ORIGINAL RESEARCH

RELATIONSHIP OF CORONARY LIPID CORE PLAQUES AND PLASMA XANTHINE OXIDOREDUCTASE ACTIVITY: EVALUATED WITH NEAR-INFRARED SPECTROSCOPY INTRAVASCULAR ULTRASOUND

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ABSTRACT
Previous research has linked raised serum uric acid levels to increased coronary lipid plaque. Xanthine oxidoreductase (XOR) is a purine metabolism rate-limiting enzyme that is thought to play an essential role in coronary atherosclerosis. However, the link between coronary lipid plaque and XOR remains unknown. Patients with stable coronary artery disease who had elective percutaneous coronary intervention using near-infrared spectroscopy intravascular ultrasound (NIRS-IVUS) guidance were included in the study. Based on a prior publication, they were categorised into three groups: high, normal, and low plasma XOR activity. The researchers looked at quantitative coronary angiography and grayscale IVUS. The primary endpoint was NIRS-IVUS assessment of coronary lipid plaques in a nontarget artery with lipid core burden index (LCBI) and maximum LCBI in 4 mm (maxLCBI4mm). Out of 68 patients, 11, 31, and 26 were classed as having low, normal, or high XOR activity. Among the three groups, the high XOR activity group had the longest lesion length, the smallest minimum lumen diameter, and the highest percentage of diameter stenosis in a nontarget artery. Grayscale IVUS analysis revealed that the high XOR activity group had a lower lumen area than the rest. In a nontarget vessel, LCBI (102.1 ± 56.5 vs 65.6 ± 37.8, p = 0.04) and maxLCBI4mm (474.4 ± 171.6 vs 347.4 ± 181.6, 294.0 ± 155.9, p = 0.04) were considerably greater in the high XOR group than in the low and normal groups. In patients with stable coronary artery disease, higher XOR activity was related to coronary lipid-rich plaque in a nontarget vessel.

INTRODUCTION
Gout and the development of cardiovascular illnesses such as hypertension, heart failure, stroke, and coronary artery disease are linked to hyperuricemia (CAD) [1]. Previous research has found a link between elevated serum uric acid (SUA) levels and higher lipid content of coronary artery plaque as measured by integrated backscatter-intravascular ultrasound.
suggesting that SUA levels could be used as a surrogate marker for vulnerable plaque in CAD patients. However, whether a high SUA level is a cause of coronary artery disease is debatable, and the mechanism is unknown [1]. Xanthine oxidoreductase (XOR) is a rate-limiting enzyme that converts hypoxanthine to xanthine and xanthine to uric acid in the last two steps of purine metabolism. XOR produces reactive oxygen species (ROS) and is thought to play a role in the development of susceptible plaque in CAD patients [2,4]. However, the relationship between plasma XOR activity and coronary lipid plaque has only been studied in a few studies. The goal of this study was to see if there was a link between plasma XOR activity and coronary lipid core plaque measured by near-infrared spectroscopy (NIRS) in patients with stable CAD.

METHODS
Patients with stable CAD who underwent elective percutaneous coronary intervention (PCI) at MKCG Medical College were prospectively included for a period of 1 year and 6 months. Acute coronary syndrome (ACS), hemodialysis, and the use of an XOR inhibitor were all substantial exclusion factors. A total of 80 patients were enrolled, but the following subjects were excluded:

(1) the NIRS-IVUS system was not used at the discretion of the operator (n = 5),
(2) the NIRS-IVUS catheter failed to cross neither the culprit nor the non-culprit arteries (n = 6), and
(3) the XOR inhibitor was used (n = 1).
As a result, the current study included 68 patients. Consent had been gathered from all the patients beforehand. During PCI, blood samples were taken from all patients in the fasting state before intravenous heparin injection. Plasma XOR activity was measured using a very sensitive method that combined liquid chromatography and triple quadruple mass spectrometry with stable isotope-labeled xanthine [5,6]. Patients were categorised into three groups based on plasma XOR activities: low 33 pmol/100 mL/h, normal 33 to 120 pmol/100 mL/h, and high >120 pmol/100 mL/h, according to a prior publication [7]. SUA, LDL and HDL cholesterol, triglycerides, fasting blood sugar, glycosylated haemoglobin, and serum creatinine were all measured.

QAngio XA was used to examine coronary angiography quantitatively (Version 7.1). A program automatically measured the reference vessel diameter, minimum lumen diameter, percentage diameter stenosis, and lesion length.

After intracoronary nitrate injection, all PCI procedures were conducted under NIRS-IVUS guidance. The NIRS-IVUS catheter system included a 3.2 Fr rapid-exchange catheter, a pullback and rotation device, and a console (TVC imaging systems, Infraredx, Burlington, VT). The NIRS-IVUS catheter was inserted into the target vessel and nontarget vessels before predilation if possible, and then pulled back from the distal section to the ostium of the coronary artery or guiding catheter. Predilation was allowed and NIRS-IVUS analysis was performed before stent placement if the NIRS-IVUS catheter could not pass the target lesion. The coronary arteries were not examined when NIRS-IVUS could not cross nontarget vessels. The operator was urged to picture as much as possible in both target and nontarget boats in every circumstance.TVC imaging devices were used to examine NIRS data prior to stent placement to offer a quantitative estimate of the amount of lipid core plaque. The
fraction of yellow pixels acquired from the chemogram, an image map resulting from the NIRS data, were used to calculate the total lesion lipid core burden index (LCBI) and the maximal lipid core burden index in 4 mm (maxLCBI4 mm) [8]. When NIRS-IVUS was used to examine two nontarget vessels, the one with the highest maxLCBI4 mm was determined to be the nontarget vessel. According to the consensus document, grayscale IVUS was also examined using computerised planimetry (EchoPlaque 3.0, Indec Systems, Mountain View, CA) [9,10].

Lumen and external elastic membrane cross-sectional areas and plaque burden at the site of minimum lumen area within the total measured segment and within the maxLCBI4mm segment were measured [11]. All NIRS-IVUS analyses were performed by experienced operators who were blinded to patients’ characteristics. The primary end point of the present study was the relation between XOR activities and LCBI or maxLCBI4mm in a non-target vessel as predilation in the culprit vessel significantly alters these indices [12].

JMP Pro 13 software was used for statistical analysis (SAS Institute, Cary, NC). All information is presented as a mean, standard deviation, or frequency (percent). Analysis of variance was used to compare continuous variables. The chi-square test or Fisher's exact test were used to compare categorical data. The log-transformed XOR activity was employed as a continuous variable to equalise the skewed distribution. For continuous variables, the Pearson correlation coefficient was employed. The linear regression analysis was used to accomplish the univariable analysis. To identify the independent predictors of LCBI and maxLCBI4mm, the related factors in univariable analyses (p <0.20) were included in the multivariable model. A statistically significant value of p <0.05 was used.

**RESULTS**

Low, normal, and high XOR activity groups were assigned to 26 (38%) patients, 31 (46%) patients, and 11 (16%) patients, respectively. Table 1 shows the baseline patient characteristics. SUA level and log-XOR activity had no significant relationship (r = 0.002, p = 0.98).

**Table 1: Baseline patient characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>XOR activity</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (n = 26)</td>
<td>Normal (n = 31)</td>
</tr>
<tr>
<td>Age</td>
<td>71.2 ± 11.5</td>
<td>70.0 ± 9.8</td>
</tr>
<tr>
<td>Men</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Body mass index</td>
<td>22.1 ± 3.7</td>
<td>24.0 ± 2.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sugar (mg/dl)</td>
<td>129± 84</td>
<td>119± 32</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>140± 71</td>
<td>143± 70</td>
</tr>
<tr>
<td>LDL-C</td>
<td>94± 27</td>
<td>87± 24</td>
</tr>
</tbody>
</table>
HDL-C 51± 16 49± 11 55±30 0.60
eGFR 70.6 ± 16.1 69.5 ±20.3 77.6 ±13.5 0.34
HbA1c (%) 6.2±1.2 6.4±0.9 6.5±1.0 0.60
Serum uric acid 5.5±1.5 5.4±1.7 5.6±0.6 0.96

Medication
Dual antiplatelet therapy 25 30 10 1
Oral anticoagulant 1 6 0 0.1
ACE-I or ARB 11 13 8 0.54
β-blocker 7 14 5 0.40
Calcium channel blocker 11 14 3 0.80
Diuretic 3 3 2 0.86
Statin 23 23 9 0.23

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCI = percutaneous coronary intervention; XOR = xanthine oxidoreductase. Values are mean ± standard deviation, or n (%). Dyslipidemia was defined by HDL-C 140 mg/dl, triglyceride >150 mg/dl, or taking lipid lowering medications.

Angiographic and gray-scale IVUS findings are provided in Table 2. Among the three groups, the high XOR activity group had a longer lesion length, smaller minimum lumen diameter, and a higher proportion of diameter stenosis in a non-target channel, according to quantitative coronary angiography (Table 2). In a nontarget vessel, gray-scale IVUS analysis revealed a considerably lower lumen area and numerically larger plaque burden in the high XOR activity group than in the others.

Table 2: Angiographic findings

<table>
<thead>
<tr>
<th>Variable</th>
<th>XOR activity</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Predilation performed</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Nontarget coronary artery</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Right</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

Quantitative coronary angiography

<table>
<thead>
<tr>
<th>Nontarget vessel</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Minimum lumen diameter</td>
<td>1.86 ± 0.56</td>
<td>1.97 ± 0.61</td>
</tr>
<tr>
<td>Reference diameter</td>
<td>2.80 ± 0.75</td>
<td>2.80 ± 0.64</td>
</tr>
<tr>
<td>Lesion length</td>
<td>8.5 ± 6.6</td>
<td>6.9 ± 3.9</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td>32.6 ± 12.6</td>
<td>29.3 ± 12.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Target vessel</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Minimum lumen diameter</td>
<td>0.92 ± 0.44</td>
<td>0.96 ± 0.41</td>
</tr>
<tr>
<td>Reference diameter</td>
<td>2.43 ± 0.59</td>
<td>2.70 ± 0.83</td>
</tr>
<tr>
<td>Lesion length</td>
<td>34.1 ± 18.4</td>
<td>27.4 ± 12.5</td>
</tr>
</tbody>
</table>
XOR = xanthine oxidoreductase. Values are mean ± standard deviation, or n (%).

Pull-back length of NIRS-IVUS in a target vessel (74.3±20.2 vs 74.7±22.8 vs 81.7±24.3 mm, p = 0.63) and a nontarget vessel (66.0±25.7 vs 63.4±21.2 vs 72.6±23.9 mm, p = 0.59) did not significantly differ among the 3 groups. Compared with the low and normal XOR activity groups, the high XOR activity group had significantly higher LCBI (55.6±37.8 vs 65.6±48.5 vs 102.1 ±56.5, p = 0.04) and maxLCBI4mm (294.0±155.9 vs 347.4±181.6 vs 474.4±171.6, p = 0.04) in a nontarget vessel, whereas there were no significant differences of LCBI (95.4±70.5 vs 97.1±68.2 vs 71.4±65.8, p = 0.57) and maxLCBI4mm (463.4±218.7 vs 412.1±211.8 vs 325.5±172.2, p = 0.21) in a target vessel. Multivariable analyses showed previous coronary artery bypass grafting and logXOR activity as significant independent predictors of LCBI in a nontarget vessel, and log-XOR activity as predictors of maxLCBI4mm with marginal significance. During a follow-up of 12.0±6.5 months, 1 patient in the normal XOR group died and 2 in the high XOR group had a myocardial infarction.

DISCUSSION

The present study showed that high XOR activity was found in 16% of patients with stable CAD who underwent elective PCI. Patients in the high XOR activity group had significantly smaller minimum lumen diameter and area, longer lesion length, and higher LCBI and maxLCBI4mm in a nontarget vessel. Multivariable analysis demonstrated that XOR activity was associated with higher LCBI and maxLCBI4mm. To the best of our knowledge, this is the first study investigating the impact of XOR activity on coronary lipid core plaque.

We previously reported that elevated SUA level was correlated with greater lipid content of coronary plaque in non-culprit lesions in patients with ACS [2]. A subsequent study confirmed this finding in patients with ACS and stable CAD, although the relationship was not significant in patients with stable CAD [3]. No significant relation between elevated SUA levels and greater lipid plaque was observed in the present study probably due to different study populations (ie, ACS vs stable CAD). In these reports, [2,3] XOR was speculated as a key factor to promote atherosclerotic plaque formation. However, the direct relation between XOR activity and coronary lipid plaque has not been studied. It was difficult to accurately measure plasma XOR because the activity is much lower in humans than in animals [13]. In the present study, a recently developed assay was used to quantify human XOR activity [5,6]. Utilizing this novel and sensitive method, Otaki et al determined the reference interval of XOR activity as 33 to 120 pmol/100 mL/h based on the results for 95% of normal control subjects, indicating only 2.5% of normal control have high XOR activity [7]. In contrast, high XOR activity was observed in 16% of the present study population, suggesting that patients with CAD are likely to have higher XOR activity. The prevalence of current smoking was significantly higher in the high XOR group than in the low and normal XOR groups in this study, which is in line with the previous reports [13]. After the adjustment with smoking...
status, higher XOR activity was indicated as an independent predictor of greater lipid core plaques. XOR pathways are one of the major ROS-generating systems in the vascular vessels. XOR plays physiologic roles in inflammatory signaling, the regulation of nitric oxide production, and vascular function in the purine metabolism, whereas uric acid itself may have a protective role in vascular alterations. The ROS generated by XOR induces adipogenesis, endothelial dysfunction, and myocyte activation, leading to atherosclerosis [14]. It is plausible that higher XOR activity increases the risk of having vulnerable plaque beyond the SUA level.

The present study demonstrates that LCBI and maxLCB–BI4mm in a nontarget vessel assessed by NIRS-IVUS were significantly higher in the high XOR activity group. Although there is no head-to-head comparison, it is conceivable that NIRS-IVUS is one of the most accurate in vivo technologies for detecting lipid-rich plaque. The specificity of NIRS-IVUS in detecting coronary atheroma was reported to be up to 99% in various types of segments (eg, calcification and small plaque burden) using histology as a gold standard [15]. Both LCBI and maxLCBI4mm in a nontarget vessel have been shown to have a prognostic impact in recent studies. The ATHEROREMO-NIRS study indicated that patients with LCBI ≥43 (the median value in the study) in a nontarget vessel had a higher rate of cumulative 1-year events, a composite of death, nonfatal ACS, and unplanned coronary revascularization, compared with their counterpart (16.7% vs 4.0%, p = 0.01) [16]. Another retrospective study showed LCBI ≥77 in nontarget vessels as a predictor of cardiovascular events [17]. Patients with the highest quartile of maxLCB–BI4mm (≥360) in a nontarget vessel in the combined dataset of the ATHEROREMO-NIRS and IBIS-3-NIRS substudies were reported to have the highest risk of major adverse cardiac during the median follow-up of 4.1 years [18]. A prospective, single-center observational registry also showed that the major adverse cardiovascular and cerebrovascular events were more frequently observed in patients with maxLCBI4mm ≥400 in the non-culprit segment than in the counterpart [8]. The LCBI and maxLCBI4mm in the high XOR activity group (ie, 102.1±56.5 and 474.4±171.6) were numerically higher than the cutoff values in the previous studies, indicating that coronary lipid core plaques in high XOR activity group in the present study are clinically significant. Recently, a large-scale prospective cohort confirmed the predictive impact of LCBI and maxLCBI4mm [19].

There is no clinical study examining the efficacy of SUA or XOR lowering therapy to reduce coronary lipid plaque and subsequent coronary events following PCI. XOR inhibitors such as allopurinol have been shown to improve endothelial function and oxidative stress in patients with stable CAD [20]. A previous placebo-controlled randomized trial found that allopurinol significantly reduced the progression of carotid intima-media thickness [21]. Although a recent randomized control trial did not show the benefit of SUA lowering therapy in reducing coronary events, [22] active intervention in patients with high XOR activity might improve clinical outcomes.

**LIMITATIONS**

There are some limitations in the present study. This was a single-center study, and the sample size was relatively small. Future studies with large sample size are warranted to confirm our study results and elucidate the relation of XOR activity with associated factors (eg, smoking). NIRS-IVUS was used to assess coronary lipid plaque in the present study;
however, the impact of other modalities enabling precise analysis of coronary plaque morphology (eg, optical coherence tomography) is unknown [23,24]. Although oxidative stress is one of the key factors in the process of XOR-induced atherosclerosis, oxidative stress markers (eg, isoprostanes, 8-hydroxy-2’-deoxyguanosine, and thiobarbituric acid reactive substances) were not assessed in the present study.

CONCLUSION
In conclusion, high XOR activity was observed in 16% of patients who underwent elective PCI. Patients with high XOR activity had significantly smaller coronary lumen and area, longer lesion length, and higher LCBI and maxLC BI4mm in a nontarget vessel, showing that elevated XOR activity was associated with a coronary lipid-rich plaque inpatients with stable CAD.

REFERENCES
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