Journal of Cardiology 61 (2013) 144–148

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Uric acid and high sensitive C-reactive protein are associated with subclinical thoracic aortic atherosclerosis

Mustafa Gür (MD)[a,*], Durmuş Yıldıray Şahin (MD)[a], Zafer Elbasan (MD)[a], Gülhan Yüksel Kalkan (MD)[a], Ali Yıldız (MD)[b], Zekeriya Kaya (MD)[b], Betül Özaltun (MD)[a], Murat Çaylı (MD)[a]

[a] *Adana Numune Education and Research Hospital, Department of Cardiology, Adana, Turkey*
[b] *Harran University, School of Medicine, Department of Cardiology, Şanlıurfa, Turkey*

ARTICLE INFO

Article history:
Received 5 July 2012
Received in revised form 23 August 2012
Accepted 26 August 2012
Available online 16 November 2012

Keywords:
Uric acid
Aorta
Atherosclerosis
C-reactive peptide
Intima media

ABSTRACT

Background and purpose: The detection of atherosclerotic lesions in the aorta by transesophageal echocardiography (TEE) is a marker of diffuse atherosclerotic disease. Hyperuricemia is a well-recognized risk factor for cardiovascular diseases. However, no data are available concerning the relationship between serum uric acid (UA) and subclinical thoracic aortic atherosclerosis. We aimed to investigate the association between thoracic aortic atherosclerosis and serum UA level.
Methods: We studied 181 patients (mean age 46.3 ± 8 years) who underwent TEE for various indications. Four different grades were determined according to intima–media thickness (IMT) of thoracic aorta. UA and other biochemical markers were measured with an automated chemistry analyzer.
Results: TEE evaluation characterized thoracic aortic intimal morphology as Grade 1 in 69 patients, Grade 2 in 52 patients, Grade 3 in 31 patients, and Grade 4 in 29 patients. The highest UA level was observed in patients with Grade 4 IMT when compared with Grade 1 and 2 IMT groups ($p < 0.001$ and $p = 0.014$, respectively). UA levels in patients with Grade 3 and Grade 2 IMT were also higher than patients with Grade 1 IMT group ($p < 0.001$, for all). In multiple linear regression analysis, IMT was independently associated with UA level ($\beta = 0.350$, $p < 0.001$), age ($\beta = 0.219$, $p = 0.001$), total cholesterol ($\beta = -0.212$, $p = 0.031$), low-density lipoprotein cholesterol ($\beta = 0.350$, $p = 0.001$), and high sensitivity C-reactive protein (hsCRP) levels ($\beta = 0.148$, $p = 0.014$).
Conclusion: Uric acid and hsCRP levels are independently and positively associated with subclinical thoracic atherosclerosis.

Introduction

Uric acid (UA) is the final product of purine nucleotides metabolism. UA is a major antioxidant in human plasma [1]. However, UA has a more complex relationship to oxidative stress, possessing both scavenging properties and oxidizing and radical-forming properties [2,3]. Serum UA is an independent risk factor for cardiovascular disease [4,5]. Ultrasonographically measured carotid intima–media thickness (IMT) is a marker for atherosclerotic disease [6] and serum UA levels were reported to be positively correlated with subclinical carotid atherosclerosis (AS) [7,8].

Aortic atherosclerotic lesions detected on transesophageal echocardiography (TEE) are markers of diffuse atherosclerotic disease [9,10] and thoracic aortic IMT was reported as an earlier marker of preclinical AS than carotid IMT [11]. We hypothesized that UA level may be related to thoracic AS, but the association between thoracic aortic AS and serum UA level remains to be investigated in humans. Therefore, in the present study, we aimed to assess the relationship between thoracic aortic AS with serum UA level and other biochemical markers such as low-density lipoprotein (LDL) and high sensitive C-reactive protein (hsCRP) in patients undergoing TEE examination for various indications.

Methods

Subjects

Of the 549 TEE procedures performed between January 2011 and May 2012 in our clinic, we evaluated 181 patients who had non-atherosclerotic heart disease who underwent TEE examination for various indications (86 male, 95 female; mean age 45.2 ± 8.4 years), which included evaluation and management of atrial fibrillation (62 patients), valvular heart disease (30 patients for mitral valve

* Corresponding author at: Adana Numune Education and Research Hospital, Department of Cardiology, Adana 01150, Turkey. Tel.: +90 5052661824; fax: +90 322 338 33 69.
E-mail address: drmugur@yahoo.com (M. Gür).

0914-5087/$ – see front matter © 2012 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jjcc.2012.08.023

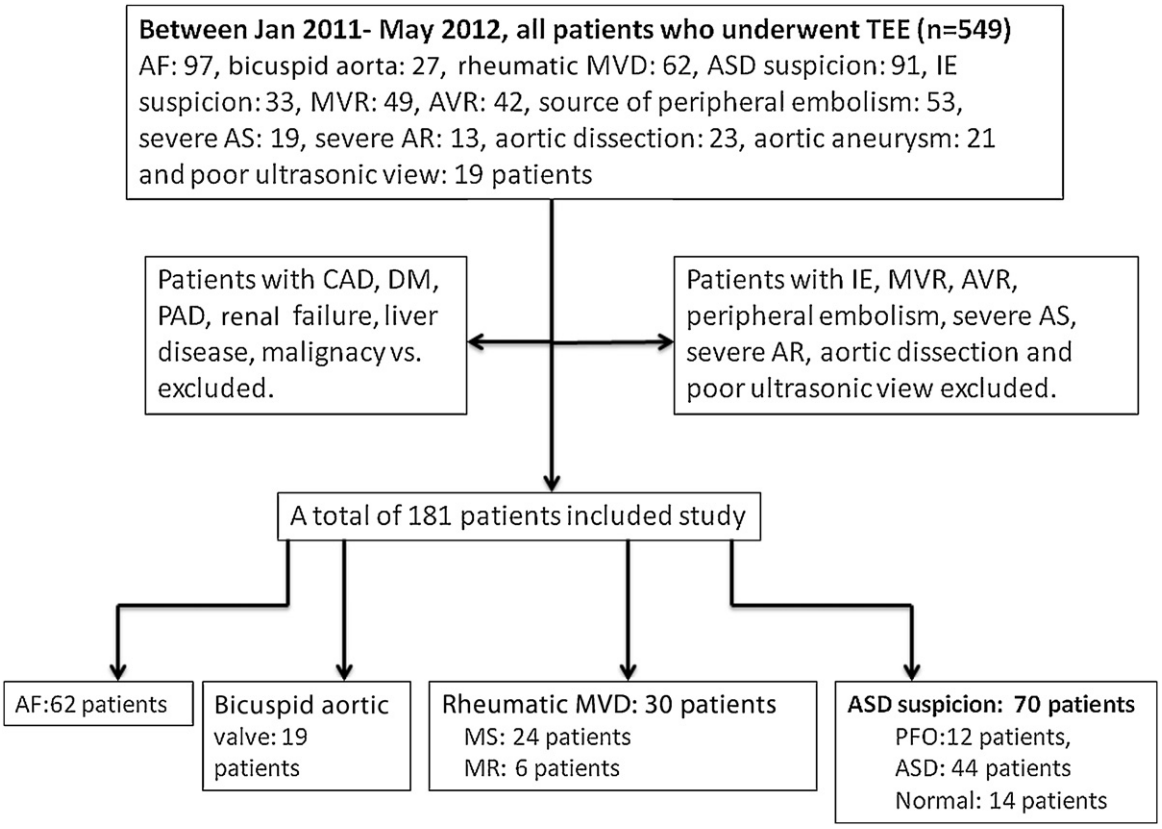

Fig. 1. Flow diagram of the study. TEE, transesophageal echocardiography; AF, atrial fibrillation; MVD, mitral valve disease; ASD, atrial septal defect; IE, infective endocarditis; MVR, mitral valve replacement; AVR, aorta valve replacement; AS, aortic stenosis; AR, aortic regurgitation; CAD, coronary artery disease; PAD, peripheral artery disease; DM, diabetes mellitus; MS, mitral stenosis; MR, mitral regurgitation; PFO, patent foramen ovale.

disease, 19 patients for aortic valve disease), and suspected atrial septal defect (70 patients) (Fig. 1).

Patients with known coronary artery disease or clinical signs of ischemic heart disease, heart failure, peripheral vascular disease, kidney and liver diseases, malignancy, hypertension, diabetes mellitus, and patients with history of carotid artery surgery or stroke besides current smokers were excluded from the study. We also excluded patients with familial hypercholesterolemia, aortic dissection, or aortic aneurysm, as well as the patients with poor ultrasonographic recording quality with no clear delineation of the intima–media complex. In addition, patients taking anti-oxidant drugs, diuretics, vitamins, and alcohol were also excluded from the study. Positive exercise treadmill test was also an exclusion criterion in our study. Institutional ethics committee approved the study and written informed consent for participation in the study was obtained from all individuals.

Age and gender were recorded and body mass index (BMI) was computed as weight divided by height squared (kg/m^2).

Transthoracic and transesophageal echocardiography

Transthoracic echocardiography and TEE were performed in all study subjects by using a commercially available system (Vivid 7®, GE Medical Systems, Horten, Norway). Left ventricular ejection fraction (EF) was determined by Teichholz method [12].

All patients underwent TEE by using a multiplane transesophageal transducer after a 4-h fasting period prior to the procedure. Subjects were placed in left decubitus with the left arm under the head, which was kept in a flexed position after oropharyngeal anesthesia with lidocaine spray. The transducer was introduced for visualization of the cardiac and aortic structures into the esophagus and gastric cavity through the mouth. An experienced cardiologist blinded to other laboratory results performed TEE. TEE was well tolerated by all patients, and there were no complications. A well-standardized protocol, which has been previously described, was applied to cardiac examinations in all patients [9]. All studies were recorded on videotape recorder and were interpreted independently by an experienced observer.

IMT of the thoracic aorta was graded using a previously described classification [9]. The thoracic aorta was considered normal (Grade 1) when the intimal surface was smooth and continuous without lumen irregularities or increased echo density, with an intimal thickness less than 1.0 mm. Grade 2 was defined as a simple atherosclerotic plaque with increased echo density of the intima extending <3.0 mm into the aortic lumen. Grade 3 was defined as an atherosclerotic plaque extending ≥3.0 mm and <5.0 mm into the aortic lumen. In Grade 4, the atherosclerotic plaque was ≥5.0 mm in thickness.

Blood sampling

Blood samples were obtained following an overnight fasting state just before TEE examination. Blood samples were centrifuged at 3000 rpm for 10 min. Plasma samples were stored at −70 °C until analysis for UA, hsCRP, triglyceride, total cholesterol, LDL, high-density lipoprotein (HDL), and fasting glucose.

Measurement of biochemical markers

Plasma UA, triglyceride, total cholesterol, LDL, HDL concentrations, and fasting glucose were measured with an automated chemistry analyzer (Aeroset, Abbott, Abbott Park, IL, USA) by using

Table 1
Comparison of demographic, clinical, and laboratory characteristics in groups.

Variables	Grade 1 ($n=69$)	Grade 2 ($n=52$)	Grade 3 ($n=31$)	Grade 4 ($n=29$)	p-Value (ANOVA)
Age (years)	42.3 ± 8.4[a]	44.7 ± 8.2[aa]	47.4 ± 7.0	50.6 ± 7.2	**<0.001**
Male gender n (%)	24 (34.8)	27 (51.9)	18 (58.1)	17 (58.6)	**0.05**[×]
BMI (kg/m^2)	26.7 ± 2.9	26.9 ± 3.6	26.4 ± 5.0	27.1 ± 3.1	0.869
SBP (mmHg)	117.5 ± 11.4	117.6 ± 12.7	119.5 ± 13.8	117.2 ± 12.3	0.887
DBP (mmHg)	74.4 ± 6.7	73.7 ± 9.2	74.5 ± 9.9	75.2 ± 8.5	0.882
EF (%)	65.8 ± 3.7	65.4 ± 3.7	65.7 ± 4.3	66.3 ± 3.7	0.681
Glucose (mg/dl)	86.5 ± 8.5	85.2 ± 10.0	87.4 ± 9.9	87.1 ± 6.8	0.697
TC (mg/dl)	187.7 ± 34.7[b]	206.3 ± 31.5	211.0 ± 30.3	210.2 ± 32.2	**<0.001**
LDL (mg/dl)	114.3 ± 30.0[c]	132.9 ± 30.1[cc]	144.2 ± 27.0	146.025.8	**<0.001**
TG (mg/dl)	143.7 ± 64.1	158.9 ± 73.2	149.8 ± 64.6	132.1 ± 53.4	0.331
HDL (mg/dl)	44.7 ± 9.9[d]	41.6 ± 8.9[dd]	36.8 ± 7.7	37.8 ± 6.5	**<0.001**
Creatinine (mg/dl)	0.74 ± 0.16[e]	0.83 ± 0.18	0.80 ± 0.19	0.83 ± 0.16	**0.011**
Urea (mg/dl)	30.8 ± 10.4	32.5 ± 9.8	29.8 ± 6.0	30.3 ± 7.2	0.546
hsCRP (mg/dl)	0.78 ± 0.64[f]	1.0 ± 0.77	1.19 ± 1.07	1.11 ± 0.99	0.082
Uric acid (mg/dl)	3.91 ± 0.76[b]	4.74 ± 0.69[g]	4.91 ± 0.78	5.17 ± 0.74	**<0.001**
AF n (%)	24 (29)	16 (30.8)	11 (35.5)	11 (37.9)	0.922[×]
VHD n (%)	15 (21.7)	20 (38.5)	6 (19.4)	8 (27.6)	0.148[×]
ASD suspicion n (%)	27 (39.1)	21 (40.4)	12 (38.7)	10 (34.5)	0.963[×]

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; EF, ejection fraction; TC, total cholesterol; LDL, low-density lipoprotein; TG, triglyceride; HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; AF, atrial fibrillation; VHD, valvular heart disease; ASD, atrial septal defect.
Significance p values ($p<0.05$) were indicated in boldface.
[a] $p=0.004$ vs. Grade 3 group, $p<0.001$ vs. Grade 4 group.
[aa] $p=0.002$ vs. Grade 4 group.
[b] $p<0.001$ vs. Grade 2, 3 and 4.
[c] $p<0.001$ vs. Grade 3 and 4, $p=0.001$ vs. Grade 2.
[cc] $p=0.05$ vs. Grade 4.
[d] $p<0.001$ vs. Grade 3 and 4.
[dd] $p=0.017$ vs. Grade 3 group.
[e] $p=0.003$ vs. Grade 2, $p=0.014$ vs. Grade 4.
[f] $p=0.022$ vs. Grade 3.
[g] $p=0.014$ vs. Grade 4.
[×] Chi square test.

commercial kits (Abbott). HsCRP was measured with an autoanalyzer (Aeroset) by using a commercial spectrophotometric kit (Scil Diagnostics GmbH, Viernheim, Germany).

Statistical analysis

All analyses were conducted using SPSS 17.0 (SPSS for Windows 17.0, Chicago, IL, USA). Continuous variables were expressed as mean ± S.D. and categorical variables were expressed as percentages. Comparison of categorical variables between the groups was performed using the Chi square (χ^2) test. Analysis of normality was performed with the Kolmogorov–Smirnov test. Analysis of variance (ANOVA) was used in the analysis of continuous variables. A stratified post hoc analysis of echocardiographic, clinical, and laboratory variables was performed according to the grade of thoracic aortic IMT. Scheffe and Tamhane's T2 tests were used according to homogeneity test results. The correlation between aortic IMT and clinical and laboratory parameters was assessed by the Pearson correlation test. Multiple linear regression analysis was performed to identify the independent predictors of aortic IMT by including the parameters, which were correlated with aortic IMT in bivariate analysis. Standardized β-regression coefficients and their significance from multiple linear regression analysis were reported. A two-tailed $p<0.05$ was considered statistically significant.

Results

TEE evaluation characterized thoracic aortic intimal morphology as Grade 1 in 69 patients (38.1%), as Grade 2 in 52 patients (28.7%), as Grade 3 in 31 patients (17.1%), and as Grade 4 in 29 patients (16%).

Comparison of demographic, clinical and laboratory characteristics in groups

Comparison of demographic, clinical and laboratory characteristics in groups is shown in Table 1. Age and gender were different among the groups ($p<0.001$, $p=0.05$, respectively). Total cholesterol level in the Grade 1 group was lower than in the Grade 2, 3, and 4 groups ($p<0.001$, for all). LDL cholesterol level in Grade 1 group was lower compared with Grade 2, 3, and 4 groups ($p=0.001$, $p<0.001$, and $p<0.001$, respectively). Also, LDL cholesterol level in Grade 2 group was lower than in Grade 4 group ($p=0.05$). HDL cholesterol level in Grade 1 group was lower than Grade 3 and 4 groups ($p<0.001$ for both). HDL cholesterol level in the Grade 2 group was lower than in the Grade 3 group ($p=0.017$). Creatinine level in the Grade 1 group was lower than in the Grade 2 and Grade 4 groups ($p=0.003$, $p=0.014$, respectively).

The highest UA level was observed in patients with Grade 4 IMT ($p<0.001$ and $p=0.014$, compared with Grade 1 and 2 groups, respectively). UA level of patients with Grade 3 and Grade 2 IMT were also higher than patients with Grade 1 IMT ($p<0.001$, for all). HsCRP level of Grade 1 group was lower than Grade 3 group ($p=0.022$). HsCRP level in the Grade 4 group was higher than in the Grade 1 group, but this was not statistically significant ($p=0.072$).

Bivariate and multivariate relationships of thoracic aortic IMT

Bivariate and multivariate relationships of thoracic aortic IMT are shown in Table 2. Thoracic aortic IMT was associated with age ($r=0.356$, $p<0.001$), gender ($r=0.154$, $p=0.039$), total cholesterol ($r=0.241$, $p<0.001$), LDL cholesterol ($r=390$, $p<0.001$), HDL cholesterol ($r=-0.331$, $p<0.001$), creatinine level ($r=0.155$, $p=0.037$), hsCRP level ($r=0.183$, $p=0.014$), and UA level ($r=0.491$, $p<0.001$) in bivariate analysis.

Table 2
Bivariate and multivariate relationships of thoracic aortic intima–media thickness.

	Pearson correlation coefficient	*p*-Value	Standardized β regression coefficients[a]	*p*-Value
Age	0.356	**<0.001**	0.219	**0.001**
Gender	0.154	**0.039**	0.042	0.507
TC	0.241	**<0.001**	−0.212	**0.031**
HDL	−0.331	**<0.001**	−0.115	0.081
LDL	0.390	**<0.001**	0.350	**0.001**
Creatinine	0.155	**0.037**	−0.027	0.674
hsCRP	0.183	**0.014**	0.148	**0.014**
Uric acid	0.491	**<0.001**	0.350	**<0.001**
AF	0.023	0.754		
VHD	−0.026	0.729		
ASD suspicion	−0.028	0.710		

TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high sensitivity C-reactive protein; AF, atrial fibrillation; VHD, valvular heart disease; ASD, atrial septal defect.
Significance *p* values ($p < 0.05$) were indicated in boldface.
[a] Multiple linear regression analysis.

In multiple linear regression analysis, IMT was independently correlated with UA level ($\beta = 0.350$, $p < 0.001$), age ($\beta = 0.219$, $p = 0.001$), total cholesterol ($\beta = -0.212$, $p = 0.031$), LDL cholesterol ($\beta = 0.350$, $p = 0.001$), and hsCRP levels ($\beta = 0.148$, $p = 0.014$). The relationship between thoracic aorta IMT and UA is shown in Fig. 2.

Bivariate and multivariate relationships of uric acid

UA level was associated with age ($r = 0.152$, $p = 0.041$), gender ($r = 0.251$, $p = 0.001$), total cholesterol ($r = 0.298$, $p < 0.001$), LDL cholesterol ($r = 0.351$, $p < 0.001$), HDL cholesterol level ($r = -0.344$, $p < 0.001$), creatinine ($r = 0.189$, $p = 0.011$) levels, and IMT of thoracic aorta ($r = 0.491$, $p < 0.001$).

In multiple linear regression analysis, UA level was independently correlated with gender ($\beta = 0.149$, $p = 0.023$), HDL cholesterol level ($\beta = -0.196$, $p = 0.004$), and thoracic aortic IMT ($\beta = 0.373$, $p < 0.001$).

Bivariate and multivariate relationships of thoracic aortic IMT within the normal LDL cholesterol range (127 patients)

After the high LDL cholesterol values were excluded (>155 mg/dl), LDL cholesterol levels did not differ among the groups ($p = 0.814$). According to bivariate analysis, thoracic aortic IMT was significantly associated with age ($r = 0.336$, $p < 0.001$), UA (0.373, $p < 0.001$), and hsCRP ($r = 0.247$, $p = 0.005$). Multivariate regression analysis showed that the IMT was independently related to age ($\beta = 0.274$, $p = 0.001$), UA ($\beta = 0.340$, $p < 0.001$), and hsCRP levels ($\beta = 0.226$, $p = 0.004$).

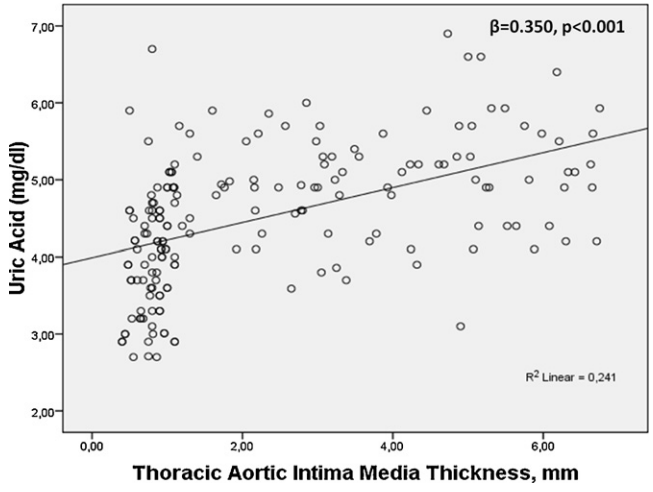

Fig. 2. The relationship between thoracic aorta intima–media thickness and uric acid.

Discussion

The present study is the first in the literature, which evaluated the relationship between UA level and thoracic aorta IMT in patients without clinical manifestation of atherosclerotic cardiovascular disease whom were referred for evaluation by TEE. The main finding of this study is that UA and hsCRP levels are independently associated with thoracic aorta IMT and these relationships persisted even after taking into account traditional cardiovascular risk factors.

The detection of atherosclerotic lesions on TEE in the aorta is a marker of diffuse atherosclerosis [9,10]. Takasu et al. showed that thoracic aortic calcification was associated with increasing severity of carotid atherosclerotic burden as measured by carotid IMT [13]. Recently, it was reported that aortic IMT was an earlier marker than carotid IMT of preclinical AS [11]. In recent years, with the development of preventive medicine, several studies on predictors or risk factors of AS were conducted and plenty of factors in this regard have been considered.

In this cross-sectional study, we demonstrated that thoracic aorta IMT is increased in the subjects with higher serum UA concentrations. This finding is important as it may imply a tendency to enhanced atherosclerosis in subjects with higher serum UA concentrations in early stages of life. Previous epidemiological studies have demonstrated an inverse association between levels of UA and atherosclerosis in humans [4,7,8]. In the study of Tavil et al., there were significant correlations between carotid IMT measurement, serum UA level, and other major atherosclerotic risk factors [7]. In that study, the authors reported that higher serum UA levels were associated with atherogenesis independent of hypertension. In another study, Erdogan et al. reported that increased serum UA concentration, even in physiological range, is a risk factor for increased carotid IMT, reduced flow-mediated dilation, and increased aortic stiffness independent of other cardiovascular risk factors, and of factors related to the metabolic syndrome in healthy subjects [8]. An independent relationship between thoracic aorta IMT and serum UA level in the present study supports findings of previous studies reporting UA as a risk factor for initial AS [7,8].

Endothelial dysfunction plays a crucial role in the pathogenesis of vascular diseases [14] as development of endothelial dysfunction is regarded as a pioneer of atherosclerosis. Endothelial dysfunction might be enhanced by an imbalance characterized by reduced nitric oxide production and/or increased reactive oxygen species production [14,15]. In vivo studies have demonstrated that UA can induce endothelial dysfunction by exerting anti-proliferative

effects on the endothelium and by impairing nitric oxide production [2,16,17]. By the way of these mechanisms UA behaves as a pro-oxidant in vascular cells, increasing lipid oxidization, impairing endothelium-dependent vasodilation, and thereby potentially giving rise to cardiovascular disease risk [2,3,18]. Conversely, increased UA concentrations may be a compensatory mechanism trying to counteract oxidative stress [19,20]. In previous studies, with increased thoracic aortic IMT, oxidative stress is increased [21,22]. Therefore, highest UA level in Grade 4 IMT may be associated with increased oxidative stress. However, oxidative stress markers were not investigated in the present study.

The role of chronic inflammatory process in the development of atherosclerosis has been demonstrated in laboratory and experimental investigations [23] and hsCRP, the most widely used marker of inflammation, has been reported to be independently associated with cardiovascular diseases in a variety of clinical settings, including healthy subjects [24,25]. An independent association of hsCRP levels with thoracic aorta IMT in the present study supports previous studies revealing the role of chronic inflammatory process, evidenced by increased hsCRP levels, in the development of atherosclerosis [23,24].

Coronary artery disease risk factors such as age, male gender, hypertension, hyperlipidemia, and smoking have been associated with aortic AS [26,27]. In the present study, coronary risk factors such as serum lipid levels and age were independently associated with thoracic IMT. However, the impact of diabetes and hypertension on thoracic AS could not be concluded in our study as patients with hypertension and diabetes were excluded from the study. Data revealing an association of grade of thoracic aorta AS and serum lipid levels, in the present study, support Matsuzaki et al. who concluded that hypertension and hypercholesterolemia might be important risk factors for the development of atherosclerotic lesions in the thoracic aorta in relatively younger patients [26] and Nishino et al. who identified hypercholesterolemia as a predictor of thoracic aortic plaques [28].

In our study, UA level was associated with HDL cholesterol level and gender besides aortic IMT in multiple linear regression analysis and these findings were consistent with literature revealing an inverse relationship between UA and HDL levels [7,29].

Study limitation

In our study, the patient population was enrolled from a diverse population with several disease states, however thoracic aorta IMT was not related to diagnosis of these patients. Additionally, coronary angiography was not performed in our patients although the diagnosis of coronary artery disease has been excluded according to clinical characteristics and patient history, electrocardiography, and treadmill exercise test. Endothelial dysfunction was not investigated in our study, although such an analysis would add to the value of the present study.

In conclusion, UA and hs-CRP are independently associated with subclinical thoracic atherosclerosis. Increases in both UA and hsCRP may be crucial biochemical markers for initial AS.

References

[1] So A, Thorens B. Uric acid transport and disease. J Clin Invest 2010;120:1791–9.
[2] Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin–angiotensin system. J Hypertens 2008;26:269–75.
[3] Patterson RA, Horsley ET, Leake DS. Prooxidant and antioxidant properties of human serum ultrafiltrates toward LDL: important role of uric acid. J Lipid Res 2003;44:512–21.
[4] Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 1999;131:7–13.
[5] Sato Y, Fujiwara H, Takatsu Y. Biochemical markers in heart failure. J Cardiol 2012;59:1–7.
[6] O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson Jr SK. Carotid artery intima and media thickness as a risk factor of myocardial infarction and stroke in older adults. N Engl J Med 1999;340:14–22.
[7] Tavil Y, Kaya MG, Oktar SO, Sen N, Okyay K, Yazici HU, Cengel A. Uric acid level and its association with carotid intima–media thickness in patients with hypertension. Atherosclerosis 2008;197:159–63.
[8] Erdogan D, Gullu H, Caliskan M, Yildirim E, Bilgi M, Ulus T, Sezgin N, Muderrisoglu H. Relationship of serum uric acid to measures of endothelial function and atherosclerosis in healthy adults. Int J Clin Pract 2005;59:1276–82.
[9] Rohani M, Jogestrand T, Ekberg M, van der Linden J, Källner G, Jussila R, Agewall S. Interrelation between the extent of atherosclerosis in the thoracic aorta, carotid intima–media thickness and the extent of coronary artery disease. Atherosclerosis 2005;179:311–6.
[10] Belhassen L, Carville C, Pelle G, Monin JL, Teiger E, Duval-Moulin AM, Dupouy P, Dubois Rande JL, Gueret P. Evaluation of carotid artery and aortic intima–media thickness measurements for exclusion of significant coronary atherosclerosis in patients scheduled for heart valve surgery. J Am Coll Cardiol 2002;39:1139–44.
[11] Harrington J, Peña AS, Gent R, Hirte C, Couper J. Aortic intima media thickness is an early marker of atherosclerosis in children with type 1 diabetes mellitus. J Pediatr 2010;156:237–41.
[12] Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic–angiographic correlations in the presence of absence of asynergy. Am J Cardiol 1976;37:7–11.
[13] Takasu J, Budoff MJ, Katz R, Rivera JJ, O'Brien KD, Shavelle DM, Probstfield JL, O'Leary D, Nasir K. Relationship between common carotid intima–media thickness and thoracic aortic calcification: the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 2010;209:142–6.
[14] Drexler H, Hornig B. Endothelial dysfunction in human disease. J Mol Cell Cardiol 1999;31:51–60.
[15] Dijkhorst-Oei LT, Stroes ES, Koomans HA, Rabeling TJ. Acute simultaneous stimulation of nitric oxide and oxygen radicals by angiotensin II in humans in vivo. J Cardiovasc Pharmacol 1999;33:420–4.
[16] Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. Semin Nephrol 2005;25:39–42.
[17] Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, Krotova K, Block ER, Prabhakar S, Johnson RJ. Hyperuricemia induces endothelial dysfunction. Kidney Int 2005;67:1739–42.
[18] Puddu P, Puddu GM, Cravero E, Vizioli L, Muscari A. The relationships among hyperuricemia, endothelial dysfunction, and cardiovascular diseases: molecular mechanisms and clinical implications. J Cardiol 2012;59:235–42.
[19] Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci USA 1981;78:6858–62.
[20] Sevanian A, Davies KJ, Hochstein P. Serum urate as an antioxidant for ascorbic acid. Am J Clin Nutr 1991;54:1129–34.
[21] Demirbag R, Yilmaz R, Kunt AS, Gur M, Ulucay A, Unlu D. Relationship between plasma total antioxidant capacity and thoracic aortic intima–media thickness. Echocardiography 2006;23:183–8.
[22] Gur M, Yilmaz R, Demirbag R, Yildiz A, Kocyigit A, Celik H, Cayli M, Polat M, Bas MM. Lymphocyte DNA damage is associated with increased aortic intima–media thickness. Mutat Res 2007;617:111–8.
[23] Ross R. Atherosclerosis—an inflamatory disease. N Engl J Med 1999;340:115–26.
[24] Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836–43.
[25] Heo JM, Park JH, Kim JH, You SH, Kim JS, Ahn CM, Hong SJ, Shin KH, Lim DS. Comparison of inflammatory markers between diabetic and nondiabetic ST segment elevation myocardial infarction. J Cardiol 2012;60:204–9.
[26] Matsuzaki M, Ono S, Tomochika Y, Michishige H, Tanaka N, Okuda F, Kusukawa R. Advances in transesophageal echocardiography for the evaluation of atherosclerotic lesions in thoracic aorta—the effects of hypertension, hypercholesterolemia, and aging on atherosclerotic lesions. Jpn Circ J 1992;56:592–602.
[27] Tribouilloy CM, Peltier M, Iannetta-Peltier MC, Zhu Z, Andréjak M, Lesbre JP. Relation between low-density lipoprotein cholesterol and thoracic aortic atherosclerosis. Am J Cardiol 1999;84:603–5.
[28] Nishino M, Masugata H, Yamada Y, Abe H, Hori M, Kamada T. Evaluation of thoracic aortic atherosclerosis by transesophageal echocardiography. Am Heart J 1994;127:336–44.
[29] Desai MY, Dalal D, Santos RD, Carvalho JA, Nasir K, Blumenthal RS. Association of body mass index, metabolic syndrome, and leukocyte count. Am J Cardiol 2005;97:835–8.