>
<td>27</td>
<td>348</td>
<td>179</td>
<td>554</td>
</tr>
<tr>
<td></td>
<td>% by uric acid level</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

The study of our group of man and women revealed a considerable prevalence rate of hypertension among patients with hyperuricemia/gout. A total of 354 patients had hypertension, of which 139 female individuals and 215 male persons.

25.7% of women with increased uric acid levels had hypertension, while the percentage of hypertensive men with increased sUA levels was 28.6%. 27.3% of patients with increased sUA levels of both sexes had hypertension, i.e. each one out of four patients with increased sUA values had hypertension.

Hypertensive women with elevated uric acid levels were 33.8%, 31.6% man with hypertension had elevated uric acid levels. In total, 32.5% of hypertensive patients of both sexes had elevated uric acid levels, i.e. uric acid values were increased in 1 of 3 hypertensive patient.

Two hundred subjects of our study had chronic heart failure, NYHA functional class II-IV, mean age 71.2 years-
table 2.

In all patient's serum creatinine, eGFR, ejection fraction (EF) and sUA levels were measured.
Table 2: Descriptive statistics of age, serum creatinine levels, eGFR, ejection fraction (EF) and uric acid levels.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34</td>
<td>94</td>
<td>71.19</td>
<td>0.774</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>40</td>
<td>410</td>
<td>113.74</td>
<td>3.883</td>
</tr>
<tr>
<td>eGFR</td>
<td>12</td>
<td>178</td>
<td>60.21</td>
<td>1.913</td>
</tr>
<tr>
<td>EF</td>
<td>20</td>
<td>70</td>
<td>46.56</td>
<td>0.860</td>
</tr>
<tr>
<td>Uric acid</td>
<td>107</td>
<td>1299</td>
<td>484.62</td>
<td>12.359</td>
</tr>
</tbody>
</table>

The etiology of heart failure was as follows: IHD in 33.5% (67 pts), Acquired valve disorders in 27.5% (55 pts), Hypertensive disease in 37.5% (75 pts), Congenital valve disorder in 1.5% (3 pts).

No statistically significant relationship was established between heart failure etiology and uric acid levels. No statistically significant relationship was found between age and sex, and uric acid levels in heart failure patients (P>0.05). The lack of statistical significance of the relationship between uric acid levels and age is probably due to the prevailing number of patients over 65 years of age (73%) of both sexes.

The distribution of sUA values depending on the type of diabetes mellitus in heart failure patients is presented in Figure 2. Serum uric acid values were dependent on the presence of diabetes mellitus and its type with statistically significant differences (P=0.049). The relative increase in uric acid levels was highest in patients with insulin-dependent diabetes (94.4%).

In patients with heart failure without concomitant diabetes mellitus, the observed Mean sUA value was 486.82 μmol/L. The Mean sUA level in patients with insulin-dependent diabetes was 540.71 μmol/L, and 481.22 μmol/L in patients with insulin-independent diabetes. No statistically significant differences were found for the Mean values of sUA between both types of diabetes mellitus (P>0.05).

The potential association between sUA values and ejection fraction was also investigated. Among patients with
ejection fraction below 50%, 16 patients had normal sUA levels and 97 had increased levels. No statistically significant difference was found between ejection fraction and sUA values ($P>0.05$).

Serum uric acid levels divided into two groups – normal and increased in patients with heart failure and atrial fibrillation, are presented in Table 3.

<table>
<thead>
<tr>
<th>Atrial fibrillation</th>
<th>Uric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td>% by atrial fibrillation</td>
<td>10.3%</td>
</tr>
<tr>
<td>% by uric acid</td>
<td>31.3%</td>
</tr>
<tr>
<td>No</td>
<td>22</td>
</tr>
<tr>
<td>% by atrial fibrillation</td>
<td>21.4%</td>
</tr>
<tr>
<td>% by uric acid</td>
<td>68.8%</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
</tr>
<tr>
<td>% by atrial fibrillation</td>
<td>16.0%</td>
</tr>
<tr>
<td>% by uric acid</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Table 3: Uric acid values in patients with heart failure and atrial fibrillation (in percentages).

89.7% of patients with atrial fibrillation had increased sUA levels. Atrial fibrillation was present in 51.8% of the patients with hyperuricemia and a statistically significant relation between the sUA levels and atrial fibrillation was found ($P=0.036$). The increased levels of sUA are a significant risk factor for atrial fibrillation OR=1.141, 95% CI (1.01; 1.287). These data support the findings of other authors showing that increased uric acid levels are risk markers for atrial fibrillation [20,21].

Oxidative stress and inflammation are associated with development of atrial fibrillation, while uric acid itself is a biomarker for oxidative damage and inflammation by xanthine oxidase activation, which plays, at least to a certain degree, an important role in the development of atrial fibrillation. It is generally known that pro-inflammatory mediators could alter atrial electrophysiological properties and structural substrates leading to left atrial (LA) structural and electrical remodeling [21,22,24,25].

The relationship between uric acid levels and creatinine levels, glomerular filtration rate, in-hospital diuretic dose and ejection fraction were estimated by Spearman’s rank correlation coefficient.

A very strong statistically significant negative correlation ($\rho=-0.911$, $P<0.0001$, $D=82.99\%$) was observed between creatinine and glomerular filtration rate (eGFR). The correlation between creatinine and ejection fraction was weak, statistically significant and negative ($\rho=-0.185$, $P=0.009$, $D=3.42\%$). The correlation between creatinine and in-hospital diuretic dose was moderate, statistically significant and positive ($\rho=0.318$, $P<0.0001$, $D=10.12\%$). The correlation between creatinine and uric acid levels was considerable, statistically significant and positive ($\rho=0.514$, $P<0.0001$, $D=26.42\%$). The correlation between glomerular filtration rate (eGFR) and uric acid levels was moderate, statistically significant and negative ($\rho=-0.452$, $P<0.0001$, $D=20.43\%$). The correlation between ejection fraction and uric acid levels was weak, statistically significant and negative ($\rho=-0.190$, $P=0.007$, $D=3.61\%$). Between in-hospital diuretic dose and uric acid levels a weak, statistically significant and positive correlation was found ($\rho=0.297$, $P<0.0001$, $D=8.82\%$).

The significance of uric acid level as a prognostic marker is further increased by its relationship with renal function and diuretic dose.
A very small number of patients, only 13 (6.5%), had received UA lowering drugs (such as allopurinol) prior to their admission to the clinic, and their therapy had not been adequately titrated based on sUA levels. Upon discharge from the clinic, 30 patients were prescribed allopurinol at a dose of 100 mg, 32 patients at a dose of 200 mg and 8 patients – at a dose of 300 mg.

**Discussion**

Many clinical and epidemiological studies have demonstrated that sUA levels are associated with the risk for hypertension, heart failure, atrial fibrillation and diabetes mellitus [9,11,14,15,19,20].

The present study has found that the prevalence of hyperuricemia was 33.9% in the common group of 1242 patients and up to 84% in the group of 200 patients with heart failure.

The main conclusions from the study are:

- Almost half of the patients with overweight and obesity (BMI > 25) had increased uric acid levels. Statistically significant differences in the BMI values based on uric acid levels (P=0.002) were seen.
- The incidence rates of hyperuricemia among young subjects were low (6.2% in the age group of up to 44 years), significantly increased up to 46.5% in the group of patients over 45 years, and up to 47.7% in female individuals aged over 65 years.
- High levels of sUA were associated with high incidence of arterial hypertension. Nearly every one of four patients with high uric acid value from both sexes had hypertension.
- In heart failure patients, a significant correlation between sUA levels and presence of diabetes mellitus was found, with increased uric acid levels in 94.4% of patients with insulin-dependent diabetes mellitus.
- A statistically significant correlation between increased uric acid values and atrial fibrillation was found in heart failure patients. Hyperuricemia represents a risk for atrial fibrillation with OR=1.141, 95%CI (1.01; 1.287).
- A considerable, statistically significant and positive correlation was found between creatinine and uric acid levels in patients with heart failure, while the correlation between in-hospital diuretic dose and uric acid values was weak, although statistically significant.
- The number of patients treated with UA-lowering drugs was surprisingly small.

The present study has found that the prevalence of hyperuricemia in the studied group of Bulgarian patients was considerably higher (33%) compared to reported data for other populations in Europe. The estimated prevalence of hyperuricemia in European countries and the USA is 2% to 18% of the general population [5,6].

The prevalence of hyperuricemia is age dependent. In the present study, the incidence rates of hyperuricemia were low in younger subjects and significantly higher among adults; in women the incidence was highest after 65 years of age, and in men – between 45 and 65 years of age, which showed a trend for decreased incidence after 65 years of age. Our data are very similar to the results from some Asian studies in which age has been reported as a risk factor for hyperuricemia in women. The increase in sUA levels with age might be due to impaired renal function, use of diuretics and hypertension, very common among elderly patients [16].

The prevalence of hyperuricemia as demonstrated in this and other similar studies, might be associated with increasing prevalence of overweight and obesity. Higher adiposity, weight gain and higher BMI index are strong risk factors for gout. Hyperuricemia has been associated with obesity by increased urate production and reduced excretion.

The present study also analyzed the association between heart failure and hyperuricemia. The presence of hyperuricemia reflects increased XO activity in HF.

The XO enzyme system is an important source of free oxygen radicals. They ensure the pathophysiological link between UA and a great variety of harmful undesirable processes including increased cytokine production, cell apoptosis and endothelial dysfunction. Therefore, serum UA might be an important metabolic marker in HF. According to the available literature data, a cut-off point for sUA level of 565 μmol/l is a marker for poor prognosis [11,12]. The assessment of UA provides additional information irrespective of other well-established parameters such as clinical status, functional capacity and renal function.

With some exceptions, patients with higher sUA levels were with more advanced heart failure and atrial fibrillation. Among different types of rhythm disorders, atrial fibrillation plays a particularly important role for increasing cardiovascular morbidity and mortality. Patients with atrial fibrillation are at increased risk for heart failure, stroke and dementia. Age, male sex, rheumatic heart disease, arterial hypertension, congenital heart disease, hyperthyroidism, chronic renal disease and diabetes mellitus are common risk factors for atrial fibrillation. The accumulation of uric acid in atrial myocytes may lead to ionic and structural atrial remodeling which itself is a substrate for onset of atrial fibrillation. Since inflammation seems to contribute to great extent for the electrical and structural remodeling, typical for atrial fibrillation, it is logical to assume that allopurinol, an inhibitor of uric acid synthesis, might be beneficial for atrial fibrillation prevention. This hypothesis certainly needs further clinical investigations.
We have no definite answer to the question whether a decrease in sUA levels in patients with heart failure will lead to better clinical outcomes. While xanthine oxidase inhibitors are widely used for the treatment of gout patients, the evidence from large randomized clinical trials on the cardiovascular safety of these drugs is limited and controversial [4,7,13,17,18,19].

In the studied cohort the number of patients with HF and hyperuricemia who had received treatment with UA-lowering drugs (as allopurinol) was surprisingly small. The number of patients with adequate allopurinol dosing was even smaller.

According to recent publications, a dosage regimen of allopurinol 300 mg daily has been associated with reduction in cardiovascular events [17,18,19]. We still have no definite answer to the question whether a decrease in sUA levels in patients with heart failure might lead to better clinical outcomes. While xanthine oxidase inhibitors are widely used in treating gout patients, the evidence from large randomized clinical trials on the cardiovascular safety of these drugs is limited and controversial.

The CARES study in patients with gout and CV disease compared cardiovascular outcomes associated with the most widely used UA-lowering drugs febuxostat and allopurinol. The study results have shown similar incidence rates of CV events but higher CV and all-cause mortality in the group with febuxostat compared to the group receiving allopurinol [17].

Other two smaller studies-OPT-HF, including 405 patients and EXACT-HF with 253 patients with HrEF-have not shown an improvement of the clinical status despite the significant reduction in sUA levels [4,18,19].

Several study reviews have demonstrated that the use of allopurinol is associated with lower mortality in patients with cardiovascular diseases [7,9,12,23]. Discrepancies between the studies could be explained by different allopurinol doses used. The underuse of urate-lowering substances and the use of drugs potentially increasing sUA levels, along with genetic variations in the population, might contribute to the prevalence of gout and hyperuricemia.

Our study presents several limitations:

- Uricemia is not routinely evaluated in all patients in the clinical practice.
- Patient sample does not cover all geographical regions of our country.
- The study did not include treatment analysis except for the heart failure group.

**Conclusion**

This study is the first one to evaluate the epidemiology of hyperuricemia in Bulgaria. Hyperuricemia is common in more than 30% of the patients with cardiovascular disease from the study and remains inadequately treated despite the increasing evidence on its importance as an independent cardiovascular risk factor. The increased level of uric acid is a significant risk factor for atrial fibrillation.

**Declaration of conflicting interests:** The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding:** The authors received no financial support for the research, authorship, and/or publication of this article.

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