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Serum uric acid level and subclinical coronary atherosclerosis in asymptomatic individuals: An observational cohort study

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HIGHLIGHTS

- The association between serum uric acid and CAD showed conflicting results.
- High serum uric acid level is an independent predictor of non-calcified vulnerable plaque.
- Screening for CAD might be considered in individuals with hyperuricemia.

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ABSTRACT

Background and aims: There are limited data on the association between serum uric acid (SUA) level and subclinical coronary atherosclerosis. This study investigated the influence of SUA level on subclinical coronary atherosclerosis, as detected by coronary computed tomography angiography (CCTA), in an asymptomatic population.

Methods: We evaluated 6431 asymptomatic individuals (mean age 53.6 ± 7.6 years, 4691 men [72.9%]) with no prior history of coronary artery disease, who voluntarily underwent laboratory tests and CCTA as part of a general health examination. The participants were stratified into quartiles according to their SUA levels. Coronary atherosclerotic plaques (calcified, mixed, and non-calcified plaques) were assessed using CCTA. Logistic regression analysis was used to determine the association between SUA levels and subclinical coronary atherosclerosis.

Results: The prevalence of any atherosclerotic, calcified, mixed, and non-calcified plaques increased with SUA quartiles (all $p < 0.001$). After adjustment for cardiovascular risk factors, there were no statistically significant differences in the adjusted odds ratios for calcified plaque (1.19; 95% CI 0.98–1.46; $p = 0.080$) and mixed plaque (1.25; 95% CI 0.94–1.67; $p = 0.132$) in the fourth SUA quartile compared to the first quartile. However, the adjusted odds ratios for any atherosclerotic plaque (1.39; 95% CI 1.16–1.68; $p < 0.001$) and non-calcified plaque (1.38; 95% CI 1.11–1.72; $p = 0.004$) were significantly higher in the fourth SUA quartile.

Conclusions: In asymptomatic individuals, high SUA level was an independent predictor of non-calcified plaques, suggesting an increased cardiovascular risk.

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1. Introduction

High serum uric acid (SUA) level is the main prerequisite for gout [1], and it might be associated with obesity, hypertension, glucose intolerance, insulin resistance, and dyslipidemia, which are the known risk factors for coronary artery disease (CAD) [2]. The potential association between high SUA level and CAD has not been elucidated. Previous studies have suggested the proatherogenic property of uric acid, which might prompt vascular smooth cell proliferation and cause endothelial dysfunction [3]. Endothelial dysfunction is believed to play a key role in the early development of atherosclerosis and precedes plaque formation [4]. However, although the association of SUA level with CAD has been investigated in previous studies, the results are conflicting [5–7]. Several studies have demonstrated a relation between SUA and CAD independently of traditional risk factors for coronary artery disease [5], while other studies did not support these findings [6,7].

With the advent of multidetector-row computed tomography, coronary computed tomography angiography (CCTA) has shown to be effective in comprehensively evaluating coronary atherosclerosis, including lesion location, severity, and plaque characteristics [8]. A recent meta-analysis with CCTA showed that the specific characteristics of atherosclerotic plaques determine the different risks of future cardiovascular events [9]. However, there are limited data regarding the association between SUA and subclinical coronary atherosclerosis in asymptomatic individuals. Therefore, we investigated the relationship between SUA and the characteristics of atherosclerotic plaques, using a large cohort of asymptomatic individuals who voluntarily underwent CCTA for early detection of CAD.

2. Patients and methods

2.1. Study population

Between January 2007 and December 2011, 9269 consecutive South Korean individuals aged ≥20 years, who had undergone self-referred CCTA evaluation as part of a general health examination at the Health Screening and Promotion Center in the Asan Medical Center, were included. Among these, 7129 (76.9%) agreed to participate in the present study. Possible risks associated with CCTA were explained, and written informed consent was obtained from each participant. We excluded individuals with 1) a previous history of angina or myocardial infarction; 2) abnormal resting electrocardiography results, i.e., pathological Q waves, ischemic ST segments or T-wave changes, or left bundle-branch blocks; 3) insufficient medical records; 4) structural heart disease; 5) a previous history of open heart surgery or percutaneous coronary intervention; 6) a previous cardiac procedure; 7) unmeasured SUA; and 8) renal insufficiency (creatinine > 1.5 mg/dL). Finally, 6431 subjects were enrolled and analyzed (Fig. 1). This study was approved by the local Institutional Review Board of the Asan Medical Center, Seoul, Korea.

2.2. Clinical and laboratory measurements

Basic demographic data of study participants were acquired from a database maintained by the Health Screening and Promotion Center at the Asan Medical Center. Past medical history, including that of angina, myocardial infarction, stroke, structural heart disease, open heart surgery, percutaneous coronary intervention, previous cardiac procedures,

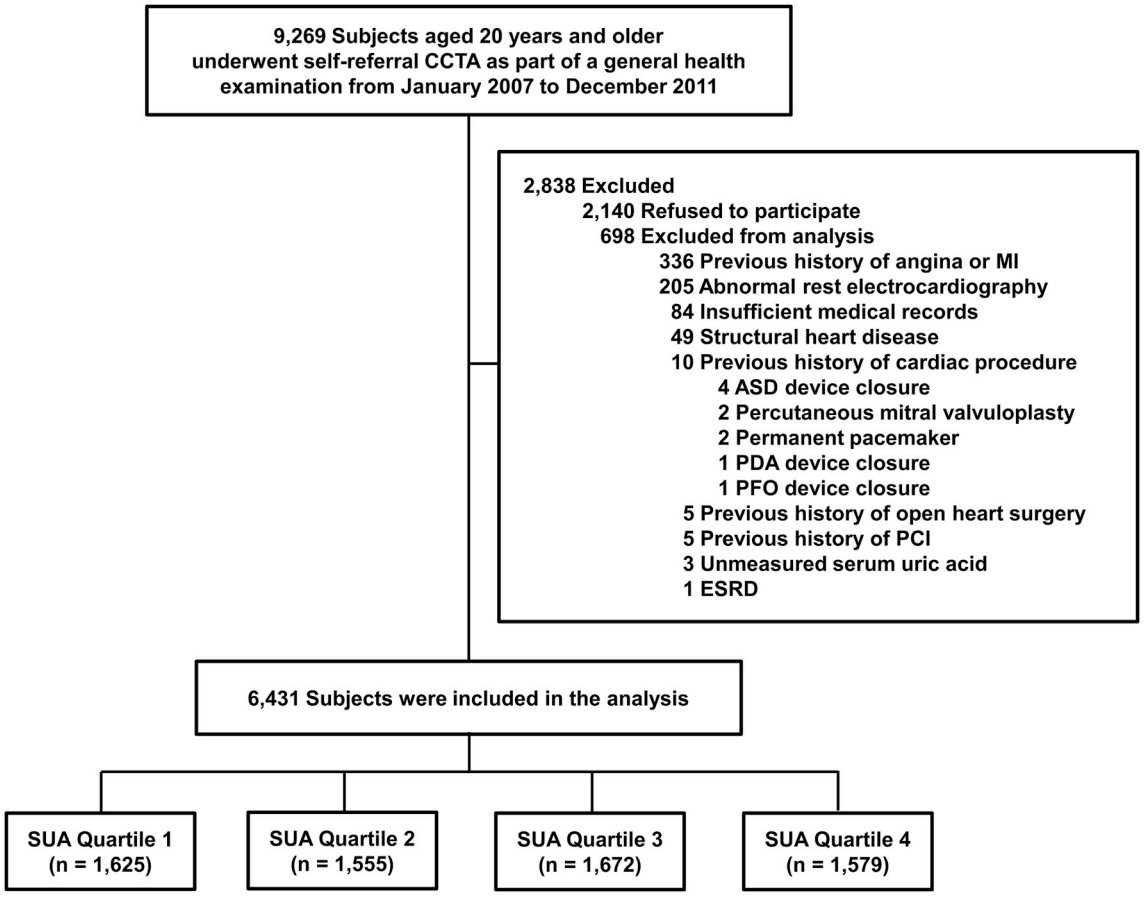

Fig. 1. Overview of the study population.
CCTA = coronary computed tomographic angiography; MI = myocardial infarction; ASD = atrial septal defect; PDA = patent ductus arteriosus; PFO = patent foramen ovale; PCI = percutaneous coronary intervention; ESRD = end-stage renal disease; SUA = serum uric acid.

diabetes mellitus, hypertension, hyperlipidemia, and smoking status, was obtained from the responses in the systemized self-report questionnaires issued to the participants prior to the general health examination [10].

Height, weight, waist circumference, and blood pressure of study participants were measured in a standard manner. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). After overnight fasting, blood samples were drawn early in the morning. The concentrations of SUA, fasting plasma glucose, hemoglobin A1c (HbA1c), creatinine, fasting total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein (hs-CRP) were measured [10]. The estimated glomerular filtration rate was calculated based on the Cockcroft & Gault formula.

Obesity was defined as a BMI $\geq$25 kg/m^2 on the basis of an Asian-specific cutoff point as recommended in the World Health Organization. Diabetes mellitus was defined as a fasting plasma glucose concentration $\geq$126 mg/dL, HbA1c $\geq$ 6.5%, or a self-reported history of diabetes mellitus and/or use of antidiabetic medication. Hypertension was defined as blood pressure $\geq$130/80 mmHg or a self-reported history of hypertension and/or use of anti-hypertensive medication. Hyperlipidemia was defined as total cholesterol $\geq$240 mg/dL or use of an anti-hyperlipidemic medication. A family history of CAD was defined as having a first-degree relative of any age with CAD, as mentioned in the self-report questionnaire [10].

2.3. CCTA image acquisition and analysis

CCTA was conducted using either single-source 64-slice CT (LightSpeed VCT, GE, Milwaukee, WI, USA) or dual-source CT (SOMATOM Definition, Siemens, Erlangen, Germany). A standard scanning protocol was used, as previously described [8]. All CCTA scans were analyzed using a dedicated workstation by experienced cardiovascular radiologists (DHY, JWK, and THL) according to the guidelines of the Society of Cardiovascular Computed Tomography. A coronary artery calcium (CAC) score was measured and categorized by scores of 0, 1 to 10, 11 to 100, 101 to 400, and > 400. Coronary artery calcification was defined as CAC > 10 [11]. Plaques were defined as structures larger than 1 mm^2 within and/or adjacent to the vessel lumen, which clearly could be distinguished from the lumen and surrounding pericardial tissue. Plaques containing calcified tissue involving > 50% of the plaque area (density > 130 Hounsfield units) were classified as calcified. Plaques with < 50% calcium in the plaque area were classified as mixed. Plaques without any calcium were classified as non-calcified [12]. The contrast-enhanced portion of the coronary lumen was semi-automatically traced at the site of maximal stenosis and compared with the mean value of the proximal and distal reference sites. Significant stenosis was defined as diameter stenosis $\geq$50% [8].

2.4. Statistical analysis

Categorical variables are expressed as frequencies with percentages, and continuous variables, as the mean and standard deviation. Between-group comparisons were performed using Pearson's chi-square test or Fisher's exact test for categorical variables, and the one-way analysis of variance or Kruskal–Wallis test for numerical variables, as appropriate. Univariable and multivariable analyses were performed using a logistic regression model to analyze the association between SUA and subclinical coronary atherosclerosis on CCTA. Based on previous epidemiologic studies [13,14], we selected clinically important variables such as age, sex, obesity, diabetes mellitus, hypertension, hyperlipidemia, current smoking, a family history of CAD, and hs-CRP $\geq$2 mg/L. Multivariable logistic regression analyses were performed using these covariates. Unadjusted and adjusted odds ratios with 95% confidence intervals for the logistic regression were calculated. All reported p-values are two-sided, and $p < 0.05$ was considered statistically significant. Data manipulation and statistical analyses were performed using SPSS software (Version 18; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

Among the 6431 individuals (mean age, 53.6 ± 7.6 years) in the study, 72.9% were male. The baseline characteristics of the study participants according to the quartiles of SUA are summarized in Table 1. BMI, waist conference, prevalence of male sex, hypertension, hyperlipidemia, current smoking, and obesity significantly increased with the SUA category. Levels of systolic and diastolic blood pressure, low-density lipoprotein cholesterol, and triglycerides were higher in increasing SUA quartiles.

3.2. CCTA findings

CCTA findings according to the quartiles of SUA are shown in Table 2. The mean CAC score of the study participants was 40.8 ± 140.0, and it increased with the SUA category ($p < 0.001$). Atherosclerotic plaques were found in 2698 (41.8%) individuals. Calcified, non-calcified, and mixed plaques were detected in 1808 (28.1%), 1179 (18.3%), and 570 (8.9%) participants, respectively. The prevalence of any atherosclerotic, calcified, non-calcified, or mixed plaque significantly increased with the SUA quartiles (all $p < 0.001$). Among the study participants, 494 (7.7%) had significant coronary artery stenosis ($\geq$50% diameter stenosis) in at least one coronary artery on CCTA. Significant stenosis in the left main, left anterior descending, left circumflex artery, and right coronary arteries was observed in 23 (0.4%), 328 (5.1%), 161 (2.5%), and 143 (2.2%) participants, respectively. Significant stenosis also increased with the SUA category ($p < 0.001$).

3.3. Association between SUA and subclinical atherosclerosis

The association between SUA and subclinical atherosclerosis is described in Table 3. On univariable analysis, the increasing quartiles of SUA were significantly associated with coronary artery calcification (defined as CAC score > 10), and any atherosclerotic, calcified, non-calcified, and mixed plaques. Compared to the first quartile of SUA, the third and fourth quartiles also had a significant association with significant coronary artery stenosis.

After adjustment for cardiovascular risk factors (age, sex, obesity, diabetes mellitus, hypertension, hyperlipidemia, current smoking, family history of CAD, and hs-CRP), there were no statistically significant differences in the adjusted odds ratios for coronary artery calcification (1.19; 95% confidence interval [CI] 0.97–1.46; $p = 0.090$), calcified plaque (1.19; 95% CI 0.98–1.46; $p = 0.080$), and mixed plaque (1.25; 95% CI 0.94–1.67; $p = 0.132$) in the fourth SUA quartile compared to the first quartile. However, the adjusted odds ratios for any atherosclerotic plaque (1.39; 95% CI 1.16–1.68; $p < 0.001$) and non-calcified plaque (1.38; 95% CI 1.11–1.72; $p = 0.004$) were significantly higher in the fourth SUA quartile.

4. Discussion

The main finding of our study was that SUA level was an independent predictor of non-calcified plaques on CCTA in asymptomatic individuals after adjusting for cardiovascular risk factors. However, SUA level showed no association with either calcified or mixed plaques.

It is known that CAC scores are good predictors of cardiovascular events [15]. Although several studies have investigated the association between SUA level and CAD, the results have been conflicting. Some studies showed the significant relationship between SUA level and CAC

Table 1
Baseline characteristics of the study population according to the quartiles of serum uric acid.

Characteristics	Overall (n = 6431)	Serum uric acid				
		Quartile 1 ≤4.6 mg/dL (n = 1625)	Quartile 2 4.7–5.5 mg/dL (n = 1555)	Quartile 3 5.6–6.5 mg/dL (n = 1672)	Quartile 4 ≥6.6 mg/dl (n = 1579)	*p* value
Age, years	53.6 ± 7.6	54.0 ± 7.7	54.5 ± 7.3	53.5 ± 7.5	52.7 ± 7.6	< 0.001
Male sex	4691 (72.9)	554 (34.1)	1095 (70.4)	1498 (89.6)	1544 (97.8)	< 0.001
Body mass index, kg/m^2	24.6 ± 2.9	23.3 ± 2.9	24.4 ± 2.7	25.1 ± 2.8	25.7 ± 2.7	< 0.001
Waist circumference, cm	85.9 ± 8.3	81.2 ± 8.3	85.2 ± 7.8	87.5 ± 7.6	89.5 ± 7.2	< 0.001
Systolic blood pressure, mmHg	120.1 ± 13.1	117.2 ± 14.0	119.4 ± 12.9	121.4 ± 12.6	122.5 ± 12.2	< 0.001
Diastolic blood pressure, mmHg	76.9 ± 10.4	73.5 ± 10.9	76.3 ± 9.9	78.3 ± 9.9	79.5 ± 9.9	< 0.001
Diabetes mellitus	1024 (15.9)	244 (15.0)	263 (16.9)	298 (17.8)	219 (13.9)	0.009
Hypertension	3519 (54.7)	691 (42.5)	806 (51.8)	986 (59.0)	1036 (65.6)	< 0.001
Hyperlipidemia	2001 (31.1)	426 (26.2)	471 (30.3)	539 (32.2)	565 (35.8)	< 0.001
Current smoker	1524 (23.7)	196 (12.1)	361 (23.2)	475 (28.4)	492 (31.2)	< 0.001
Obesity	2822 (43.9)	429 (26.4)	633 (40.7)	813 (48.7)	947 (60.0)	< 0.001
Family history of coronary artery disease[a]	983 (15.3)	245 (15.1)	233 (15.0)	270 (16.1)	235 (14.9)	0.724
Fasting blood glucose, mg/dL	104.9 ± 20.8	104.2 ± 24.6	104.8 ± 20.9	105.4 ± 18.7	105.1 ± 18.3	< 0.001
Hemoglobin A1c	5.7 ± 0.8	5.7 ± 0.9	5.8 ± 0.8	5.7 ± 0.7	5.7 ± 0.7	< 0.001
Total cholesterol, mg/dL	195.5 ± 34.3	193.6 ± 34.7	193.6 ± 33.4	195.9 ± 34.8	198.8 ± 34.0	< 0.001
Low-density lipoprotein cholesterol, mg/dL	121.3 ± 30.1	117.6 ± 30.2	120.1 ± 29.0	122.7 ± 30.3	125.0 ± 30.2	< 0.001
High-density lipoprotein cholesterol, mg/dL	53.4 ± 13.5	59.0 ± 14.5	53.7 ± 13.1	51.5 ± 12.4	49.4 ± 12.1	< 0.001
Triglyceride, mg/dL	134.1 ± 85.7	107.3 ± 66.7	126.7 ± 83.9	140.8 ± 85.4	162.0 ± 95.2	< 0.001
Creatinine, mg/dL	0.9 ± 0.2	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	< 0.001
Glomerular filtration rate, mL/min	89.9 ± 19.3	86.8 ± 18.1	89.9 ± 19.0	91.8 ± 19.2	91.3 ± 20.6	< 0.001
High-sensitivity C-reactive protein ≥2 mg/L	58 (0.9)	18 (1.1)	14 (0.9)	12 (0.8)	14 (0.9)	0.703

Values are shown as the mean ± standard deviation or number (%).
[a] Coronary artery disease in a first-degree relative of any age.

score [16], and reported that SUA level was an independent predictive factor of CAC score [7], whereas other studies did not support this finding [6]. In the present study, on univariable analysis, coronary artery calcification was significantly associated with SUA level. However, after adjustment for cardiovascular risk factors, this association did not persist.

Few studies have focused on the association between SUA level and characterization of coronary atherosclerotic plaques by CCTA. A systemic review showed that non-calcified plaques might tend to progress and lead to an increased risk of acute coronary syndrome events, while calcified plaques are more resistant to changes in size [9]. Another study involving CCTA described that non-calcified plaques were associated with the culprit lesions in patients with subsequent acute coronary syndrome [17]. Further, even in asymptomatic subjects, non-calcified plaques were related to cardiac events, defined as cardiac death, acute coronary syndrome, and revascularization with stable angina [18]. In our study, after adjustment for cardiovascular risk factors, calcified or mixed plaques did not associate with SUA levels. However, non-calcified plaques had an increased odds ratio only in individuals classified under the fourth quartile of SUA. Therefore, considering the findings of previous reports and those of the present study, high SUA level might be an independent risk factor for non-calcified plaque, which is as a vulnerable plaque with potential cardiac risk.

The role of uric acid in atherosclerosis has not yet been elucidated. Several studies have suggested the proatherogenic property of uric acid; uric acid might prompt vascular smooth cell proliferation and cause endothelial dysfunction, resulting in atherosclerosis and coronary calcification [3]. On the contrary, other studies have described that uric acid, as a general antioxidant in the body, may have a protective role in atherosclerosis, and that high SUA level reflected oxidative stress, endothelial dysfunction, and slow coronary artery flow [19]. Whether uric acid has a pathogenic effect on the development of atherosclerosis or it is only a marker of atherosclerosis during a protective process is still

Table 2
Comparison of coronary computed tomography angiographic findings according to the quartiles of serum uric acid.

Variables	Overall	Serum uric acid				
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* value
Mean coronary artery calcium score	40.8 ± 140.0	25.1 ± 107.3	39.2 ± 131.8	46.3 ± 151.1	52.5 ± 160.5	< 0.001
Coronary artery calcium score, no. (%)						< 0.001
0	4144 (64.7)	1216 (75.1)	992 (64.1)	1032 (61.9)	904 (57.4)	
1–10	598 (9.3)	113 (7.0)	143 (9.2)	164 (9.8)	178 (11.3)	
11–100	1026 (16.0)	181 (11.2)	260 (16.8)	284 (17.0)	301 (19.1)	
101–400	490 (7.6)	94 (5.8)	119 (7.7)	139 (8.3)	138 (8.8)	
> 400	151 (2.4)	16 (1.0)	34 (2.2)	48 (2.9)	53 (3.4)	
Any atherosclerotic plaque, no. (%)	2698 (41.8)	490 (30.2)	654 (42.1)	734 (43.9)	811 (51.4)	< 0.001
Plaque characteristics, no. (%)						
Calcified plaque	1808 (28.1)	326 (20.1)	454 (29.2)	503 (30.1)	525 (33.2)	< 0.001
Non-calcified plaque	1179 (18.3)	212 (13.0)	264 (17.0)	330 (19.7)	373 (23.6)	< 0.001
Mixed plaque	570 (8.9)	99 (6.1)	128 (8.2)	149 (8.9)	194 (12.3)	< 0.001
Significant stenosis, no. (%)	494 (7.7)	92 (5.7)	105 (6.8)	140 (8.4)	157 (9.9)	< 0.001

Values are shown as the mean ± standard deviation or number (%).

Table 3
Association between serum uric acid level and coronary computed tomography angiographic findings.

Variables	Univariable		Multivariable	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Coronary artery calcification[a]				
Quartile 1 (reference)	1		1	
Quartile 2	1.65 (1.39–1.95)	< 0.001	1.11 (0.91–1.34)	0.315
Quartile 3	1.77 (1.50–2.01)	< 0.001	1.05 (0.86–1.28)	0.656
Quartile 4	2.05 (1.74–2.41)	< 0.001	1.19 (0.97–1.46)	0.090
Any atherosclerotic plaque				
Quartile 1 (reference)	1		1	
Quartile 2	1.68 (1.45–1.95)	< 0.001	1.11 (0.94–1.32)	0.223
Quartile 3	1.81 (1.57–2.10)	< 0.001	1.03 (0.86–1.23)	0.770
Quartile 4	2.45 (2.12–2.83)	< 0.001	1.39 (1.16–1.68)	< 0.001
Calcified plaque				
Quartile 1 (reference)	1		1	
Quartile 2	1.64 (1.40–1.94)	< 0.001	1.13 (0.94–1.37)	0.198
Quartile 3	1.72 (1.46–2.01)	< 0.001	1.05 (0.86–1.27)	0.653
Quartile 4	1.99 (1.69–2.33)	< 0.001	1.19 (0.98–1.46)	0.080
Non-calcified plaque				
Quartile 1 (reference)	1		1	
Quartile 2	1.36 (1.12–1.66)	0.002	1.02 (0.83–1.26)	0.848
Quartile 3	1.64 (1.36–1.98)	< 0.001	1.11 (0.90–1.38)	0.324
Quartile 4	2.06 (1.71–2.48)	< 0.001	1.38 (1.11–1.72)	0.004
Mixed plaque				
Quartile 1 (reference)	1		1	
Quartile 2	1.38 (1.05–1.82)	0.020	0.91 (0.68–1.22)	0.519
Quartile 3	1.51 (1.16–1.96)	0.002	0.88 (0.66–1.18)	0.395
Quartile 4	2.16 (1.68–2.78)	< 0.001	1.25 (0.94–1.67)	0.132
Significant stenosis				
Quartile 1 (reference)	1		1	
Quartile 2	1.21 (0.90–1.61)	0.203	0.88 (0.65–1.20)	0.421
Quartile 3	1.52 (1.16–2.00)	0.002	1.02 (0.75–1.39)	0.879
Quartile 4	1.84 (1.41–2.40)	< 0.001	1.26 (0.93–1.72)	0.142

CI = confidence interval.
Covariates in the multivariable model include age, sex, obesity, diabetes mellitus, hypertension, hyperlipidemia, current smoking status, family history of coronary artery disease, and high-sensitivity C-reactive protein ≥2 mg/L.
[a] Coronary artery calcification is defined as coronary artery calcium score > 10.

unclear. Therefore, large-scale randomized studies should be conducted to investigate the role of reduction in uric acid levels in the progression of atherosclerosis.

Our study has several limitations. First, it was conducted in a single center, and all research participants had voluntarily visited the hospital for general health screening. Therefore, there is a potential for selection bias. Second, as our study participants were exclusively Korean, the applicability of our findings to other ethnic groups may be limited. Third, since this is an observational study, only the association between high SUA and atherosclerosis can be shown, but not causality. Even so, we have outlined plausible ways in which SUA may promote atherosclerosis whereas the reverse phenomenon of atherosclerosis causing high SUA would have to be considered highly speculative, complex and multifactorial. Fourth, calcified plaques and higher CAC scores may have led to an overestimation of significant coronary artery stenosis. Fifth, CCTA has potential shortcomings, including radiation hazards, use of contrast, and higher cost. Therefore, although this study enrolled only volunteers, the use of CCTA in asymptomatic individuals with high SUA level cannot be justified. Finally, we did not obtain the medical history of gouty arthritis which could play an important role in potential confounder. Despite these limitations, we believe that this study may have a clinical implication in revealing an independent association between high SUA level and subclinical coronary atherosclerosis in asymptomatic individuals.

In conclusion, in this large cross-sectional study of asymptomatic individuals undergoing CCTA, high SUA level was associated with non-calcified plaques, suggesting an increased risk of cardiovascular events.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

DH Lim, Y Lee, and GM Park were involved in the conception, design, or planning of the study. GM Park, SW Lee, YH Kim, DH Yang, JW Kang, TH Lim, HK Kim, and J Choe were involved in the acquisition of data. DH Lim, Y Lee, GM Park, SW Choi, and YG Kim were involved in the analysis of data. DH Lim, GM Park, S Hong, YG Kim, CK Lee and B Yoo were involved in the interpretation of results. DH Lim, Y Lee and GM Park substantially contributed to drafting of the manuscript.

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