Prognostic value of pericoronary adipose tissue attenuation in patients with non-alcoholic fatty liver disease with suspected coronary artery disease

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Abstract

Pericoronary adipose tissue (PCAT) attenuation on coronary computed tomography angiography (CTA) has been emerged as a marker of pericoronary inflammation. We aimed to investigate the prognostic value of PCAT attenuation in patients with non-alcoholic fatty liver disease (NAFLD). We enrolled 232 NAFLD patients with suspected coronary artery disease and underwent coronary CTA. NAFLD was defined by abdominal CT as the ratio of hepatic attenuation to spleen attenuation less than 1.0. PCAT attenuation values were assessed by the crude analysis of mean CT attenuation value of the left anterior descending artery (LAD) and right coronary artery (RCA). As coronary CTA findings, luminal stenosis and high-risk plaque features were examined. Primary outcome was the composite of cardiovascular (CV) death, nonfatal acute coronary syndrome, and hospitalization for heart failure. During a median follow-up of 4.9 years, 17 patients had CV events. LAD-PCAT attenuation in patients with CV events was higher than that without CV events (−66.9 ± 7.0 versus −70.5 ± 6.6; p = 0.032), while RCA-PCAT attenuation was not. LAD-PCAT attenuation and high-risk plaque features were independent predictors of CV events. The addition of LAD-PCAT attenuation to high-risk plaque features increased the C-statistics and global chi-square from 0.66 to 0.75 (p = 0.042) and 6.8 to 12.7 (p = 0.015), respectively. The net reclassification achieved by adding LAD-PCAT attenuation to high-risk plaque features was 0.494 (p = 0.041). High-LAD-PCAT attenuation was an independent predictor of CV events in NAFLD patients, regardless of CTA-verified high-risk plaque features. In addition, LAD-PCAT attenuation had an incremental prognostic value over high-risk plaque features.

Keywords Non-alcoholic fatty liver disease · Computed tomography angiography · Cardiovascular disease · Inflammation

Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most common liver disease worldwide [1]. The prevalence of NAFLD patients in Japan is around 30% and it is estimated that the number will further increase in the future [2, 3]. NAFLD is associated with not only liver-related but also cardiovascular (CV) mortality [4]. Therefore, the prevention of CV events in NAFLD patients is gaining importance as a public health measure. The current NAFLD practice guideline recommends aggressive modification of CV risk factors such as obesity, diabetes mellitus, dyslipidemia, and hypertension in all NAFLD patients [5]. With the increasing global prevalence of NAFLD and healthcare costs, a diagnostic approach to help identify NAFLD patients who will benefit from aggressive prevention therapy is needed. Coronary computed tomography angiography (CTA) is used to evaluate coronary artery disease noninvasively [6, 7]. In addition to evaluation of stenosis, coronary CTA identifies characteristics of plaque composition. Previous studies reported the significant association between high-risk plaque features assessed on coronary CTA and CV events in various patients and clinical settings [8–10]. Earlier, we have reported that high-risk plaque features also increased the likelihood of CV events in NAFLD patients.
Pericoronary adipose tissue (PCAT) attenuation on coronary CTA, which indicates pericoronary inflammation, has recently been developed and reported to have incremental prognostic value over high-risk plaque features [12, 13]. However, the prognostic value of PCAT attenuation in patients with NAFLD remains unclear.

This study aimed to investigate the predictive capability and prognostic value of PCAT attenuation, quantified by coronary CTA, for CV events in NAFLD patients.

**Materials and methods**

**Study design and study population**

This study is a post hoc analysis of PCAT attenuation from a prospective cohort study that evaluated the impact of hepatic steatosis on coronary artery disease and its prognosis. The principal study design has been described previously [4]. Briefly, patients who underwent coronary CTA for suspected stable coronary artery disease at Okayama University from August 2011 to December 2016 were enrolled in this cohort study. All patients underwent the simultaneous examination of hepatic steatosis by an abdominal non-contrast computed tomography (CT) scan before cardiac imaging. The following patients were excluded: history of coronary artery disease, heavy alcohol consumption (> 20 g of alcohol per day), known liver disease, using oral corticosteroid or amiodarone, coexisting active tumor, and < 1 year of follow-up. Figure 1 shows the flow diagram of this study. In the principal study, we enrolled 1148 patients. Among them, 247 patients were diagnosed as NAFLD and were included in the primary analysis. Fifteen patients were excluded because we were unable to extract the segmentation of the coronary artery due to technical difficulties. Finally, 232 NAFLD patients were included in this study. The current study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the institutional review board of the Okayama University Graduate School of Medicine. All the enrolled patients provided written informed consent to participate.

**Assessment of NAFLD**

An abdominal non-contrast CT scan was performed just before the cardiac scan on the same day. Hepatic and splenic Hounsfield attenuations were measured using the maximum circular regions of interest in the liver and spleen. The regions of interest > 100 mm² included two areas that were aligned with the anterior–posterior dimension of the right liver lobe and one that was aligned with the spleen. A liver-to-spleen ratio < 1.0 was set as the cutoff for the diagnosis of NAFLD [14]. In addition, fibrosis-4 index was calculated as a liver fibrosis marker in all patients.

**Outcomes**

The patients were followed up prospectively from the date of coronary CTA. Clinical follow-up information was obtained from a review of medical records or telephone interviews blinded to CT results. In this study, CV events were defined as the composite of CV death, nonfatal acute coronary syndrome, and admission due to heart failure. The details of event definition were provided previously [15].

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**Fig. 1** Flow diagram of this study

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[Image of flow diagram]
Coronary CTA analyses

Coronary CTA images were performed using a Definition Flash scanner (Siemens Medical Solutions, Erlangen, Germany), as previously described [4]. On coronary CTA analysis, we evaluated coronary artery segments with a diameter > 2 mm and defined plaque characteristics in accordance with the Society of Cardiovascular Computed Tomography [16]. Two experienced cardiovascular imaging researchers (K.O. and T.M.) interpreted the coronary CTA findings. High-risk plaque features were defined as positive remodeling, low-attenuation plaque, and spotty calcification. We defined positive remodeling as having an index of > 1.1. Plaques with a CT attenuation number < 30 Hounsfield units were defined as low-attenuation plaques. Spotty calcification was defined as a calcium burden length < 1.5 times the vessel diameter and a width less than two-thirds of the vessel diameter. Stenosis was significant if there was luminal narrowing of > 50% in any coronary artery.

PCAT attenuation analyses

PCAT attenuation was analyzed using a dedicated workstation (Aquarius iNtuition Edition version 4.4.13; TeraRecon Inc., Foster City, CA, USA). PCAT attenuation was measured in HU of the proximal 40 mm of the left anterior descending artery (LAD) and 10–50 mm segments of the right coronary artery (RCA) as previously described [12, 17]. PCAT was defined as the adipose tissue located within a radial distance from the outer vessel wall equal to the diameter of the coronary vessel, and adipose tissue was defined as all voxels with an attenuation between −190 HU and −30 HU. Based on the above, PCAT attenuation was automatically calculated as the mean CT attenuation value. Representative images of PCAT attenuation analysis are shown in Fig. 2. Two investigators (M.N. and T.N.), who were blinded to the clinical and CT data, performed the PCAT attenuation analysis.

Risk factors

At baseline, standardized questionnaires were used to collect information about demographics, alcohol use, medical history, medication use, and smoking status. Detailed definitions of risk factors have been previously described [18]. Obesity was defined as a body mass index ≥ 25.0 kg/m² according to the International Obesity Task Force recommendation [19]. As a liver fibrosis marker, fibrosis-4 index was calculated using the following formula: age (years) × AST (U/L)/[ALT (U/L)]^{1/2} × platelet count (10⁹/L) [20].

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median with interquartile range. Dichotomous variables were expressed as numbers and percentages. Differences in continuous variables between the two groups were analysed using Student’s t test and the Mann–Whitney U test, as appropriate. Categorical data were compared using χ² and Fisher’s tests, as appropriate. In subsequent analysis, LAD-PCAT attenuation was used because LAD-PCAT attenuation was more closely associated with prognosis than RCA-PCAT attenuation in our study. Kaplan–Meier curves were used to estimate cumulative rates of CV events. Differences between time-to-event curves were compared by log-rank tests. Cox regression analyses to ascertain the association between PCAT attenuation and CV events, and the results were reported as hazard ratios (HR) with 95% confidence intervals (CI). We conducted a multivariate Cox
regression analysis including factors with \( p \) value < 0.05 in the univariate analysis to ascertain the independent predictors of CV events. The incremental prognostic value of PCAT attenuation was assessed by receiver operating characteristics (ROC) curve analysis and global chi-square tests. C-statistics were calculated from the ROC curves and compared using the Delong test. The category-free net reclassification improvement was also calculated. All reported \( p \) values were two sided, and statistical significance was set at \( p < 0.05 \). Statistical analyses were performed using SPSS statistical software (Version 28; IBM Corp., Armonk, NY, USA) and the R statistical package (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

### Results

#### Patient characteristics and coronary CTA findings

The mean age of the study population was 61 years, 154 (67%) were men, and the mean fibrosis-4 index was 1.6. Significant stenosis and high-risk plaque features were detected in 69 (30%) and 124 (53%) patients, respectively. The mean LAD- and RCA-PCAT attenuation were \(-70.2 \pm 6.7\) and \(-69.1 \pm 7.3\) HU, respectively. During the follow-up (median, 4.9 years), 17 patients had CV events, including cardiac death (\( n = 2 \)), acute coronary syndrome (\( n = 10 \)), and admission due to heart failure (\( n = 5 \)). The comparison of baseline patient characteristics and coronary CTA results between patients with and without CV events are shown in Table 1. The patients with CV events had higher fibrosis-4 index than those without CV events (2.1 ± 1.2 versus 1.5 ± 1.1; \( p = 0.032 \)). As regards

| Table 1 | Comparison of baseline characteristics between patients with and without cardiovascular events |
|---------|--------------------------------------------------|
|         | All | Cardiovascular events | \( p \) value* |
|         | N   | Present | Absent |
| Age, years | 232 | 17 | 215 | 0.463 |
| Male gender | 154 (67) | 11 (65) | 143 (67) | 0.879 |
| Body mass index, kg/m\(^2\) | 26±4 | 25±4 | 26±4 | 0.251 |
| Hypertension | 168 (72) | 14 (82) | 154 (72) | 0.341 |
| Diabetes mellitus | 96 (41) | 7 (41) | 89 (41) | 0.986 |
| Dyslipidemia | 135 (58) | 9 (53) | 126 (59) | 0.649 |
| Current smoker | 65 (28) | 5 (29) | 60 (28) | 0.894 |
| Obesity\(^b\) | 141 (61) | 11 (65) | 130 (61) | 0.730 |
| Atrial fibrillation | 20 (9) | 3 (18) | 17 (8) | 0.170 |
| Beta blocker | 59 (25) | 7 (41) | 52 (24) | 0.121 |
| Calcium channel blocker | 88 (38) | 7 (41) | 81 (38) | 0.775 |
| ACE-I or ARB | 105 (45) | 10 (59) | 95 (44) | 0.243 |
| Statin | 70 (33) | 6 (35) | 70 (33) | 0.817 |
| eGFR, mL/min/1.73m\(^2\) | 73±16 | 73±15 | 73±16 | 0.971 |
| Total cholesterol, mg/dL | 193±33 | 197±44 | 193±34 | 0.667 |
| LDL cholesterol, mg/dL | 118±33 | 120±41 | 118±33 | 0.810 |
| Hemoglobin A1c, % | 6.6±1.4 | 6.9±1.5 | 6.6±1.4 | 0.411 |
| Fibrosis-4 index | 1.6±1.1 | 2.1±1.2 | 1.5±1.1 | 0.032 |
| Significant stenosis (>50%) | 69 (30) | 8 (47) | 61 (28) | 0.105 |
| High-risk plaque features | 124 (53) | 14 (82) | 110 (51) | 0.013 |
| LAD-PCAT attenuation, HU | \(-70.2 \pm 6.7\) | \(-66.9 \pm 7.0\) | \(-70.5 \pm 6.6\) | 0.032 |
| RCA-PCAT attenuation, HU | \(-69.1 \pm 7.3\) | \(-67.1 \pm 5.0\) | \(-69.3 \pm 7.5\) | 0.248 |

Data are presented as mean±standard deviation or number (%).

ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; eGFR: estimated glomerular filtration rate; LAD: left anterior descending artery; LDL: low-density lipoprotein; HU: Hounsfield units; PCAT: pericoronary adipose tissue; RCA: right coronary artery

*Comparisons between patients with and without cardiovascular events

Obesity was defined as body mass index ≥ 25 kg/m\(^2\)
to coronary CTA results, patients with CV events had higher prevalence of high-risk plaque features (82% versus 51%; \( p = 0.012 \)).

**Association of PCAT attenuation and CV events**

LAD-PCAT attenuation in patients with CV events was significantly higher than that without CV events (−66.9 ± 7.0 versus −70.5 ± 6.6; \( p = 0.032 \)) while RCA-PCAT attenuation did not differ between the two groups (−67.1 ± 5.0 versus −69.3 ± 7.5; \( p = 0.248 \)) (Fig. 3). The ROC curve analysis showed that the optimal cut-off value of LAD-PCAT attenuation to predict CV events was −66.6 HU (sensitivity 58.8%, specificity 73.0%). Kaplan–Meier analysis showed that patients, whose LAD-PCAT attenuation level exceeded the threshold of ≥ −66.6 HU, had more CV events than those, whose LAD-PCAT attenuation level remained below the threshold (\( p = 0.017 \), log-rank test) (Fig. 4). Based on the univariate Cox regression analyses, high-risk plaque features (hazard ratio [HR], 4.116; 95% confidence interval [CI], 1.181–14.342; \( p = 0.026 \)), and LAD-PCAT attenuation above threshold (HR, 3.004; 95% CI, 1.158–7.792; \( p = 0.024 \)) were significantly associated with CV events, while significant stenosis (HR, 2.320; 95% CI, 0.893–6.026; \( p = 0.084 \)) was not (Table 2). The multivariate Cox regression analysis showed that LAD-PCAT attenuation was independent predictor of CV events after adjustment for high-risk plaque features (HR, 3.321; 95% CI, 1.277–8.635; \( p = 0.014 \)).

**Incremental prognostic value of PCAT attenuation over high-risk plaque features**

The addition of LAD-PCAT attenuation to high-risk plaque features increased the C-statistics and global chi-square from 0.66 to 0.75 (\( p = 0.042 \)). Similarly, adding LAD-PCAT attenuation to high-risk plaque features significantly increased the global chi-square value from 6.8 to 12.7 (\( p = 0.015 \)). The net classification achieved by adding LAD-PCAT attenuation to high-risk plaque features was 0.494 (\( p = 0.041 \)). Thus, the addition of LAD-PCAT attenuation to high-risk plaque features...

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Fig. 3 The comparisons of pericoronary adipose tissue attenuation in the left anterior descending artery and right coronary artery between patients with and without cardiovascular events. Boxplots showing the comparison pericoronary adipose tissue attenuation between patients with and without cardiovascular events. *LAD* left anterior descending artery; *PCAT* pericoronary adipose tissue; *RCA* right coronary artery

Fig. 4 Impact of pericoronary adipose tissue attenuation on prognosis in non-alcoholic fatty liver disease patients. Kaplan–Meier curve showing the cumulative incidence of cardiovascular events in NAFLD patients stratified by the threshold (−66.6 HU). *HU* Hounsfield units; *NAFLD* non-alcoholic fatty liver disease; *PCAT* pericoronary adipose tissue
features resulted in an improvement in the risk reclassification for CV events in NAFLD patients.

Discussion

To our knowledge, this is the first study to demonstrate that increased LAD-PCAT attenuation was associated with CV events in NAFLD patients. In addition, addition of LAD-PCAT attenuation to coronary CTA derived high-risk plaque features significantly improved the ability of risk classification in NAFLD patients with suspected coronary artery disease.

Growing evidence showed that high-risk plaque features on coronary CTA are significant factors associated with increased risk of CV events in various populations and clinical settings [8–10]. We previously reported that high-risk plaque features on coronary CTA was significantly associated with CV events even in NAFLD patients with suspected coronary artery disease [11]. Recently, PCAT attenuation, a novel method for the non-invasive quantification of coronary inflammation, has been developed and demonstrated to have prognostic value over high-risk plaque features on coronary CTA [12, 13, 21]. However, it was unknown whether these results could be applied directly to NAFLD patients because NAFLD patients represent low-grade inflammatory states and have increased coronary inflammation [22], [23]. Our study demonstrated the prognostic value of LAD-PCAT attenuation in NAFLD patients, suggesting the concurrent assessment of PCAT attenuation during coronary CTA could be helpful in identifying NAFLD patients at higher risk for future CV events.

The relationship between high-PCAT attenuation and increased risk of CV events in NAFLD patients can be inferred by previous reports. The stage of liver histological severity is strongly associated with both liver-related and CV mortalities [24], [25]. The circulating levels of monocyte chemoattractant protein 1 (MCP1), known as pro-inflammatory cytokines, increase in tandem with the liver histological severity of NAFLD, suggesting a pathophysiological link between liver histological severity and CV mortality in NAFLD patients [26]. Serum level of MCP1 also has been reported to have positive correlation with PCAT attenuation [27]. Considering these previous reports, we believe that there is a strong relationship between liver histological severity and PCAT attenuation. Future studies are needed to investigate the direct relationship between histological severity and PCAT attenuation in NAFLD patients.

| Table 2 Factors associates with cardiovascular events |
|-----------------------------------------------------|
| **Univariate** & **Multivariate** |
| Hazard ratio (95% CI) & p value | Hazard ratio (95% CI) & p value |
| Age, per y1 years | 1.016 (0.973–1.061) | 0.475 |
| Male gender | 0.890 (0.329–2.407) | 0.818 |
| Body mass index, per 1 kg/m² | 0.906 (0.796–1.032) | 0.139 |
| Hypertension | 1.789 (5.14–6.232) | 0.361 |
| Diabetes mellitus | 0.724 (0.273–1.922) | 0.517 |
| Dyslipidemia | 0.723 (0.279–1.879) | 0.506 |
| Current smoker | 1.172 (0.412–3.329) | 0.766 |
| Obesity | 0.957 (0.358–2.648) | 0.958 |
| Atrial fibrillation | 3.159 (0.901–11.075) | 0.072 |
| Beta blocker | 2.643 (0.999–6.992) | 0.050 |
| Calcium channel blocker | 1.229 (0.468–3.230) | 0.675 |
| ACE-I or ARB | 1.803 (0.686–4.739) | 0.232 |
| Statin | 1.039 (0.384–2.811) | 0.940 |
| eGFR, per 1 mL/min/1.73 m² | 0.996 (0.965–1.028) | 0.815 |
| Total cholesterol, per 1 mg/dL | 1.005 (0.991–1.019) | 0.506 |
| LDL cholesterol, per 1 mg/dL | 1.003 (0.988–1.018) | 0.694 |
| Hemoglobin A1c, per 1% | 1.054 (0.762–1.457) | 0.750 |
| Fibrosis-4 index, per 1 index | 1.276 (0.898–1.647) | 0.061 |
| Significant stenosis (> 50%) | 2.320(0.893–6.026) | 0.084 |
| High-risk plaque features | 4.116 (1.181–14.342) | 0.026 |
| LAD-PCAT attenuation (≥ −66.6 HU) | 3.004 (1.158–7.792) | 0.024 |

ACE-I angiotensin-converting enzyme inhibitor; ARB angiotensin-receptor blocker; eGFR estimated glomerular filtration rate; LAD left anterior descending artery; LDL low-density lipoprotein; HU Hounsfield units; PCAT pericoronary adipose tissue
Elnabawi et al. recently reported that PCAT attenuation was a dynamic marker [28]. This suggests its potential role as a therapeutic effect index. The practice guideline of NAFLD recommends aggressive modification of risk factors in all patients with NAFLD [5]. Our result suggests that the treatment with reducing PCAT attenuation may potentially prevent CV events in NAFLD patients. Further studies are warranted to assess whether PCAT attenuation targeted medical treatment will result in improved outcome and whether assessment of PCAT attenuation is helpful to identify NAFLD patients who will benefit from aggressive prevention therapy.

Limitations

This study has several limitations that need to be addressed. First, several previous reports have highlighted that RCA-PCAT attenuation is a more reproducible measurement of pericoronary inflammation compared to LAD-PCAT attenuation [12], while this study showed no significant differences in RCA-PCAT attenuation between patients with and without CV events. The number of patients with NAFLD included in this study was relatively small. Thus, the statistical power of the study was hampered by the small sample size. In addition, our study included only Asian population. The volume of fat surrounding coronary arteries in Asian population may be less than that in Caucasian population. Thus, ethnical differences may affect this result. Second, we used abdominal non-contrast CT to diagnose NAFLD without histological confirmation of liver status, which is the gold standard for diagnosing NAFLD. Therefore, we were unable to assess histological severity of NAFLD. However, histological diagnosis of NAFLD for a large population is difficult to accomplish and adds a risk for some complications [29]. Third, our study population only consisted of NAFLD patients with suspected coronary artery disease. Therefore, selection bias cannot be excluded.

Conclusions

In conclusion, high-LAD-PCAT attenuation was an independent predictor of CV events in NAFLD patients, regardless high-risk plaque features on coronary CTA. In addition, LAD-PCAT attenuation had an incremental prognostic value over high-risk plaque features in this population. LAD-PCAT attenuation assessment was a viable tool for CV risk prediction in NAFLD patients.

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