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Pericoronary Adipose Tissue Density, Inflammation, and Subclinical Coronary Artery Disease Among People With HIV in the REPRIEVE Cohort

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Background. Pericoronary adipose tissue (PCAT) may influence plaque development through inflammatory mechanisms. We assessed PCAT density, as a measure of pericoronary inflammation, in relationship to coronary plaque among people with human immunodeficiency virus (HIV [PWH]) and to a matched control population.

Methods. In this baseline analysis of 727 participants of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) Mechanistic Substudy, we related computed tomography–derived PCAT density to presence and extent (Leaman score) of coronary artery disease (CAD), noncalcified plaque, coronary artery calcium (CAC), and vulnerable plaque features using multivariable logistic regression analyses. We further compared the PCAT density between PWH and age, sex, body mass index, CAC score, and statin use–matched controls from the community-based Framingham Heart Study (N = 464), adjusting for relevant clinical covariates.

Results. Among 727 REPRIEVE participants (age 50.8 ± 5.8 years; 83.6% [608/727] male), PCAT density was higher in those with (vs without) coronary plaque, noncalcified plaque, CAC >0, vulnerable plaque, and high CAD burden (Leaman score >5) ($P < .001$ for each comparison). PCAT density related to prevalent coronary plaque (adjusted odds ratio [per 10 HU]: 1.44; 95% confidence interval, 1.22–1.70; $P < .001$), adjusted for clinical cardiovascular risk factors, body mass index, and systemic immune/inflammatory biomarkers. Similarly, PCAT density related to CAC >0, noncalcified plaque, vulnerable plaque, and Leaman score >5 (all $P \leq .002$). PCAT density was greater among REPRIEVE participants versus Framingham Heart Study (−88.2 ± 0.5 HU versus −90.6 ± 0.4 HU; $P < .001$).

Conclusions. Among PWH in REPRIEVE, a large primary cardiovascular disease prevention cohort, increased PCAT density independently associated with prevalence and severity of coronary plaque, linking increased coronary inflammation to CAD in PWH.

Keywords. pericoronary adipose tissue; HIV; coronary plaque; coronary artery disease; inflammation.

People with human immunodeficiency virus (HIV [PWH]) have a significantly higher prevalence of coronary artery disease (CAD) compared with the general population [1–3]. Although traditional risk factors explain only a portion of the risk increase [4], other factors, including immune activation and inflammation [5–12], are thought to contribute. The composition of pericoronary adipose tissue (PCAT) surrounding the coronary arteries can be used as an index of vascular inflammation [13]. The composition of PCAT is assessed by its density, measured in Hounsfield units (HU) on computed tomography (CT). Epidemiologic studies have associated increased PCAT density with more than 2 times the elevated risk of all-cause and cardiac mortality in patients with stable chest pain [14] and the general population with high-risk coronary artery plaque morphology and acute coronary syndrome [15, 16]. A recent meta-analysis demonstrated a pooled hazard ratio for

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major adverse cardiovascular events (MACEs) of 3.29 (1.88–5.76) in the general population [17]. However, it is unknown whether increased PCAT density relates to coronary plaque or is increased in PWH compared with the general population.

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) was designed to assess the effects of a primary prevention strategy in PWH at low-to-moderate traditional atherosclerotic cardiovascular disease (ASCVD) risk [18, 19]. REPRIEVE has recently been closed for a robust efficacy signal (35% reduction in MACE in daily pitavastatin vs placebo) [20]. Here, leveraged REPRIEVE mechanistic substudy baseline data assessed PCAT density in relationship to detailed coronary plaque indices, traditional risk and critical pathways of inflammation, and immune activation for the first time in PWH [8]. Furthermore, we compared PCAT density between PWH and matched controls from the community-based Framingham Heart Study (FHS).

METHODS

Study Population and Clinical Characteristics

REPRIEVE enrolled 7769 women and men (age 40–75 years) with low-to-moderate traditional ASCVD risk [19, 21], receiving antiretroviral therapy, asymptomatic without prior clinical cardiovascular disease, and not receiving statins [21]. Participants with active systemic infections and serious non-HIV illnesses were excluded. Thirty-one U.S. sites (mainly from the AIDS Clinical Trials Group) coenrolled 805 participants in the REPRIEVE Mechanistic Substudy (A5333s) between May 2015 and February 2018 [18]. For full exclusion criteria, see Supplementary Text 1.

Analogous data on PCAT density was assessed in a control group of asymptomatic participants in the multidetector CT substudy of the Offspring, Third Generation, and Omni cohorts of the community-based FHS [22] not on statin therapy. Control subjects were matched 1:1 without replacement in advance before PCAT measurements for age, sex, body mass index (BMI), coronary artery calcium (CAC) score, and statin use. The matching criteria included age ±2 years, sex 1:1, BMI ±2 kg/m^2, and CAC in the same category (0, 1–10, 11–100, 101–400, or >400) (Figure 1).

The institutional review boards of the Massachusetts General Hospital (REPRIEVE) and the Boston University Medical Center (FHS) approved the study protocols. All research sites obtained institutional review board/ethics committee approval and written informed consent from the participants.

CT Image Acquisition

All CT scans in REPRIEVE were acquired on ≥64-slice CT scanners using standard protocols, including acquisition of a standardized electrocardiogram (ECG)-synchronized noncontrast

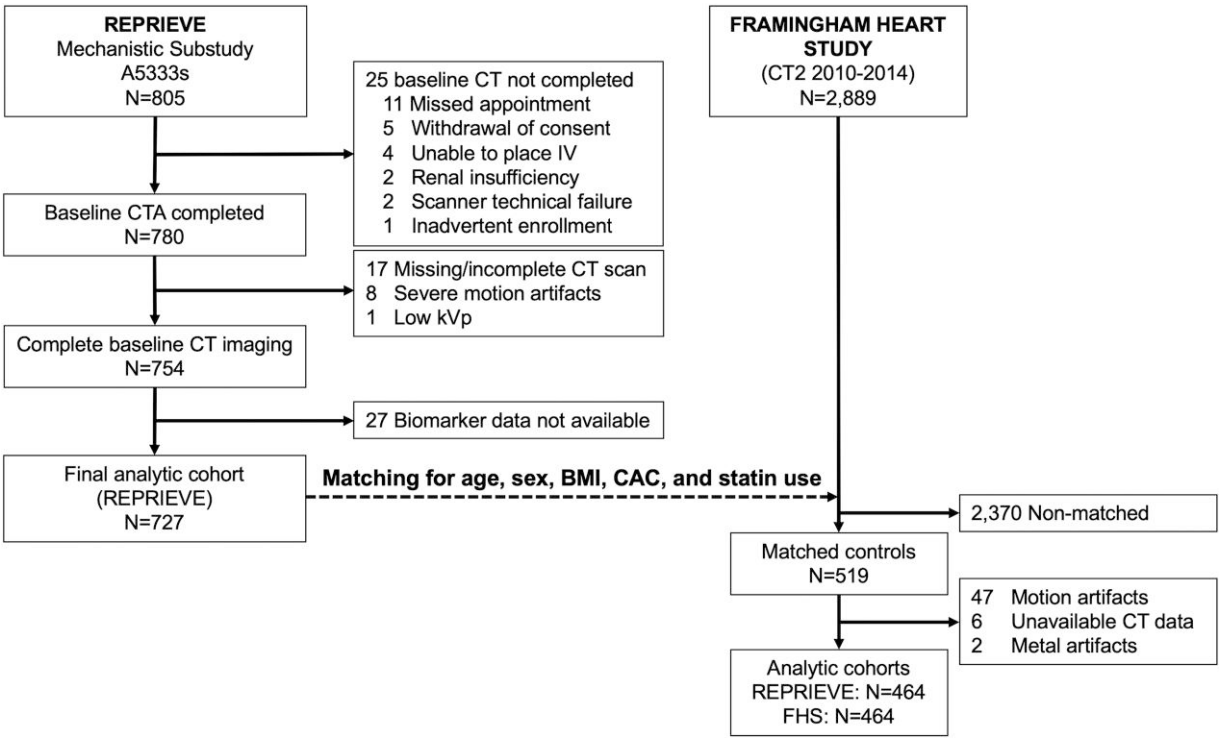

Figure 1. Consort diagram. ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAC, coronary artery calcium; CT, computed tomography; CTA, CT angiography; FHS, Framingham Heart Study.

CAC scoring scan and subsequent contrast-enhanced coronary CT angiography [18]. FHS cardiac CT scans consisted exclusively of ECG-synchronized noncontrast CAC scoring performed as in REPRIEVE using standardized acquisition parameters (120 kVp, ECG synchronization, 2.5- to 3-mm slice thickness, and field of view <250 mm) [22].

Assessment of Presence, Extent, and Composition of CAD on Cardiac CT

A central core laboratory quantified CAC on noncontrast CT images using standard methods in both REPRIEVE and FHS [23]. In REPRIEVE, contrast-enhanced coronary CT angiography scans were available and assessed for the presence, extent, and composition of atherosclerotic plaques using the standard 18-segment SCCT model [24]. Plaques were categorized by stenosis degree (0%, 1%–49%, 50%–69%, 70%–99%, and 100%) [24], composition (including noncalcified plaque), and assessed for vulnerability based on low attenuation (plaque with density <30 HU), positive remodeling (>1.1 remodeling index), and napkin ring sign (low central density core and ring-like peripheral hyperdensity) [8, 25]. The Leaman score, based on the number of affected segments, plaque location, stenosis degree, and plaque composition, provided information on coronary plaque burden [26].

Measurement of Pericoronary Adipose Tissue Density

PCAT density was determined similarly in both REPRIEVE and FHS participants in a representative area around the proximal 4 cm of the right coronary artery (RCA). PCAT is part of the epicardial adipose tissue that directly surrounds the coronary arteries. Supplementary Text 2 provides detailed descriptions of the measurement methods. Figure 2 shows representative examples.

Plasma Biomarkers of Immune Activation and Inflammation

Monocyte chemoattractant protein-1, high-sensitivity interleu kin-6, lipoprotein-associated phospholipase 2, oxidized low-density lipoprotein, and high-sensitivity C-reactive protein were assessed as previously published [8] and included in the multivariate modeling.

Statistical Methods

Continuous variables were presented as mean ± standard deviation or medians (25th–75th percentiles) and categorical variables as absolute and relative frequencies. PCAT density comparisons were performed using the Kruskal–Wallis test and logistic regression modeling. Odds ratios (ORs) were calculated per 10 HU higher PCAT density, ~25% of the measured range of PCAT density. Adjustments were performed for: ASCVD risk score, BMI, and substance use (model 1); model 1 + systemic inflammatory and immune activation biomarkers (model 2); or model 2 with individual cardiovascular risk factors instead of ASCVD risk score, including age, sex, race, and smoking (model 3). Biomarkers were log2-transformed and then divided by 0.32 to give effects per 25% increase of biomarker value. A sensitivity analysis included HIV-related indices in the modeling. A supplementary analysis was conducted for PWH without plaque in the proximal- or mid-RCA, assessing PCAT density's relation to plaque elsewhere.

Finally, a matched-cohort analysis compared PCAT density between REPRIEVE and FHS participants using a paired *t* test and general least squares random effects models adjusting for smoking and race. Statistical analyses were performed using Stata version 17.1 (StataCorp), and 2-sided *P* values <.05 were considered significant. The sample size was based on available data.

RESULTS

REPRIEVE Study Population

A total of 727 REPRIEVE Mechanistic Substudy participants had CT imaging suitable for PCAT and plaque assessment and provided immune/inflammatory biomarker data (Figure 1). Demographic characteristics, including substance use, are shown in Table 1 and footnote. Waist circumference cutoffs are per World Health Organization guidelines [27]. Viral load was suppressed in the great majority of participants.

PCAT Density in Relation to Demographic, Traditional Cardiovascular Risk Factors, and Anthropometric Measures

Among the 727 analyzed participants, the mean PCAT density was −88.0 ± 10.5 HU. Male sex, Black race, current smoking, and current or former substance use were associated with higher PCAT density. In contrast, higher BMI and waist circumference were associated with lower PCAT density (Table 1).

Relationship of PCAT Density to HIV Parameters

PCAT density was not associated with the duration of HIV infection or the length or type of antiretroviral therapy. Although HIV RNA was less than the lower level of quantification in 88% of REPRIEVE participants, higher PCAT density was marginally associated with a greater percentage of quantifiable HIV RNA ($P = .039$) (Table 1).

PCAT Density and CAD in People With HIV

Comparison of PCAT Density By Plaque Phenotype in PWH

Higher PCAT density was seen among those with coronary plaque, increasing stenosis degree and CAC, noncalcified plaques, vulnerable plaques, and increasing Leaman score (all $P < .001$; Table 2 and Figure 3). For example, PCAT density was −87.0 (−93.9 to −79.6) versus −90.4 (−96.3 to −83.6) HU in those with and without plaque, respectively ($P < .001$). See Figure 2*B* for representative examples.

In modeling, increased PCAT density was significantly associated with presence of coronary artery plaque (OR = 1.30; 95% confidence interval [CI]: 1.13–1.50; $P < .001$; OR per 10 HU increase in PCAT density). This association remained significant after adjustment for ASCVD risk score, BMI, substance use (model 1: adjusted OR [aOR] = 1.26; 95% CI: 1.09–1.47;

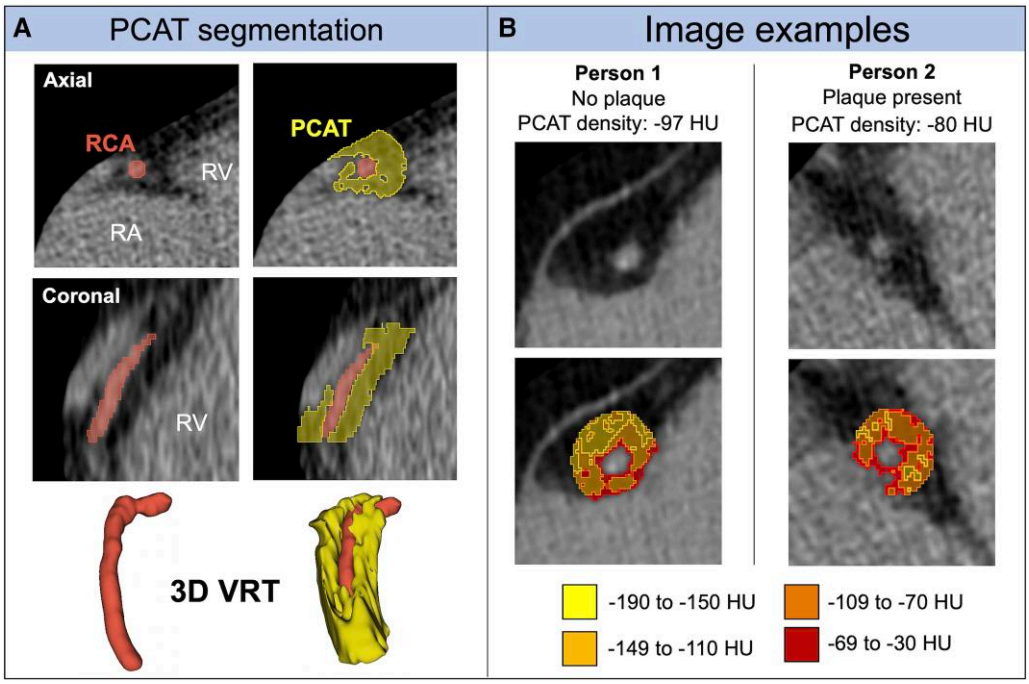

Figure 2. Pericoronary adipose tissue on noncontrast cardiac computed tomography. *A,* Segmentation of PCAT surrounding the right coronary artery to measure PCAT density. *B,* Examples of patients with and without CAD and correspondingly higher PCAT density in the patient with CAD. 3D VRT, 3-dimensional volume rendering technique; CAD, coronary artery disease; HU, Hounsfield unit; PCAT, pericoronary adipose tissue; RA, right atrium; RCA, right coronary artery; RV, right ventricle; VRT, volume-rendering technique.

$P = .002$), and model 1 + systemic inflammatory biomarkers (model 2: aOR = 1.38; 95% CI: 1.18–1.62; $P < .001$). Similar results were seen after correcting for individual cardiovascular risk factors instead of ASCVD risk score (Table 3). Supplementary Table 1 provides results per 1 standard deviation difference in PCAT density. Similarly, PCAT density was significantly associated with noncalcified plaque, any CAC, vulnerable plaque, and Leaman score >5 (Supplementary Tables 2–5). In fully adjusted models, the aORs were 1.33; 95% CI: 1.13–1.57; $P = .001$ for noncalcified plaque; 1.64, 95% CI: 1.37–1.97; $P < .001$ for CAC > 0; 1.34, 95% CI: 1.11–1.62; $P = .002$ for vulnerable plaque; and 1.81, 95% CI: 1.44–2.28; $P < .001$ for Leaman score >5).

Supplementary Analysis

Using an identical technique to ours, Takahashi et al demonstrated MACE in 14.2% versus 5.6% in those with higher PCAT density ≥ −93.55 HU [28]. We analyzed the data in our study using this clinically relevant cutoff from the literature. Using this cutoff, 70% of the PWH versus 60% in the FHS in the current study ($P = .01$) demonstrated pericoronary inflammation. In REPRIEVE, of the 70% above the threshold, 52% had any plaque versus 42% in the 30% of the population below the threshold ($P = .01$).

In addition, 17% of the REPRIEVE population demonstrated coronary artery plaque in the proximal, mid, or both RCA segments where PCAT density was measured. In a supplementary analysis limited to the 83% of participants without proximal- or mid-RCA plaque, PCAT density around the proximal RCA was similarly associated with coronary artery plaque in other coronary segments (aOR = 1.39; 95% CI: 1.15–1.69; $P = .001$; Supplementary Table 6).

Finally, adjustment for HIV-specific parameters, including antiretroviral therapy duration, CD4 cell count, HIV-RNA, and abacavir exposure did not affect any of the relationships between PCAT density and CT-derived CAD characteristics (aORs = 1.31–1.78; $P \leq .005$; Supplementary Table 7).

PCAT Density in PWH Versus Controls

Overall, 464 REPRIEVE subjects were matched for age, sex, BMI, statin use, and CAC with corresponding FHS participants (Figure 1). Supplementary Table 8 details the characteristics of the REPRIEVE and FHS groups. PCAT density was significantly, but modestly, higher in REPRIEVE compared with matched controls in the FHS (PCAT density: -88.2 ± 0.5 HU vs -90.6 ± 0.4 HU; $P < .001$). The difference in PCAT density remained similar in magnitude and significant in random-effects modeling, further controlling for smoking and race (coefficient: 1.86 HU; 95% CI: .44–3.28; $P = .010$; Supplementary Table 9). As in REPRIEVE, increased PCAT density related to the presence of CAC in the FHS participants with a generally similar OR (OR = 1.58 per 10 HU, 95% CI: 1.34–1.82; $P < .001$).

Table 1. Detailed Baseline Demographics, Risk Factors, Comorbidities, and Other Descriptors in all REPRIEVE Participants and Stratified by PCAT Density

Demographics	n/N (%), Mean ± SD, or Median (25%–75%)	PCAT Density–HU Median (25%–75%)	*P* Value
Age, y	50.8 ± 5.8	…	
Age categories, y			.998
40–44	102 (14.0)	−88.8 (−95.9 to −80.3)	
45–49	208 (28.6)	−88.8 (−95.9 to −80.3)	
50–54	228 (31.4)	−88.6 (−94.2 to −82.4)	
55–59	135 (18.6)	−89.1 (−94.6 to −82.0)	
≥60	54 (7.4)	−88.5 (−94.6 to −79.8)	
Sex			.026
Female	119 (16.4)	−91.0 (−97.2 to −83.6)	
Male	608 (83.6)	−88.2 (−94.6 to −80.9)	
Race	…	…	<.001
White	388 (53.4)	−89.5 (−95.7 to −82.7)	
Black or African American	257 (35.4)	−86.4 (−92.8 to −78.6)	
Asian	10 (1.4)	−89.8 (−91.5 to −85.0)	
Other	72 (9.9)	−90.3 (−96.7 to −82.6)	
Ethnicity			.004
Hispanic or Latino	176 (24.2)	−90.7 (−96.0 to −84.8)	
Not Hispanic or Latino	541 (74.4)	−87.8 (−94.6 to −80.4)	
Unknown	10 (1.4)	−91.4 (−94.2 to −78.7)	
Behavioral risk factors			
Smoking status			.003
Current	176 (24.2)	−86.7 (−92.8 to −78.4)	
Former	227 (31.3)	−88.9 (−95.3 to −82.0)	
Never	323 (44.5)	−89.8 (−95.9 to −81.2)	
Substance use[a]			<.001
Current	16 (2.2)	−80.2 (−86.3 to −75.7)	
Former	357 (49.2)	−87.1 (−93.0 to −79.9)	
Never	352 (48.6)	−91.2 (−97.0 to −83.5)	
Cardiovascular risk factors			
Family history of premature disease			.529
Yes	164 (22.6)	−89.8 (−95.5 to −82.5)	
No	540 (74.5)	−88.4 (−94.8 to −81.0)	
Unknown	21 (2.9)	−88.2 (−95.3 to −80.5)	
Prior statin use			.586
Yes	57 (7.8)	−88.3 (−92.6 to −80.9)	
No	670 (92.2)	−88.9 (−95.3 to −81.2)	
History of hypertension			.861
Yes	228 (31.4)	−88.0 (−95.3 to −81.6)	
No	499 (68.6)	−88.9 (−94.8 to −81.1)	
Median ASCVD risk score, %	4.5 (2.6–6.8)	…	
ASCVD risk categories, %			.613
<2.5	168 (23.1)	−89.4 (−95.2 to −81.7)	
2.5–4.9	238 (32.7)	−89.0 (−95.2 to −80.8)	
5.0–7.4	177 (24.4)	−88.3 (−95.8 to −81.6)	
7.5–9.9	98 (13.5)	−87.9 (−94.6 to −81.6)	
≥10.0	46 (6.3)	−87.3 (−92.4 to −79.7)	
Metabolic risk factors and orthometric measures			
BMI, kg/m^2	27.3 ± 4.4	…	
BMI categories, kg/m^2			.001
<18.5	8 (1.1)	−79.0 (−99.1 to −74.1)	
18.5–24.9	238 (32.7)	−86.6 (−92.3 to −79.0)	
25–29.9	295 (40.6)	−90.0 (−95.8 to −82.0)	
30–34.9	142 (19.5)	−90.1 (−95.7 to −84.0)	
≥35	44 (6.1)	−89.3 (−95.8 to −83.2)	
Waist circumference, cm	95.6 ± 11.9	…	

Table 1. Continued

Demographics	n/N (%), Mean ± SD, or Median (25%–75%)	PCAT Density–HU Median (25%–75%)	*P* Value
Waist circumference categories			<.001
High (male: ≥102 cm; female ≥88 cm)	220 (31.9)	−90.9 (−95.5 to −84.2)	
Normal (male: <102 cm; female <88 cm)	469 (68.1)	−87.7 (−94.3 to −79.9)	
HIV parameters			
HIV RNA, copies/mL			.039
<LLQ	633 (88.2)	−89.2 (−95.3 to −81.6)	
LLQ, <400	70 (9.8)	−86.8 (−91.9 to −79.6)	
≥400	15 (2.1)	−83.0 (−92.3 to −76.4)	
Total ART use			.742
<5 y	117 (16.1)	−89.6 (−95.2 to −79.7)	
5–9.9 y	190 (26.1)	−89.1 (−94.8 to −82.0)	
≥10 y	420 (57.8)	−88.3 (−94.9 to −81.2)	
ART regimen by class			.991
NRTI + INSTI	325 (44.7)	−88.6 (−95.3 to −81.6)	
NRTI + NNRTI	190 (26.1)	−89.0 (−95.8 to −81.2)	
NRTI + PI	121 (16.6)	−89.4 (−93.9 to −80.8)	
NRTI-sparing	21 (2.9)	−86.6 (−95.1 to −82.8)	
Other NRTI-containing	70 (9.6)	−88.3 (−94.2 to −80.8)	
Abacavir exposure			.834
Yes	246 (33.9)	−88.7 (−95.1 to −81.6)	
No	479 (66.1)	−88.8 (−94.8 to −81.1)	
CD4, cells/mm^3			.779
<350	110 (15.1)	−88.3 (−94.8 to −80.5)	
350–499	145 (19.9)	−89.0 (−95.2 to −81.9)	
≥500	472 (64.9)	−88.8 (−95.0 to −81.2)	
Nadir CD4, cells/mm^3			.186
<50	157 (21.6)	−88.9 (−96.3 to −81.8)	
50–199	212 (29.2)	−89.3 (−95.7 to −82.9)	
200–349	196 (27.0)	−88.6 (−94.3 to −80.4)	
≥350	140 (19.3)	−88.7 (−93.4 to −81.2)	
Unknown	22 (3.0)	−84.5 (−90.9 to −75.3)	

[a]Substance use among PWH was classified as current (2.2%) or former (49%) (IV drug [current: 0%, former: 11.2%], cocaine [current: 1.2%, former: 45.8%], or methamphetamine [current: 1.1%, former: 19.7%]. *P* values were obtained using a nonparametric Kruskal–Wallis test.

Abbreviations: ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HIV, human immunodeficiency virus; HU, Hounsfield unit; INSTI, integrase strand transfer inhibitors; LLQ, lower level of quantification; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PCAT, pericoronary adipose tissue; PI, protease inhibitor; REPRIEVE, Randomized Trial to Prevent Vascular Events in HIV.

DISCUSSION

The current study leveraged the large REPRIEVE cohort to analyze PCAT density, a novel imaging marker of local coronary inflammation, and its association with coronary artery plaque in PWH. Moreover, we compared PCAT density in PWH with matched controls from the community-based FHS to investigate HIV's relationship with increased coronary inflammation. This study revealed 2 main findings. First, PCAT density was strongly associated with critical CT indices of subclinical CAD in PWH, independent of cardiovascular risk factors, body composition, and immune activation biomarkers. Second, we observed significantly higher coronary inflammation in REPRIEVE than in an age-, sex-, BMI-, statin use–, and CAC-matched FHS population.

PCAT Density as a Novel Marker of Vascular Inflammation

PCAT is an important fat depot with a unique location. PCAT surrounds coronary arteries without a connective tissue barrier, making it susceptible to inflammatory mediators released by inflamed vessel walls [29]. Moreover, PCAT contains immune cells such as macrophages and T lymphocytes [30] and is thought to have paracrine functionality. The less differentiated smaller PCAT adipocytes have a secretory profile favoring local production of pro-inflammatory cytokines (eg, interleukin-6 [IL-6], IL-8, monocyte chemoattractant protein 1) and less adiponectin, potentially contributing to vascular wall inflammation [31]. Indeed, ex vivo studies have demonstrated that vessel-derived inflammatory cytokines (eg, tumor necrosis factor-alpha, IL-6, interferon-gamma) inhibit human preadipocyte differentiation and lower adipocyte lipid content [13]. This effect leads to a higher connective tissue-to-lipid volume ratio, regional fibrosis, and increased PCAT density on CT. In contrast, obesity leads to a higher adipocyte lipid content, a lower connective tissue-to-lipid ratio, and lower PCAT density on CT [13], reflected in our study by a lower PCAT density in those with higher BMI and waist circumference (Table 1).

Table 2. CT-Derived CAD Indices in all Participants and by PCAT Density

	n/N (%)	PCAT Density, HU Median (25%–75%)	*P* Value
Participants with any plaque			<.001
No	371 (51.0)	−90.4 (−96.3 to −83.6)	
Yes	356 (49.0)	−87.0 (−93.9 to −79.6)	
Number of noncalcified segments			<.001
0 segments with noncalcified plaque	436 (60.0)	−90.1 (−95.7 to −82.5)	
1–2 segments with noncalcified plaque	234 (32.2)	−87.5 (−94.1 to −80.1)	
≥3 segments with noncalcified plaque	57 (7.8)	−84.0 (−90.6 to −78.9)	
Stenosis			<.001
No (stenosis 0%)	371/715 (51.9)	−90.4 (−96.3 to −83.6)	
Mild (stenosis 1%–49%)	319/715 (44.6)	−87.2 (−94.0 to −79.4)	
Moderate (stenosis 50%–69%)	16/715 (2.2)	−83.5 (−88.9 to −79.9)	
Severe (stenosis ≥70% or ≥50% left main)	9/715 (1.3)	−84.0 (−91.7 to −79.0)	
CAC score			<.001
CAC = 0	452/698 (64.8)	−90.2 (−96.2 to −83.5)	
CAC = 1–100	173/698 (24.8)	−85.3 (−92.9 to −78.7)	
CAC = 101–400	61/698 (8.7)	−84.3 (−92.7 to −77.8)	
CAC >400	12/698 (1.7)	−83.9 (−89.5 to −79.9)	
Vulnerable plaque features			
Any vulnerable plaque			<.001
No	563 (77.4)	−89.5 (−95.7 to −81.9)	
Yes	164 (22.6)	−85.3 (−92.8 to −79.2)	
Vulnerable plaque category			
Positive remodeling			<.001
No	568 (78.1)	−89.4 (−95.6 to −81.9)	
Yes	159 (21.9)	−85.5 (−92.9 to −79.0)	
Low-attenuation plaque			.530
No	683 (94.0)	−88.9 (−95.2 to −81.1)	
Yes	44 (6.1)	−86.6 (−94.2 to −82.5)	
Napkin ring sign			.342
No	704 (96.8)	−88.6 (−94.8 to −81.1)	
Yes	23 (3.2)	−89.6 (−98.7 to −83.9)	
Leaman score			<.001
0	371/715 (51.9)	−90.4 (−96.3 to −83.6)	
>0–5	230/715 (32.2)	−88.3 (−95.1 to −80.8)	
>5	114/715 (15.9)	−83.9 (−90.7 to −77.9)	

Leaman score reflects coronary artery disease burden based on the number of segments with plaque, plaque location, stenosis degree, and plaque morphology. *P* values were obtained using a nonparametric Kruskal–Wallis test.

Abbreviations: CAC, coronary artery calcium; CT, computed tomography; HU, Hounsfield unit; PCAT, pericoronary adipose tissue.

Therefore, we adjusted our multivariable analyses for BMI and showed that PCAT density is associated with CAD characteristics independent of obesity. Moreover, elevated ^{18}F-sodium fluoride uptake on positron emission tomography has been correlated with increased subcutaneous adipose tissue density in animal studies (rho = 0.69, $P < .001$) in which adipocyte size is driven by the infiltration of activated macrophages and insulin resistance [13]. Elevated ^{18}F-sodium fluoride uptake has been linked to increased lesion-specific PCAT density in high-risk plaques, suggesting a role of coronary inflammation in the development of CAD [32].

Increased PCAT Density is Strongly Related to Coronary Plaque in PWH

In REPRIEVE, the prevalence of coronary artery plaques was relatively high (49%) despite an overall low to moderate ASCVD risk of 4.5% [8]. This important observation aligns with prior investigations in PWH [11, 33] and indicates that low-clinical-risk individuals may develop CAD through unique pathophysiological pathways. In this regard, increased arterial inflammation may promote CAD among PWH. Prior data demonstrated increased arterial inflammation using (technetium-99 m–tilmanocept single photon emission computed tomography/CT) and ^{18}F-2-deoxy-glucose positron emission tomography among virologically controlled PWH [5, 12]. However, these studies assessed aortic radiotracer uptake without assessing coronary artery inflammation. We now show that PCAT density, as an index of local coronary inflammation, relates not only to presence of plaque but to critical plaque features in this population, including vulnerable plaque and plaque burden (ie, Leaman score), known to relate to clinical disease [26]. This finding was robust, and a 10-HU

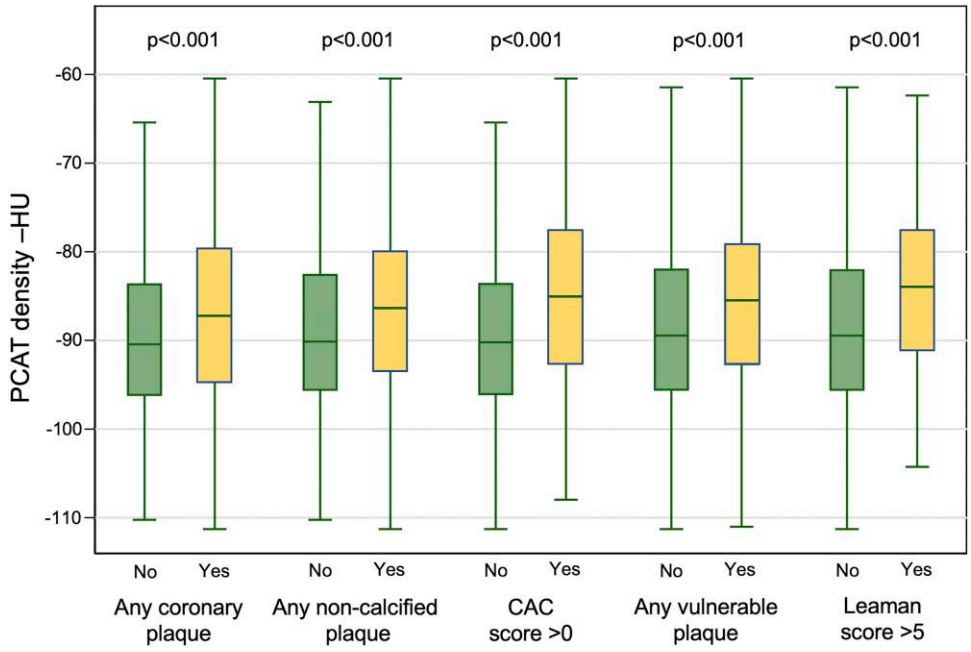

Figure 3. PCAT density differences by CT findings. Higher PCAT density in REPRIEVE participants with coronary plaques, noncalcified plaques, coronary calcium score >0, vulnerable plaques, and increased coronary artery disease burden (Leaman score >5). Each boxplot displays the median (solid horizontal line), interquartile range (box), and 1.5 interquartile ranges of the upper and lower quartiles (whiskers). Leaman score reflects coronary artery disease burden based on the number of segments with plaque, plaque location, stenosis degree, and plaque composition. *P* values were obtained using a nonparametric Kruskal–Wallis test. CAC, coronary artery calcium; CT, computed tomography; HU, Hounsfield unit; PCAT, pericoronary adipose tissue; REPRIEVE, Randomized Trial to Prevent Vascular Events in HIV.

Table 3. Uni- and Multivariable Regression Results Comorbidities Versus Presence of Plaque

	Univariable			Model 1			Model 2			Model 3		
Any Coronary Plaque	OR	95% CI	*P* Value	OR	95%CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
PCAT density (per 10 HU)	1.30	1.13–1.50	<.001	1.26	1.09–1.47	.002	1.38	1.18–1.62	<.001	1.44	1.22–1.70	<.001
Age, y	…	…		…	…		…	…		1.10	1.07–1.13	<.001
Sex (male)	…	…		…	…		…	…		2.18	1.34–3.56	.002
Race												
White	…	…		…	…		…	…		ref.	…	
Black or African American	…	…		…	…		…	…		0.69	.46–1.03	.066
Asian	…	…		…	…		…	…		1.61	.39–6.72	.513
Other	…	…		…	…		…	…		0.98	.56–1.70	.941
ASCVD, %	…	…		1.16	1.10–1.22	<.001	1.14	1.08–1.21	<.001	…	…	
BMI, kg/m^2	…	…		1.01	.97–1.04	.619	1.01	.97–1.04	.772	1.02	.98–1.06	.272
Substance abuse	…	…		1.26	.93–1.72	.134	1.20	.87–1.65	.265	1.23	.87–1.72	.237
Smoking (current)	…	…		…	…		…	…		1.27	.84–1.92	.259
MCP-1, pg/mL	…	…		…	…		1.09	.99–1.20	.066	1.06	.96–1.17	.259
IL-6, pg/mL	…	…		…	…		1.05	1.00–1.11	.048	1.06	1.00–1.12	.041
LpPLA2, ng/mL	…	…		…	…		1.19	1.10–1.28	<.001	1.15	1.06–1.25	.001
oxLDL, mU/L	…	…		…	…		1.09	.99–1.20	.090	1.13	1.02–1.25	.021
hsCRPm mg/L	…	…		…	…		1.02	.98–1.07	.342	1.03	.99–1.08	.179

P values were obtained with logistic regression modelling.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; HU, Hounsfield unit; IL-6, interleukin 6; LpPLA2, lipoprotein-associated phospholipase A2; MCP-1, monocyte chemoattractant protein 1; OR, odds ratio; oxLDL, oxidized low-density lipoprotein; PCAT, pericoronary adipose tissue.

difference in pericoronary fat density was associated with a 44% higher risk of coronary plaque, independent of clinical ASCVD risk and inflammatory indices. To provide perspective, a 1-percentage point difference in ASCVD risk score, representing approximately 25% of the median risk score of 4.5% in REPRIEVE, was associated with a 14% higher risk of coronary plaque in this model. Providing further clinical context, Takahashi et al demonstrated MACE in 14.2% versus 5.6% in

those with PCAT density ≥ −93.55 HU. A higher percentage of PWH in REPRIEVE met this clinically relevant cutoff than in the FHS.

Of note, our results were in line with data from the Cardiovascular RISk Prediction using Computed Tomography study, revealing that perivascular inflammation around the proximal segments of the major coronary arteries without detectable CAD was associated with high-risk plaque features elsewhere [14].

Relationship of PCAT Density to CAD is Independent of Systemic Inflammation

Interestingly, PCAT density's association with CAD was independent of systemic inflammatory and immune activation indices, highlighting the important paracrine nature of pericoronary inflammation with respect to plaque as suggested in prior studies [13, 17]. Moreover, the relationship of PCAT to plaque remained significant controlling for HIV-related indices. Indeed, assessing PCAT density allows us to evaluate an index of local coronary inflammation in juxtaposition to the coronary artery wall, which may influence plaque independent of systemic inflammatory indices.

Comparison of PWH to FHS Controls

We compared PCAT density in PWH with FHS controls for the first time, showing a modestly higher PCAT density in PWH compared with age, sex, BMI, CAC, and statin use–matched controls. This observation remained significant in a model further adjusting for relevant covariates not used in the matching. The magnitude of this difference in PCAT density between FHS and controls was about two-thirds the difference between those with and without plaque among PWH in REPRIEVE. Furthermore, the magnitude of the relationship between PCAT density and CAD, at least as assessed by CAC, available in both studies, is generally similar.

Optimal Imaging of Pericoronary Adipose Tissue Density

Although there are patented artificial intelligence–enhanced algorithms (eg, CaRi-HEART algorithm [34] fat attenuation index) [13, 14], we chose to assess PCAT density using the noncontrast highly standardized (consistent 120 kVp and slice thickness) coronary artery calcium scans available from both studies [35] to minimize the effect of technical confounding and harmonize the measurement across studies. This method successfully showed a robust association of PCAT density with CAD in both REPRIEVE and FHS and has been used successfully by other groups assessing pericoronary inflammation [28, 35]. Furthermore, our data suggest that assessing PCAT density from low-cost, low-radiation, and noncontrast calcium scoring, recommended for primary prevention, may be a valuable strategy to identify those at increased risk for CAD in PWH with low traditional cardiovascular risk.

Strengths and Limitations

To the best of our knowledge, this is the first study investigating pericoronary inflammation in PWH. We assessed PCAT density in a large, well-phenotyped primary prevention cohort of PWH and compared it with data in a well-known community-based cohort, controlling for traditional risk factors and key systemic inflammatory indices. The REPRIEVE population was recruited from ACTG sites across the United States and represents the HIV population here in terms of race, gender, and substance use [36]. The current study is cross-sectional, limiting causal conclusions between PCAT and CAD. In our comparison to controls from the FHS, we matched key covariates and controlled for differences in the study populations. There may be other differences in CT technique that may influence our results, but we used a uniform method to assess PCAT from standardized noncontrast images across both studies to limit any differences. Future studies with other more racially diverse control populations are needed to confirm these results. We hypothesized that there might be a difference in the relationship of PCAT density to plaque characteristics, though this relationship was similar for CAC in both REPRIEVE and FHS. Future studies should investigate the relationship between PCAT density and increased hard clinical endpoints and compare the relationship of PCAT to other CAD indices among PWH and control populations.

CONCLUSIONS

Among PWH living in the United States at low-to-moderate cardiovascular risk, PCAT density was associated with a higher prevalence of CAD, CAC, vulnerable plaque, and overall plaque burden. This relationship remained significant adjusting for cardiovascular risk factors, anthropometric measures, and systemic inflammatory indices. Moreover, PCAT density was higher among PWH in REPRIEVE compared with FHS controls, suggesting higher vascular inflammation in PWH. PCAT density may thus represent a novel marker of vascular and subclinical coronary pathology. Future studies should assess the mechanisms of increased perivascular inflammation in PWH and how strategies to affect PCAT density may affect plaque and future events. Early identification of CAD risk markers such as PCAT density may help to optimize ASCVD preventive strategies among PWH.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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