Impact of Serum Uric Acid Levels on Coronary Plaque Stability Evaluated Using Integrated Backscatter Intravascular Ultrasound in Patients with Coronary Artery Disease

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Aim: Because the prevalence of hyperuricemia is lower in females than in males, the association between hyperuricemia and cardiovascular disease has been frequently reported in females. Increased serum uric acid levels are associated with the presence of cardiovascular risk factors such as hypertension, renal dysfunction, insulin resistance, and metabolic syndrome. However, it is controversial whether hyperuricemia is an independent risk factor for coronary artery disease in both the genders. The purpose of this study was to investigate the relationship between serum uric acid levels and coronary plaque components assessed using integrated backscatter intravascular ultrasound (IB-IVUS) in males and females.

Methods: In total, 385 patients (298 males and 87 females) who underwent percutaneous coronary intervention using IB-IVUS were divided into three groups in each gender according to their serum uric acid levels. We characterized tissue from coronary plaques in culprit lesions.

Results: Serum uric acid levels significantly correlated with percent lipid volume ($r=0.37$) and inversely correlated with percent fibrous volume ($r=-0.35$). Multivariate analysis showed that the uric acid level was independently associated with lipid-rich plaques (odds ratio 2.43, 95% confidence interval 1.75–3.47). The prevalence of lipid-rich plaques increased with increasing uric acid levels in both genders.

Conclusion: Increased serum uric acid levels were associated with larger lipid content plaques in both genders.

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Key words: Uric acid, Intravascular ultrasound, Plaque component

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Introduction

Several epidemiological studies have reported that hyperuricemia, the presence of excess uric acid in the blood, is associated with cardiovascular disease^{1, 2}. Serum uric acid levels are affected by body mass index, physique, kidney dysfunction, and hypertension.

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Therefore, it is controversial whether hyperuricemia is an independent risk factor for coronary atherosclerosis³. The effect of hyperuricemia on coronary atherosclerosis evaluated by intravascular ultrasound (IVUS) or coronary computed tomographic angiography has been reported⁴⁻⁶. However, it remains to be determined whether serum uric acid levels are associated with coronary plaque components.

In general, serum uric acid levels are higher in male than female populations. Estrogen has been reported to promote the clearance of uric acid⁷. Serum uric acid levels increase after menopause in females but are still lower than those in males. Females have low risks for being overweight and high alcohol intake, which

Table 1. Patient characteristics

	All (n=385)	Male			P value	Female			P value	Interaction P with gender
		T1M (n=100)	T2M (n=97)	T3M (n=101)		T1F (n=29)	T2F (n=29)	T3F (n=29)		
Age, years	69.1 ± 10.9	69.5 ± 8.8	65.5 ± 11.7*	68.7 ± 11.6	0.024	72.6 ± 7.8	73.6 ± 11.1	74.1 ± 10.1	0.836	0.286
Body mass index, kg/m ²	23.6 ± 3.2	22.9 ± 2.8	23.9 ± 3.6	24.4 ± 3.1*	0.011	22.9 ± 3.6	22.7 ± 3.1	24.4 ± 2.9	0.171	0.431
Hypertension	278 (72%)	58 (59%)	71 (73%)	77 (76%) [†]	0.017	22 (76%)	24 (83%)	27 (93%)	0.174	0.624
Diabetes mellitus	161 (42%)	46 (46%)	44 (45%)	34 (33%)	0.133	11 (38%)	8 (28%)	19 (65%) [§]	0.010	0.002
Dyslipidemia	246 (64%)	53 (53%)	60 (62%)	75 (74%) [†]	0.026	21 (72%)	18 (62%)	20 (69%)	0.693	0.200
Current smoking	89 (23%)	27 (27%)	32 (33%)	28 (27%)	0.606	1 (3%)	1 (3%)	0	0.439	0.471
ACS	130 (33%)	41 (41%)	21 (22%) [†]	35 (35%)	0.013	11 (38%)	11 (38%)	7 (24%)	0.426	0.131
LDL cholesterol, mg/dl	100.4 ± 33.9	95.3 ± 33.8	96.9 ± 35.0	102.3 ± 32.3	0.301	108.8 ± 33.7	107.3 ± 35.0	106.0 ± 34.3	0.955	0.620
HDL cholesterol, mg/dl	49.3 ± 11.9	50.1 ± 11.0	47.3 ± 11.9	48.3 ± 12.1	0.239	52.1 ± 15.1	52.6 ± 11.9	50.6 ± 9.4	0.834	0.611
eGFR, ml/min/1.73 m ²	72.7 ± 24.1	82.2 ± 22.6	75.0 ± 21.9	63.2 ± 18.3 ^{†§}	<0.001	82.3 ± 34.1	69.1 ± 22.7	59.2 ± 23.9 [†]	0.011	0.681
Uric acid, mg/dl	5.5 ± 1.4	4.2 ± 0.6	5.6 ± 0.3	7.2 ± 1.0	<0.001	3.7 ± 0.7	4.9 ± 0.3	6.6 ± 1.1	<0.001	0.430
LVEF, %	59.6 ± 12.6	57.4 ± 12.6	58.9 ± 12.9	60.9 ± 12.8	0.209	59.3 ± 11.9	64.3 ± 11.2	59.2 ± 11.9	0.256	0.257
Concomitant medications										
Statins	181 (45%)	36 (36%)	53 (55%)	46 (46%)	0.072	9 (31%)	13 (45%)	17 (59%)	0.274	0.329
Anti-hyperuricemics	58 (14%)	7 (7%)	14 (14%)	30 (30%) ^{†§}	<0.001	1 (3%)	1 (3%)	3 (10%)	0.453	0.868
Diuretics	68 (17%)	9 (9%)	16 (17%)	19 (19%)	0.108	4 (14%)	5 (17%)	12 (41%) ^{**}	0.032	0.318
β blockers	174 (43%)	44 (44%)	45 (46%)	42 (42%)	0.793	16 (55%)	13 (45%)	8 (28%)	0.095	0.221
RAA inhibitors	278 (72%)	71 (71%)	71 (73%)	70 (69%)	0.832	23 (79%)	20 (69%)	23 (79%)	0.577	0.494

Data are expressed as n (%) for categorical variables and mean ± standard deviation for continuous variables. * $p < 0.05$ vs T1, [†] $p < 0.01$ vs T1, [‡] $p < 0.05$ vs T2, [§] $p < 0.01$ vs T2.

ACS, acute coronary syndrome; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; RAA, renin angiotensin aldosterone system

are associated with elevated serum uric acid levels⁸. Moreover, it was reported that the impact of hyperuricemia on cardiovascular disease is greater in females than in males^{9, 10}. Therefore, we investigated the association between serum uric acid levels and cardiovascular disease by sex.

Integrated backscatter (IB)-IVUS has recently been developed to analyze coronary plaque tissue characteristics more precisely than gray-scale IVUS^{11, 12}. Coronary plaque components analyzed using IB-IVUS were reported to be well correlated with histological findings¹². Lipid-rich plaque evaluated using IB-IVUS was associated with future cardiovascular events¹³ and no re-flow phenomenon during percutaneous coronary intervention (PCI)¹⁴. In the present study, we investigated the impact of serum uric acid levels on coronary plaque components, as assessed by IB-IVUS in patients who underwent PCI.

Materials and Methods

Study Population

From July 2009 to November 2012, 401 patients underwent PCI using IB-IVUS in our hospital. Sixteen patients on hemodialysis were excluded, and the

remaining 385 patients were enrolled in the study. All patients gave written informed consent. The protocol was approved by the institution's Human Investigation Committee. Procedures were performed in accordance with the Declaration of Helsinki.

Measurement of Serum Uric Acid Levels

Blood samples were obtained on admission to the hospital. The serum uric acid levels were determined by an enzymatic method using the uricase-peroxidase system¹⁵.

IVUS Measurement

We characterized tissue from coronary plaques in culprit lesions in patients with acute coronary syndrome (ACS) or stable angina pectoris. IB-IVUS examinations were performed with the IVUS imaging system (VISIWAVE, Terumo, Tokyo, Japan) and a 40-MHz, 5 Fr IVUS imaging catheter (ViewITTM, Terumo). IB-IVUS images were captured at a speed of 0.5 mm/s using a motorized pull-back system. Plaque analysis was performed in the range of culprit lesions at 1-mm axial intervals. Plaque volume was calculated as the sum of plaque plus media in each cross-sectional area. IB data for each tissue component were calcu-

Table 2. IVUS characteristics

	Male				Female				Interaction P with gender
	T1M (n=100)	T2M (n=97)	T3M (n=101)	P value	T1F (n=29)	T2F (n=29)	T3F (n=29)	P value	
Lesion length, mm	18.0 (13.0-22.0)	15.0 (11.7-19.8)	17.5 (13.0-24.0)	0.065	20.5 (12.4-28.0)	17.2 (11.1-25.0)	14.0 (10.4-24.0)	0.138	0.208
Plaque volume, mm ³	145.0 (100.2-193.7)	138.2 (97.6-217.2)	148.8 (108.0-213.2)	0.175	170.6 (105.5-219.3)	147.5 (88.5-219.7)	114.1 (78.7-185.2)	0.224	0.084
% lipid volume	46.3 ± 13.4	49.6 ± 13.8	56.9 ± 12.9 ^{†‡}	<0.001	47.0 ± 10.8	45.8 ± 13.1	55.4 ± 11.7 ^{†‡}	0.006	0.526
% fibrous volume	43.8 ± 9.5	41.7 ± 9.8	36.6 ± 9.4 ^{†‡}	<0.001	43.3 ± 7.0	43.9 ± 9.3	37.9 ± 9.0 ^{†‡}	0.014	0.612
% dense fibrous volume	7.4 ± 4.1	6.5 ± 4.1	4.9 ± 3.3 ^{†‡}	<0.001	7.1 ± 3.8	7.7 ± 3.9	5.1 ± 2.8 ^{†‡}	0.018	0.447
% calcification volume	2.5 ± 2.3	2.2 ± 2.5	1.5 ± 1.6 [†]	0.005	2.5 ± 1.8	2.4 ± 1.8	1.6 ± 1.6	0.087	0.907

Data are expressed as mean ± standard deviation or median (interquartile range). [†] $p < 0.01$ vs T1. [‡] $p < 0.01$ vs T2.

Fig. 1. Simple linear regression analysis showing the relationship between serum uric acid levels and coronary plaque components: (A) % lipid volume and (B) % fibrous volume.

lated as average power levels using a fast Fourier transform, measured in decibels, of the frequency component of backscattered signals from a small volume of tissue. On the basis of previous data, we applied the manufacturer's default settings of the IB-IVUS¹³⁾. IB-IVUS analysis classified the color-coded tissue into four major components by IB scores measuring backscattered signals from the tissue: blue (lipid), green (fibrosis), yellow (dense fibrosis), and red (calcification)¹⁶⁾. Quantitative volumetric IB-IVUS analysis was performed to calculate volumes of lipid, fibrosis, dense fibrosis, and calcification from the sum of the areas of the respective tissue types in each cross-sectional area. Then, the percentage volume of each component was calculated: % lipid volume = $100 \times \text{lipid volume} / \text{plaque volume}$, % fibrous volume = $100 \times \text{fibrous volume} / \text{plaque volume}$, % dense fibrous volume = $100 \times \text{dense$

fibrosis volume / plaque volume, and % calcified volume = $100 \times \text{calcified volume} / \text{plaque volume}$. Conventional IVUS analysis was performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies¹⁷⁾. Coronary plaques with a lipid area >65% have been reported to be associated with the development of ACS¹³⁾. We defined lipid-rich plaques as having a lipid volume >65%. It was reported that the percentage of lipid content is different between ACS and stable angina pectoris (SAP)¹⁸⁾. Therefore, subgroup analysis that divided the patients into ACS and SAP groups was performed.

Statistical Analysis

Continuous variables with normal distribution are

Table 3. Univariate and multivariate logistic analyses for lipid rich plaque

	Lipid rich plaque				Interaction P with gender	Interaction P with ACS
	Univariate		Multivariate			
	OR (95%CI)	<i>P</i> value	OR (95%CI)	<i>P</i> value		
Age, 1 increase	1.13 (0.85-1.51)	0.414				
Body mass index, 1 SD (3.2) increase	1.13 (0.84-1.51)	0.406				
Hypertension	2.27 (1.12-5.11)	0.021	1.85 (0.86-4.42)	0.119		
Diabetes mellitus	1.05 (0.59-1.84)	0.864				
Dyslipidemia	1.29 (0.72-2.39)	0.403				
Current smoking	1.34 (0.68-2.83)	0.407				
Statin use	1.06 (0.60-1.86)	0.834				
Uric acid, 1 SD (1.4) increase	2.48 (1.84-3.43)	<0.001	2.43 (1.75-3.47)	<0.001	0.685	0.016
eGFR, 1 SD (24.1) increase	0.71 (0.51-0.96)	0.028	1.08 (0.74-1.55)	0.689		

SD, standard deviation; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome

presented as the mean $\pm$ SD. Analysis of variance was used for continuous variables, and a chi-square test was used for categorical variables in comparisons between the three groups. When there was statistical significance of differences between the three groups, we performed post-hoc analysis using Tukey's test or the Bonferroni method. Simple linear regression analysis was performed to investigate the relationship between serum uric acid levels and IVUS parameters. Univariate and multivariate logistic analyses were used to identify independent predictors for lipid-rich plaques. Significant predictors selected in the univariate analysis were entered into the multivariate analysis. Interaction test was performed to take account of interaction with each subgroup. A p value < 0.05 was considered statistically significant. All statistical analyses were performed with a standard statistical program package (JMP version 9.0, SAS Institute Inc., Cary, NC, USA).

Results

Clinical Characteristics

Study patients were divided into three groups in each gender according to tertile of serum uric acid level (Male: T1M < 5.0 mg/dl, $n = 100$; T2M $5.0 - 6.2$ mg/dl, $n = 97$; T3M > 6.2 mg/dl, $n = 101$. Female: T1F < 4.6 mg/dl, $n = 29$; T2F $4.6 - 5.3$ mg/dl, $n = 29$; T3F > 5.3 mg/dl, $n = 29$).

The clinical characteristics of male and female patients are summarized in **Table 1**. There were no significant differences in the prevalence of current smoking, serum cholesterol levels, and left ventricular ejection fraction examined by echocardiography among the three groups in either gender. There were significant differences in body mass index; the prevalence of hypertension, dyslipidemia, and ACS; and the

usage of antihyperuricemics between the three groups in males. However, there was no significant interaction with gender. Group T3M had a lower estimated glomerular filtration rate (eGFR) than groups T1M and T2M. Group T3F had a lower eGFR than group T1F and had a higher prevalence of diabetes mellitus than group T2F. There were no significant differences in the use of renin-angiotensin aldosterone system inhibitors among the three groups in either gender.

Association between Coronary Plaque Components and Serum Uric Acid Levels

There were no significant differences in total plaque volume among the three groups in either gender (**Table 2**). Group T3M and T3F had higher % lipid volume, and lower % fibrous and % dense fibrous volume than the other groups in both genders.

Simple linear regression analysis revealed that serum uric acid levels correlated significantly with % lipid volume ($r = 0.371$, $p < 0.001$; **Fig. 1A**) and inversely correlated with % fibrous volume ($r = -0.347$, $p < 0.001$; **Fig. 1B**).

We evaluated the predictors for lipid-rich plaques (**Table 3**). Univariate analysis showed that hypertension, eGFR, and uric acid levels were significantly associated with lipid-rich plaque formation. In multivariate analysis, the uric acid level was independently associated with the presence of lipid-rich plaques. However, there was interaction between the predictive ability of serum uric acid levels for lipid-rich plaques and ACS. **Fig. 2** shows the prevalence rate of lipid-rich plaques in each tertile in both genders. Group T3M had a significantly higher prevalence of lipid-rich plaques than groups T1M and T2M. Groups T2F and T3F had a significantly higher prevalence of lipid-rich plaques than group T1F. There was no interaction

Fig. 2. The prevalence of lipid-rich plaques in each tertile of serum uric acid level in males and females. Study patients were divided into three groups in each gender according to tertile of serum uric acid level (male: T1M, low tertile; T2M, intermediate tertile; T3M, high tertile. Female: T1F, low tertile; T2F, intermediate tertile; T3F, high tertile). * $p < 0.01$ vs. T1M; † $p < 0.01$ vs. T2M; and ** $p < 0.05$ vs. T1F.

with gender (interaction $p = 0.269$).

There was no significant difference in the prevalence rate of lipid-rich plaques between the three groups in the SAP group ($p = 0.084$, interaction $p = 0.041$; **Fig. 3**). However, the prevalence rate of lipid-rich plaques in group T3 in ACS group was significantly greater than that in groups T1 and T2.

Discussion

The present study revealed that elevated serum uric acid levels were associated with higher percentage lipid volume and lower percentage fibrous volume in target coronary plaques. After adjustment for confounding factors, higher serum uric acid levels were independently associated with lipid-rich plaques.

It remains controversial whether asymptomatic hyperuricemia causes cardiovascular disease. Association between serum uric acid levels and coronary artery disease is frequently obscured by other comorbid cardiovascular risk factors such as hypertension, kidney dysfunction, and metabolic syndrome^{3, 19}. Several epidemiological cohort studies showed that the impact of hyperuricemia on cardiovascular diseases is

greater in females than in males⁹, and that a modest increase in serum uric acid levels to ≥ 6.0 mg/dl is associated with cardiovascular disease in females²⁰. It was reported that high concentration of serum uric acid was correlated with coronary endothelial microvascular dysfunction in only women²¹. Recently, it was reported that elevated serum uric acid levels are associated with lipid-rich plaques⁶. However, they analyzed the relationship between uric acid levels and plaque components without taking account of gender difference in serum uric acid levels. In the present study, the prevalence of lipid-rich plaques increased with increasing serum uric acid levels (≥ 4.6 mg/dl) in female patients. Japanese guidelines for the treatment of hyperuricemia and gout recommend that the serum uric acid should be < 6.0 mg/dl in both genders²². A more stringent control of uric acid levels in females may be required.

Verdecchia *et al.* reported that low serum uric acid, i.e., < 4.5 mg/dl in males and < 3.2 mg/dl in females, increased cardiovascular events²³. Because uric acid is a potent antioxidant, it has been suggested that the levels of reactive oxygen species may increase when serum uric acid levels decrease significantly²⁴.

Fig. 3. The prevalence of lipid-rich plaques in each tertile of serum uric acid level in acute coronary syndrome and stable angina pectoris. Patients were divided into three groups according to tertile of serum uric acid level (T1, T1M+T1F; T2, T2M+T2F; T3, T3M+T3F). Data were expressed as number of patients with lipid-rich plaque/number of patients in each subgroup. ACS, acute coronary syndrome; SAP, stable angina pectoris.

However, we did not observe a so-called “J curve” relationship between serum uric acid levels and % lipid plaque volume in the present study.

Several mechanisms have been proposed for the involvement of hyperuricemia in coronary atherosclerosis. Macrophages infiltrate into injured vascular endothelial cells and form foam cells by the incorporation of oxidized low-density lipoprotein cholesterol or remnants, which facilitate lipid-rich plaque formation²⁵⁾. Hyperuricemia was reported to induce vascular endothelial injury through production of neutrophil extracellular traps^{26, 27)}. Xanthine oxidoreductase (XOR), which is the rate-limiting enzyme of uric acid production, is reportedly expressed in macrophages²⁸⁾. Lipid accumulation in, and macrophage infiltration into, injured vascular endothelia are inhibited by XOR inhibitors^{29, 30)}. Activated XOR may promote atherosclerotic plaque formation through lipid accumulation into the plaque. Recently, XOR was reported to promote macrophage interleukin-1 β secretion via activation of the NOD-like family receptor, pyrin domain-containing 3 inflammasome³¹⁾. It was reported that uric acid can induce smooth muscle proliferation^{32, 33)},

free radical formation³⁴⁾, and oxidative stress³⁵⁾, which all play roles in the development of arteriosclerosis. However, the causal relationship between hyperuricemia and coronary artery disease is still unclear. There are no criteria for treatment of asymptomatic hyperuricemia to prevent coronary artery disease. In the present study, we showed that elevated serum uric acid was associated with lipid-rich plaque in both genders.

Clinical Implication

It is still unknown whether lowering serum uric acid levels will provide stabilizing effect on coronary plaques. However, because a smaller increase in serum uric acid levels is associated with lipid-rich plaques in females than in males, more stringent control may be needed to reduce future cardiovascular events in females. Moreover, because it was reported that non-culprit coronary lesions with ACS patients are associated with the lipid-rich plaques¹⁸⁾, lowering serum uric acid may be beneficial for secondary prevention in patients with hyperuricemia who underwent PCI.

Limitations

The present study has several limitations. First, it was performed in only one medical center. A randomized controlled multicenter study is required to investigate the causal relationship between hyperuricemia and coronary artery disease. Second, we considered lipid-rich plaque to be vulnerable plaque, but several other factors are related to plaque vulnerability³⁶⁾. Third, predictive ability of serum uric acid levels for lipid-rich plaque was qualified only in patients with ACS. Further prospective study is needed to reveal the impact of serum uric acid on lipid-rich plaque in SAP.

Conclusion

Increased serum uric acid levels were associated with larger lipid content and smaller fibrosis of coronary plaques, as assessed by IB-IVUS in both genders. Lipid-rich plaque was associated with higher serum uric acid levels, particularly in patients with ACS. Lowering serum uric acid levels may be an option to stabilize vulnerable coronary plaques.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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