Coronary Plaque Characteristics in Patients With Mild Chronic Kidney Disease – Analysis by 320-Row Area Detector Computed Tomography –

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Background: The differences in the coronary plaque characteristics between patients with mild chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] 30–59 ml·min⁻¹·1.73m⁻²) and those without CKD (eGFR ≥60) by 320-row area detector computed tomography (CT) have not been studied.

Methods and Results: We enrolled 487 patients undergoing coronary CT angiography with suspected stable coronary artery disease (mean age: 66.6±10.8 years, 131 with mild CKD) and analyzed 6,352 segments. All coronary plaques were characterized for the presence of vessel remodeling, plaque consistency, and the disposition of coronary calcification, and a plaque with positive vessel remodeling and/or low-attenuation was defined as high risk. The number of diseased segments per patient was higher in mild CKD patients than in those without CKD (4.61±3.83 vs. 2.95±3.11, P<0.0001). The prevalence of severe stenosis (≥70% luminal diameter) was significantly higher in cases of mild CKD than in no CKD (35.1% vs. 19.4%, P=0.0003), but there was no significant difference in the prevalence of high-risk plaque (13.0% vs. 9.8%, P=0.3189).

Conclusions: The severity of coronary artery stenosis was higher in the patients with mild CKD, though there was no significant difference in the prevalence of high-risk plaque. We suggest that the high risk of coronary events in patients with CKD is related to the severity of stenosis rather than to the characteristics of plaque. (Circ J 2012; 76: 1436–1441)

Key Words: Area detector computed tomography; Chronic kidney disease; Coronary artery disease; Plaque characteristics

Chronic kidney disease (CKD) promotes the development of atherosclerosis and increases the risk of cardiovascular disease (CVD) in the general population. It is well known that death is far more common than initiation of dialysis at all stages of CKD. In Japan, one-eighth of adults have CKD, with their number exceeding 13 million. As well as in the United States and Europe, CKD has been reported to be an independent risk factor for CVD in the general Japanese population.

Coronary computed tomographic angiography (CCTA) has a pivotal role in the noninvasive evaluation of coronary atherosclerosis. It provides valuable information not only about coronary stenosis, but also the plaque characteristics. CCTA is, moreover, of prognostic import in coronary artery disease (CAD). The presence of obstructive CAD detected by CCTA has a prognostic impact on the prediction of all-cause mortality and cardiac events. We previously reported that patients demonstrating positively remodeled coronary segments with low-attenuated plaques were especially at high risk of developing acute coronary syndrome (ACS).

Evaluation of coronary atherosclerosis by CCTA in patients with CKD has been difficult because of the risk of contrast-
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induced nephropathy (CIN). But the introduction of 320-row area detector CT (ADCT) has enabled whole-heart volumetric acquisition in a single gantry rotation. Compared with conventional 64-slice or less multidetector CT (MDCT), modern scanners, including ADCT, enable imaging with less motion artifact, lowering the dose of contrast medium needed, and hence extending the potential use of imaging in some patients with CKD.

The purpose of this study was to evaluate the coronary plaque burden and plaque characteristics using ADCT, and to compare them between patients with mild CKD (estimated glomerular filtration rate [eGFR] 30–59 ml · min$^{-1}$ · 1.73 m$^{-2}$) and those without CKD (eGFR ≥60).

Methods

Study Group
From November 2007 to March 2011, we retrospectively studied 993 consecutive subjects undergoing CCTA for suspected CAD. Of these, we enrolled 487 patients (mean age: 66.6±10.8 years, 300 men, 131 with mild CKD) and excluded 506 patients: 191 after coronary artery surgery, 148 after percutaneous coronary intervention (PCI), 113 suspected ACS, 20 on dialysis therapy, 2 with advanced CKD (eGFR <30), 14 with lack of data regarding renal function, 1 after kidney transplantation, 3 with Kawasaki disease, and 14 with poor image quality (Figure). In all subjects, height (cm), body weight (kg), blood pressure (systolic and diastolic BP), serum levels of triglycerides (TG), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), creatinine (Cr), proteinuria (PU), fasting blood glucose, hemoglobin A$\text{c}$, smoking status (current vs. nonsmoker) and medications used were recorded as cardiovascular risk factors. We calculated eGFR using the abbreviated equation modified by the Japanese Society of Nephrology for Japanese based on the Modification of Diet in Renal Disease (MDRD) study: $0.741 \times 175 \times [\text{age} (\text{years})]^{0.203} \times [\text{serum Cr} (\text{mg/dl})]^{-1.154} \times [0.742 \text{ if female}].$ Based on the eGFR of enrolled subjects, mild CKD was defined as ranging from 30 to 59 ml · min$^{-1}$ · 1.73 m$^{-2}$ and no CKD was defined as eGFR ≥60. PU was checked by dipstick urinalysis and assessed qualitatively. All patients were divided into 4 groups (–, 1+, 2+, 3+). The result of ‘1+’ or more was regarded as positive. Body mass index was calculated as body weight divided by height squared (kg/m$^2$). Hypertension (HT) was defined as current systolic/diastolic BP >140/90 mmHg or use of antihypertensive agents. Hyperlipidemia was defined as LDL-C >140 mg/dl or TG >200 mg/dl or use of cholesterol-lowering agents. Diabetes mellitus (DM) was considered present if the patient was taking insulin or oral hypoglycemic agents or had previously been diagnosed with DM. Old myocardial infarction was based on a self-reported history.

CCTA Protocol
CCTA was performed using a 320-ADCT (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) with 0.5-mm detector elements, rotation speed of 350, 375, and 400 ms. Scanner settings of 350–450 mA and 100–135 kV were used. For the contrast-enhanced scan, 20.4 mgI · kg$^{-1}$ · s$^{-1}$ contrast medium was injected for 12 s followed by 20 ml of saline at 3.0 ml/s. We had no treatment for the prevention of CIN. All scans were performed during a single breath-hold. Isosorbide dinitrate spray was provided immediately before CCTA. The entire heart was imaged in 1–3 beats (depending on heart rate) and the ECG was registered simultaneously for prospective

Figure. Study population. Of a total of 993 patients, 131 with mild CKD and 356 with no CKD were analyzed after excluding 506 patients. CKD, chronic kidney disease; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary aorta bypass graft; HD, hemodialysis.
Coronary artery segments with a diameter >2 mm within and/or adjacent to the artery lumen, clearly distinguishable from the vessel lumen and surrounding pericardial tissue were defined as a structure >1 mm in size (SC). Manual inspection, in both cross-section and longitudinal view, was chosen for analysis.

Volumetric data were reconstructed with half or segmented reconstruction. After acquisition of the reconstructed volumetric data, images were transferred to a workstation (ZIOSTATION System 1000, Amin/ZIO, Tokyo, Japan). The study was approved by the Institutional Review Board and the Ethics Committee of Fujita Health University.

Image Analyses
On CT images, coronary arteries were divided into 15 segments based on the recommendations of the American Heart Association.20 Coronary artery segments with a diameter ≥2 mm were evaluated for the presence of plaques. Coronary plaques were defined as a structure >1 mm² within and/or adjacent to the artery lumen, clearly distinguishable from the vessel lumen and surrounding pericardial tissue.12 All coronary artery segments were evaluated by 2 experienced observers unaware of the clinical history of the patients.

Atherosclerotic lesions were classified visually as mild (<50% luminal diameter), moderate (50–69%), or severe (≥70%). We defined the plaque consistency based on our previously published data from a comparison of CCTA and intravascular ultrasound (IVUS).9 The plaques were reported as either calcified or noncalcified (NCP). NCP was classified into 2 categories: low-attenuation plaque (LAP: NCP ≤30 HU) and intermediate attenuation plaques (IAP: 30 HU < NCP ≤150 HU). Plaque calcification was classified into 2 categories: spotty calcification (SC: <3 mm in size) and large calcification (LC: larger than SC). Manual inspection, in both cross-section and longitudinal reconstruction, was used for defining the remodeling index (lesion area/reference segment). The remodeling index was reported as positive remodeling (PR) when the area at the plaque site was at least 21% larger than the reference segment. In our previous study, we showed that positively remodeled coronary segments with low-attenuation plaques on CCTA was characteristic of lesions in ACS,23 with patients having such lesions at the phase with the least amount of coronary artery motion being chosen for analysis.

Table 1. Patients’ Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=487)</th>
<th>Mild CKD (n=131)</th>
<th>No CKD (n=356)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.6±10.8</td>
<td>71.8±6.9</td>
<td>64.6±11.4</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Male sex</td>
<td>300 (61.6%)</td>
<td>81 (61.8%)</td>
<td>219 (61.5%)</td>
<td>0.949</td>
</tr>
<tr>
<td>BMI</td>
<td>22.8±3.6</td>
<td>22.9±3.6</td>
<td>22.8±3.6</td>
<td>0.676</td>
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<tr>
<td>DM</td>
<td>119 (24.4%)</td>
<td>37 (28.2%)</td>
<td>82 (23.0%)</td>
<td>0.235</td>
</tr>
<tr>
<td>HT</td>
<td>301 (61.8%)</td>
<td>92 (70.2%)</td>
<td>209 (58.7%)</td>
<td>0.0231*</td>
</tr>
<tr>
<td>HL</td>
<td>273 (56.1%)</td>
<td>82 (62.6%)</td>
<td>191 (53.7%)</td>
<td>0.0826</td>
</tr>
<tr>
<td>PU</td>
<td>46 (9.5%)</td>
<td>25 (19.1%)</td>
<td>21 (6.9%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Current smoker</td>
<td>85 (17.5%)</td>
<td>25 (19.1%)</td>
<td>60 (16.9%)</td>
<td>0.486</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>0.79±0.22</td>
<td>1.02±0.20</td>
<td>0.71±0.15</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>eGFR (ml·min⁻¹·1.73m⁻²)</td>
<td>71.1±16.3</td>
<td>51.2±7.8</td>
<td>78.4±11.9</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>CM volume (ml)</td>
<td>48.7±9.8</td>
<td>47.9±9.3</td>
<td>48.9±10.0</td>
<td>0.464</td>
</tr>
</tbody>
</table>

Table 2. Coronary Artery Stenosis and Plaque Characteristics in Mild CKD and No CKD Groups

<table>
<thead>
<tr>
<th>Patients</th>
<th>Total (n=487)</th>
<th>Mild CKD (n=131)</th>
<th>No CKD (n=356)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No plaque</td>
<td>142 (29.0%)</td>
<td>23 (17.3%)</td>
<td>119 (33.4%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Prevalence of any plaque</td>
<td>345 (70.8%)</td>
<td>108 (82.4%)</td>
<td>237 (66.6%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Prevalence of moderate stenosis</td>
<td>186 (38.2%)</td>
<td>65 (49.6%)</td>
<td>121 (34.0%)</td>
<td>0.0015*</td>
</tr>
<tr>
<td>Prevalence of severe stenosis</td>
<td>115 (23.6%)</td>
<td>46 (35.1%)</td>
<td>69 (19.4%)</td>
<td>0.0003*</td>
</tr>
<tr>
<td>Prevalence of multivessel disease</td>
<td>48 (9.9%)</td>
<td>24 (18.3%)</td>
<td>24 (6.7%)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Prevalence of high-risk plaque</td>
<td>52 (10.7%)</td>
<td>17 (13.0%)</td>
<td>35 (9.8%)</td>
<td>0.3189</td>
</tr>
<tr>
<td>Prevalence of low-attenuation plaque</td>
<td>33 (6.7%)</td>
<td>10 (7.5%)</td>
<td>23 (6.5%)</td>
<td>0.519</td>
</tr>
<tr>
<td>Prevalence of plaque with positive remodeling</td>
<td>44 (9.0%)</td>
<td>13 (9.8%)</td>
<td>31 (8.7%)</td>
<td>0.7141</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Segments</th>
<th>Total (n=487)</th>
<th>Mild CKD (n=131)</th>
<th>No CKD (n=356)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>No. of segments including any plaque</td>
<td>3.4±1.41</td>
<td>4.6±3.83</td>
<td>2.9±3.11</td>
<td>&lt;0.0001*</td>
</tr>
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<td>No. of segments including large calcification</td>
<td>0.8±1.86</td>
<td>1.7±2.88</td>
<td>0.57±1.23</td>
<td>0.0001*</td>
</tr>
<tr>
<td>No. of segments including spotty calcification</td>
<td>2.2±2.34</td>
<td>2.6±2.53</td>
<td>2.0±2.25</td>
<td>0.0166*</td>
</tr>
<tr>
<td>No. of segments including intermediate attenuated plaque</td>
<td>0.9±1.45</td>
<td>1.0±1.50</td>
<td>0.90±1.43</td>
<td>0.1239</td>
</tr>
<tr>
<td>No. of segments including high-risk plaque</td>
<td>0.1±0.41</td>
<td>0.15±0.39</td>
<td>0.12±0.41</td>
<td>0.3376</td>
</tr>
<tr>
<td>No. of segments including low-attenuation plaque</td>
<td>0.08±0.31</td>
<td>0.09±0.34</td>
<td>0.07±0.31</td>
<td>0.5081</td>
</tr>
<tr>
<td>No. of segments including plaque with positive remodeling</td>
<td>0.1±0.33</td>
<td>0.11±0.36</td>
<td>0.10±0.32</td>
<td>0.7018</td>
</tr>
</tbody>
</table>

Data are n (%) or mean±SD. P-values indicate the difference between patients with mild CKD and those with no CKD; *P<0.05.

CKD, chronic kidney disease; BMI, body mass index; DM, diabetes mellitus; HT, hypertension; HL, hyperlipidemia; PU, protein urea; Cr, creatinine; eGFR, estimated glomerular filtration rate; CM, contrast medium.

Cardiovascular study in patients with mild chronic kidney disease: Current smoking status and inflammatory markers affect coronary outcomes

KAWAI H et al.

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Coronary Plaque in Patients With Mild CKD

We divided all patients into 2 groups (mild CKD and no CKD) and compared their baseline characteristics. There were statistically significant differences in age, HT, and PU, in addition to Cr and eGFR (Table 1). Of 487 patients, 345 (70.8%) had plaque, 186 (38.2%) had moderate stenosis, 115 (23.6%) had severe stenosis, and 48 (9.9%) had multivessel disease (Table 2). Compared with the patients with no CKD, those with mild CKD had significantly higher prevalences of some plaque (82.4% vs. 66.6%, P<0.001), moderate stenosis (49.6% vs. 34.0%, P=0.0015), severe stenosis (35.1% vs. 19.4%, P=0.0003), and multivessel disease (18.3% vs. 6.7%, P=0.0001). Concerning the characteristics of the plaque, there were significant differences in the number of segments containing LC (1.7±1.88 vs. 0.57±1.23, P=0.0001) and SC (2.6±2.53 vs. 2.08±2.25, P=0.0166). On the other hand, no significant difference was noted in the prevalence of HRP (13.0% vs. 9.8%, P=0.3189). Of the plaque with PR, the mean value of the remodeling index was 1.38±0.19 (1.32±0.14 vs. 1.40±0.21, P=0.4111). Patients with severe stenosis had a higher prevalence of male sex, CKD, DM, HT, and PU. Patients with multivessel disease had a higher prevalence of male sex, CKD, DM, and HT. Patients with HRP had a higher prevalence of male sex, obesity, and DM (Table 3). Table 4 shows the results of the multivariate logistic regression analysis for prediction of severe stenosis and multivessel disease. After adjusting for sex, CKD, DM, HT, and PU, the patients with CKD had a higher risk of severe stenosis (odds ratio [OR] 2.08, 95% confidence interval [CI] 1.30–3.32, P=0.024), and multivessel disease (OR 2.86, 95% CI 1.52–5.39, P=0.013).

**Statistical Analyses**
All data are presented as mean±SD for continuous and frequency (percentage) for categorical variables. The mean values for 2 groups were compared with chi-square tests for categorical and Wilcoxon signed-rank sum test for continuous variables. Those variables significant at P<0.05 were included in the logistic regression analysis to determine whether mild CKD was independently associated with any CCTA findings. All analyses were performed with JMP Version 8, (SAS Institute, Cary, NC, USA) and a P<0.05 was considered as statistically significant.

**Results**
We defined a plaque with LAP and/or PR as high-risk plaque (HRP).

**Discussion**
The present study demonstrated the presence of coronary atherosclerosis already patients with mild CKD. The prevalence of significant stenosis was higher in patients with mild CKD than in patients with no CKD, though there was no significant difference in the prevalence of HRP between the 2 groups. To our knowledge, few studies are available regarding the CCTA findings of patients with CKD, and none for the pre-CKD stage to mild CKD. Furthermore, this is the first study to focus on the characteristics of coronary plaque specifically in patients with CKD.

Several reports have shown an association between coronary stenotic severity and a patient's prognosis. It has been reported that obstructive CAD (≥50% luminal narrowing) detected by CCTA has both independent and incremental value in predicting all-cause mortality independent of conventional risk factors. Furthermore, severe CAD (eg, multivessel...
There are many studies of plaque characteristics using IVUS. A few studies using IVUS have focused on volume and characteristics of coronary plaque in CKD patients. Nicholls et al described a meta-analysis of IVUS studies comparing coronary atherosclerotic volume in CKD patients and concluded that mildly impaired renal function was not associated with a greater burden of atherosclerosis. Miyagi et al performed integrated backscatter IVUS before elective PCI in patients with SAP. They reported that eGFR showed a significant negative correlation with lipid volume and a significant positive correlation with fibrous volume in coronary plaques. But the studied coronary arteries were limited to the culprit lesions of PCI, and so the findings might not reflect the extent of atherosclerosis throughout the whole coronary arterial tree. There has been poor understanding of why CKD is an independent risk factor for CAD in the pathology of coronary plaque. It is not well known whether the increased incidence of coronary events is related to increased severity of stenosis or plaque vulnerability. The present study demonstrated that patients with mild CKD had significantly more severe coronary lesions, but did not have more HRP. We thus suggest that the high risk of coronary events in patients with CKD is related to the severity of stenosis.

DM is a remarkable feature underlying many coronary risk factors, and numerous papers have noted the association between DM and coronary atherosclerosis detected by CCTA. Although CKD is also a significant risk factor, few reports have focused on coronary plaque burden and characteristics revealed on CCTA in such patients. We attribute this to the fact that CCTA using contrast material has been regarded as an inappropriate modality for patients with CKD because of the risk of developing CIN. To the best of our knowledge, only 2 papers have described the coronary atherosclerosis in patients with CKD evaluated by CTA. Cho et al studied 4,297 subjects who underwent CTA as part of a general health evaluation and they concluded that early CKD is an independent risk factor for CAD, with the presence of PE useful for risk stratification. Despite the great number of patients with CKD evaluated using 64-slice MDCT, detailed coronary data were not provided. Mitsutake et al studied 313 patients (including 95 patients with CKD) who underwent CCTA and showed that eGFR levels in the group of patients with triple-vessel disease were significantly lower than those in patients without stenosed vessels. They concluded that CKD might contribute to the severity of CAD associated with progression of coronary artery calcification.

There are several guidelines for the use of contrast media, but there is no clear-cut criterion for CCTA when evaluating patients with CKD. It is well known that the clinical course of CIN depends on the baseline renal function, although it is also reported that the ratio of incidence of CIN is 2.2-fold greater for intraarterial contrast material administration compared with intravenous administration. Microshovers of cholesterol emboli have been shown to occur in up to 50% of PCI in which a catheter is passed through the aorta, and they may be a cause of the increased risk for CIN. Several reports of CAG have shown that the prevalence of severe stenosis is higher in patients with CKD than in those without CKD, but it was reported that patients with renal dysfunction had more frequent vascular complication after invasive CAG. If there is any doubt about being able to obtain a good image quality on CCTA for evaluating coronary atherosclerosis in spite of high-dose contrast medium use, one would hesitate to subject patients with CKD to CCTA examination. But as we noted previously, ADCT provides excellent coronary images with lower-dose contrast medium compared with 64-slice or less MDCT. In a previous paper, asymptomatic CKD patients were screened by 64-MDCT with a contrast medium bolus volume twice as great as that used by us. For CKD patients requiring CCTA after other checkups, CCTA with low-dose contrast medium by ADCT would be a reasonable option.

**Study Limitations**

First, a limited number of patients in a single center were enrolled for the study and were observed retrospectively. Although the P-value is higher than 0.05, the prevalence of HRP tended to be higher in patients with mild CKD than in those with no CKD. To clear up this contradiction we need a large-population study that examines the prognosis of the studied patients. Second, not all patients with suspected CAD were enrolled in this study. The attending physicians made the decision to select patients for CCTA, thereby increasing the possibility of sampling and observational biases, especially for the patients with CKD. Finally, patients with advanced CKD (eGFR <30) or on hemodialysis were excluded from this study.
Conclusions

Our results indicate that the number of coronary segments with plaque is increased even in mild CKD. The prevalence of significant stenosis, especially multivessel stenosis, is also increased in mild CKD, although the difference in the prevalence of HRP between the 2 groups was not significant. We suggest that the high risk of coronary events in patients with CKD is related to the severity of stenosis rather than to the characteristics of the plaque.

References


