Serum uric acid and carotid artery intima media thickness in patients with masked hypertension

Mustafa CALISKAN[1], MD; Aytekin GUVEN[2], MD; Ozgur CIFTCI[2], MD; Mehmet OZULKU[3], MD; Murat GUNDAY[3], MD; Irfan BARUTCU[4], MD

[1]Istanbul Medeniyet University School of Medicine, Dept. of Cardiology, Istanbul; [2]Baskent University School of Medicine, Dept. of Cardiology, Konya; [3]Baskent University School of Medicine, Dept. of Cardiovascular Surgery, Konya; [4]Medipol University School of Medicine, Dept. of Cardiology, Istanbul, Turkey.

Background Serum uric acid is related to hypertension and cardiovascular diseases. Masked hypertension is associated with an increase in cardiovascular risk. The aim of our study was to evaluate the serum uric acid level and its relationship with carotid intima-media thickness (IMT) in patients with masked hypertension.

Subjects and methods A total of 114 untreated masked hypertension patients (62 men, 52 women; mean age 44.6 ± 7.9 years) and 38 controls (20 men, 18 women; mean age 44.8 ± 7 years) were included in the study. All patients underwent 24-hour ambulatory blood pressure. Serum uric acid and carotid IMT were measured.

Results Serum uric acid was significantly higher in masked hypertension patients when compared to the control group (5.14 ± 1.42 mg/dl, 4.84 ± 1.45 mg/dl, $P = 0.01$). Masked hypertension patients had significantly higher carotid IMT than control subjects (0.58 ± 0.09, 0.52 ± 0.09, $P < 0.001$). The masked hypertension group was also divided into two groups according to the median value of the serum uric acid levels (median value: 5 mg/dl). Carotid IMT was significantly higher in patients with a higher uric acid when compared to those with a lower uric acid ($P < 0.001$). We also found that the serum uric acid level was a good predictor of increased carotid IMT at the receiver-operating characteristic curve. The area under the curve was 66% (95% confidence interval, 0.56-0.77), and the serum uric acid level was significantly predictive of a high carotid IMT ($P = 0.001$).

Conclusions Our data suggest that the uric acid levels were significantly higher in the masked hypertension group and elevated uric acid levels were associated with increased carotid IMT, indicating that elevated serum uric acid levels might contribute to the increase in cardiovascular risk in masked hypertension.

Keywords *Uric acid – carotid intima-media thickness – masked hypertension.*

INTRODUCTION

Uric acid is a major product of the purine metabolism in humans. Extensive epidemiologic and experimental evidence now suggests that serum uric acid is a relevant risk factor for cardiovascular and renal disease, particularly in patients with hypertension, heart failure, or diabetes[1]. Hyperuricaemia predicts mortality in patients with heart failure or coronary heart disease, cerebrovascular events in individuals with diabetes, and cardiac ischaemia in hypertension[2-5]. The mechanisms by which uric acid may engender organ damage is still incompletely understood, but there is increasing evidence that endothelial dysfunction is a fundamental mechanism whereby this substance may affect cardiovascular and renal function and structure[6]. The association of hyperuricaemia with hypertension has long been recognized[7]. Elevated serum uric acid levels have been associated with increased risk for developing hypertension[8-12].

The ultrasound-based measurement of carotid intima-media thickness (IMT) has become a standard for non-invasive assessment of arteriosclerosis. Increased

Address for correspondence:

Prof. Aytekin GUVEN, M.D.,
Baskent University School of Medicine, Dept. of Cardiology,
Konya, Turkey.
E-mail: aytekinguven@hotmail.com

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carotid IMT is a structural marker of early atherosclerosis related to vascular risk factors, and predicting cardiovascular events in different population groups[13,14].

Masked hypertension, which is often defined as isolated ambulatory hypertension, is a clinical condition characterized by normal clinic blood pressure measurements but elevated values at home measurements or during ambulatory blood pressure monitoring. Until recently, little attention has been paid to this condition, but recent evidence demonstrates that masked hypertension is a significant predictor of target organ damage and cardiovascular disease[15-17].

Currently, there is no study investigating the relationship among serum uric acid levels and carotid IMT and masked hypertension. Therefore, the present study was designed to evaluate serum uric acid levels and carotid IMT in masked hypertension subjects and to compare them to those of normotensive control subjects.

SUBJECTS AND METHODS

Study populations

A total of 114 subjects for the untreated masked hypertension group and 38 healthy subjects for the control group were consecutively selected from our cardiology outpatient clinic.

Exclusion criteria were evidence of coronary artery disease, peripheral vascular diseases, secondary hypertension, chronic heart failure, diabetes mellitus, renal or hepatic dysfunction, stroke, haematological disease, cancer, thrombocytopenia, systemic inflammatory conditions, auto-immune disease, smoking, alcohol consumption and use of antithrombotic drugs. The study was conducted according to the recommendations set forth by the Declaration of Helsinki on Biomedical Research Involving Human Subjects. Written informed consent was obtained from each subject, and our institutional ethics committee approved the study protocol.

Measurement of blood pressure

At the medical office blood pressure (BP) was measured with a mercury sphygmomanometer with an appropriate cuff. After a 5-10 minute resting period, the measurements were taken from the patient's bare right arm, which was supported and maintained at the heart level. Three measurements were taken and averaged as the mean systolic and diastolic pressure values.

In the same study period, all subjects underwent non-invasive 24-h ambulatory blood pressure monitoring on a daily activity. BP and heart rate were measured every 15 min during the daytime (between 07.00 AM and 23.00 PM) and every 30 min during nighttime (between 23.00 PM and 07.00 AM) by the oscillometric method using an automatic monitoring device (Spacelabs Medical Inc., Model 90207, Redmond, Virginia USA).

Classification of study population according to blood pressure

Participants were classified into two groups based on their office BP and 24-h ambulatory BP values: normotension (mean office BP < 140/90 mmHg and daytime ambulatory BP < 135/85 mmHg), masked hypertension (mean office BP < 140/90 mmHg, and daytime ambulatory BP ≥ 135/85 mmHg). This definition of masked hypertension is based on the European Society of Hypertension and European Society of Cardiology guidelines.

Carotid intima-media thickness measurement

A high resolution 7.5-MHz linear array transducer (EUB 6500; Hitachi, Tokyo, Japan) was used to scan the two common carotid arteries longitudinally. With the subject in the supine position, longitudinal scanning was performed from the common carotid artery to the bifurcation point. After the bifurcation of the common carotid artery had been confirmed, the carotid IMT was measured from the far wall of the right carotid artery within 10 mm proximal to the bifurcation. The IMT, defined as the distance between the intima-luminal interface and the media-adventitial interface, was measured as previously described[18]. Three points were measured on one scan, which was synchronized with the R-wave peaks on the electrocardiogram to avoid possible errors resulting from variable arterial compliance. Mean carotid IMT was calculated from six measurements on two scans. One investigator who was unaware of the subjects' clinical data carried out all the measurements. The ultrasound images were recorded by videotape for off-line analysis. No subject had atheromatous plaque or a localized lesion in the imaged region. The intraobserver coefficient of variation for carotid IMT was 1.4%.

Laboratory analyses

Venous blood samples were obtained from each participant after overnight fasting for the determination of serum glucose, serum creatinine, and lipid profile (total cholesterol, triglycerides, and low and high lipoprotein cholesterol), according to established methods. Serum uric acid levels were measured by an enzymatic colorimetric method on an autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA). Plasma levels of high sensitive C-reactive protein were measured by means of particle-enhanced immunonephelometry with the Behring

nephelometer method using N Latex CRP mono reagent (Behring Werke, Marburg, Germany).

Statistical analyses

SPSS statistical software (SPSS for Windows, version 17.0, Inc., Chicago, IL, USA) was used for all statistical calculations. Categorical variables were expressed as number and proportions, while continuous variables were expressed as mean ± standard deviation. The chi square (χ^2) test was used to compare groups regarding categorical variables. Continuous variables were compared with the Student *t*-test (while comparing parametric variables between masked hypertension patients and controls) or Mann-Whitney *U* test (while comparing non-parametric variables between masked hypertension patients and controls). Correlation analysis was performed using the Pearson or Spearman tests. Linear regression analysis was used to explore the independent determinants of carotid IMT. The masked hypertension group was also divided into two groups according to the median value of the serum uric acid levels (median value: 5 mg/dl). Lower and higher uric acid groups were compared using the Student's *t*-test for multiple comparisons. The receiver-operating characteristic (ROC) curve was determined to evaluate the predictive performance of serum uric acid to detect high carotid IMT. The area under the ROC curve (AUC), and its standard error were calculated. A *P* value of < 0.05 was considered significant.

RESULTS

In total, 152 subjects were included in the study. The masked hypertension group consisted of 114 patients (62 men, 52 women; mean age 44.6 ± 7.9 years), and the control group consisted of 38 subjects (20 men, 18 women; mean age 44.8 ± 7 years). The demographic and baseline characteristics of the study population are shown in table 1.

Masked hypertension subjects had significantly higher 24-h systolic and diastolic BP values than control subjects ($P < 0.001$). Mean office BP and ambulatory BP values of study population are shown in table 1.

Table 1 Baseline clinical characteristics of the study populations.

	Control group (n = 38)	Masked hypertension (n = 114)	*P* value
Age (years)	44.8 ± 7.0	44.6 ± 7.9	NS
Male/female	20/18	62/52	NS
BMI (kg/m^2)	27.3 ± 2.2	27.4 ± 2.4	NS
Heart rate (beats/min)	69.3 ± 9.9	70.9 ± 6.8	NS
Office SBP (mmHg)	124.0 ± 7.5	130.9 ± 5.8	NS
Office DBP (mmHg)	76.9 ± 5.8	78.6 ± 6.6	NS
Ambulatory 24-h SBP (mmHg)	120.2 ± 11.2	140.9 ± 6.7	< 0.001
Ambulatory 24-h DBP (mmHg)	75.4 ± 7.6	84.6 ± 9.6	< 0.001
Ambulatory daytime SBP (mmHg)	125.5 ± 8.2	146.5 ± 7.2	< 0.001
Ambulatory daytime DBP (mmHg)	72.2 ± 6.7	90.4 ± 6.1	< 0.001
Ambulatory nighttime SBP (mmHg)	110.5 ±5.6	130.6 ± 6.5	< 0.001
Ambulatory nighttime DBP (mmHg)	70 ± 5.5	75.5 ±7.1	< 0.001
Total cholesterol (mg/dl)	190.2 ± 27.6	192.2 ± 30.5	NS
HDL-cholesterol (mg/dl)	47.6 ± 11.6	45.9 ± 8.9	NS
LDL-cholesterol (mg/dl)	116.2 ± 21.8	118.1 ± 23.7	NS
Triglycerides (mg/dl)	134.9 ± 48.7	139.5 ± 58.1	NS
hs-CRP (mg/l)	2.42 ± 1.89	3.18 ± 2.09	0.01
Creatinine (mg/dl)	0.87 ± 0.15	0.89 ± 0.16	NS
Fasting blood glucose (mg/dl)	92.6 ± 6.2	94.3 ± 8.9	NS
Uric acid (mg/dl)	4.84 ± 1.45	5.14 ± 1.42	0.01
Carotid IMT (mm)	0.52 ± 0.09	0.58 ± 0.09	< 0.001

NS: not significant, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, BP: blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, IMT: intima-media thickness.

Uric acid was significantly higher in masked hypertension patients when compared to the control group (5.14 ± 1.42 mg/dl, 4.84 ± 1.45 mg/dl, $P = 0.01$). Plasma hs-CRP levels were significantly higher in patients with masked hypertension than in normotensive healthy subjects (3.18 ± 2.09 mg/l, 2.42 ± 1.89 mg/l, $P = 0.01$).

Masked hypertension patients had a significantly higher carotid IMT than control subjects (0.58 ± 0.09, 0.52 ± 0.09, $P < 0.001$).

The masked hypertension group was also divided into two groups according to the median value of the serum uric acid levels (mean value: 5 mg/dl for masked hypertension patients). Carotid IMT and hs-CRP levels were significantly higher in patients with a higher uric acid level of the masked hypertension patients when compared to patients with a lower uric acid level of the masked hypertension patients ($P < 0.001$, $P = 0.03$, respectively, table 2).

There was a significant positive correlation between carotid IMT and uric acid (r = 0.295, $P < 0.001$) and hs-CRP levels (r = 0.176, $P = 0.02$), ambulatory 24-h systolic BP (r = 0.253 $P < 0.001$), ambulatory 24-h diastolic BP (r = 0.301 $P < 0.001$) in masked hypertension subjects. (table 3).

Linear regression analysis suggested that serum uric acid level ($\beta = 0.014$, $P = 0.002$) and ambulatory 24-h diastolic BP ($\beta = 0.002$, $P < 0.001$) were independent predictors of carotid IMT in masked hypertension patients.

We also demonstrated that uric acid level was an accurate predictor of high carotid IMT at the ROC curve. The area under the curve (AUC) was 66% (95% CI: 0.56-0.77), and the uric acid levels were significantly predictive of high carotid IMT ($P = 0.001$). Serum uric acid level had a sensitivity of 61.6% and specificity of 70.3% (cut-off ≥ 4.85) to detect patients with higher carotid IMT values ($P = 0.001$). The area under the ROC curve (AUC) = 0.666 (figure 1).

Table 2 Laboratory and carotid IMT values of masked hypertension patients according to median uric acid levels (5 mg/dl)

	MH patients with lower uric acid (n = 60)		MH patients with higher uric acid (n = 54)		*P* value
	Male (n = 38)	Female (n = 22)	Male (n = 35)	Female (n = 21)	
Carotid IMT	0.54 ± 0.06	0.55 ± 0.07	0.66 ± 0.06	0.62 ± 0.09	< 0.001
hs-CRP					
Median	3.1	2.4	3.5	4.8	0.03
Interquartile range	1.3-4.4	1.2-4.1	1.5-5.2	2.1-5.7	
Creatinine					
Median	1	0.8	1	0.8	NS
Interquartile range	0.9-1	0.7-0.9	0.9-1.1	0.7-0.8	
Total cholesterol					
Median	200	189	202	179	NS
Interquartile range	182-217	171-207	179-220	158-204	
HDL-C					
Median	42	47	41	51	NS
Interquartile range	40-46	43-51	38-47	40-63	
LDL-C					
Median	128	119	129	120	NS
Interquartile range	105-142	102-128	101-135	98-138	
Triglycerides					
Median	170	159	174	163	NS
Interquartile range	127-202	92-193	105-210	82-196	
Ambulatory daytime SBP (mmHg)	136 ± 12	134 ± 18	140 ± 11	136 ± 16	NS
Ambulatory daytime DBP (mmHg)	86 ± 7	86 ± 11	89 ± 8	86 ± 13	NS
Ambulatory nighttime SBP (mmHg)	122 ± 10	123 ± 16	128 ± 11	125 ± 19	NS
Ambulatory nighttime DBP (mmHg)	75 ± 7	77 ± 10	78 ± 10	76 ± 12	NS
Non-dipper n (%)	5 (13.1)	4 (18.1)	7 (20)	3 (14.2)	NS

MH: masked hypertension, NS: not significant, HDL: high-density lipoprotein, LDL: low-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, IMT: carotid intima-media thickness, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Table 3 Partial correlation coefficient (r) and *P* value between carotid IMT and various risk parameters in patients with masked hypertension.

	Univariate correlations coefficient	*P* value
Age (year)	0.114	0.13
hs-CRP (mg/l)	0.176	0.02
Total cholesterol (mg/dl)	0.035	0.64
Triglycerides (mg/dl)	0.022	0.77
HDL cholesterol (mg/dl)	–0.091	0.24
LDL cholesterol (mg/dl)	0.082	0.28
Uric acid (mg/dl)	0.295	< 0.001
Ambulatory 24-h SBP (mmHg)	0.253	< 0.001
Ambulatory 24-h DBP (mmHg)	0.301	< 0.001

hs-CRP: high-sensitivity C-reactive protein, SBP: systolic blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein; IMT: intima-media thickness.

DISCUSSION

The main finding of this study is that uric acid, hs-CRP levels and carotid IMT are significantly higher in the masked hypertension subjects than normotensive healthy subjects. Second, there is a positive correlation between uric acid and hs-CRP levels in masked hypertension subjects. Thirdly, there is a significant positive correlation between uric acid and carotid IMT in masked hypertension subjects. These results may indicate that elevated serum uric acid levels are associated with the increased cardiovascular risk in masked hypertension.

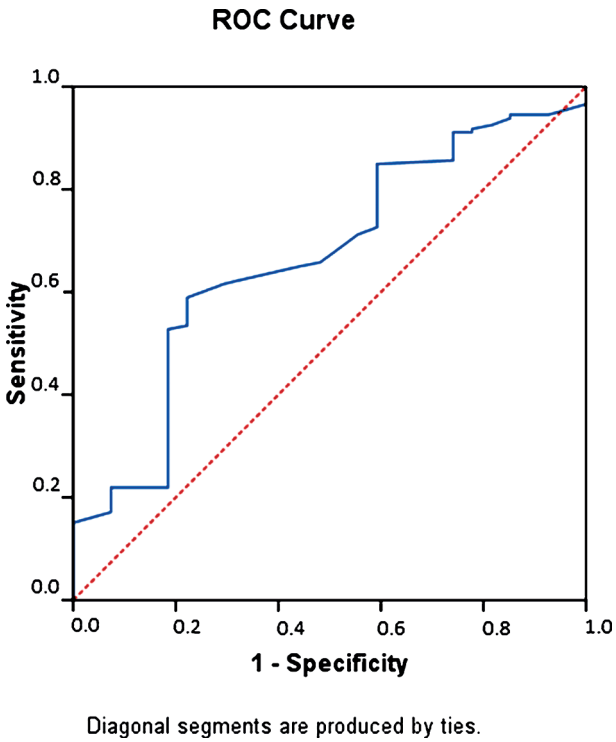

Fig. 1 Receiver-operating characteristic (ROC) curve analysis of serum uric acid levels for carotid intima-media thickness. Diagonal segments are produced by ties. AUC, area under the ROC curve (AUC = 0.666, *P* = 0.001).

Potential mechanisms between uric acid level and the risk of developing hypertension have been investigated in experimental studies. It has been shown that hyperuricaemia causes hypertension and renal vascular injuries through the activation of the renin-angiotensin system[19,20]. It has also been shown that uric acid causes renal afferent arteriopathy and tubulointerstitial disease, leading to hypertension in a rodent model of hyperuricaemia[20]. Uric acid also affects vascular smooth muscle cell proliferation and inhibits nitric oxide production and thereby leads to endothelial dysfunction[21,22].

A variety of studies have reported that hyperuricaemia is associated with hypertension. Hyperuricaemia was observed in 25-60% of untreated hypertensive patients[23]. Higher serum uric acid levels were also found in 89% of children with primary hypertension[24]. In addition, uric acid is independently associated with prehypertension. The National Health and Nutrition Examination Survey (NHANES) reported that the multivariable-adjusted odds ratio for prehypertension was 1.96 in subjects with uric acid above 6 mg/dL in comparison to those with uric acid below 4 mg/dL[25]. A larger survey that enrolled 14,451 adults free of hypertension confirmed the above findings[26]. These study results suggest that uric acid may have a role in the early pathogenesis of hypertension.

Fang et al. analysed data from the NHANES I Epidemiologic Follow-up Study and concluded that both systolic and diastolic blood pressure were associated with increasing serum uric acid levels in the general

population[27]. Verdecchia et al. recruited 1,720 untreated adult hypertensive subjects and measured their blood pressure and biochemistry[28]. This study demonstrated that hypertensive patients with high levels of serum uric acid were associated with higher office and ambulatory systolic blood pressure than those with lower uric acid levels.

Jones et al. measured 24-h ambulatory blood pressure and serum uric acid in 104 children referred for possible hypertension[29]. They found that uric acid was significantly associated with 24-h and nocturnal diastolic blood pressure, independent from sex, ethnicity, and body mass index. Uric acid was also significantly associated with increased risk of diastolic hypertension, with an odds ratio of 2.1 after adjusting for confounding factors in these children. Serum uric acid appears to be an important marker of high blood pressure in adults and in children[29].

In the Framingham Heart Study, 3,329 participants free of hypertension were investigated to determine the relationship of serum uric acid to hypertension incidence. In that study, hypertension incidence increased progressively from 9.8% for the lowest quartile to 15.6% for the top quartile of serum uric acid during 4 years of follow-up[30]. Accordingly, we found higher uric acid levels in masked hypertension patients than in the normotensive control group. We also found a positive correlation between uric acid and ambulatory 24-h systolic BP values in masked hypertension subjects.

Carotid IMT measured by ultrasonography is used as a surrogate marker for atherosclerotic disease and can be used to predict clinical events. Tavil et al. found that carotid IMT was increased in patients with hypertension independently of hyperuricaemia when compared with control subjects[31]. However, subjects presenting with both hypertension and hyperuricaemia had increased carotid IMT compared to those with normal uric acid levels. In addition, there were significant associations between carotid IMT measurement, serum uric acid level, and other major atherosclerotic risk factors[31]. A cross-sectional evaluation of the ARIC study population in white and black U.S. individuals showed that serum uric acid levels were associated with IMT in both sexes. However, this association lost its significance in women and was reduced in men after adjustment for other risk factors[32].

Our study implicated that subjects with masked hypertension have increased carotid IMT and serum uric acid levels were an independent predictor of carotid IMT in masked hypertension patients. Another significant finding was that carotid IMT was significantly higher in patients with higher uric acid levels when compared to patients with lower uric acid levels in masked hypertension patients.

Although endothelial dysfunction has been reported as the factor responsible for hyperuricaemia in cardiovascular disease, other related hormonal and cytokine effects of uric acid-mediated pro-inflammation and proliferation on vascular smooth muscle cells (SMCs) are also important[33]. The increased CRP levels are a risk factor for cardiovascular diseases[34]. Uric acid-induced expression of CRP has been observed previously in human vascular SMCs and endothelial cells[35]. More importantly, uric acid was found to be associated with several inflammatory markers, including CRP and IL-6, in a population-based study[36,37]. Thus, these results imply that uric acid may induce endothelial dysfunction and vascular inflammation reaction, which play pivotal roles in the pathogenesis of atherosclerosis[38].

In our study, we found higher hs-CRP levels in masked hypertension patients than in the normotensive control group. Also, we found that hs-CRP is significantly higher in patients with higher uric acid levels when compared to lower uric acid levels of the masked hypertension patients.

STUDY LIMITATIONS

Our study has some limitations. First, a small number of individuals were included in this study. Second, our findings could not be extrapolated to all masked hypertension patients because we excluded patients with smoking, diabetes, obesity, renal failure, ischaemic heart disease and peripheral vascular disease, and therefore, the study does not provide information about the association between the serum uric acid levels and carotid IMT in the overall group of patients with masked hypertension.

CONCLUSION

To our knowledge, this is the first study to evaluate uric acid, hs-CRP levels and carotid IMT in masked hypertension. We found that patients with masked hypertension have higher uric acid and hs-CRP levels and increased carotid IMT when compared to normotensive control subjects. Our results may suggest that patients with masked hypertension are prone to endothelial dysfunction. However, further large-scale studies are needed to clarify whether endothelial dysfunction could contribute to increase the cardiovascular risk in patients with masked hypertension.

CONFLICT OF INTEREST: none.

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