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

Purpose: Pericoronary adipose tissue (PCAT) attenuation on coronary computed tomography angiography (CTA) has emerged as a marker for pericoronary inflammation. We investigated the prognostic value of PCAT attenuation in patients with non-alcoholic fatty liver disease (NAFLD).

Methods: We enrolled 232 patients with NAFLD and suspected coronary artery disease who underwent coronary CTA. NAFLD was defined by abdominal computed tomography (CT) as a ratio of hepatic attenuation to spleen attenuation of <1.0 . PCAT attenuation values were assessed by crude analysis of the mean CT attenuation values of the left anterior descending artery (LAD) and right coronary artery (RCA). Luminal stenosis and high-risk plaque features were examined as coronary CTA findings. The primary outcome was a composite of cardiovascular (CV) death, nonfatal acute coronary syndrome, and hospitalization for heart failure.

Results: During a median follow-up of 4.9 years, 17 patients experienced 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 the high-risk plaque features was 0.494 ($p=0.041$).

Conclusion: High LAD-PCAT attenuation was an independent predictor of CV events in patients with NAFLD regardless of CTA-verified high-risk plaque features. Additionally, LAD-PCAT attenuation had incremental prognostic value over high-risk plaque features.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide [1]. The prevalence of NAFLD in Japan is approximately 30%, and this number is expected to further increase in the future [2, 3]. NAFLD is associated with both liver-related and cardiovascular (CV) mortality [4]. Therefore, prevention of CV events in patients with NAFLD is gaining importance as a public health measure. The current NAFLD practice guidelines recommend aggressive modification of CV risk factors, such as obesity, diabetes mellitus, dyslipidemia, and hypertension, in all patients with NAFLD [5]. With the increasing global prevalence of NAFLD and healthcare costs, a diagnostic approach to help identify patients with NAFLD who will benefit from aggressive prevention therapy is needed.

Coronary computed tomography angiography (CTA) is used to noninvasively evaluate CAD. In addition to evaluating stenosis, coronary CTA identifies the characteristics of plaque composition. Previous studies have reported the significant association between high-risk plaque features assessed on coronary CTA and CV events in various patients and clinical settings [6–8]. Previously, we have reported that high-risk plaque features also increase the likelihood of CV events in patients with NAFLD [9]. 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 [10, 11]. 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 using coronary CTA, for CV events in patients with NAFLD.

Materials And Methods

Study design and study population

This study was 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 between August 2011 and December 2016 were enrolled in this cohort study. All patients underwent simultaneous examination of hepatic steatosis using abdominal non-contrast computed tomography (CT) 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, use of oral corticosteroids or amiodarone, coexisting active tumors, and <1 year of follow-up. Figure 1 presents the flow diagram of this study. In the principal study, we enrolled 1148 patients. Among them, 247 patients were diagnosed with NAFLD and 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 patients with NAFLD were included in this study. This study was conducted according to the principles of the Declaration of Helsinki and approved by the institutional review board of the Okayama University Graduate School of Medicine. All the enrolled patients provided written informed consent for participation.

Assessment of NAFLD

An abdominal non-contrast CT scan was performed immediately before the cardiac scan on the same day. Hepatic and splenic Hounsfield attenuations were measured using the maximum circular ROIs in the liver and spleen. The regions of interest $>100 \text{ mm}^2$ included two areas that were aligned with the anteroposterior 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 cut-off for the diagnosis of NAFLD [12]. Additionally, the fibrosis-4 index was calculated as a marker of liver fibrosis in all the patients.

Outcomes

Patients were followed up prospectively from the date of the coronary CTA. Clinical follow-up information was obtained from a review of medical records or telephone interviews blinded to the CT results. Here, CV events were defined as a composite of CV death, nonfatal acute coronary syndrome, and admission due to heart failure. The details of the event definition have been previously provided [13].

Coronary CTA analyses

Coronary CTA images were obtained 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 of >2 mm and defined plaque characteristics in accordance with the Society of Cardiovascular Computed Tomography [14]. Two experienced cardiovascular imaging researchers (K.O. and T.M.) interpreted coronary CTA findings. High-risk plaque features were defined as positive remodeling, low-attenuation plaque, and spotty calcification. We defined positive remodeling as an index >1.1. Plaques with a CT attenuation number <30 Hounsfield units were defined as low-attenuation. Spotty calcification was defined as a calcium burden length <1.5 of the vessel diameter and a width less than two-thirds of the vessel diameter. Stenosis was considered 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 in 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 [10, 15]. PCAT was defined as 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, the PCAT attenuation was automatically calculated as the mean CT attenuation value. Representative images of the PCAT attenuation analysis are illustrated in Figure 2. Two investigators (M.N. and T.N.), who were blinded to the clinical and CT data, performed PCAT attenuation analysis.

Risk factors

At baseline, standardized questionnaires were used to collect information on demographics, alcohol use, medical history, medication use, and smoking status. Detailed definitions of the risk factors have been previously described [16]. Obesity was defined as a body mass index ≥ 25.0 kg/m² according to the International Obesity Task Force recommendation [17]. As a liver fibrosis marker, fibrosis-4 index was calculated using the following formula: age (years) $\times$ AST (U/L)/[ALT (U/L)^{1/2} $\times$ platelet count (10⁹/L)] [18].

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation or median with interquartile range. Dichotomous variables are expressed as numbers and percentages. Differences in continuous variables between the two groups were analyzed using Student's t-test and Mann–Whitney U-test, as appropriate. Categorical data were compared using χ^2 and Fisher's tests, as appropriate. In the subsequent analysis, LAD-PCAT attenuation was used because it was more closely associated with prognosis than RCA-PCAT attenuation in our study. Kaplan–Meier curves were used to estimate the cumulative rates of CV events. Differences between the time-to-event curves were compared using the log-rank test. Cox regression

analyses were used to ascertain the association between PCAT attenuation and CV events, and the results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). We conducted a multivariate Cox regression analysis including factors with a 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 using receiver operating characteristic (ROC) curve analysis and global chi-square tests. C-statistics were calculated from 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 the 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%) patients 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 patients (53%), respectively. The mean LAD-PCAT and RCA-PCAT attenuation were -70.2 ± 6.7 and -69.1 ± 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). A comparison of baseline patient characteristics and coronary CTA results between patients with and without CV events is shown in Table 1. Patients with CV events had a higher fibrosis-4 index than those without CV events (2.1 ± 1.2 versus 1.5 ± 1.1 , p=0.032). Regarding coronary CTA results, patients with CV events had a higher prevalence of high-risk plaque features (82% vs. 51%; p=0.012).

Table 1

Comparison of baseline characteristics between patients with and without cardiovascular events.

	All	Cardiovascular events		p-value ^a
		Present	Absent	
N	232	17	215	
Age, years	61 ± 13	63 ± 13	61 ± 13	0.463
Male sex	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
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/1.73 m 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
HemoglobinA1c, %	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

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

^aComparisons between patients with and without cardiovascular events.^bObesity was defined as body mass index ≥ 25 kg/m².

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.

	All	Cardiovascular events		p-value ^a
		Present	Absent	
High-risk plaque features	124 (53)	14 (82)	110 (51)	0.013
LAD-PCAT attenuation, HU	-70.2 ± 6.7	-66.9 ± 7.0	-70.5 ± 6.6	0.032
RCA-PCAT attenuation, HU	-69.1 ± 7.3	-67.1 ± 5.0	-69.3 ± 7.5	0.248
Data are presented as mean ± standard deviation or number (%).				
^a Comparisons between patients with and without cardiovascular events.				
^b Obesity was defined as body mass index ≥ 25 kg/m ² .				
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.				

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) (Figure 3). The ROC curve analysis indicated that the optimal cut-off value of LAD-PCAT attenuation for predicting CV events was -66.6 HU (sensitivity 58.8%, specificity 73.0%). The Kaplan–Meier analysis revealed 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) (Figure 4). Based on the univariate Cox regression analyses, high-risk plaque features (HR 4.116; 95% confidence interval [CI], 1.181–14.342; p=0.026) and LAD-PCAT attenuation above the 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 revealed that LAD-PCAT attenuation was an independent predictor of CV events after adjusting for high-risk plaque features (HR, 3.321; 95% CI, 1.277–8.635; p=0.014).

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 sex	0.890 (0.329–2.407)	0.818		
Body mass index, per 1 kg/m ²	0.906 (0.796–1.032)	0.139		
Hypertension	1.789 (0.514–6.232)	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		
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 m ²	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		

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.

	Univariate	Multivariate		
HemoglobinA1c, per 1%	1.054 (0.762–1.457)	0.750		
Fibrosis-4 index, per 1 index	1.276 (0.989–1.647)	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	4.523 (1.291–15.841)	0.018
LAD-PCAT attenuation (≥ -66.6 HU)	3.004 (1.158–7.792)	0.024	3.321 (1.277–8.635)	0.014
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.				

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 the 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 the high-risk plaque features was 0.494 ($p=0.041$). Thus, the addition of LAD-PCAT attenuation to high-risk plaque features improved the risk reclassification of CV events in patients with NAFLD.

Discussion

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

Growing evidence indicates that high-risk plaque features on coronary CTA are significant factors associated with increased risk of CV events in various populations and clinical settings [6–8]. We have previously reported that high-risk plaque features on coronary CTA were significantly associated with CV events, even in patients with NAFLD and suspected coronary artery disease [9]. Recently, PCAT attenuation, a novel method for non-invasive quantification of coronary inflammation, has been developed and demonstrated to have prognostic value over high-risk plaque features on coronary CTA [10, 11, 19]. However, whether these results could be applied directly to patients with NAFLD is known because they represent low-grade inflammatory states and have increased coronary inflammation [20,

21]. Our study demonstrated the prognostic value of LAD-PCAT attenuation in patients with NAFLD, suggesting that the concurrent assessment of PCAT attenuation during coronary CTA could be helpful in identifying patients with NAFLD who are at a higher risk for future CV events.

The relationship between high PCAT attenuation and increased risk of CV events in patients with NAFLD can be inferred from previous reports. The stage of liver histological severity is strongly associated with both liver-related and CV mortalities [22, 23]. The circulating levels of monocyte chemoattractant protein 1 (MCP1), a pro-inflammatory cytokine, increase in tandem with the liver histological severity of NAFLD, suggesting a pathophysiological link between liver histological severity and CV mortality in patients with NAFLD [24]. Serum MCP1 levels have also been reported to be positively correlated with PCAT attenuation [25]. Hence, liver histological severity and PCAT attenuation may have a strong relationship. Further studies are needed to investigate the direct relationship between histological severity and PCAT attenuation in patients with NAFLD.

Recently, Elnabawi et al. have reported that PCAT attenuation is a dynamic marker [26], which suggests its potential role as a therapeutic index. The practice guidelines for NAFLD recommend aggressive modification of risk factors in all patients with NAFLD [5]. Our results suggest that treatment with reduced PCAT attenuation may prevent CV events in patients with NAFLD. Further studies are warranted to assess whether PCAT attenuation-targeted medical treatment will result in improved outcomes and whether assessment of PCAT attenuation is helpful in identifying patients with NAFLD who will benefit from aggressive prevention therapy.

Limitations

This study has several limitations that should be considered. First, the sample size was limited because this was a single-center study with a few patients with NAFLD who experienced CV events. Thus, the power of the study was hampered, leading to the finding that there was no significant difference in RCA-PCAT attenuation between patients with and without CV events. Our results should be confirmed in a larger population, and require further validation. Second, we used abdominal non-contrast CT to diagnose NAFLD without histological confirmation of the liver status, which is the gold standard for diagnosing NAFLD. Therefore, we were unable to assess the histological severity of the NAFLD. However, histological diagnosis of NAFLD in a large population is difficult and poses a risk of complications [27]. Third, our study population consisted only of patients with NAFLD with suspected coronary artery disease. Therefore, a selection bias cannot be excluded.

Conclusions

High LAD-PCAT attenuation was an independent predictor of CV events in patients with NAFLD, regardless of high-risk plaque features on coronary CTA. Additionally, LAD-PCAT attenuation had an incremental prognostic value over high-risk plaque features in this population. The LAD-PCAT attenuation assessment is a viable tool for predicting CV risk in patients with NAFLD.

Declarations

Acknowledgments

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Competing Interests

All authors declare no conflicts of interest regarding the materials presented in this article.

Author Contributions

Ethics Approval

This study was conducted according to the principles of the Declaration of Helsinki and approved by the institutional review board of the Okayama University Graduate School of Medicine.

Consent to Participate

All the enrolled patients provided written informed consent for participation.

Consent to publish

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Figures

Figure 1

Flow diagram of this study

Figure 2

Representative case of pericoronary adipose tissue attenuation measured by coronary computed tomography (CT) angiography. Pericoronary adipose tissue attenuation was defined as the mean computed tomography attenuation value between -190 HU and -30 HU within a radial distance equal to the diameter of the vessel

Figure 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 of pericoronary adipose tissue attenuation between patients with and without cardiovascular events. PCAT, pericoronary adipose tissue; LAD, left anterior descending artery; PCAT, pericoronary adipose tissue; RCA, right coronary artery

Figure 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 patients with NAFLD stratified by the threshold (-66.6 HU). HU, Hounsfield units; NAFLD, non-alcoholic fatty liver disease; PCAT, pericoronary adipose tissue