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Effect of Pericardial Fat Volume and Density on Markers of Insulin Resistance and Inflammation in Patients with Human Immunodeficiency Virus Infection

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Abstract

Treated HIV infection is characterized by ectopic fat deposition, a persistent inflammatory state, and increased cardiometabolic risk. In this secondary analysis of a placebo controlled trial of rosuvastatin among 147 HIV+ subjects (median age 46; 78% male) on stable antiretroviral therapy, we aimed to evaluate longitudinal associations between CT measures of pericardial fat (PCF) volume and density, insulin resistance and inflammation. We measured PCF volume and density (mean attenuation in Hounsfield Units) by non-contrast gated computed tomography at baseline and week 96. Homeostatic model of insulin resistance was calculated from fasting insulin and glucose at entry, 24, 48, and 96 weeks. At baseline, insulin resistance correlated positively with PCF volume and negatively with density. Similarly divergent correlations of volume and density were observed with waist:hip ratio, nadir CD4+ count, and duration of antiretroviral therapy. In a linear mixed model, PCF density was associated with insulin resistance independent of PCF volume, body mass index, metabolic syndrome, and biomarkers of immune activation and systemic inflammation; however, baseline PCF measures were not associated with longitudinal changes in insulin resistance. Soluble CD163, a marker of monocyte activation, positively correlated with PCF volume and was associated with insulin resistance in linear models. Statin treatment assignment did not affect PCF volume or density change (both $p > 0.8$). In conclusion, the quantity and quality (i.e. radiodensity) of PCF are differentially related to insulin resistance and inflammation in patients with treated HIV infection.

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Keywords

HIV; pericardial fat; insulin resistance; inflammation

Introduction

Persons living with HIV infection remain at elevated risk for cardiometabolic disease despite the declining toxicity of newer generations of antiretroviral therapy (ART)[1]. Pericardial fat (PCF)—fat that surrounds the heart and coronary arteries—may have a direct and causal effect on cardiovascular disease[2], but may also serve as a useful imaging biomarker of this systemic metabolic risk and inflammation in this population[3]. Therefore, the primary objective of this study was to determine whether baseline PCF volume and density independently predict changes in insulin resistance over time. Secondary objectives were: (A) to determine clinical correlates of PCF volume and density; (B) to evaluate the relation of PCF volume and density to biomarkers of systemic inflammation and immune activation; (C) to evaluate the effect of statin therapy on PCF; and (D) to determine predictors of PCF volume and density change over time.

Methods

Our study is a secondary analysis of data from the Stopping Atherosclerosis and Treating Unhealthy Bone with RosuvastatiN in HIV (SATURN-HIV) trial—a 96 week randomized, double-blind trial of rosuvastatin 10mg daily vs. placebo among HIV-infected patients on ART with LDL-cholesterol ≤130mg/dL and evidence of increased inflammation and/or T-cell activation [high sensitivity C-reactive protein (hs-CRP) ≥2mg/L and/or CD8+CD38+HLA-DR+ T-cells ≥19%][4]. All participants were ≥18 years of age without known coronary disease or diabetes, and on stable ART for at least 3 months with HIV-1 RNA <1,000 copies/mL. Full inclusion and exclusion criteria can be found at clinicaltrials.gov (NCT01218802). The study was approved by the Institutional Review Board of University Hospitals Cleveland Medical Center, and all participants signed written informed consent.

Self-reported demographics, smoking status, and medical history (including duration and type of ART) were obtained along with a targeted physical exam including height, weight, waist, and hip measurements. Ten-year Framingham risk for coronary heart disease was determined using a published risk calculator[5]. Blood was drawn after at least a 12-hour fast for lipoprotein analysis, glucose and insulin levels in real time in the hospital clinical lab and stored for batched measurements of biomarkers as described below. HIV-1 RNA level and CD4+ cell count were obtained as part of routine clinical care. Nadir CD4+ T-cell count was defined as the lowest recorded CD4+ count in the subject's medical record. Whole body dual-energy absorptiometry (DEXA; Lunar Prodigy Advance, GE Healthcare, USA) was used to measure total and regional (trunk vs. peripheral) fat distribution at baseline and 96 weeks as previously described[3].

Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated from fasting glucose and insulin levels at weeks 0, 24, 48, and 96 using the following formula: [glucose (mg/dl) × insulin (mg/dl)] ÷ 405.[6]

All subjects had a non-contrast electrocardiogram-gated cardiac CT for calcium scoring at baseline and 96 weeks. Scans were performed on a 64-slice multidetector scanner (Somatom Sensation 64, Siemens Medical Solutions, USA) with 30 × 0.6mm collimation, 330ms rotation time, and 120kV tube voltage. Three-millimeter slices were obtained from the carina to the diaphragm with prospective gating at 60% of the R-R interval. We defined calcified coronary lesions as areas of ≥6 pixels with density >130 Hounsfield units (HU) and used the Agatston method to quantify coronary calcium score. We separately assessed both PCF volume and density from the baseline and 96 week scans. A single reader (CTL) blinded to randomization arm and subject characteristics performed all measurements using Aquarius iNtuition Cloud (Terarecon, San Mateo, CA USA). Pericardial fat volumes were measured using the same semi-automatic segmentation technique used in the Framingham Heart Study [3,7]. The region of interest was first obtained by manually tracing the pericardial borders. Fat tissue was defined as pixels within a window of −195 to −45 HU, and PCF was then selected as all fat tissue within the pericardial sac. Pericardial fat density was measured as the mean attenuation of PCF on three consecutive axial slices through the center of the heart. The intra-class correlation for density measurements was excellent at 0.953.

Soluble baseline levels of biomarkers of inflammation and monocyte activation were measured at baseline and 96 weeks from frozen plasma samples stored at −80°C and analyzed in batch. Cystatin C and hs-CRP were measured by particle enhanced immunonepholometric assays on a BNII nephelometer (Siemens, Munich, Germany). Interleukin-6 (IL-6), soluble tumor necrosis factor-α receptor 1 (sTNF-RI), soluble CD14 (sCD14), and soluble CD163 (sCD163) were measured by ELISA (R&D Systems, Minneapolis, MN). Inter-assay variability has been previously reported and generally ranged between 0.4–18%[3,4,8]. We measured cellular markers of immune activation at baseline using peripheral blood mononuclear cells isolated from whole blood using the Ficoll-Hypaque method. Cryopreserved cells were then analyzed in batch on a MACS Quant flow cytometer (Miltenyi Biotec, Bergisch Gladbach, Germany) as previously described[9]. T-cell activation was defined as co-expression of HLA-DR and CD38 on CD4+ and CD8+ T-cells. Two monocyte populations of interest (expressed as a proportion of total monocytes) were used for this analysis: (1) $CD14^{dim}CD16+$ (variably referred to as “patrolling” or “non-classical” monocytes), and (2) CD14+CD16+ or “inflammatory” monocytes.

Baseline characteristics and study variables were first described by treatment group using median (interquartile range) for continuous variables and frequency (%) for categorical variables. We then assessed the distribution of all variables and natural log-transformed those that were non-normally distributed for all subsequent analyses.

Relations between our primary explanatory variables of interest (PCF volume and density) and our outcomes of interest (HOMA-IR, clinical variables, body composition, and biomarkers of inflammation) were first assessed at baseline using scatter plots and Pearson correlation coefficients. After confirming that changes in HOMA-IR over time were linear,

we used linear mixed modeling with random intercept and slope to describe the relationship between PCF measures and HOMA-IR, accounting for the within-patient correlation of measurements obtained at different weeks on the same patient. An initial model included PCF measures and their interactions with time as well as main effects and interactions with time for other covariates that were significantly correlated ($p<0.05$) in univariable analyses; all time interaction terms not involving PCF measures with $p>0.15$ were then removed. There was no evidence of significant multicollinearity in this model (all variance inflation factors <4); however, because of significant baseline correlation between PCF volume and BMI, we repeated the model leaving out BMI to assess whether this altered the association between PCF and HOMA-IR.

Differences in 96-week PCF volume and density change between statin and placebo groups were assessed using t-tests. Correlations between 96 week changes in PCF volume and density and changes in body composition and inflammation were assessed with scatter plots and Pearson correlation coefficients. Confidence intervals for correlation coefficients were calculated using the Fisher z-transformation. Finally, we separately assessed predictors of both PCF volume and density changes using hierarchical multiple linear regression models adjusted for covariates in four stages: (1) demographics and clinical variables, (2) body composition, (3) HIV parameters; (4) biomarkers of inflammation and immune activation. Age, race, and sex were forced into each model and factors found to be statistically significant ($p<0.05$) were carried forward into each subsequent model. In the fourth stage, interactions of treatment group with all other significant factors were tested; however, since none were significant, no interaction terms were included in the final model.

Statistical analyses were performed using SAS version 9.4 (SAS Institute; Cary, NC). Additional figures were created using GraphPad Prism version 6.07 (GraphPad Software, Inc.; La Jolla, CA). A p-value <0.05 was considered statistically significant.

Results

Overall, 147 subjects were enrolled in SATURN-HIV and 118 subjects completed all assessments through 96 weeks of follow-up. The reasons for screen failure and loss-to-follow-up have been previously described (see Supplemental Figure 1)[4]. Baseline characteristics by category of PCF volume and radiodensity are shown in Table 1. Median (IQR) age was 46 (40–53) years; approximately three-quarters were male and two-thirds African American. Although median current CD4+ T-cell count was high, over half had a history of CD4+ <200 cell/μl. Half of subjects were on PI-based ART. A quarter were obese (BMI >30kg/m^2) and nearly two-thirds were current smokers. Although no subjects had diabetes (this was an exclusion criteria), over a third demonstrated at least a modest amount of insulin resistance (HOMA-IR >2.5) at baseline.

At baseline, median (IQR) PCF volume was 68 (47–92) ml and modestly skewed at the upper limit. Median PCF density was −86.8 (−88.7 to −84.95) HU and was normally distributed. In further analyses involving PCF measures, the natural log of PCF volume and untransformed value of PCF density were used. HOMA-IR correlated positively with

Ln(PCF volume) (r = 0.432, p<0.001) and negatively with PCF density (r= −0.274, p<0.001; Figure 1).

In a multivariable linear mixed model of insulin resistance over 96 weeks, baseline PCF density was inversely associated with Ln(HOMA-IR) independent of Ln(PCF volume), BMI, metabolic syndrome, and biomarkers of immune activation and systemic inflammation; however, baseline PCF measures were not associated with longitudinal changes in HOMA-IR (p for time interaction terms >0.05; Table 2). When BMI was removed from the model, both Ln(PCF volume) (adj β = 0.409, p<0.001) and PCF density (adj β = −0.041, p=0.046) were independently associated with Ln(HOMA-IR). Ninety-six week changes in Ln(HOMA-IR) were not correlated with 96-week changes in Ln(PCF volume) or density (both p>0.4).

Similarly to the correlations seen with HOMA-IR, clinical variables such as age and lipoprotein profiles tended to demonstrate divergent correlations with PCF volume and density (Figure 2A). In contrast to volume, PCF density did not correlate with measures of total body adiposity (BMI r=0.057 and total body fat r=−0.034, both p>0.4), but was negatively correlated to waist-hip ratio (−0.337, p<0.001). Interestingly, markers of more severe HIV disease history (lower nadir CD4+ and longer duration of ART or PI use) were associated with higher PCF volume and lower density (Figure 2A). Over 96 weeks, changes in Ln(PCF volume) were strongly correlated to changes in DEXA measures of total and regional adiposity [r=0.67, 0.65, and 0.64 for total, trunk, and limb fat, respectively; all p <0.0001]; however, PCF density changes were unrelated to body fat changes [all r <0.02; all p >0.8]. Changes in Ln(PCF volume) and PCF density did not correlate with changes in lean mass [both r<0.1; p>0.2].

Among the soluble and cellular biomarkers of inflammation and immune activation measured in our study, IL-6, sTNF-RI, cystatin C, and sCD163 were most strongly related to PCF volume and/or density at baseline (Figure 2B). In linear mixed models of insulin resistance, Ln(sCD163) was the only biomarker of inflammation and immune activation that was positively associated with Ln(HOMA-IR) independent of PCF volume or density (Table 2). Changes in select biomarkers over 96 weeks were weakly but positively associated with Ln(PCF volume) change [r=0.20, 0.24, and 0.20 for Ln(IL-6), Ln(sTNF-RI), and Ln(sCD163), respectively; all p<0.04] and PCF density change [r=0.19, 0.23, 0.18; all p<0.05].

There was no observed effect of statin therapy on changes in Ln(PCF volume) or density over 96 weeks in our study [p=0.96 and p=0.81 for volume and density change, respectively]. The full hierarchical regression models of predictors of PCF volume and density change over time are shown in Supplemental Tables 1 and 2. Baseline lean body mass and nadir CD4+ count were positively associated with PCF density change, while duration of ART and hs-CRP were inversely associated with density change over 96 weeks.

Discussion

Pericardial fat volume and density were independently related to insulin resistance at baseline but did not predict changes in insulin resistance over time in this placebo-controlled trial of rosuvastatin for patients with treated HIV infection. Adjustment for a clinical measure of total body adiposity (BMI) attenuated the relationship of HOMA-IR with PCF volume, but PCF density remained associated. Additionally, we describe differential associations of PCF volume and density with markers of inflammation and immune activation and with the legacy effects of a longer duration of ART/PI use and lower nadir CD4+ count. Finally, rosuvastatin therapy was not associated with change in PCF volume or density.

As reported previously, rosuvastatin 10mg daily significantly increased fasting insulin levels and HOMA-IR compared to placebo in SATURN-HIV[10]. Only 3 people (1 statin; 2 placebo), however, developed a fasting glucose >126 mg/dL by week 96[10]. In this current study, we sought to further explore whether PCF volume and density were related to the observed changes in insulin resistance. Since PCF measures were only associated with HOMA-IR at baseline and not over time, they are more likely markers rather than causes of insulin resistance.

Ours is the first study to evaluate the radiodensity of PCF in patients with treated HIV infection. We confirm cross-sectional and longitudinal findings from the general population that fat density on CT is inversely associated with cardiometabolic risk[11–13] and further extend these findings to a population of HIV infected patients. Our observation that baseline PCF density and changes over time are inversely correlated with ART and PI duration and positively associated with nadir CD4+ T-cell count may reflect persistent subclinical fat abnormalities in patients who have a legacy of long-standing, more-severe HIV-infection and who have been exposed to toxic ART regimens in the past. These data complement prior studies associating PCF volume with longer duration of ART[14,15] and extent of CD4+ recovery[16].

What does the radiodensity of a fat depot ultimately tell us about the tissue characteristics? Mean CT attenuation of adipose tissue is strongly and inversely correlated with visceral adipocyte diameter ($r = -0.76$, $p<0.001$) in non-human primates[17]; however, radiodensity may also be determined by other tissue characteristics such as vascularity[18,19]. Larger, less dense, and poorly vascularized adipocytes may experience more oxidative stress leading to metabolic dysfunction and production of pro-inflammatory adipocytokines[19]. Importantly, however, there may be significant regional variation of adipose tissue characteristics, particularly within the pericardium[20], and this may be reflected in regional variation of radiodensity[21]. Future studies in the HIV+ and general populations should consider more granular characterization of PCF volumes and radiodensity by location within the pericardium.

Fat abnormalities in persons living with HIV have been associated with inflammation and immune activation. In our study, IL-6, sTNF-RI, cystatin C, and sCD163 were most strongly related to PCF volume and/or density, while cellular markers of immune activation were not.

We extend our prior study of PCF volume[3] to show that PCF density correlates with these biomarkers in the opposite direction. One interesting marker of monocyte activation—sCD163—was further related to insulin resistance independent of PCF volume or density. Soluble CD163 is associated with both obesity [22] and insulin resistance [23] in the general population. Because of consistently observed associations of fat volume and density with IL-6, sTNF-RI, sCD163, and cystatin C, future studies of fat in HIV might focus on these soluble markers.

As a secondary analysis of a randomized trial, our results should be considered hypothesis generating. Nonetheless, our study has many strengths including the longitudinal design and robust characterization of inflammation and immune activation markers. The use of CT allowed us to characterize fat radiodensity in addition to volume; however, our methods did not distinguish between epicardial and intra-myocardial fat as some MRI studies of HIV have done[15]. As we have previously reported[4], there was ~20% attrition over 96 weeks in this trial. Although this reduced study power, it is unlikely to have introduced substantial bias since baseline characteristics remained similar among those with complete 96-week data. We performed a fair number of statistical tests, but since this was a hypothesis generating study, we chose not to adjust p-values for multiple comparisons. Our study was predominantly male and African American. Finally, although our study was designed to include subjects with higher levels of baseline inflammation, our results may not be generalizeable to HIV-infected patients without chronic inflammation; however, most patients with treated HIV infection have some level of residual inflammation and less than 10% of screened subjects were excluded because they failed to meet our inflammation entry criteria[4].

In conclusion, both quantity and quality (i.e. density) of PCF are differentially related to insulin resistance and inflammation in subjects with treated HIV infection. This study focused on the relationship between PCF and markers of systemic metabolic disease and inflammation. Future studies should explore PCF density as a marker of subclinical coronary and structural heart disease risk in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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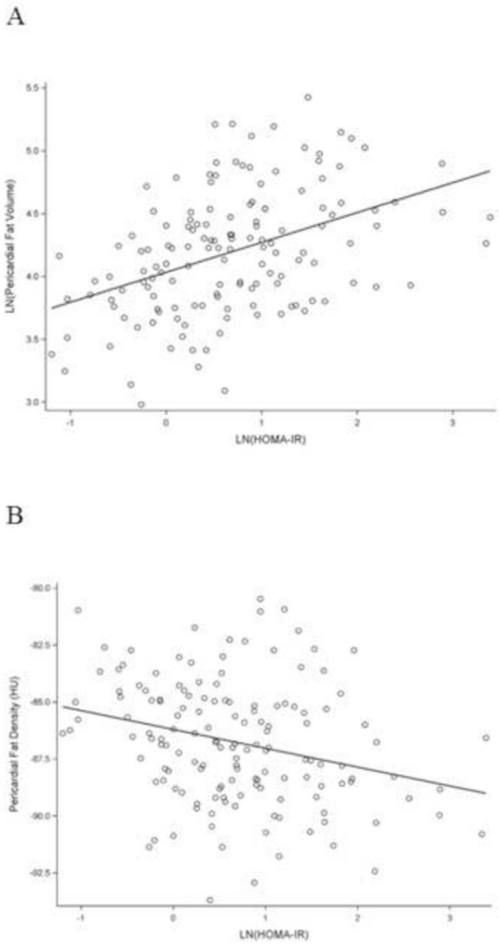

Figure 1.

At baseline, insulin resistance correlated positively with (A) pericardial fat volume [r = 0.432, p=<0.001] and negatively with (B) pericardial fat density [r= −0.274, p<0.001]. Pericardial fat volume and homeostatic model assessment of insulin resistance (HOMA-IR) were log-transformed prior to analyses. HOMA-IR, homeostatic model assessment of insulin resistance; HU, Hounsfield Units.

Figure 2A

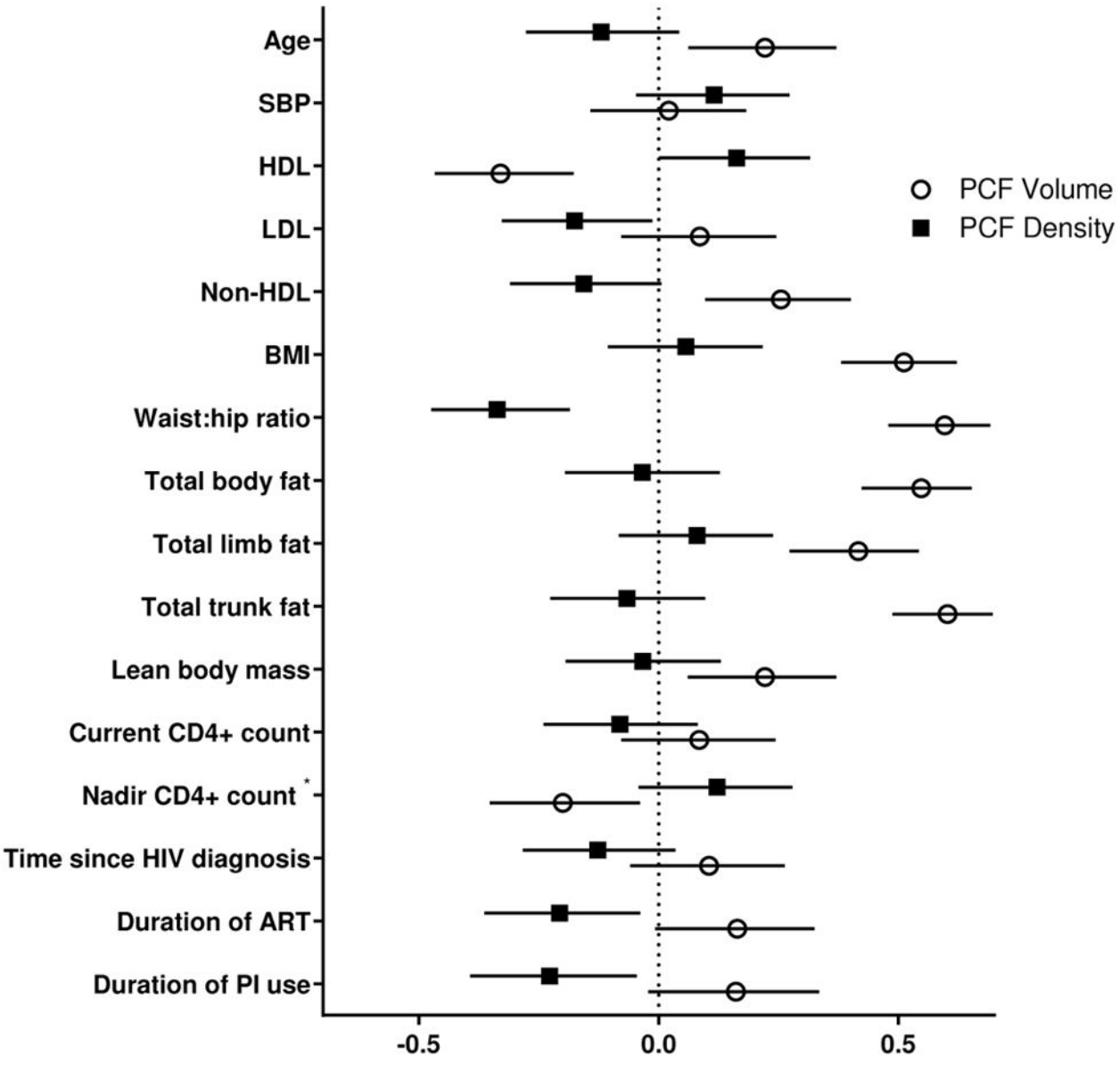

Figure 2B

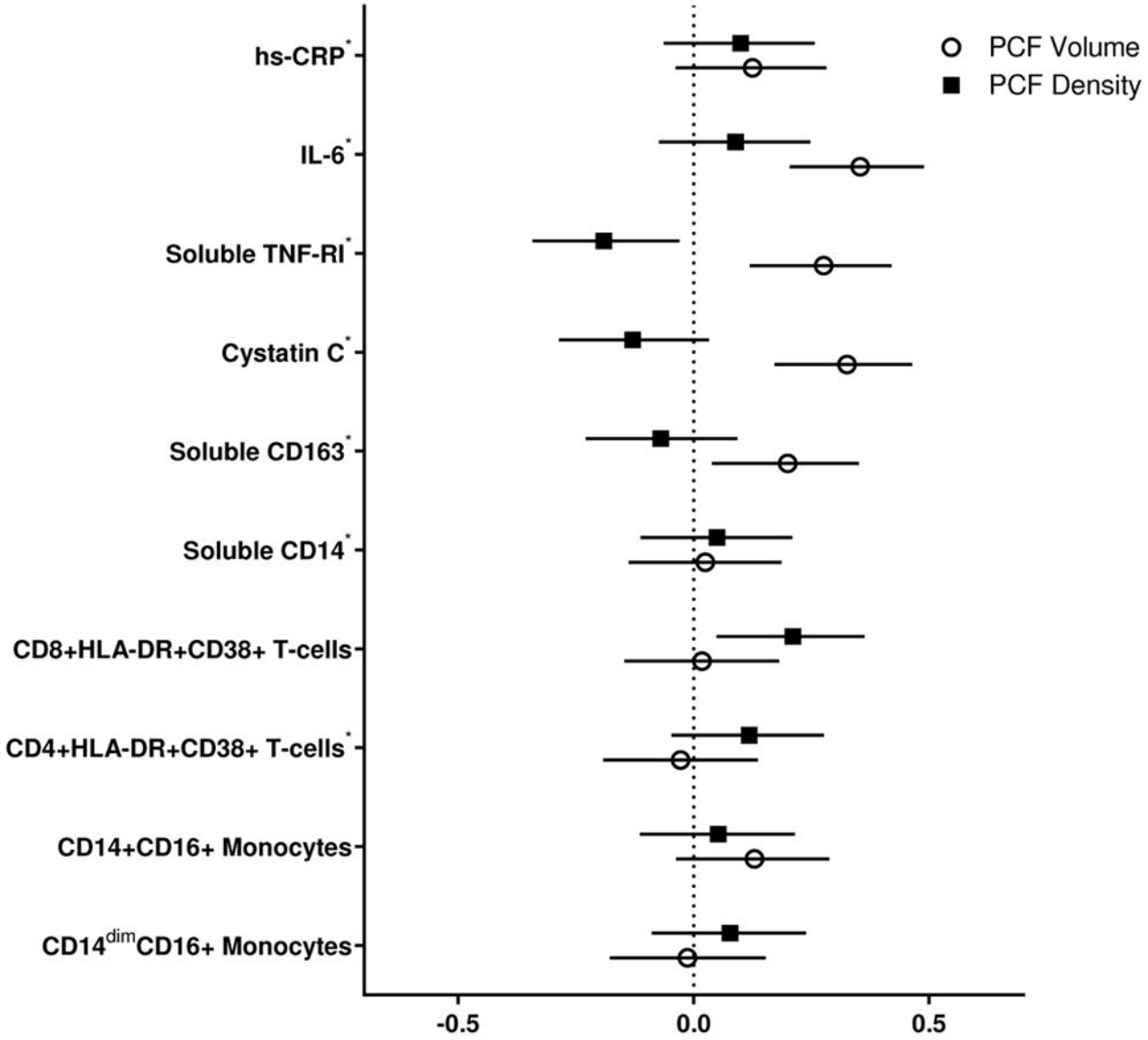

Figure 2.

Correlation of natural logarithm of pericardial fat volume and density with (A) baseline clinical variables, body composition, and HIV parameters and (B) markers of inflammation and immune activation. The plotted point estimates for volume (open circle) and density (closed square) represent the Pearson correlation coefficient with 95% confidence interval. * = Non-normally distributed variables were log-transformed prior to analyses. Nadir CD4+ T-cell count was defined as the lowest recorded CD4+ count in the subject's medical record. ART, antiretroviral therapy; BMI, body mass index; HDL, high density lipoprotein; hs-CRP, high sensitivity C-reactive protein; HLA, human leukocyte antigen; IL-6, interleukin-6;

LDL, low-density lipoprotein; PCF, pericardial fat; SBP, systolic blood pressure; TNF-RI, tumor necrosis factor alpha receptor 1.

Table 1

Subject characteristics by category of pericardial fat (PCF) volume and density

	Low PCF volume High PCF density* (N=49)	Low PCF volume Low PCF density (N=25)	High PCF volume High PCF density (N=25)	High PCF volume Low PCF density (N=48)
Age (years)	46 (40, 49)	44 (34, 52)	47 (41, 53)	49 (41, 54)
Male	73%	84%	68%	85%
African American	86%	64%	64%	54%
HIV Duration (years)	10 (6, 15)	12 (5, 17)	11 (6, 19)	13 (7, 19)
Current CD4+ Count (cells/μl)	559 (425, 734)	589 (418, 893)	688 (441, 885)	640 (449, 861)
Nadir CD4+ Count (cells/μl)	214 (117, 317)	183 (127, 308)	188 (95, 253)	150 (51, 276)
HIV-1 RNA ≤48 copies/ml	67%	80%	80%	81%
Antiretroviral Therapy Duration (years)	4 (2, 8)	8 (4, 12)	5 (3, 9)	7 (4, 10)
Current Protease Inhibitor Use	37%	76%	44%	50%
Protease inhibitor duration (years)	2 (0.3, 4)	5 (3, 9)	4 (0, 8)	4 (0.2, 9)
Body Mass Index (kg/m^2)	24 (22, 27)	26 (23, 29)	34 (26, 41)	28 (26, 32)
Total Limb Fat (kg)	6.2 (3.3, 10.6)	7.9 (4.7, 11.2)	16.0 (6.4, 21.0)	10.5 (7.2, 13.0)
Total Trunk Fat (kg)	7.7 (4.5, 11.5)	11.9 (9.0, 13.9)	20.0 (12.8, 25.1)	15.6 (12.3, 19.0)
Systolic Blood Pressure (mmHg)	120 (109, 132)	122 (110, 132)	118 (112, 128)	122 (113, 131)
Anti-hypertensive Medication Use	22%	8%	24%	35%
High Density Lipoprotein Cholesterol (mg/dL)	56 (43, 63)	49 (40, 54)	39 (33, 53)	42 (35, 53)
Low Density Lipoprotein Cholesterol (mg/dL)	87 (70, 107)	102 (88, 122)	105 (85, 116)	97 (84, 114)
Homeostatic Model Assessment of Insulin Resistance ≥ 2.5	22%	36%	44%	47%
Current Smoking	69%	44%	80%	58%
Framingham Score (% 10-year risk)	2 (1, 6)	3 (1, 5)	4 (2, 8)	6 (2, 9)
Coronary Artery Calcium Score 1 – 100	24%	16%	32%	33%
Coronary Artery Calcium Score > 100	10%	8%	8%	10%

*Low is <median and high is ≥median. Median PCF volume = 67.75; Median PCF density = −86.83

Continuous variables are presented as median (interquartile range); categorical variables as a percentage

Table 2

Linear mixed model of the relationship between pericardial fat and insulin resistance.

	HOMA-IR†			
	Beta	**95% CI**		**P-value***
Baseline variables				
Pericardial fat volume (ml)†	0.148	−0.113	0.412	0.264
Pericardial fat density (HU)	**−0.067**	**−0.108**	**−0.026**	**0.001**
Treatment (statin vs. placebo)	−0.079	−0.278	0.122	0.429
Non-HDL (mg/dl)	0.002	−0.001	0.005	0.187
Metabolic syndrome (yes vs. no)	**0.503**	**0.254**	**0.725**	**<.0001**
Body Mass Index (kg/m^2)	**0.037**	**0.020**	**0.055**	**<.0001**
Soluble CD163 (ng/ml)†	**0.487**	**0.253**	**0.722**	**<.0001**
Soluble CD14 (ng/ml)†	−0.220	−0.496	0.048	0.123
Current smoker (yes vs. no)	**−0.247**	**−0.428**	**−0.064**	**0.010**
Longitudinal variables				
Time (weeks)	**0.056**	**0.008**	**0.099**	**0.018**
weeks * treatment	0.002	0.000	0.005	0.106
weeks * PCF volume†	0.001	−0.002	0.004	0.569
weeks * PCF density	0.000	0.000	0.001	0.095
weeks * soluble CD163†	−0.003	−0.006	0.000	0.076

* = Bolded values represent p <0.05.

† = Non-normally distributed variables were log-transformed prior to analyses. CI, confidence interval; HDL, high-density lipoprotein; HOMA-IR, Homeostatic model assessment of insulin resistance; HU, Hounsfield Units; PCF, pericardial fat.