ABSTRACT:

Purpose: To assess the role of asymptomatic hyperuricemia for the presence and severity of coronary arterial calcium (CAC) in adults with different cardiovascular (CV) pathology and its association with conventional CV risk factors.

Material/Methods: Adults (n=81) of both genders were divided into controls: with moderate- to high risk without known CVD; AF-group: CVD-patients with paroxysmal or persistent atrial fibrillation in sinus rhythm, HF–group: heart failure subjects with preserved ejection fraction. A structured interview was performed at admittance for evaluation of the classical CVD risk factors. CAC score (CACS) was determined by multislice computed tomography. Routine laboratory parameters, including uric acid (UA), were extracted from medical documentation. Descriptive statistics, Mann-Whitney U-test, one-way ANOVA, chi-square test, Spearman’s correlation, and multiple linear regression analysis were applied. The predictive power of serum UA was evaluated using receiver operating characteristic (ROC) analysis. Statistical significance was considered at p<0.05.

Results: Serum UA was significantly higher in subjects with CACS=1-99AU (p=0.030), and with CACS ≥100AU (p=0.067) vs. patients without CACS. Within the UA tertiles, highest CACS was found in the tertile with highest serum UA. UA revealed positive relation with CACS (r=0.35, p=0.002), age (r=0.25, p=0.027), body mass index (0.27, p=0.017), waist circumference (r=0.44, p<0.0001), triglycerides (r=0.29, p=0.001), and creatinine (r=0.54, p<0.0001). Multiple linear regression analysis revealed significant association between UA as dependent variable and waist circumference (β=0.63, p=0.061), serum triglycerides (β=0.37, p=0.028), creatinine levels (β=0.45, p<0.0001).

Conclusions: Asymptomatic hyperuricaemia could be an important metabolic factor negatively affecting the chronic cardio-vascular pathology besides the conventional risk factors.

Keywords: uric acid, cardiovascular diseases, coronary arterial calcification

INTRODUCTION

Classically, hyperuricaemia is associated with gout; however recent evidence show that high serum uric acid (UA) may cause chronic inflammatory process and could result in various vascular alterations including hypertension and atherosclerosis [1, 2]. In vascular smooth muscle cells (VSMC) UA can induce monocyte chemoattractant protein-1 and cyclooxygenase-2 (COX-2), stimulating their proliferation and inflammatory responses [3]. Hyperuricaemia can reduce the production or activity of nitric oxide (NO) in endothelial cells, thus promoting endothelial dysfunction, increasing vascular tone, and may contribute to arterial stiffness [4]. High levels of UA can cause oxidative stress through LDL oxidation, which can reduce coronary flow [5].

A clinical study was shown that high UA levels are prognostic predictor in patients with heart failure [6]. High UA has been found to be associated with mortality in patients with acute myocardial infarction [7], and in subjects with acute coronary artery disease [8]. Elevated UA is associated with an increased risk of subsequent clinical cardiovascular events [9] and death in patients with stable coronary artery disease [8]. In addition, UA was independently related to the severity of coronary artery calcification (CAC) in adults without prior coronary artery disease, in asymptomatic individuals, and in relatively young individuals who are not at risk for CVD [1, 10].

Although there is an abundance of evidence, supporting the hypothesis that UA may be involved in the pathology of atherosclerosis regardless of conventional risk factors [11], its role as a risk factor for CAC remains controversial. Some studies report a significant association between UA and CAC [10, 12] while others did not found any relationship [13, 14].

The main hypothesis of the current study is that...
asymptomatic hyperuricaemia could be an important metabolic factor negatively affecting the chronic cardio-vascular pathology besides the conventional risk factors. Revealing the role of UA in the pathogenesis of vascular calcification could serve a basis for the usage of UA as a cheap and non-invasive screening tool for patients subject to invasive and expensive CAC measurement.

Therefore, the present prospective study aimed to assess serum UA levels in adult patients with different CVD pathology and their associations with CAC and with conventional CVD risk factors.

MATERIALS AND METHODS:
The study was approved by the local Ethical Committee at the Medical University of Varna (Protocol No 75/07.06.2018). Written informed consent was obtained from all participants in the study.

Patients
The current study included 81 participants (57 females, 24 males), admitted at the Cardiology Clinics of the University Hospital–Varna between October 2018 and January 2020. Patients without known CVD but with estimated moderate- to high risk for CVD (n=43) served as controls. According to the underlying pathology, the patients with CVD (n=38) were stratified into two subgroups: atrial fibrillation (AF) group – subjects with paroxysmal or persistent atrial fibrillation in sinus rhythm; heart failure (HF) group – heart failure patients with preserved ejection fraction (ejection fraction>40%) and in sinus rhythm at the time of hospitalization. A structured interview was carried out at admittance in the hospital for evaluation of the classical risk factors, such as age, CVD-history, smoking status, presence and duration of arterial hypertension (AH), hyperlipidemia, type-2 diabetes mellitus. Hypertension was defined as blood pressure (BP) >140/90 mmHg at the time of examination or with a history of elevated BP and on antihypertensive therapy. Hyperlipidemia was defined as elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) or triglycerides (TG) according to the ESC Guidelines cut-off values [15, 16] and/or on lipid lowering medications. All patients underwent a physical examination for heart rate, BP, weight, height, and waist circumference (WC). WC below 88cm for females and below 102cm for males was considered as normal; WC above 88cm for women and above 102cm for men was an indicator for abdominal obesity. Body mass index (BMI) was calculated as weight/height² (kg/m²). BMI below 24.9kg/m² was considered as normal; BMI between 25.0kg/m²-29.9kg/m² indicated overweight, and obesity was defined as BMI above 30.0kg/m² [2, 17]. From the study were excluded patients with proven ischemic heart disease or stroke, cardiomyopathies, type-1 diabetes mellitus, chronic renal disease IV stage or more (with eGFR<30 mL/min/1.73m²), known thyroid gland diseases, and active cancer.

Coronary artery calcification measurement
CAC was assessed by multislice computed tomography examination on Siemens Somatom Definition (Dual Source 2x64) CT scanner (Siemens Medical Solutions USA, Inc., Malvern, PA, USA) using standardized imaging protocols. Thirty to forty consecutive tomographic slices were obtained at 3mm intervals, 1cm below the carina and progressing caudally to include the entire coronary tree. Scans were interpreted by a single trained physician blinded to the clinical characteristics of the patients. CAC was defined as a lesion of >130 Hounsfield units, with an area equal to 3 pixels. Coronary artery calcium score (CACS) was calculated using the Agatston criteria [18]. The presence of CAC was defined as an Agatston score >0 Agatston units (AU). According to the CACS results, the patients were classified into one of the following categories: CACS=0AU (absence of coronary calcium), CACS 1-99AU, and CACS e”100AU.

Laboratory measurements
Routine laboratory parameters – glucose, urea, creatinine, UA, TC, TG, HDL-cholesterol (HDLC), and LDL-C for each patient were extracted from the medical documentation. These parameters were measured in fasting blood using biochemical analyzer (ADVIA-1800 Chemistry System, Siemens Healthcare GmbH, Erlangen, Germany) at admittance in the hospital. Castelli risk indexes (TC/HDL-C and LDL-C/HDL-C) and estimated glomerular filtration rate (eGFR) were calculated.

Statistical analysis
Data were presented as mean±standard deviation, median (interquartile range, IQR 25th–75th percentile) or number (n), and percentage (%), as appropriate.

Data analysis was performed on GraphPad Prism v.8.3. (GraphPad Software, San Diego, CA USA) and SPSS v.23 (SPSS Inc., Chicago, IL, USA). Standard statistical methods, such as descriptive statistics, Mann-Whitney U-test for non-normally distributed interval data, and one-way analysis of variance (ANOVA) including Bonferroni correction, were used. For categorical data, chi-square test or Fisher’s exact test were applied. The relationship between continuous variables was evaluated by Spearman’s correlation analysis, and if significant relation was found, a multiple linear regression analysis was applied to test for important predictors of UA as a dependent variable. Receiver operating characteristic (ROC) analysis was performed for evaluation of the predictive power of serum UA. All statistical analyses were two-tailed and statistical significance was considered at p<0.05.

RESULTS:
Patients’ characteristics
Table 1 represents the baseline characteristics of the participants in the study. The females were 69% of all patients, 65% in the control group, 68% in the AF group, and 87.5% in the HF group. Obesity was observed in 33.8% of the entire group with prevalence among the HF patients (50.0%). Current smokers dominated in the control group (37.2%) vs AF (13.6%) and HF (12.5%) group. More than 85% of our patients were with AH with median duration of 10 years (IQR 4–15 years). Hyperlipidemia was present in 80% of the patients, while diabetes was observed only in 10.3% of the participants. Almost 90% of all participants did not report a family history of early ischemic heart disease (IHD).

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Data are presented as mean ± SD and percent (%) as appropriate. UA – uric acid; BMI – body mass index; WC – waist circumference; AH – arterial hypertension; TC – total cholesterol; TG – triglycerides; HDL-C – high density lipoproteins cholesterol; LDL-C – low density lipoproteins cholesterol.

**Uric acid and conventional risk factors for CVD**
Significant elevation of serum UA was observed with BMI and WC (fig. 1, fig. 2) and with the presence of AH (fig. 3). No significant differences in UA levels were found with age, hyperlipidemia, and smoking.

![Fig. 1. Uric acid levels according to body mass index.](https://www.journal-imab-bg.org)
The central line represents the distribution median.
Serum UA median for BMI ≤ 24.9 kg/m²: 266.0 mmol/L, IQR 229.0 - 364.0 mmol/L; for BMI 25.0-29.9 kg/m²: median 362.0 mmol/L, IQR 305.0-471.0 mmol/L; for BMI ≥30 kg/m²: median 361.0 mmol/L, IQR 301.0-409.0 mmol/L.

**Fig. 2.** Uric acid levels according to waist circumference.

The central line represents the distribution median.
Serum UA for normal WC (WC ≤ 88 cm for women, WC ≤ 102 cm for men): median 305.5 mmol/L, IQR 242.0-368.8 mmol/L; abdominally obese (WC > 88 cm for women, WC > 102 cm for men): median 366.5 mmol/L, IQR 304.3-409.8 mmol/L. BMI – body mass index; WC – waist circumference.

**Fig. 3.** Uric acid levels according to the presence of arterial hypertension.

The central line represents the distribution median.
Serum UA median of patients with AH: 360.0 mmol/L (IQR 288.0-412.0 mmol/L); patients without AH: 256.0 mmol/L (IQR 217.5-313.5 mmol/L). UA – uric acid; AH - arterial hypertension.

For the entire studied cohort, Spearman correlation analysis indicated low or moderate positive relation of serum UA with age (r=0.25, p=0.027), BMI (r=0.27, p=0.017), WC (r=0.44, p<0.0001), TG (r=0.29, p=0.0095), and strong positive correlation with creatinine (r=0.54, p<0.0001). The correlation with AH duration was borderline significant (r=0.22, p=0.075). Significant associations were found in the moderate- to high-risk patients without known CVD, strong positive relation of serum UA with BMI (r=0.53, p=0.0003), WC (r=0.62, p<0.0001), AH duration (r=0.40, p=0.015), TG (r=0.45, p=0.002), creatinine (r=0.72, p<0.0001), and borderline significant correlation with TC/HDL (r=0.28, p=0.069). Multiple linear regression analysis revealed associations between UA as a dependent variable and TG (β=0.43, p=0.028), creatinine (β=0.45, p<0.0001), and WC (β=0.63, p=0.061).

Serum UA was significantly lower in women than in men (303.5 mmol/L, IQR 244.3-377 mmol/L vs 370.5 mmol/L, IQR 349.3-428.8 mmol/L; p<0.0006).

As in our study, the females prevail, we stratified the UA levels into tertiles by gender (table 2).

**Table 2.** Tertiles of serum uric acid levels stratified by gender.

| Tertile | serum UA levels (mmol/L) |
|---------|--------------------------|
|         | males (n) | females (n) |
| 1       | ≤ 361.18 (8) | ≤ 262.60 (19) |
| 2       | 361.19 – 413.98 (8) | 262.70 – 360.30 (18) |
| 3       | > 413.99 (8) | > 360.40 (19) |

UA – uric acid

Across the UA tertiles age, WC, TG, and creatinine were significantly different. In the 3-rd UA tertile, age and WC were higher than in the 1-st UA tertile. Creatinine levels were significantly elevated in the 2-nd and in the 3-rd tertile. The same tendency was observed for TG levels. There were no significant changes for the other lipid parameters (table 3).

**Table 3.** Characteristics of the study population stratified by serum uric acid tertiles.

| Parameter               | tertile 1     | tertile 2     | tertile 3     | p         |
|-------------------------|---------------|---------------|---------------|-----------|
| Age (years)             | 55.3±12.3     | 61.3±11.7     | 66.4±100      | 0.004     |
| BMI (kg/m²)             | 27.2±5.0      | 29.0±6.6      | 29.7±5.6      | 0.301     |
| WC (cm)                 | 89.2±13.8     | 95.9±16.5     | 99.3±16.6     | 0.081     |
| Duration of AH (years)  | 7.0±7.4       | 11.0±9.2      | 10.6±6.3      | 0.192     |
Data are presented as mean±SD.
BMI – body mass index; WC – waist circumference; AH – arterial hypertension; TC – total cholesterol; TG – triglycerides; HDL-C – high density lipoproteins cholesterol; LDL-C – low density lipoproteins cholesterol.

The frequency of AH presence increased gradually across the UA tertiles from 74.1% for the first, 95.3% for the second and up to 100% for the third tertile. The same tendency for increasing severity of CVD pathology across the UA tertiles was also observed. The frequency of CVD severity was gradually increased across the UA tertiles for both AF and HF patients (from 18.51% for the 1-st tertile to 34.65% for the 3-rd tertile for AF participants and from 7.41% for the 1-st tertile to 34.65% for the 3-rd tertile for HF patients).

Uric acid and CAC score

Median CACS for the entire studied population was 26.2AU (IQR 0.0-221.3AU). It gradually increases with the severity of CVD pathology: CACS=0.0AU (IQR 0.0-43.1AU) for moderate- to high-risk patients without known CVD; CACS=112.9AU (IQR 1.5-409.9AU) for AF patients, and CACS=220.6AU (IQR 53.5-387.4AU) for the HF-group. Without coronary calcium deposits were 37 participants (45.7%) of the entire studied population, with coronary calcium were 44 cases (54.3%).

Stratification by CACS revealed gradual elevation of serum UA across the subgroups (fig. 4). Serum UA was significantly higher by 16.1% in the subjects with CACS 0-1AU (p=0.030), by 16.5% in those with CACS ≥100AU (p=0.067) compared to patients without coronary calcium.

The central line represents distribution median. UA levels for different CACS categories: 317.5mmol/L (IQR 254.5-365.3mmol/L) for CACS0-1AU; 368.5mmol/L (IQR 306.5-420.3mmol/L) for CACS 1-99AU; 370.0mmol/L (IQR 245.0-448.0mmol/L) for CACS≥100AU; CACS – coronary arterial calcium score; UA – uric acid.

The serum UA correlated significantly and positively with CACS in the entire studied population (r=0.35, p=0.002). Across the CACS groups, significant correlations were present with creatinine for all CACS groups (r=0.54, p=0.0006, for CACS 0-1AU); (r=0.53, p=0.055, for CACS 1-99AU); (r=0.50, p=0.009, for CACS ≥100AU). Only in the group with CACS 0-1AU were indicated significant associations with BMI (r=0.39, p=0.02), WC (r=0.58, p=0.0003), TG (r=0.46, p=0.004), with borderline significance with age (r=0.28, p=0.085) and with AH duration (r=0.31, p=0.095). Multiple linear regression analysis revealed significant association between UA as a dependent variable and CACS for the entire studied population (β=0.26, p=0.049).

Within the UA tertiles, highest CAC was found in the group with the highest serum UA (3-rd tertile) (fig. 5). The participants with CACS ≥100AU comprise 58.3% in the 3-rd tertile, while the patients with CACS=0 were only 33.3% in the same UA subgroup.
Coronary arterial calcium score across serum UA tertiles.

![Graph showing coronary arterial calcium score across serum UA tertiles.](image)

The central line represents distribution median. CACS 0.0AU (IQR 0.0-206.1AU) for the 1-st UA tertile; CACS 0.0AU (IQR 0.0-60.7AU) for the 2-nd UA tertile; CACS 175.1AU (IQR 1.3-463.1AU) for the 3-rd UA tertile. UA – uric acid; CACS – coronary arterial calcium score.

To assess whether the association of serum UA and CAC is modified by conventional CVD risk factors, such as the presence of AH, hyperlipidemia, age, gender, and obesity indexes we stratified the participants by these risk factors. Across the UA tertiles, the highest prevalence of CAC according to conventional risk factors was observed in the 3-rd tertile with the highest serum UA (table 4).

**Table 4.** Prevalence of CAC (in %) across the uric acid tertiles according to conventional CVD risk factors.

| CVD risk factor          | Tertile 1 | Tertile 2 | Tertile 3 |
|-------------------------|-----------|-----------|-----------|
| Age ≥ 64 years          | 87.5      | 54.54     | 88.9      |
| BMI ≥ 30 kg/m²          | 50.0      | 50.0      | 77.8      |
| Abdominal obesity       | 62.5      | 50.0      | 86.7      |
| Present AH              | 55.0      | 45.8      | 76.0      |
| Present hyperlipidemia  | 40.0      | 37.5      | 71.7      |

CAC – coronary artery calcium; CVD – cardiovascular disease; BMI – body mass index; AH – arterial hypertension.

**Uric acid as a predictive factor for CAC**

Receiver operating characteristic (ROC) analysis was performed to evaluate the impact of UA as a predictive factor for CAC. The AUC value of 0.638 (p=0.039) revealed weak predictive power for serum UA when tested alone without taking into account the impact of conventional CVD risk factors. A set of conventional risk factors (BMI, presence of AH, smoking, serum creatinine, TC, and TG) revealed AUC 0.727 (p=0.001). When UA was added to the tested CVD risk factors, almost no difference was found in the predictive power for CAC (AUC 0.732, p=0.0009) (fig. 6).

![Graph showing receiver operating characteristic (ROC) analysis evaluating the predictive impact of UA for CAC.](image)

AUC 0.638 (p=0.039) when UA tested alone; AUC 0.727 (p=0.001) for a set of conventional risk factors (BMI, presence of AH, smoking, serum creatinine, TC, and TG); AUC 0.732, p=0.0009 when UA was added to the tested CVD risk factors;

UA – uric acid; AUC – area under the ROC curve; BMI- body mass index; AH – arterial hypertension; TC – total cholesterol; TG – triglycerides; CVD – cardiovascular disease.

**DISCUSSION:**

This prospective study aimed to evaluate (1) whether serum UA levels differ between subgroups of adult patients with different CVD pathology compared to controls at increased risk; (2) the associations between serum UA and CAC as well as with conventional CVD risk factors; (3) the predictive power of serum UA for the development of CAC.

In patients with AF and HF, we found significantly higher UA levels than in participants with moderate-to-high risk without known CVD. Our results are in line with the findings of a case-control study examining Greek patients with AF and establishing an association between serum UA and AF [19]. The increased relative risk for AF patients with high serum UA compared to those with normal UA was reported by a recent meta-analysis evaluating six cross-sectional studies (n=7930) and three cohort studies (138306 subjects without AF) [20]. It is considered that...
oxidative stress plays a role in the pathogenesis of AF. Neurohormonal and inflammatory factors could activate xanthine oxidase, increase serum UA levels and the production of reactive oxygen species (ROS), and thus favor the development of oxidative stress [21]. Relationship between increased oxidative stress and AF was reported in patients after coronary bypass surgery and AF recurrence [22]. Moreover, experimental studies have shown that oxidative stress induces NO decrease and the development of AF [23, 24]. The role of serum UA in HF incidence and development is not completely understood. There are studies reporting that high serum UA is associated with an increased risk of incident HF [25]. It is suggested that upregulation of xanthine oxidase and ROS formation by serum UA may contribute to numerous pathological processes related to HF such as cardiac hypertrophy, myocardial fibrosis, and contractility impairment. In addition, being a pro-inflammatory substance serum, UA can trigger complex pro-inflammatory cascades and thus may contribute to HF development and progression [10]. Moreover, therapy with xanthine oxidase inhibitors results in improvement of hemodynamics and clinical outcomes in HF patients [26, 27].

In this study, we established that CACS significantly increases with the serum UA levels. Highest coronary calcium we found in patients with the highest serum UA levels (3-rd tertile). The same tendency for gradual elevation of serum UA across CACS subgroups was also confirmed by subgroup analysis. Our results correspond to the findings of Kim et al. (2017) who demonstrated that serum UA was independently associated with CACS severity [10]. Another study was found a positive relationship between serum UA and CACS in 663 asymptomatic middle-aged patients [12]. A recent systematic review and meta-analysis reported that serum UA is associated with increased risk of CAC development and progression in asymptomatic subjects [1, 28] and is an independent predictor for the development of moderate CAC in subjects with no or minimal CAC [29]. Although the molecular mechanism is not fully understood, it is suggested that UA as pro-oxidant may stimulate VSMC production of superoxide radical by COX-2 and thus contribute to atherosclerosis. As a pro-inflammatory agent, UA induces vascular inflammation and arterial intimal calcification by activation of inflammatory cascades mediated by receptor activator of NF-κB ligand, colony stimulating factor-1, tumor necrosis factor-α, bone morphologic protein, and macrophage infiltration. Alotgether, these processes further contribute to VSMC activation and proliferation and arterial intimal calcification [30, 31, 32]. Some authors speculate that individuals with high serum UA are at greater risk for developing more severe CAC than in subjects with lower serum UA levels [10]. On the contrary, others have shown that serum UA is not associated with the presence or severity of CAC [33, 34].

In our study serum, UA was significantly associated with conventional CVD risk factors. For the entire population and across the CACS groups, serum UA significantly correlated with age, BMI, WC, TG and creatinine. Similar results were also found in other studies [1, 29]. Increased serum UA with age was reported by a longitudinal population-based study controlled for BMI and alcohol consumption [34]. Increasing of serum UA with obesity indexes was also found in a cross-sectional study on 3529 overweight and obese subjects [35]. A possible mechanism through which serum UA contributes to the pathogenesis of obesity-related CVD is via upregulation of renin-angiotensin system expression and angiotensin II secretion in response to oxidative stress induced by UA in adipocytes [36]. Regarding the associations between serum UA, TG and creatinine, our results are in line with the findings of other authors for increasing tendency for TG and creatinine levels with serum UA [1, 37]. UA as a final product of purine metabolism is mainly eliminated by the kidneys in the urine. Thus, impaired kidney function associated with higher serum creatinine and lower eGFR could be related to higher serum UA. In our study, we found a significant positive association between serum UA and creatinine. It is considered that elevated serum UA may indicate an altered kidney function and is a risk factor for hypertension and CVD events [38, 39, 40].

ROC curve analysis evaluating, the impact of UA as a predictive factor for CAC revealed weak predictive power for serum UA when tested alone without taking into account the impact of other classical CVD risk factors. A set of conventional risk factors, such as BMI, presence of AH, smoking, creatinine, total cholesterol, and triglyceride levels showed higher AUC than that of UA. When UA was added to the model, the predictive power for coronary artery calcification was almost the same. This is probably due to the small number of participants in our study. No significant difference between the AUC of serum UA and that of classical risk factors for CVD was indicated in a retrospective study on 4461 adult participants [29]. The authors reported significant improvement of the predictive power (by 13%) when serum UA was combined with the tested CVD risk factors.

The main limitation of our study was the small number of participants. However, the stratification into subgroups according to the CVD pathology and CAC severity may help for better evaluation the role of serum UA as a biomarker. We did not have data on dietary intake, which could modify serum UA levels. Because our study is not longitudinal, we could not assess causal relations between serum UA, CACS and other confounders.

CONCLUSIONS:
In conclusion, we found a significant increase of serum UA levels with the severity of CVD pathology and CACS in adults ranging from moderate or high-risk patients without known CVD to CVD subjects with AF or HF. Serum UA was associated with conventional CVD risk factors such as age, obesity indexes, duration of AH, TG and creatinine. Nowadays, it is considered that asymptomatic hyperuricaemia is an important metabolic factor negatively affecting the chronic cardiovascular pathology. Therefore, lowering serum UA levels by a healthier lifestyle may be a useful strategy for lowering CVD events.
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