Association between Renal Dysfunction and the Mixed Plaque of Coronary Artery on Computed Tomographic Angiography

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Coronary artery plaque is related to development of coronary artery disease (CAD), and chronic kidney disease is associated with CAD. However, the association of renal dysfunction (RD) with coronary artery plaque characteristics has not been fully elucidated. We evaluated the association between RD and coronary artery plaque characteristics in patients with suspected CAD, who underwent multislice computed tomographic angiography (CTA). A total of 918 patients were classified into 4 groups: group with no plaque (NP) (48.9%), group with calcified plaque (CP) (16.0%), group with noncalcified plaque (NCP) (22.4%), and group with mixed plaque (MP) (12.7%). NCP is considered as rupture-prone soft plaque, and CP as more stable lesion. The mean of estimated glomerular filtration rate (eGFR) was 82.5 ± 15.4 mL/min/1.73m², and the prevalence of RD (defined as eGFR < 60 mL/min/1.73m²) was 6.3%. The prevalence of RD was 3.3% in the NP group, 10.2% in the CP group, 5.3% in the NCP group, and 14.5% in the MP group (P < 0.001 by ANOVA tests). The adjusted odds ratio for RD was 3.38 (95% confidence interval, 1.27 - 9.04) for the MP group, compared with the NP group. The presence of RD showed an independent association with the MP counts (r = 0.155, P < 0.001); however, there was no association between RD and other plaque characteristics. In conclusion, RD is associated with MP rather than CP or NCP, compared with NP, which may reflect one of the developmental processes of CAD in patients with RD.

Keywords: calcified plaque; computed tomographic angiography; coronary artery plaque; mixed plaque; renal dysfunction

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Cardiovascular disease (CVD) is the most frequent cause of morbidity and mortality in patients with chronic kidney disease (CKD) (Parfrey and Foley 1999). Renal dysfunction and coronary artery disease (CAD) are known to have a strong association, which is subsequently the predominant cause of death in these patients. The associated mechanism is multifactorial and is not completely understood (Moe and Chen 2008).

Coronary artery plaque and CVD are known to have a strong association. Coronary atherosclerotic plaque characteristics, rather than plaque size or the degree of coronary artery stenosis, has been shown to be an important determinant of the evolution and disruption of the plaque (Kragel et al. 1989; Falk et al. 1995). Coronary calcified atherosclerotic plaque (CP) reflects later stages of atherosclerosis and may indicate more stable lesions (Goldstein et al. 2000), and CP represents only a limited portion of the overall atherosclerotic plaque burden (Rumberger et al. 1995). Noncalcified atherosclerotic plaque (NCP) is considered a feature of early atherosclerosis (Stary et al. 1995) and might be associated with acute coronary syndrome (Schuijf et al. 2007). In a study using integrated backscatter intravascular ultrasound (IB-IVUS), Miyagi et al. (2010) reported on an association of impaired renal function with a higher percentage of a lipid volume and lower percentage of fibrous volume in coronary artery plaque; however, they enrolled patients with known CAD who were referred for coronary percutaneous intervention, and a small number of patients were enrolled. Little is known about the characteristics of coronary artery plaque associated with renal dysfunction.

Multislice computed tomographic coronary angiography (CTA) is a non-invasive technique used for assessment of coronary artery stenosis and coronary artery plaque characteristics. A recent study has demonstrated the feasibility...
of differentiation of CP, NCP, and mixed plaques (MP) according to density measurements within plaque by CTA (Schroeder et al. 2001). Thus, this study was designed to evaluate the association of renal dysfunction and coronary artery plaque characteristics detected by CTA.

**Subjects and Methods**

Nine hundred and eighteen consecutive individuals without a previous diagnosis of CAD who underwent CTA between January 2008 and December 2009 were included in this cross-sectional study. All of the enrolled subjects visited the outpatient clinic for evaluation of their chest pain or discomfort. Subjects with known CVD (history of myocardial infarction, prior stent placement, or bypass grafting) were excluded. Baseline demographic data, history of hypertension, hyperlipidemia, diabetes mellitus (DM), and smoking were collected. Hypertension was defined as a self-reported history of hypertension and/or use of antihypertensive medication or blood pressure ≥ 140/90 mmHg. DM was defined as a self-reported history of diabetes and/or receiving antidiabetic treatment or a fasting plasma glucose ≥ 126 mg/dl. Smoking was defined as any cigarette smoking within one year of CTA. Height, body weight, and blood pressure were measured in all patients. Total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol, hemoglobin, albumin, blood urea nitrogen (BUN), calcium, phosphorus, and creatinine level were measured after a fasting period of at least 8 hr < 30 days before the CTA evaluation. Creatinine was measured using the rate-blanked and compensated Jaffé method with calibration of the automated systems (Hitachi High-Tech, Tokyo, Japan). The level of kidney function was ascertained by the estimated glomerular filtration rate (eGFR) using the formula developed and validated in the Modification of Diet in Renal Disease (MDRD) study (Levey et al. 2003). And the Korean coefficients for MDRD study equations were applied (Lee et al. 2010). Renal dysfunction was defined as an eGFR < 60 ml/min/1.73m².

All CTA examinations were performed using a Somatom Definition dual-source CT scanner (Siemens Medical Systems, Forchheim, Germany). Each patient’s heart rate was monitored prior to each scan. In the absence of contraindications, patients with a heart rate > 65 beats/min received an oral β-blocker (20–40 mg propranolol orally, Dongkwang Pharm, Seoul, Korea) as the preferred method for slowing the heart rate. Prior to the helical scan, a non-enhanced electrocardiographically gated scan, prospectively triggered at 75% of the RR interval, was performed for measurement of the coronary artery calcification score (CACS) and for determination of the start and end positions of the helical scan. A sublingual pill of 0.6 mg nitroglycerin (Hana Pharm, Seoul, Korea) was administered immediately before the contrast injection. A bolus of 80 ml iodinated contrast (Ultravist370, Bayer Schering Pharma, Berlin, Germany), followed by 50 to 80 ml of saline, were administered by power injection. The scan parameters were 64 × 0.625 mm collimation, rotation time 0.35 seconds, tube voltage 120 kV, and tube current 600 mA. Radiation-reduction algorithms using electrocardiographic modulation were used in order to reduce radiation exposure (mA) during systole and end-diastole. After scan completion, multiphasic reconstruction of the multidetector computed tomographic angiographic scans was performed, with reconstructed images from 70% to 80% by 5% and 5% to 95% by 10% increments. All images were evaluated on a 3-dimensional image analysis workstation (Leonardo, Siemens Medical Systems, Forchheim, Germany). Coronary arteries were divided into 15 segments according to a modified American Heart Association classification. Plaques were defined as structures > 1 mm² within and/or adjacent to the vessel lumen, which could be clearly distinguished from the lumen and surrounding pericardial tissue. Plaques occupied by calcified tissue covering more than 50% of the plaque area (density > 130 Hounsfield unit in native scans) were classified as CP, plaques with < 50% calcium were classified as MP, and plaques without calcium were classified as NCP (Schroeder et al. 2001; Leber et al. 2003, 2005). Coronary arteries without visual stenotic lesions were defined as no plaque (NP). We classified all patients into 4 dominant plaque groups, including NP, CP, NCP, and MP, according to the most frequent plaques or plaques that were associated with the most significant stenosis on CTA.

All studies were interpreted by a single experienced observer who was unaware of patient clinical data. The institutional review board approved the study protocol, and all patients gave informed consent.

Continuous variables are expressed as the means ± s.d., whereas categorical variables are presented as absolute values and percentage. Differences among groups were tested with one-way ANOVA for continuous variables and with chi-square test for categorical variables. For assessment of the independent association of the different plaque subtypes with kidney function, all variables of P-values of less than 0.10 were entered into multivariable logistic and linear regression analysis. A P-value < 0.05 was considered statistically significant. Exceptionally, corrected P-value < 0.05/3 was considered significant as a solution for multiple testing problem on the logistic regression analysis. All analyses were performed using the SPSS 13.0 statistical package (SPSS Inc., Chicago, IL., USA).

**Results**

Baseline characteristics of the study population are listed in Table 1. In 918 patients, 448 patients (48.9%) were classified as the NP group, 147 patients (16%) as the CP group, 206 patients (22.4%) as the NCP group, and 117 patients (12.7%) as the MP group. The mean patient age was 57 ± 12 years, and the number of male patients was 439 (47.8%). The average of eGFR was 82.5 ± 15.4 ml/min/1.73 m², and the number of renal dysfunction patients was 58 (6.3%). Patients with predominantly MP showed the lowest levels of eGFR, compared with other plaque groups. Among the four groups, age, DM, hypertension, smoking, and eGFR showed significant differences. Patients in the MP group were older than those in other groups. Compared with other groups, the NCP group included more patients with DM and hypertension. Albumin levels of the CP group were significantly lower, compared with other groups.

Multiple logistic regression analysis for predictors of coronary artery plaque characteristics is shown in Table 2. After adjustment for confounding variables, including age, gender, current smoking, DM, hypertension, and serum albumin, renal dysfunction was found to be an independent risk factor for MP (odds ratio 3.38, 95% confidence interval 1.27 - 9.04, P = 0.015). Significant risk factors for CP were age, gender, serum phosphorus and serum albumin, but not renal dysfunction, in multivariable analysis. Age, gender, and DM were independent risk factors for NCP in multi-
variable analysis. As shown in Fig. 1, the MP group had the only significant odds ratio for renal dysfunction, as compared to the NP group.

Table 3 presents the results of multivariable linear regression analysis for prediction of MP counts. Significant variables associated with MP counts were age, hypertension, and renal dysfunction in univariable analysis. After adjustment for covariables, including age, gender, DM, and hypertension, renal dysfunction was independently associated with MP counts. Patients with three or more MP counts had lower eGFR than control patients ($P = 0.018$) (Fig. 2).

**Discussion**

The results of this study demonstrated a correlation between renal dysfunction and the plaque characteristics detected on CTA. Renal dysfunction was found to be an independent risk factor of MP in patients with suspected CAD. Several studies have reported on the association between coronary plaque characteristics and CVD. The Framingham Heart Study identified traditional CVD risk factors related to coronary plaque characteristics (Bamberg et al. 2008; Weiner et al. 2008; Yun et al. 2009; Cheng et al. 2010; Nasir et al. 2010). Schuijf et al. (2007) reported an association of plaques with low Hounsfield units with acute coronary syndrome; they showed that the MP type accounts for half of stenotic vessels in patients with acute coronary syndrome (Kunimasa et al. 2005; Schuijf et al. 2007). Henneman et al. (2008) reported that patients with obstructive multivessel CAD have a larger proportion of MP (55%), as compared with patients with non-obstructive CAD, which suggests that MP may be associated with multivessel CAD. In addition, recent studies have suggested that lipid-rich plaque is more frequently seen in patients with metabolic syndrome or insulin resistance (Amano et al. 2007, 2008). Therefore, identification of the coronary plaque composition would be important in determination of the risk of CVD. Few studies of the relationship between renal dysfunction and coronary plaque characteristics have been conducted. Miyagi et al. (2010) demonstrated an
association of kidney function and coronary plaque composition. A lower eGFR was strongly predictive of lipid-rich composition in coronary plaque (Miyagi et al. 2010). They used IB-IVUS and only studied patients with known CAD who were referred for coronary percutaneous intervention. IB-IVUS is an invasive technique performed on an inpatient basis, while CTA is non-invasive and can be performed on an outpatient basis. No prior study using CTA for investigation of the association between CKD and coronary artery plaque characteristics has been conducted.

Dellegrottaglie et al. (2006) reported a significant association between the CACS and renal function related parameters (GFR, hemoglobin, albumin, calcium, phosphate, and parathyroid hormone). In contrast, Scholte et al. (Scholte et al. 2008) reported a relatively high proportion of NCP, regardless of calcium scores, in patients with a high risk of CAD. Large lipid cores are considered to be histologic markers for plaque vulnerability, which is directly related to a risk of plaque rupture (Davies et al. 1993; Fernandez-Ortiz et al. 1994). Therefore, CACS may be a limited value for determining the risk of CAD, and the composition of coronary artery plaque might have an influence on the risk of CAD, rather than CACS.

The presence of impaired kidney function has been reported to be an independent risk factor for CVD (Anavekar et al. 2004; Go et al. 2004). These reports are consistent with our data showing an association of characteristics and number of MP with the presence of renal dys-

![Graph](image1)

**Fig. 1.** Adjusted hazard ratio of renal dysfunction according to coronary artery plaque characteristics.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P</td>
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<tr>
<td>Age (1-years increment)</td>
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<td>Male vs. female</td>
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<td>0.523</td>
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<td>Hypertension (yes or no)</td>
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<td>&lt; 0.001</td>
</tr>
<tr>
<td>Renal dysfunction (yes or no)</td>
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<td>&lt; 0.001</td>
</tr>
</tbody>
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![Graph](image2)

**Fig. 2.** Comparison of estimated glomerular filtration rate according to the number of mixed plaque counts.

![Graph](image3)

**Table 3.** Multivariable linear regression analysis between clinical and laboratory variables and mixed plaques counts.
function. It is possible that MP could be a connector between renal dysfunction and CVD.

The results of this study showed that renal dysfunction was not associated with the presence of CP. It may be because few subjects with severe renal dysfunction were enrolled in this study. Consequently, a larger effect of age, gender, and phosphorus levels might have attenuated subtle effects of renal dysfunction. In addition, Gruberg et al. (2005) showed that chronic renal insufficiency in the absence of dialysis is not associated with calcium burden in plaques; these results are consistent with our data.

Although significant, an association between renal function and MP counts was weak ($r = 0.155$). MP counts may be a crude method to evaluate quantitative burden of MP. Some studies have reported the quantitative measurements of plaque areas, remodeling index, and plaque volume by CTA (Achenbach et al. 2004; Leber et al. 2005, 2006; Uetani et al. 2010). Unfortunately we could not evaluate those precise measurements. Further study could be needed to evaluate the association between renal dysfunction and quantitative burden of plaque characteristics.

A previous study reported an association of lipid profiles with an increased MP and NCP burden (Cheng et al. 2010); the results of this study are not consistent with these prior findings. This study showed an association of total cholesterol and HDL levels with MP, as compared with NP, on univariable analysis, but no association with MP on multivariable analysis. This may be attributed to differences in ethnicity or a relative smaller body mass index in our study.

Specific medical therapy may affect coronary artery plaque. Goh et al. (2010) demonstrated that statin therapy reduces progression of calcified plaques. Inoue et al. (2010) showed that statin treatment results in a decrease in the plaque and necrotic core volumes. In contrast, Cheng et al. (2009) indicated that there were no associations between statin therapy and the contribution of CP, NCP, and MP. Unfortunately, we did not collect detailed information on medications, which could be very critical. Further studies are needed.

Many previous studies have demonstrated correlation of a low albumin level with the clinical and radiological presence of atherosclerosis in CKD patients (Foley et al. 1996; Beddu et al. 2002; Joki et al. 2006; Weiner et al. 2008). Our data also showed that serum albumin levels were a significant risk factor for CP, as compared with NP. However, low albumin levels were associated with the presence of MP on univariable analysis but not on multivariable analysis. Further study is needed for elucidating the relationship between differences of coronary artery characteristics and albumin. Proteinuria, one of markers of renal dysfunction, has been reported to be associated with CAD (de Zeeuw et al. 2006). Proteinuria may also predict subsequent risk of CAD (Perkovic et al. 2008). The association between proteinuria and coronary artery plaque characteristics is still unclear.

This study has some limitations. This study had few participants with severe renal dysfunction who had an eGFR < 30mL/min/1.73m². CTA would not have been performed on stage 4 or 5 CKD patients due to the risk of radiocontrast induced nephropathy; therefore a large scale study will be needed to support the conclusion. eGFR was calculated using only one measurement of serum creatinine. An arbitrary definition of renal dysfunction is also a limitation of the current study. We excluded patients with a history of CAD. Since clinically overt CAD can affect the kidney function in many different ways (Hilleges et al. 2003; Elsayed et al. 2007), this exclusion may reduce these confounding factors. Also, CTA can be applied to the patients without history of CAD in a practical point.

In conclusion, renal dysfunction is associated with MP rather than CP or NCP, compared with NP. These findings suggest that it could be one of the developmental processes of CAD in patients with renal dysfunction.

**Acknowledgments**

Supported by intramural grant of Gachon University Gil Hospital.

**Conflict of Interest**

The authors have no financial conflict of interest.

**References**


Cheng, V.Y., Nakazato, R., Dey, D., Gurudev, S., Tabak, J,


