ORIGINAL ARTICLE

Selected matrix metalloproteinases activity and hypertension-mediated organ damage in relation to uric acid serum level

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Abstract

Background: *Atherosclerosis is as a systemic inflammatory disease associated with the activation of many mediators, including matrix metalloproteinases (MMPs), and may be amplified by abnormal high serum uric acid (UA) concentration (hyperuricemia, HU). The aim of the study was to determine the relationship between serum UA concentration and activity of MMPs and their correlation with the hypertension-mediated organ damage (HMOD) intensity.*

Methods: *One hundred and nine patients untreated with antihypertensive, hypolipemic or urate-lowering drugs with diagnosed stage 1–2 essential hypertension were included in this study. In all participants blood pressure (BP) was measured, carotid-femoral pulse wave velocity (PWV), intima–media thickness (IMT), echocardiography and blood tests including UA, lipids and serum concentrations of MMPs (1, 2, 3, 9) were observed. The participants were divided into hyper- and normuricemic groups.*

Results: *Uric acid concentration in the whole study group positively correlated with some HMOD parameters (IMT, PWV, left ventricular mass index, left atrial dimension). Among the studied metalloproteinases only MMP-3 activity positively correlated with serum UA concentration independently of age, body mass index and serum lipids (R2 = 0.11, p = 0.048). Multivariate regression analysis showed positive association between IMT and BP, UA concentration and MMP-3 activity, independently of waist circumference and serum lipids (R2 = 0.328, p < 0.002). Patients with HU were characterized by higher activity of MMP-3 than those without (19.41 [14.45; 21.74] vs. 13.98 [9.52; 18.97] ng/mL, p = 0.016).*

Conclusions: *The present results may support the thesis that UA and the increased by UA activity of MMPs may take part in the development of HMOD, especially IMT.* (Cardiol J 2021; 28, 6: 905–913)

Key words: arterial hypertension, uric acid, hyperuricemia, matrix metalloproteinases, metabolic syndrome

Introduction

Cardiovascular disorders caused by atherosclerosis remain the main cause of morbidity and death in developed countries. Currently atherosclerosis is defined as a systemic inflammatory disease associated with the activation of many mediators and effectors, including excessive activation of matrix metalloproteinases (MMPs) [1] MMPs are a large group of zinc-dependent proteolytic enzymes which play a key role in physiological and pathological inflammatory processes, including activation of

immune cells, damage and apoptosis of endothelial cells, fibrosis and remodeling of vascular wall. Increased activity of MMPs was described in many inflammatory diseases as well as in selected cardiovascular diseases [2, 3].

Under physiological conditions MMPs are inhibited by a group of tissue inhibitors of metalloproteinases (TIMPs) [4, 5]. The collagenases (MMP-1, -8, -13, -18) are capable of breaking down interstitial collagen I, II, III. Collagen fragments are further degraded by gelatinases (MMP-2, -9), MMP-2, -9 are also involved in the degradation of collagen IV, vessel remodeling, angiogenesis, inflammation and atherosclerotic plaque rupture. Stromelysin-1 (MMP-3) and stromelysin-2 (MMP-10) play the key role in extracellular matrix protein degradation by activation of MMPs cascade [6–8].

Essential hypertension is associated with vascular wall remodeling, which may be amplified by abnormal high serum uric acid (UA) concentration Increased UA concentration is called hyperuricemia (HU). HU is a common condition which may affect up to a quarter of the adult population [9, 10]. Many factors promote the development of HU, especially: the use of a high-purine diet, sedentary lifestyle, metabolic syndrome, obesity and arterial hypertension. In most cases, HU is accompanied by high estimated cardiovascular risk [11, 12].

Uric acid is an important antioxidant, but in excessive amounts it can activate the formation of reactive oxygen species. UA participates in atherogenesis process by enhancing inflammation, causing endothelium dysfunction, vascular smooth muscle proliferation, increased platelet adhesion and lipid peroxidation [13]. In subjects with arterial hypertension HU is associated with increased risk of coronary heart disease and cardiovascular mortality [14, 15].

The action mechanism of elevated UA concentration on the progression of vascular changes has yet to be clearly identified. Available data in the literature about the relationship between HU and MMPs activity is limited.

The aim of the study was to determine the relationship between serum UA concentration and selected MMPs activity and their correlation with hypertension-mediated organ damage (HMOD).

Methods

The study group consisted of consecutive patients with diagnosed essential hypertension stage 1 or 2 (blood pressure [BP] ≥ 140/90 and < <180/110 mmHg) in accordance with the 2018 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines [16]. They were admitted within a 6 month period to the hypertension outpatient department. Subjects were both women and men aged 20–80 years. The exclusion criteria included: symptomatic gout, coronary heart disease (previous myocardial infarction, coronary angioplasty procedure or coronary artery bypass surgery), atrial fibrillation, stroke history or transient ischemic attack episode, active acute or chronic inflammatory process, cancer, kidney or liver failure and reported treatment with antihypertensive, hypolipemic or urate-lowering drugs in the prior 4 weeks.

Study procedures

All participants underwent medical examination, with office BP measurements in standard conditions, after 10 min rest, in a sitting position on the non-dominant arm with the use of the Omron M5-I oscillometric device (Omron Healthcare Co., Japan). The mean of the three measurements at 1-min intervals was taken for analysis. 24-h ambulatory blood pressure monitoring (ABPM) was also performed using a SpaceLabs 90207 recorder (SpaceLabs Inc, Richmond, Washington, USA) according to ESH/ESC recommendations [16]. The SphygmoCor (AtCor Medical, Sydney, Australia) device was used to examine arterial stiffness. Carotid-femoral pulse wave velocity (PWV) and central blood pressure in the aorta were measured according to ESC expert consensus recommendations [17, 18]. Echocardiographic examination using the Vivid 7® VingMed (GE-Healthcare Chicago, IL, USA) device was performed in accordance with the ESH/ESC guidelines for the management of hypertension [16]. The left ventricular mass (LVM) was calculated according to the Devereaux formula using the Penn convention LVM = 1.04 ([left ventricular internal diameter in diastole + + posterior wall thickness in diastole + interventricular septum thickness in diastole]3 – [left ventricular internal diameter in diastole]3) – 13.6 g [19]. Ultrasound carotid arteries were examined with intima–media thickness (IMT) measurement of common carotid artery and was carried out in accordance with recommendations of the Mannheim consensus with the use of the Vivid 7® VingMed (GE-Healthcare Chicago, IL, USA) [20].

Measurements of serum concentrations of UA, creatinine, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides were performed. Blood samples from the antecubital

vein were taken for the determination of serum concentrations of metalloproteinases (MMP-1, MMP-2, MMP-3 and MMP-9) and tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) in the morning hours before study procedures. Then the plasma was separated and samples stored at –75°C until analysis. TIMP-1 plasma concentrations were measured using an ELISA kit (Human TIMP-1 Immunoassay, Quantikine, R&D Systems Europe, Ltd. Abingdon, UK). The concentration of serum metalloproteinases was measured using kits from R&D Systems Europe Ltd, Abingdon, UK.

According to The Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) hyperuricemia was defined as UA concentration > 7 mg/dL (416 μmol/L) in men and > 5.7 mg/dL (339 μmol/L) in women [21]. Based on the cut-off values, the study group was divided into hyper- and normuricemia group.

Statistical analysis

Statistical analyses were performed with STA-TISTICA software (StatSoft, Poland), version 13.1. Nonparametric tests were used, because some of the variables studied did not have a normal distribution and study subgroups had different numbers. Groups were compared using the Mann-Witney U test and the association between variables was studied using the Spearman rank correlation. For the evaluation of association of HMOD with UA concentration, multivariate regression analysis was used. P-values < 0.05 were considered statistically significant.

Results

Relation of UA serum concentration with the hypertension-mediated organ damage and selected biochemical parameters

The body mass index (BMI) was 27.4 (24.3; 30.1) kg/m^2, office systolic blood pressure (SBP-office) was 150 (135; 162) mmHg, office diastolic blood pressure (DBP-office) was 93 (86; 100) mmHg, heart rate (HR) was 72 (66;79) bpm, creatinine was 65.9 (58.2; 74) μmol/L, PWV was 7.8 (7.1; 9.1) m/s, IMT was 0.6 (0.55; 0.75) mm, left ventricular mass index (LVMI) was 132.2 (103.9; 144) g. UA concentration in the whole study group positively correlated with: BMI, waist circumference, BP and some HMOD parameters (IMT, PWV, LVMI, left atrial dimension) and triglyceride level. UA concentration in the study group negatively correlated with HDL-C level. Among the metalloproteinases studied, only MMP-3 activity was positively correlated with UA serum concentration

(Fig. 1, Table 1). In multivariate regression analysis, after adjustment for age, BMI and serum lipids, UA associated with higher MMP-3 activity (R2 = = 0.11, beta = 0.332, p = 0.048) (Fig. 2) and PWV (R2 = 0.33, beta = 0.230, p = 0.0004), thicker IMT (R2 = 0.34, beta = 0.240, p = 0.04) and increased LVMI (R2 = 0.11, beta = 0.232, p = 0.0004).

The activity of MMP-3 correlated, like the concentration of UA, with the IMT (r = 0.292; p = 0.002) and the LVMI (r = 0.273; p = 0.009).

In further analyses, both factors, MMP-3 and UA serum activity together with waist circumference, SBP and DBP obtained in 24-h ABPM and serum lipids into the multivariate regression model were used to evaluate their influence on selected parameters of HMOD.

IMT value in this model was significantly positively associated with SBP and DBP (24-h mean values in ABPM), UA serum concentration and MMP-3 activity (R2 = 0.328, p < 0.002).

Only the SBP and DBP were significant determinants of PWV (R2 = 0.25, p = 0.0047).

The same multivariate regression model was not sufficient to explain LVMI variability in the group (p > 0.05).

Differences in clinical profiles of hypertensives with normo- or hyperuricemia

The hyperuricemic group consisted of 21 subjects (15 women, 6 men). The group with normouricaemia consisted of 88 subjects (40 women, 48 men).

Hypertensive patients with HU were characterized by higher BMI and waist circumference in comparison to patients without HU (Table 2).

In the HU group, higher SBP during daily activity and higher SBP and DBP during night-time were observed than in the normouricemic group (Table 2).

The group with HU compared to the normouricemic group had lower HDL-C values and higher triglyceride serum concentrations (Table 3).

Between-group differences in activity of selected MMPs (-1, -2, -3 and -9) and TIMP-1 were analyzed. Only for MMP-3 activity was a statistically significant difference obtained. Patients with HU were characterized by higher activity of MMP-3 in relation to patients without HU (Table 3).

There were no significant differences in the prevalence of diabetes or pre-diabetic conditions between the group with HU and the normouricamic group.

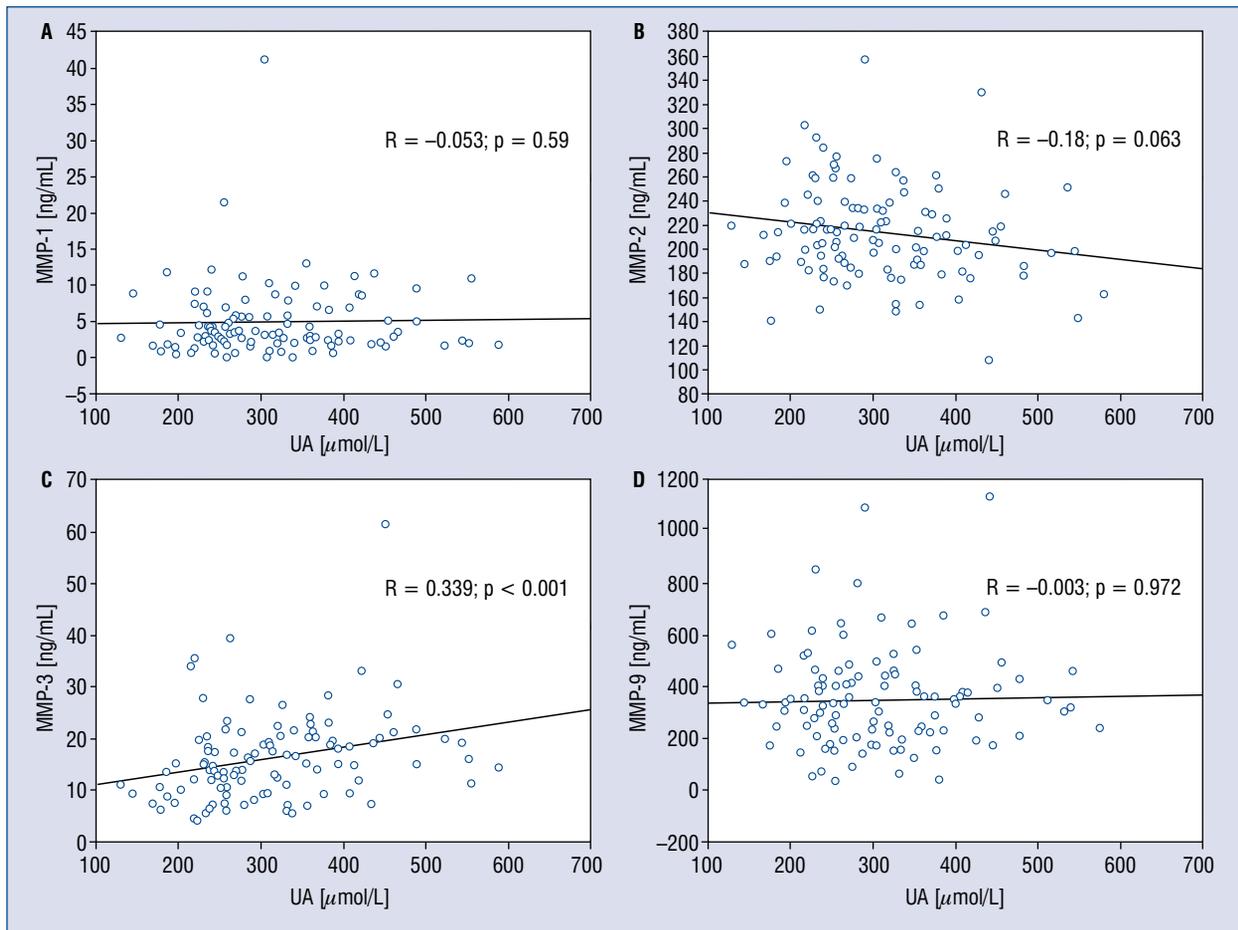The comparison of HMOD parameters between the present groups showed a greater IMT

Figure 1. A–D. The relationship between selected matrix metalloproteinase (MMP-1, -2, -3, and -9) and uric acid (UA) concentration.

of the common carotid artery and larger left atrium dimension in the M-mode parasternal long axis view in the hyperuricemic group. Patients with HU were also characterized by higher LVM, however, this difference lost significance after indexing the body surface (LVMI). There were no significant differences between the groups examined in carotid-femoral pulse wave velocity (Table 4).

Discussion

The relationship between elevated serum UA level and arterial BP is well documented in the literature. The analysis of the Framingham Study population showed positive correlations between SBP and DBP and UA [22]. The current study also observed a positive correlation of UA concentration with systolic and diastolic office BP values. A new result in the present study was a higher BP at night in patients with HU compared to normouricemic patients.

Elevated UA serum level is often recognized as an integral component of metabolic syndrome [23, 24]. The metabolic syndrome, as defined by the International Diabetes Federation in 2006, consists of: increased triglycerides and reduced HDL-C serum level, arterial hypertension, raised fasting plasma glucose or previously diagnosed type 2 diabetes and of course abdominal obesity [25]. The results the study herein, showed a positive correlation of most components of the metabolic syndrome with UA serum concentration. The hyperuricemic group was also characterized by: higher BMI, waist circumference, triglyceride concentration and lower serum HDL-C level. However, differences in the frequency of diabetes and pre-diabetes between normouricemic and hyperuricemic group were not observed.

The biochemical characteristics of the group with HU and essential hypertension in the current study was completed by higher MMP-3 activity in comparison to patients without HU. MMP-3, is a proteolytic enzyme playing a main role in the

Table 1. The correlations of serum uric acid (UA) concentration with selected variables.

Selected variable	Correlation coefficient (r) with UA	P
BMI	0.376	**< 0.001**
Waist circumference	0.486	**< 0.001**
SBP office	0.104	0.308
DBP office	0.223	**0.027**
24-h SBP	0.247	**0.025**
24-h DBP	0.238	**0.032**
SBP day	0.189	0.051
DBP day	0.256	**0.008**
SBP night	0.259	**0.008**
DBP night	0.264	**0.007**
Central BP	0.235	**0.016**
IMT	0.241	**0.012**
PWV	0.203	**0.037**
AIx-c	–0.237	**0.015**
HDL-C	–0.261	**0.006**
Triglycerides	0.362	**< 0.001**
Creatinine	0.339	**< 0.001**
MMP-1	0.053	0.590
MMP-2	–0.18	0.063
MMP-3	0.339	**< 0.001**
MMP-9	–0.003	0.972
TIMP	0.051	0.605
LVMI	0.197	**0.040**
LVM	0.376	**< 0.001**
LA (PLAX)	0.487	**< 0.001**

BMI — body mass index; SBP office — office systolic blood pressure; DBP office — office diastolic blood pressure; 24-h SBP — 24--hour systolic blood pressure; 24-h DBP — 24-hour diastolic blood pressure; SBP night — systolic nighttime blood pressure; DBP night — diastolic nighttime blood pressure; SBP day — systolic blood pressure during daily activity; DBP day — diastolic blood pressure during daily activity; BP — blood pressure; ITM — intima--media thickness; PWV — pulse wave velocity; AIx-c — central augmentation index; HDL-C — high density lipoprotein cholesterol; MMP-1, -2, -3, -9 — matrix metalloproteinase 1, 2, 3, 9; TIMP — tissue inhibitor of metalloproteinases; LVMI — left ventricular mass index; LVM — left ventricular mass, LA — left atrium dimension in PLAX presentation

Figure 2. Association between matrix metalloproteinase 3 (MMP-3) and uric acid (UA) serum levels after adjustment to: age, waist circumference, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglycerides serum concentration. Uric acid = 0.278 × MMP-3 + 259.9.

activation of other MMPs. The cascade of MMPs is responsible for the degradation of collagen and other fibrile proteins, leading to the remodeling of vascular wall, formation and destabilization of atherosclerotic plaque [26, 27].

In many diseases, MMPs are over-expressed and their over-activity leads to pathological heart and vessel remodeling, and the development of cardiovascular diseases [7, 28]. Increased activity of MMP-1, -2, -3 and -9 might also be associated
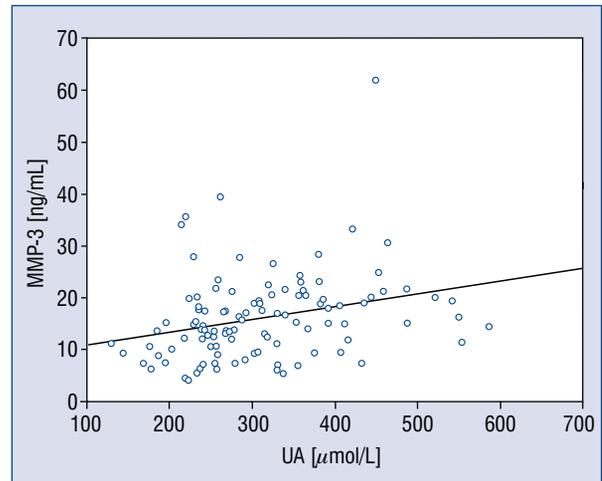
with a higher risk of death independently of other typical cardiovascular risk factors [29].

The most important result of the present study is a strong, independent association between increased activity of MMP-3 UA serum concentration in patients with mild to moderate essential arterial hypertension. The data about the association of MMP-3 activity and UA concentration in the literature is limited and includes subjects with inflammatory diseases. Increased activity of MMP-3 has been reported in gout and acute arthritis [30, 31]. In patients with lupus erythematosus a positive correlation of plasma MMP-3 and UA concentration was observed. The latter is similar to present results obtained in patients with essential arterial hypertension free of acute or chronic inflammatory diseases [32]. A positive relationship between plasma activity of collagenase-2 (MMP-2) and UA concentration in men with coronary artery disease was reported [33, 34]. Tan et al. [35] showed that higher activity of MMP-9 coexists with higher concentrations of UA and higher IMT. In opposition to the above-mentioned results in an experimental animal study performed in rats showed that UA-induced inflammation led to a decrease in MMP-9 activity [36]. Similarly, UA administration during acute phase of ischemic stroke decreased the activity of proinflammatory MMP-9 [37]. In the present study MMP-2 and MMP-9 activity did not show a significant association with UA level or HMOD parameters.

Table 2. Groups characteristics. Anthropometric and clinical data.

Selected variable	Hyperuricemic group (n = 21)	Normouricemic group (n = 88)	P (the Mann-Whitney U test)
Age [years]	52 (43; 60)	54 (42; 61)	**0.030**
Sex (no. of females)	15 (71.4%)	40 (45.5%)	0.803
Weight [kg]	88 (84; 95)	75 (65; 86)	**< 0.001**
Haight [cm]	172 (170; 176)	169 (162; 176)	0.1477
BMI [kg/m^2]	30.08 (28.4; 33.53)	26.8 (23.85; 29;48)	**< 0.001**
Waist circumference [cm]	99 (92;106)	90 (81; 97)	**< 0.001**
Heart rate [bpm]	70 (64; 75)	72 (67; 80)	0.203
SBP office [mmHg]	155 (140; 178)	150 (135; 161)	0.176
DBP office [mmHg]	94 (90; 109)	92 (85; 99)	0.073
24h SBP [mmHg]	134 (123; 138)	128 (120; 132)	0.070
24h DBP [mmHg]	82 (76; 87)	77 (72; 84)	0.118
SBP day [mmHg]	136 (125; 140)	126 (119; 133)	**0.015**
DBP day [mmHg]	83 (77; 89)	80 (74; 85)	0.092
SBP night [mmHg]	119 (112; 129)	114 (107; 121)	**0.016**
DBP night [mmHg]	73 (67; 77)	68 (62; 73)	**0.022**

Values presented as medians (interquartiles ranges) or numbers (part of the group in %). Abbreviations — see Table 1.

Table 3. Group characteristics. Biochemical blood tests.

Selected variable	Hyperuricemic group (n = 21)	Normouricemic group (n = 88)	P (the Mann-Whitney U test)
Uric acid [μmol/L]	449 (416; 487)	268 (235; 324)	**< 0.001**
MMP-1 [ng/mL]	3.51 (2.13; 8.64)	3.43 (1.99; 5.76)	0.350
MMP-2 [ng/mL]	203.8 (186.2; 218.8)	214.7 (189; 239.4)	0.233
MMP-3 [ng/mL]	19.41 (14.45; 21.74)	13.98 (9.52; 18.97)	**0.016**
MMP-9 [ng/mL]	350.1 (245.1; 432.3)	335.6 (209.9; 442.9)	0.417
TIMP [ng/mL]	92.9 (81.2; 106.8)	86.8 (80; 101.3)	0.335
Creatinine [μmol/L]	68.9 (64.2; 78.9)	65.15 (57.65; 72.55)	**0.027**
Urea [mmol/L]	6.1 (5.2; 6.8)	5.5 (4.55; 6.3)	0.0739
Total cholesterol [mmol/L]	5.43 (4.87; 5.99)	5.27 (4.57; 6.08)	0.563
LDL-C [mmol/L]	3 (2.71; 3.86)	3.21 (2.44; 3.75)	0.482
HDL-C [mmol/L]	1.17 (1.09; 1.5)	1.44 (1.19; 1.7)	**0.029**
Triglycerides [mmol/L]	1.56 (1.16; 2.18)	1.2 (0.94; 1.57)	**0.018**

Values presented as medians (interquartiles ranges). LDL-C — low density lipoprotein cholesterol; other abbreviations — see Table 1.

Lien et al. [38] studied various plasma metalloproteinase activity in atherosclerosis. Only increased MMP-3 activity showed a significant relationship with the degree of atherosclerosis in the carotid arteries. A similar result was obtained in our study. The severity of atherosclerosis in carotid arteries evaluated by IMT was related to UA and MMP-3 concentrations. Kawamoto et al. [39] showed that UA in men may increase carotid atherosclerosis independent of other factors. The authors concluded that people with hypertension and hyperuricemia are characterized by greater IMT than hypertensive patients without HU. Increased IMT in this study correlated with UA concentration independently of the BP level. Hyperuricemia may also negatively affect other HMOD indicators [40].

In a population of more than 4,000 healthy participants selected from the Generation 3 Framing-

Table 4. Selected hypertension-mediated organ damage (HMOD).

Selected HMOD	Hyperuricemic group (n = 21)	Normouricemic group (n = 88)	P (the Mann-Whitney U test)
LVMI [g/m²]	129.32 (114.72; 156.53)	123.1 (102.03; 138.93)	0.145
LVM [g]	268.62 (220.77; 331.19)	226.41 (185.76; 261.6)	**0.006**
LA (PLAX) [mm]	45 (42; 46)	40 (36; 43)	**< 0.001**
IMT [mm]	0.65 (0.6; 0.8)	0.6 (0.5; 0.75)	**0.038**
PWV [m/s]	8.4 (7.4; 8.9)	7.7 (7.1; 9.2)	0.258
c-AIx [%]	24 (14; 29)	25 (14; 33)	0.524
eGFR [mL/min/1.73 m²]	95 (82; 109)	97.5 (86; 108)	0.514

Values presented as medians (interquartiles ranges). LVMI — left ventricular mass index; LVM — left ventricular mass; LA — left atrium dimension in PLAX presentation; IMT — intima–media thickness; PWV — pulse wave velocity, c-AIx — central augmentation index; eGFR — estimated glomerular filtration rate

ham cohort, an independent positive relationship between UA level and carotid-femoral PWV was proved [41]. In a much smaller study, carried out with a group of 222 subjects with essential hypertension, a positive correlation of PWV with UA in hypertensive patients was also observed [42]. In the current study, the group of patients with essential hypertension showed a positive correlation of arterial stiffness (evaluated by carotid-femoral PWV) with UA concentration.

There are existing reports in the literature indicating that UA serum concentration is associated with decreased left ventricular function and left ventricle hypertrophy [43, 44]. In the patients of this study a positive correlation was observed between UA and LVMI and UA and the left atrium dimension. Similar results have been described by Tavil et al. [45]. The current study also performed a multivariate regression analysis of the simultaneous effect of UA and MMP-3 concentrations on the other HMODs. Analysis for LVMI did not show statistical significance. In the case of PWV, BP values played the main role, and the effects of UA and MMP-3 were not significant.

Based on these results and data from the literature, it was suspected that among different indicators of HMOD (except for) hypertension there are big differences in factors determining their development and advancement. IMT is the HMOD most closely reflecting atherosclerosis; in the present study it was associated with proinflammatory factors like UA concentration and MMP-3 activity. Results obtained herein may support the thesis that UA and increased by UA activity of MMPs may take part in the development of HMOD, especially IMT. These results are consistent with the inflammatory and free radicals hypothesis of UA side effects.

However UA may play both pro- and anti-oxidative roles, depending on its concentration, solubility and place of action (plasma or cells) [46], free radicals formed in various mechanisms in hyperuricemia [47] have a great potential to activate various inflammatory mechanisms, including the activation of metalloproteinases cascade [48].

Conclusions

In patients with primary arterial hypertension UA concentration is associated with higher MMP-3 serum activity and selected hypertension-mediated organ damage advancement, especially carotid IMT. Patients with HU and arterial hypertension are characterized by a symptom cluster typical for metabolic syndrome and more advanced structural changes in the heart and vessels as well as higher activity of MMP-3.

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