Epicardial Adipose Tissue Accumulation Is Associated With Renal Dysfunction and Coronary Plaque Morphology on Multidetector Computed Tomography

Koki Nakanishi, MD; Shota Fukuda, MD; Atsushi Tanaka, MD; Kenichiro Otsuka, MD; Haruyuki Taguchi, MD; Junichi Yoshikawa, MD; Kenei Shimada, MD

Background: Chronic kidney disease (CKD) is strongly associated with coronary artery disease (CAD), although the underlying pathophysiological mechanism remains unclear. Epicardial adipose tissue (EAT) has recently been recognized as an important source of various pro-inflammatory cytokines causing coronary atherosclerosis. This study investigated the relationship between CKD and EAT volume in association with high-risk plaque.

Methods and Results: The study included 275 patients with an estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m² who underwent multidetector computed tomography (MDCT) for the evaluation of CAD. Patients were classified, according to eGFR, into a CKD group (30 ≤ eGFR < 60 ml/min/1.73 m²) or a non-CKD group (eGFR ≥ 60 ml/min/1.73 m²). MDCT was used to assess coronary plaque morphology and EAT volume. One hundred and ten patients with CKD were more likely to be older, have higher prevalence of hypertension, lower serum HDL-C, higher serum CRP, and larger EAT volume, than those without CKD (all P<0.01). On multivariate analysis, age, hypertension, and EAT volume were significantly associated with eGFR (all P<0.01). EAT volume was associated with the presence of high-risk plaque, independent of traditional CAD risk factors (P=0.003).

Conclusions: Patients with CKD had significantly increased EAT volume, which could be associated with the presence of high-risk plaque.

Key Words: Chronic kidney disease; Coronary artery disease; Epicardial adipose tissue; Multidetector computed tomography
rent 770–850 (Omnipaque 350, Daiichi Sankyo, Tokyo, Japan) was injected
beats/min. Nitroglycerin spray is
used immediately before MDCT to improve visualization of
smaller-caliber coronary vessels through vasodilation. For the
MDCT if heart rate was >60
contrast-enhanced scans, 40–70

MDCT if heart rate was >60

The following factors were noted for each patient: hyper-
tension (blood pressure ≥140/90 mmHg on repeated mea-
urements or taking antihypertensive agents), hypercholesterolemia
(serum total cholesterol ≥200 mg/dl, or statin treatment), dia-
betes (fasting plasma glucose >126 mg/dl, taking hypoglyce-
ic drugs or insulin, or a combination of the two), and current
smoking. Body mass index (BMI) was calculated using height
and weight (kg/m²). Biochemistry was assessed using blood
takes before MDCT. For the evaluation of renal func-
tion, we assessed eGFR using the Modification of Diet in
Renal Disease equation. Serum low-density lipoprotein cho-
sterol (LDL-C) was calculated using the Friedewald equation.
In the case of triglycerides ≥400 mg/dl, serum LDL-C was
measured using direct homogeneous assay (Sekisui Medical).
The study was approved by the Institutional Review Board of
Osaka Ekisaikai Hospital, and written informed consent was
obtained before MDCT.

CT Angiography Interpretation and EAT Measurement
MDCT parameters were assessed using SYNAPSE VINCENT
(Fujifilm Medical, Tokyo, Japan). The coronary arteries were
divided into 16 separate segments ≥1.5 mm in diameter as
measured on MDCT angiogram, based on American Heart
Association classification. Each segment was classified as
interpretable or not. Patients were excluded when proximal or
mid-segment or >3 segments were uninterpretable. In the
case of plaque, plaque was also analyzed for the presence or
absence of the following 2 high-risk features: positive remodeling
(PR; remodeling index >1.1) and low-attenuation plaque
(LAP). LAP was defined as plaque with mean density <30
Hounsfield units (HU). High-risk plaque was defined as having
PR and/or LAP.

EAT was defined as the adipose tissue located within the
pericardial sac. To obtain EAT volume, there were 2 manual
ing the softwar

Table 1. Clinical Subject Characteristics vs. Presence of CKD

<table>
<thead>
<tr>
<th>CKD (n=110)</th>
<th>Non-CKD (n=165)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69±9</td>
<td>63±10</td>
</tr>
<tr>
<td>Male</td>
<td>77 (70)</td>
<td>104 (63)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>88 (80)</td>
<td>92 (56)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45 (41)</td>
<td>60 (36)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>65 (59)</td>
<td>97 (59)</td>
</tr>
<tr>
<td>Smoking</td>
<td>28 (25)</td>
<td>48 (29)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0±3.2</td>
<td>23.8±3.7</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>65 (59)</td>
<td>69 (42)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>23 (21)</td>
<td>33 (20)</td>
</tr>
<tr>
<td>CCB</td>
<td>44 (40)</td>
<td>48 (29)</td>
</tr>
<tr>
<td>Statin</td>
<td>53 (48)</td>
<td>85 (52)</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>121±39</td>
<td>119±34</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>114±35</td>
<td>117±37</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>49±12</td>
<td>54±13</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.5±2.3</td>
<td>0.8±0.6</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>49±7</td>
<td>75±12</td>
</tr>
<tr>
<td>EAT volume (ml)</td>
<td>111±41</td>
<td>81±29</td>
</tr>
</tbody>
</table>

Data given as mean±SD or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blockers; CKD, chronic kidney disease; CRP, C-reactive protein; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

uation of CAD in the setting of multiple CAD risk factors,
periodic arterial disease, or cerebrovascular disease, or abnor-
mal electrocardiogram (ECG) and echocardiography. Patients
were classified, according to eGFR, into a CKD group
(30≤eGFR<60 ml/min/1.73 m²) or a non-CKD group (eGFR
≥60 ml/min/1.73 m²).

The following factors were noted for each patient: hyper-
tension (blood pressure ≥140/90 mmHg on repeated mea-
urements or taking antihypertensive agents), hypercholesterolemia
(serum total cholesterol ≥200 mg/dl, or statin treatment), dia-
betes (fasting plasma glucose >126 mg/dl, taking hypoglyce-
ic drugs or insulin, or a combination of the two), and current
smoking. Body mass index (BMI) was calculated using height
and weight (kg/m²). Biochemistry was assessed using blood
takes before MDCT. For the evaluation of renal func-
tion, we assessed eGFR using the Modification of Diet in
Renal Disease equation. Serum low-density lipoprotein cho-
sterol (LDL-C) was calculated using the Friedewald equation.
In the case of triglycerides ≥400 mg/dl, serum LDL-C was
measured using direct homogeneous assay (Sekisui Medical).
The study was approved by the Institutional Review Board of
Osaka Ekisaikai Hospital, and written informed consent was
obtained before MDCT.

Scan Protocol and Image Reconstruction
All MDCT examinations were conducted using Somatom
Sensation 64 (Siemens Medical System, Forchheim, Germany).
The scan parameters were as follows: 64×0.6 mm collimation,
tube voltage 120 kV, gantry rotation time 330 ms, and tube cur-
rent 770–850 mAs. Each subject took 5 mg bisoprolol 2 h before
MDCT if heart rate was >60 beats/min. Nitroglycerin spray is
used immediately before MDCT to improve visualization of
smaller-caliber coronary vessels through vasodilation. For the
contrast-enhanced scans, 40–70 ml of non-ionic contrast agent
(Omnipaque 350, Daiichi Sankyo, Tokyo, Japan) was injected
i.v. at a flow rate of 4.0–5.5 ml/s followed by 30 ml of saline.
All scans were performed during a single breath hold. The raw
data were reconstructed using algorithms optimized for retro-
grade ECG-gated multislice spiral reconstruction. MDCT
analysis was performed by experienced physicians blinded to
other information.

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Results

Among the 275 patients, 110 (40%) were classified as CKD (30 ≤ eGFR < 60 ml/min/1.73 m²) and 165 (60%) as non-CKD (eGFR ≥ 60 ml/min/1.73 m²). Patients with CKD were more likely to be older (P<0.001), have a higher prevalence of hypertension (P<0.001), lower serum high-density lipoprotein cholesterol (HDL-C; P=0.001), and higher serum C-reactive protein (CRP; P=0.002), compared with the non-CKD patients (Table 1). Despite similar BMI, patients with CKD had significantly increased EAT volume than the non-CKD patients (111 ± 41 vs. 81 ± 29 ml, P<0.001). HDL-C was negatively associated with EAT volume (r=–0.25, P<0.001).

As shown in Figure A, there was a significant negative correlation between eGFR and EAT volume (r=–0.34, P<0.001), whereas no significant relationship was observed between BMI and eGFR (r=0.04, P=0.9; Figure B). On multivariate linear regression analysis age (standardized β=–0.30, P<0.001), hypertension (standardized β=–0.18, P=0.001) and EAT volume (standardized β=–0.28, P<0.001) were identified as independent factors for eGFR (Table 2). Of 275 patients, 44 patients (16%) had ≥ 1 plaque with PR and/or LAP. On multivariate logistic regression analysis hypercholesterolemia (P=0.02) and EAT volume (P=0.003) were significantly associated with as the sum of the EAT areas (step 4). Total EAT volume was calculated as the total sum of the EAT areas.

Statistical Analysis

Categorical variables are presented as frequencies, and continuous variables as mean±SD. Chi-squared test was used for comparing categorical variables and independent samples t-test or Mann-Whitney U-test for continuous variables as appropriate, according to the presence of normal distribution. Univariate and multivariate linear regression analysis was performed to investigate the relationship between eGFR and baseline variables including EAT volume. Univariate and multivariate logistic regression analysis was conducted to evaluate the impact of EAT volume on the presence of high-risk plaque. Differences were considered significant at P<0.05.

Inter-observer variability for EAT measurements was analyzed in 50 randomly selected subjects assessed by 2 independent blinded observers. Intra-observer variability was analyzed in another group of 50 subjects by the same observer at 2 different time points. The results were analyzed using both least squares fit linear regression analysis and Bland-Altman method. Statistical analysis was performed using JMP 10 (SAS Institute, Cary, NC, USA).

Table 2. Relationship Between eGFR and Clinical Variables

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standardized β (95% CI)</td>
<td>P-value</td>
<td>Standardized β (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>−0.37 (−0.76 to −0.41)</td>
<td>&lt;0.001</td>
<td>−0.30 (−0.66 to −0.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, male</td>
<td>0.07 (−0.81 to 3.3)</td>
<td>0.2</td>
<td>−0.01 (−2.2 to 1.8)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>−0.27 (−6.7 to −2.8)</td>
<td>&lt;0.001</td>
<td>−0.18 (−5.0 to −1.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>−0.03 (−2.5 to 1.5)</td>
<td>0.6</td>
<td>−0.02 (−2.1 to 1.4)</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>−0.004 (−2.0 to 1.9)</td>
<td>0.9</td>
<td>−0.03 (−2.3 to 1.2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.12 (0.11 to 4.4)</td>
<td>0.04</td>
<td>0.04 (−1.4 to 2.8)</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.004 (−0.54 to 0.58)</td>
<td>0.9</td>
<td>0.04 (−0.34 to 0.73)</td>
<td>0.5</td>
</tr>
<tr>
<td>EAT volume (ml)</td>
<td>−0.34 (−0.20 to −0.10)</td>
<td>&lt;0.001</td>
<td>−0.28 (−0.17 to −0.08)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
the presence of high-risk plaque (Table 3). The multivariate logistic regression analysis was repeated including eGFR. As a result, similar results were obtained, although P-value was slightly changed: hypercholesterolemia (P=0.02) and EAT volume (P=0.01) were risk factors for high-risk plaque.

Excellent correlation was observed in inter- and intra-observer variability of EAT measurements (r=0.99 and r=0.99, respectively). According to Bland-Altman analysis, the 95% limits of agreement for the inter- and intra-observer variabilities in EAT volume were 1.32±9.0 ml and 0.92±7.8 ml (mean±1.96 SD, respectively).

### Discussion

This study has demonstrated that CKD patients have significantly increased EAT volume compared with non-CKD patients, and that this is associated with high-risk plaque.

The worldwide rise in the number of CKD patients is threatening to reach epidemic proportions.1 Cardiovascular events are the most common cause of mortality and morbidity in patients with CKD, rather than renal failure itself.2–4 Furthermore, recent studies have shown that even mild renal disease should be considered a major risk factor for cardiovascular events.5,6 The underlying pathophysiological mechanisms, however, are still not fully elucidated. Altered fat distribution is proposed to be a key contributory factor to atherosclerosis progression in patients with CKD of any degree.21–23 Kim et al found a significant reverse correlation between visceral fat volume and eGFR in 929 patients with type 2 diabetes mellitus.21 Lamacchia et al showed increased para- and perirenal fat thickness in patients with CKD compared with those with preserved renal function on echocardiography.22 Odamaki et al demonstrated that 92 patients without diabetes who were treated with hemodialysis had significantly increased visceral fat and decreased subcutaneous fat compared with control subjects of similar BMI.23 Furthermore, an experimental study also showed a shift of subcutaneous fat to ectopic fat in uninephrectomized rats as a renal dysfunction model.24 Some recent studies investigated the impact of EAT accumulation on renal function and future cardiovascular events in patients with CKD.25–26 Kerr et al found a positive correlation between urinary albumin to creatinine ratio and single-slice EAT volume in stage 3–5 CKD patients.25 Cordeiro et al demonstrated that increased EAT volume was a predictor for future CAD events independent of traditional cardiovascular risk factors in 277 patients with stage 3–5 CKD during a median follow-up of 32 months.26 In the present study, we found significantly increased EAT volume in CKD patients compared with non-CKD patients, which was associated with high-risk plaque.

The underlying mechanisms of increased EAT volume in CKD subjects are not fully characterized, but there are several possible explanations for this. First, the obvious links have been proved between CKD and metabolic syndrome, which is also strongly associated with EAT accumulation.7,8 Furthermore, intra-abdominal visceral fat, which is an important component of metabolic syndrome, and EAT share the same origin from the splanchnopleuric mesoderm associated with the gut.9 Recent studies have demonstrated an association between adipocyte-specific parameters such as adiponectin and leptin, and CKD.10–12 Ohashi et al noted that urine albumin excretion, glomerular hypertrophy and interstitial fibrosis were significantly worse in the adiponectin knockout mice compared with wild type.31 Wolf et al showed that leptin mediated glomerular hypertrophy and sclerosis by stimulating glomerular endothelial and mesangial cell proliferation and type IV collagen production.32 Second, EAT is a source of inflammatory mediators and modulates the intrinsic autonomic nervous system,34 which would accelerate the progression of renal dysfunction. Indeed, in the present study serum CRP was significantly higher in CKD patients than in non-CKD patients. In addition, given that EAT accumulation was reported to be associated with left ventricular dysfunction,35 it may indirectly affect renal function. Finally, patients with CKD developed protein malnutrition, cachexia, and protein loss causing reduced muscle mass and insulin resistance, which in turn increased visceral fat including EAT.36 In the present study, there was a significant but weak correlation between BMI and EAT volume (r=0.29, P<0.001). Also, multivariate analysis EAT volume was associated with eGFR, independent of BMI. These observations are consistent with frequent discordances between BMI and EAT volume.3,37 Similar results are observed in the association between EAT accumulation and CAD. It remains unclear whether EAT accumulation is the cause or consequence of CKD. EAT seems to be the cause of atherosclerosis based on longitudinal experimental and clinical studies.38,39 Such a longitudinal study on EAT and CKD is required in the future.

### Study Limitations

The present study has several limitations. First, this was a single-center preliminary study, thus further large-scale studies are necessary to confirm the present findings. Furthermore, because we enrolled mild-moderate CKD subjects, the results may not be generalizable to subjects with severe renal function including hemodialysis. These limitations regarding study population may have influenced the lack of statistical associa-
tion between eGFR and diabetes in this study. Second, given the cross-sectional design of the present study, we could not establish causality. Therefore, a longitudinal study is required to prove the prognostic impact of EAT accumulation in CKD patients. Third, elevated serum CRP in patients with CKD suggests that inflammation is an important factor in the association between EAT and CKD, but detailed mechanisms remain to be resolved. Measurement of specific markers, such as leptin and adiponectin, may help to answer this question.\textsuperscript{26,32} Finally, histopathological analysis of EAT was not performed in this study. Several studies have suggested the potential usefulness of MDCT for the assessment of EAT biological characteristics.\textsuperscript{40,41} Future studies are necessary to investigate qualitative differences in EAT between CKD and non-CKD patients.

**Conclusions**

There is a close association between CKD, EAT volume, and high-risk plaque. The present findings are consistent with the hypothesis of a local pathogenic effect of EAT on coronary plaque morphology in patients with CKD. Intervention targeting EAT accumulation may have the potential to prevent or inhibit CAD in patients with CKD.

**Disclosures**

The authors declare no conflicts of interest.

**References**


