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Authors

Ketlogetswe, Kerunne S
Post, Wendy S
Li, Xiuhong
et al.

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Lower Adiponectin is Associated with Subclinical Cardiovascular Disease among HIV-infected Men

Kerunne S. KETLOGETSWE, **Wendy S. POST**, **Xiuhong LI**, **Frank PALELLA Jr**, **Lisa P. JACOBSON**, **Joseph B. MARGOLICK**, **Lawrence A. KINGSLEY**, **Mallory D. WITT**, **Adrian DOBS**, **Matthew J. BUDOFF**, and **Todd T. BROWN**
Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD (KSK, WSP); Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins University School of Medicine, Baltimore, MD (AD, TTB); Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (WSP, XL, LJ); Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health (JBM); Division of Infectious Diseases, Northwestern University Feinberg School of Medicine, Chicago, IL (FP); Department of Infectious Diseases and Microbiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA (LAK); Division of HIV Medicine, Harbor UCLA Medical Center, Torrance, CA (MDW); Harbor-UCLA LA BioMed CT Reading Center, Torrance, CA (MJB)

Abstract

Objective—To examine if altered levels of adipokines, adipose-derived peptides associated with myocardial infarction in the general population, may contribute to subclinical coronary atherosclerosis in HIV-infected persons.

Design—Nested cohort study.

Methods—We studied HIV-infected(HIV+) and HIV-uninfected(HIV−) men in the Multicenter AIDS Cohort Study with noncontrast CT to measure coronary artery calcium and regional adiposity; 75% additionally underwent coronary CT angiography to measure plaque composition and stenosis. Adiponectin and leptin levels were assessed. Multiple regression models were used to assess associations between adipokine levels and HIV disease parameters, regional adiposity, and plaque adjusted for age, race, HIV serostatus and CVD risk factors (RFs).

Results—Significant findings were limited to adiponectin. HIV+ men (n=493) had lower adiponectin levels than HIV− men (n=250) after adjusting for CVD RFs ($p<0.0001$), which became non-significant after adjustment for abdominal visceral and thigh subcutaneous adipose tissue. Among HIV+ men, lower adiponectin levels were associated with higher CD4+ T cell counts ($p= 0.004$), longer duration of antiretroviral therapy ($p= 0.006$) and undetectable HIV RNA levels ($p = 0.04$) after adjusting for age, race and CVD RFs; only CD4+ cell count remained significant after further adjustment for adipose tissue. In both groups, lower adiponectin levels

Correspondence and requests for reprints to: Todd T. Brown, MD, PhD, Division of Endocrinology, Diabetes, & Metabolism, Johns Hopkins University, 1830 East Monument Street, Suite 333, Baltimore, MD 21287. 410-502-6888. tbrown27@jhmi.edu.

WSP, FP, LAK, MJB contributed to study concept and design.
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were associated with increased odds of coronary stenosis > 50% (p <0.007). Lower adiponectin levels were associated with increased extent of plaque in HIV+ and of mixed plaque in HIV− men.

Conclusions—Adiponectin levels were lower in HIV-infected men and related to the severity of subclinical atherosclerosis, independent of traditional CVD risk factors.

Keywords

Adipokines; adiponectin; leptin; heart; subclinical coronary atherosclerosis; metabolic side effects of HIV infection; coronary CT angiography; cardiac CT

INTRODUCTION

In the era of highly active antiretroviral therapy (HAART), an increased risk of atherosclerotic heart disease has been observed in HAART-treated HIV-infected compared to HIV-uninfected persons.[1, 2] Proposed mechanisms include metabolic abnormalities including insulin resistance, dyslipidemia and diabetes mellitus, which may be partially mediated through an alteration of adipokine homeostasis.[3]

Adiponectin and leptin are adipose-derived proteins that impact insulin resistance and vascular inflammation. Adiponectin increases AMP-kinase and PPAR-α activities, fatty acid oxidation, and glucose uptake, leading to increased insulin sensitivity.[4] Leptin influences the regulation of energy balance and metabolism, and its levels fall when energy intake is limited and energy stores in fat are declining.[5] In early atherosclerosis, leptin initiates leukocyte and macrophage recruitment to the endothelial wall. Lower adiponectin levels and higher leptin levels are associated with an increased risk for myocardial infarction (MI) and stroke in the general population, independent of obesity and traditional CVD risk factors.[6–9]

Adiponectin and leptin may be dysregulated in HIV-infected persons, through either direct effects of chronic HIV infection or effects of HAART. In untreated HIV infection, lower adiponectin levels are associated with increased plasma HIV RNA concentrations; after HAART initiation, adiponectin levels increase initially, but can fall below pre-HAART levels with the development of lipodystrophy.[10–12] Because leptin levels are determined by total body fat mass (i.e., irrespective of fat distribution), HIV-infected persons with lipodystrophy have leptin levels similar to HIV-infected persons without lipodystrophy and to HIV-uninfected persons with similar total body fat mass.[13, 14] HIV-associated lipodystrophy that is accompanied by lower total body fat mass (i.e. lipoatrophy) has been associated with lower leptin levels compared to HIV- uninfected persons.[15] The relationship between adiponectin and leptin and cardiovascular disease among HIV-infected persons, however, has not been determined.

We conducted a cross-sectional analysis from the cardiovascular substudy of the Multicenter AIDS Cohort Study (MACS) to determine if levels of adiponectin and leptin: 1) were affected by HIV serostatus; 2) were differentially affected by regional adiposity among HIV-infected versus HIV-uninfected men; and 3) were associated with degree of HIV disease control and severity among HIV-infected men. We then sought to determine if the presence and extent of subclinical coronary plaque were affected by adiponectin and leptin levels independent of traditional CVD risk factors.

MATERIALS AND METHODS

Participants

MACS is an ongoing prospective observational study of men who have sex with men (MSM) in 4 sites in the United States: Baltimore, MD/Washington D.C., Chicago, IL, Los Angeles, CA, and Pittsburgh, PA.[16] MACS participants return semi-annually for a standardized interview, clinical evaluation and laboratory tests. Participants between the ages of 40–70 years, who weighed less than 300 pounds and with no history of prior cardiac surgery, percutaneous transluminal coronary angioplasty or stent placement were invited to participate in a substudy in which a non-contrast cardiac computed tomography (CT) scan to evaluate coronary artery calcium (CAC) was performed. Coronary CT angiography was also performed on consenting men not allergic to iodinated contrast media, without atrial fibrillation, without estimated glomerular filtration rate <60 ml/min/1.73 m^2 at any MACS examination or a urine protein greater than 3g/g creatinine. The study protocol was approved by the Institutional Review Board at each site, and all participants gave informed consent to participate.

Laboratory Analysis

Blood samples were collected at the CT study visit. Adiponectin and leptin were measured at the University of Vermont Laboratory for Clinical Biochemistry Research Lab (Burlington, VT) by enzyme-linked immunosorbent assays (R & D Systems, Minneapolis, MN) on plasma samples that had been stored at −70°C. The lower limit of detection for adiponectin assay was 390 ng/mL with an inter-assay coefficient of variation of 5.3–10.8%; for leptin the corresponding values were 1300 pg/mL and 5.9–6.8%. Fasting glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation when triglyceride levels were < 400 mg/dL[17] and was directly measured for men with triglyceride levels > 400mg/dL or on non-fasting samples. Serum creatinine was measured within 30 days of the CT scan and the estimated glomerular filtration rate was calculated using the MDRD equation.[18]

Other Measurements

Age, race, tobacco use, and antihypertensive and lipid medication use were assessed by self-report. Blood pressure (BP), height and weight were measured using standardized protocols. Hypertension was defined as systolic BP >140 mmHg or diastolic BP >90 mmHg, or self-reported use of an antihypertensive medication. Diabetes was defined as fasting serum glucose ≥ 126 mg/dL or use of medications to treat hyperglycemia. Among HIV-infected men, longitudinal data collected at MACS study visits included plasma HIV RNA levels, CD4+ T-lymphocyte count (most recent and nadir values used in the analysis) and duration of HAART use [16]. A history of AIDS was determined by medical record confirmation or self-reports. HAART was defined based on the DHHS/Kaiser Panel guidelines as reported use of three or more antiretroviral medications, one of which had to be a protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, one of the nucleoside reverse transcriptase inhibitors abacavir or tenofovir, an integrase inhibitor, or an entry inhibitor.[19]

Imaging Protocols

Non-contrast CT and coronary CT angiography were performed using multi-detector scanners at each site. Visceral adipose tissue (VAT) area was quantified from a single CT slice obtained at the level of the umbilicus, as previously described.[20] The amount of abdominal subcutaneous adipose tissue (SAT) was calculated by subtracting VAT fat from total abdominal fat. Thigh SAT was measured from a single slice at the mid-thigh. Body

composition CT scans were read centrally (Los Angeles Biomedical Research Institute [LA Biomed], Torrance, CA).

A non-contrast cardiac CT scan was performed to measure CAC and CAC scores were computed using the Agatston method.[21] Eligible participants underwent coronary CT angiography using radiation dose reduction techniques, as previously described [22]. The images were reviewed by 2 experienced observers unaware of the participant's clinical information. Plaque grading was performed according to the American Heart Association's 15-segment coronary artery classification grading system.[23] Within each segment, plaques with calcification comprising ≥ 50% of the plaque area were classified as calcified plaques, plaques with >0 but < 50% calcification were considered mixed plaques, and lesions without any calcium were classified as noncalcified plaques. Plaque burden was scored as none (0), mild (1), moderate (2) or severe (3). Semiquantitative measures of overall coronary artery plaque burden were calculated. The total calcified plaque (CP) score, non-calcified plaque (NCP) score, and mixed (i.e., containing both calcified and non-calcified plaque) plaque (MP) score were the sum of the scores of all identified calcified, noncalcified and mixed plaques, respectively, in the coronary segments. The total plaque score (TPS) was the sum of the CP, MP and NCP scores and thus represents the summary measure of overall plaque burden.[24] Segment stenosis was defined as 0= no plaque, 1= 1–29% (minimal) stenosis, 2= 30–49% (mild) stenosis, 3=50–69% (moderate) stenosis, or 4= ≥ 70% (severe) stenosis.

Statistical Analysis

Continuous variables are presented as means and standard deviations or medians and interquartile ranges (IQR:25%,75%). Comparisons between HIV-infected and HIV-uninfected men were performed using the Wilcoxon rank-sum test. Proportions were compared using the χ^2 test. The distributions of adiponectin and leptin were non-normal and therefore the values were log-transformed. Crude associations of adiponectin and leptin levels with categorical variables were assessed using the Kruskal-Wallis rank test and for continuous variables Pearson correlations were obtained. To evaluate whether HIV infection was associated with differences in adipokine levels, the first regression analysis included each adipokine as the dependent variable. Since 4 adipokine values were above the limit of detection and 82 leptin values were below the limit of detection, linear regression with right or left censoring was used to assess the association of each adipokine (log-transformed) with HIV serostatus, initially adjusting for age and race, then additionally for CV risk factors including BMI, hypertension medication use, systolic blood pressure among those who were not on hypertension medications, lipid medication use, total and HDL cholesterol among those who did not use lipid-lowering medications, diabetes medication use, fasting glucose levels among those who did not take hyperglycemic medications, and cumulative pack years of tobacco use. We then additionally adjusted for VAT and thigh SAT. To assess whether adipokine levels were influenced by HIV RNA and CD4+ T-lymphocyte counts among HIV-infected men, linear regression analysis was performed with each adipokine as the dependent variable and the above-mentioned HIV-related parameters, adjusting for CV risk factors and additionally for fat variables.

To evaluate whether adipokine levels were determinants of plaque presence or severity, we performed regression analyses with the different plaque measures as the dependent variables and the adipokine levels as the independent variables. Logistic regression was used to assess the relationship of each adipokine with the presence of CAC, each plaque type and coronary artery stenosis > 50%, and linear regression to assess the association with plaque extent among men with plaque present, using the same CV risk factor adjustments as above. For plaque outcomes we present results stratified by HIV serostatus. For multivariable models, missing data were imputed five times based on the distribution of covariates (age, race/ethnicity, HIV-serostatus, BMI, cumulative pack years of tobacco use, hypertension

medications, systolic BP, diabetes medications, fasting glucose, lipid lowering medications, HDL and total cholesterol) using a Markov chain Monte Carlo method, assuming multivariable normality.[25] Values for the following number of men were missing and imputed for multiple regression analyses: hypertension medication use (4), diabetes medication use (4), smoking pack-years (3), total and HDL cholesterol (3), systolic blood pressure (20), and fasting glucose (7). Statistical analyses were performed using SAS 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

There were 743 men (493 HIV-infected and 250 HIV-uninfected men) who underwent cardiac CT scanning and who had measurements of adiponectin and leptin. Of these, 555 (74.7%) also underwent coronary CT angiography (356 HIV-infected, 199 HIV-uninfected). HIV-infected men were younger, more likely to be black, actively use tobacco, and had higher fasting glucose, LDL-cholesterol and triglycerides, and lower HDL-cholesterol concentrations (Table 1). HIV-infected men had less abdominal and thigh SAT, but similar amounts of VAT.

Adipokine Associations with HIV status

HIV-infected men had lower median levels of both adiponectin and leptin than HIV-uninfected men; these differences were significant for adiponectin and borderline significant for leptin. After adjusting for age and race, the difference in adiponectin levels by HIV serostatus remained significant ($\beta = -0.16$, $p=0.003$), while the difference in leptin levels did not ($p= 0.12$). HIV serostatus-based differences in adiponectin levels persisted after adjusting for CV risk factors ($\beta = -0.15$, $p= 0.004$), but were attenuated by adjustment for either abdominal SAT or VAT ($\beta = -0.10$, $p=0.05$; and $\beta = -0.10$, $p=0.06$; respectively), and no longer existed after adjustment for thigh SAT ($\beta = 0.006$, $p=0.91$).

Adipokine Associations with Adipose Tissue Volumes

Associations between adipokine levels and adipose tissue volumes in unadjusted models stratified by HIV serostatus are shown in Table 2. Adiponectin levels had negative correlations with all three adipose tissue volumes in HIV-uninfected men and were negatively associated with VAT in HIV-infected men; in contrast, among HIV-infected men, adiponectin was not associated with abdominal SAT and was positively associated with thigh SAT. This led to a significant interaction between HIV serostatus and abdominal SAT for adiponectin level ($p= 0.02$), but this interaction was no longer significant after adjusting for CV risk factors ($p= 0.17$). The interaction by HIV serostatus for adiponectin and thigh SAT was also statistically significant in the fully adjusted models ($p= 0.0001$). Leptin was strongly positively correlated with all adipose tissue volumes in both HIV-infected and uninfected men.

Adipokine Associations with Measures of HIV disease Activity

Among HIV-infected men, after adjusting for CV risk factors, lower adiponectin levels were significantly associated with higher CD4+ T-cell counts, longer duration of HAART, and undetectable HIV RNA levels (Table 3). When all HIV disease variables were included, the association with undetectable HIV RNA levels was no longer significant (Model 3). After additionally adjusting for VAT and thigh SAT, HAART duration was no longer significant (Model 4).

Leptin levels were significantly associated with higher CD4 counts and with undetectable HIV RNA. These associations became insignificant after adjustment for CV risk factors, but a history of AIDS became significant, and this significance persisted in a multivariable

model including all HIV-clinical variables and after additional adjustment for VAT and thigh SAT.

Adipokines and Subclinical Coronary Atherosclerosis

Presence of Plaque—In models including the combined cohort (data not shown) and those stratified by HIV serostatus (Table 4), adiponectin levels were not associated with the presence of CAC or plaque of any subtype in the fully adjusted models. In contrast, lower adiponectin levels were strongly associated with presence of stenosis of 50% or more (OR per 1 log decrease in adiponectin levels 1.82 [1.18–2.78], p=0.007) among the entire cohort in the fully adjusted model. There was no interaction by HIV serostatus. In analyses stratified by HIV serostatus (Table 4), these associations remained statistically significant among both HIV-infected and -uninfected men after further adjustment for CV risk factors. Further adjustment for both VAT and thigh SAT yielded similar results (OR 1.32 [2.22–3.85], p=0.03 and OR 2.63 [1.11–6.25], p=0.003, respectively) (data not shown). Among HIV-infected men, further adjustment for HIV clinical variables (CD4+ T cell count, duration of HAART and an undetectable HIV RNA levels) did not affect the association between lower adiponectin and coronary stenosis > 50% (OR 1.72 [1.05–2.86], p=0.03). Leptin levels were not associated with the presence of plaque or coronary stenosis > 50%.

Extent of Plaque—Lower adiponectin levels were significantly associated with greater extent of NCP (β= 0.16, p= 0.003), MP (β= 0.27, p=0.002) and TP extent (β=0.28, p < 0.0001) in the whole cohort, after adjusting for age, race and serostatus. All of these associations remained statistically significant after further adjusting for CV risk factors. There was an interaction in the adiponectin and MP association by HIV serostatus: the inverse association of adiponectin to MP was greater and statistically significant among HIV-uninfected men (p for interaction=0.04 and 0.05 in age/race and CV risk factor-adjusted models, respectively) (Table 5). Lower adiponectin levels were associated with increased TP only among HIV-infected men, and further adjustment for HIV clinical variables and fat depots did not attenuate this association (β 0.21, p= 0.01). In contrast, leptin was not associated with plaque presence or extent in fully adjusted models in either HIV-infected or –uninfected men.

DISCUSSION

In this cross-sectional analysis, we observed lower serum adiponectin levels in HIV-infected men, and that lower levels of adiponectin were associated with the presence of clinically significant coronary artery stenosis and with the extent of subclinical coronary atherosclerosis. While lower serum adiponectin was associated with increased VAT regardless of HIV serostatus, the relationship between adiponectin and thigh fat differed by HIV-status, with lower adiponectin being associated with increased thigh SAT among HIV-uninfected men and lower thigh SAT in the HIV-infected men. Given the lower levels of adiponectin in the HIV-infected men studied, most of whom had undetectable plasma HIV RNA levels as a result of HAART, these findings suggest that lower levels of adiponectin may, at least in part, contribute to or mediate the higher prevalence of coronary artery disease that is seen among HAART-treated HIV infected persons compared to HIV-uninfected persons. To our knowledge, this is the first report that identifies associations between lower adiponectin levels and CTA measures of subclinical coronary atherosclerosis among HIV-infected patients.

In the general population, data regarding the association between adiponectin and measures of subclinical coronary atherosclerosis have been mixed. Low plasma adiponectin levels were suggested to predict short term CAC progression independently of other cardiovascular

risk factors in some, [26] but not all studies.[27, 28] Studies using CTA to examine the relationship between adiponectin and plaque composition have been restricted to those with clinical symptoms of CAD and have found associations between low adiponectin levels and the extent of noncalcified plaque.[29, 30]

In our population of asymptomatic individuals, we did not detect and association between adiponectin and the presence or extent of a specific plaque type among the HIV-infected men. Rather, we found that lower adiponectin levels were associated with total plaque extent and the presence of coronary stenosis >50%, suggesting that adiponectin may be more important in prevention of plaque progression rather than plaque formation in this population.

To our knowledge, there has been only one other study that has examined the relationship of adiponectin to subclinical coronary atherosclerosis among HIV-infected persons, which, similar to our study, found no association between adiponectin and CAC.[31] Our study differs from this study in that we included an HIV-uninfected group, evaluated a larger number of patients, and evaluated coronary plaque using Coronary CT angiography in addition to non-contrast CT.

It is unclear whether our findings regarding the association between lower adiponectin and subclinical atherosclerosis also suggest that lower adiponectin levels will predict cardiovascular events among HIV-infected patients. Associations between adiponectin and cardiovascular disease events in other studied populations have been inconsistent. In the Health Professionals Follow-up study, higher plasma adiponectin concentrations were associated with a lower risk of myocardial infarction in men.[32] In contrast, other studies, including a meta-analysis of 7 prospective studies failed to show an association between adiponectin and incident coronary heart disease.[33, 34] Further studies examining the relationship between adiponectin and cardiovascular events are warranted.

In contrast to our findings with adiponectin, we did not find any evidence of associations between subclinical atherosclerosis and leptin, regardless of HIV serostatus. While higher leptin levels have been associated with CV events in the general population, the association of leptin with subclinical atherosclerosis is unclear.[35, 36] Our results are in agreement with another CTA study where leptin was not associated with plaque presence or extent.[37]

In our population, adiponectin levels were lower among HIV-infected men compared to HIV-uninfected men, even after adjustment for CV risk factors, including BMI. However, after additional adjustment for thigh SAT, these differences by HIV-serostatus were no longer apparent. We also found that the direction of the association between thigh SAT and adiponectin differed by HIV-serostatus. Lower adiponectin concentrations were associated with lower thigh SAT in HIV-infected men, but higher thigh SAT in HIV-uninfected men, consistent with previous studies.[13, 14] We hypothesize that the lower thigh SAT in this heavily ART-treatment experienced population is indicative of persistent ART-induced lipoatrophy and that, despite the use of modern ART regimens, relative hypoadiponectinemia is present, which may increase CVD risk.

Among HIV-infected men, higher current CD4+ cell count, a longer duration of HAART, and an undetectable HIV RNA level were associated with lower adiponectin levels, after adjusting for CV risk factors. These HIV clinical variables are indicative of successfully treated HIV-infection, suggesting that even if HAART may normalize some of the HIV-associated changes in adiponectin, lower levels persist, possibly as a consequence of specific HAART therapies received. After further adjustment for VAT and SAT, only current CD4+ cell count remained significant, suggesting that the association of the other HIV-related factors may be reflective of prior thymidine analogue exposure resulting in lipoatrophy.

Leptin levels, in contrast, did not vary by HIV-serostatus and were closely related to the amount of SAT and VAT in both HIV-infected and uninfected men. Comparisons of leptin levels by HIV serostatus across different studies have been inconsistent, likely due to differences in study design and the selection of HIV-infected participants studied, usually based on a clinical definition of lipodystrophy.[14, 15]

There are many strengths of our study including a large sample size with contemporary HIV-uninfected controls with similar CVD risk factors and behaviors. This study used technology that allowed for more detailed characterization of coronary atherosclerosis beyond calcium scoring. However, as a cross sectional study, no inference can be made regarding the causality of lower adiponectin levels and increased subclinical coronary atherosclerosis. Our findings are consistent with, but do not prove, the hypothesis that HIV serostatus or the associated treatments affect adiponectin levels, and that these changes in adiponectin levels affect the progression of coronary plaque. Adipokine values may vary over time in response to HAART initiation and with different types of HAART. Our study only includes men and thus our findings may not be generalizable to women. Both HIV-infected and –uninfected women have been shown to have significantly higher adiponectin and leptin levels than similar men. We may have failed to detect an association between leptin and subclinical atherosclerosis because of lower leptin levels in men.[38]

In conclusion, we found that HIV-infected men have lower levels of serum adiponectin, and that levels of this adipokine are inversely associated with coronary stenosis > 50% and increasing total coronary plaque in men with plaque present. Prospective studies are needed to determine whether lower adiponectin levels are associated with increased major cardiovascular events among HIV-infected men. In addition, our findings suggest that treatments to increase adiponectin may decrease atherosclerotic coronary heart disease in HIV-infected individuals.

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Table 1

Demographic, clinical characteristics and serum levels in the study population.

	HIV + N= 493	**HIV− N= 250**	**p-value**
Age (y) mean (SD)	53.4 ± 6.0	56.0 ± 6.8	<0.0001
Race, N (%)			0.004
Black	172 (34.9)	64 (25.6)	
White	268 (54.4)	168 (67.2)	
Hispanic/Other	53 (10.8)	18 (7.2)	
Body Mass Index (kg/m^2) mean (SD)	26.0 (4.7)	27.2 (4.7)	0.001
Current smoker (%)	154 (31.7)	49 (19.7)	0.001
History of hypertension[1] (%)	236 (49.4)	114 (46.5)	0.47
Antihypertensive medication use (%)	179 (36.5)	82 (32.9)	0.33
History of diabetes[2] (%)	64 (13.1)	21 (8.5)	0.06
Diabetes medication use (%)	48 (9.8)	17 (6.8)	0.18
Fasting glucose (mg/dL) median (IQR)	98 (90–107)	96 (87–104)	0.03
Cholesterol level (mg/dL) median (IQR)			
Total	189 (163–217)	194 (167–219)	0.13
HDL	45 (37–55)	50 (42–59)	<0.0001
LDL	106 (82–130)	114 (93–141)	0.0001
Triglycerides (mg/dL) median (IQR)	148 (98–215)	106 (77–168)	<0.0001
Lipid lowering medication use (%)	178 (36.1)	82 (32.8)	0.37
Adiponectin (ng/mL) median (IQR)	5911 (3699–9725)	6900 (4944–10,628)	<0.001
Leptin (pg/mL) median (IQR)	5272 (2326–10,859)	6086 (3089–11,531)	0.06
Abdominal visceral fat area (cm^2) mean (SD)	166.0 (99.6)	155.7 (92.9)	0.19
Abdominal subcutaneous fat area (cm^2) mean (SD)	199.1 (125.7)	248.7 (126.6)	<0.0001
Thigh subcutaneous fat area (cm^2) mean (SD)	32.6 (28.7)	54.5 (30.8)	<0.0001
Current CD4+ T cell count (cells/mm^3) median (IQR)	597 (414–754)	-	
Nadir CD4+ T cell count (cells/mm^3) median (IQR)	238 (129–326)	-	
HAART Duration (years) median (IQR)	12.3 (8.7–14.0)	-	

	HIV + N= 493	HIV− N= 250	p-value
Undetectable HIV RNA (<50 copies/ml) (% of men)	81.7%	-	
Prior AIDS defining illness (%)	15.2%	-	

HDL= high density lipoprotein; LDL= low density lipoprotein

[1] systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 or use of antihypertensive medications.

[2] fasting glucose >126 mg/dl or use of glucose lowering medications.

HAART = highly active antiretroviral therapy.

Table 2

Correlation between plasma adiponectin and leptin levels and body fat depots

	Adiponectin						Leptin					
Fat Depots	**HIV+ N=493**		**HIV − N=250**		**All N=743**		**HIV+ N=493**		**HIV− N=250**		**All N=743**	
	r	**p-value**	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**	**r**	**p-value**
Abdominal Subcutaneous	−0.07	0.11	−0.29	<0.0001	−0.11	0.002	0.79	<0.0001	0.78	<0.0001	0.78	<0.0001
Abdominal Visceral	−0.32	<0.0001	−0.25	<0.0001	−0.30	<0.0001	0.57	<0.0001	0.68	<0.0001	0.60	<0.0001
Thigh Subcutaneous	0.15	0.0009	−0.24	0.0001	0.07	0.07	0.56	<0.0001	0.66	<0.0001	0.58	<0.0001

Unadjusted Pearson correlation coefficients. After adjusting for CV risk factors, significant interaction of adiponectin and thigh subcutaneous fat by serostatus (p= 0.0001).

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Table 3

Adipokine association with HIV clinical variables among 493 HIV-infected men

	Adiponectin		Leptin	
	β estimate (S.E.)	**p value**	**β estimate (S.E.)**	**p value**
CD4+ T cell count (100 cells/mm^3)				
Model 1	**−0.05 (0.01)**	**0.0001**	**0.05 (0.02)**	**0.01**
Model 2	**−0.03 (0.01)**	**0.004**	0.02 (0.01)	0.23
Model 3	**−0.03 (0.01)**	**0.01**	0.02 (0.02)	0.31
Model 4	**−0.03 (0.01)**	**0.02**	0.002 (0.01)	0.87
Nadir CD4+ T cell count (100 cells/mm^3)				
Model 1	−0.02 (0.02)	0.32	0.05 (0.03)	0.08
Model 2	−0.003 (0.02)	0.86	0.008 (0.02)	0.71
Model 3	0.007 (0.02)	0.74	0.02 (0.03)	0.51
Model 4	0.008 (0.02)	0.69	0.02 (0.02)	0.33
Years on HAART				
Model 1	**−0.03 (0.008)**	**0.0006**	0.003 (0.01)	0.83
Model 2	**−0.02 (0.007)**	**0.006**	0.003 (0.009)	0.71
Model 3	**−0.02 (0.007)**	**0.01**	0.003 (0.009)	0.76
Model 4	−0.005 (0.007)	0.44	0.01 (0.008)	0.23
Undetectable HIV RNA level				
Model 1	**−0.26 (0.08)**	**0.002**	**0.27 (0.13)**	**0.04**
Model 2	**−0.15 (0.08)**	**0.04**	0.11 (0.09)	0.27
Model 3	−0.11 (0.08)	0.18	0.09 (0.1)	0.35
Model 4	−0.09 (0.07)	0.23	0.10 (0.08)	0.21
Prior AIDS defining illness				
Model 1	0.08 (0.09)	0.36	−0.12 (0.04)	0.36
Model 2	0.02 (0.08)	0.76	**0.26 (0.1)**	**0.009**
Model 3	0.01 (0.08)	0.86	**0.29 (0.1)**	**0.004**
Model 4	0.02 (0.08)	0.80	**0.22 (0.09)**	**0.01**

Model 1= linear regression for log transformed adipokine, adjusting for age and race

Model 2= Model 1+ CV risk factors

Model 3= Model 2 + all HIV clinical variables

Model 4= Model 3 + visceral adipose tissue + thigh subcutaneous adipose tissue

CV risk factors = Body mass index, cumulative pack years tobacco use, systolic BP, antihypertensive medication use, diabetes medication use, fasting glucose, lipid medication use, total and HDL cholesterol

Table 4

Associations of adiponectin and leptin with the presence of coronary plaque by HIV serostatus after adjustment for age and race (Model 1) and adjustment for age, race, and cardiovascular risk factors (Model 2).

	ADIPONECTIN				**LEPTIN**			
	HIV+		**HIV−**		**HIV+**		**HIV−**	
NONCONTAST CT	**OR (95% CI)**	**P- value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P- value**	**OR (95% CI)**	**P- value**
Coronary artery calcium	N=493		N=250		N=493		N=250	
Model 1	1.18 (0.89–1.56)	0.24	1.09 (0.67–1.75)	0.74	1.07 (0.88–1.31)	0.48	1.24 (0.92–1.67)	0.15
Model 2	1.18 (0.85–1.61)	0.34	0.65 (0.35–11.9)	0.17	1.06 (0.78–1.43)	0.71	0.64 (0.38–1.06)	0.09
CORONARY CT ANGIOGRAPHY	N=356		N=199		N=356		N=199	
Non-calcified plaque								
Model 1	1.22 (0.85–1.75)	0.26	1.52 (0.88–2.56)	0.13	1.27 (0.98–1.65)	0.07	0.98 (0.71–1.35)	0.89
Model 2	1.05 (0.70–1.59)	0.81	1.49 (0.79–2.78)	0.21	1.04 (0.71–1.53)	0.83	0.72 (0.42–1.25)	0.24
Calcified plaque								
Model 1	**1.47 (1.04–2.08)**	**0.03**	0.80 (0.47–1.39)	0.43	1.12 (0.87–1.46)	0.38	1.09 (0.78–1.53)	0.60
Model 2	0.72 (0.49–1.07)	0.11	1.75 (0.88–3.47)	0.11	1.00 (0.68–1.48)	0.99	0.61 (0.33–1.13)	0.11
Mixed plaque								
Model 1	1.25 (0.88–1.79)	0.21	1.25 (0.72–2.17)	0.43	0.92 (0.71–1.19)	0.52	1.18 (0.84–1.65)	0.34
Model 2	1.23 (0.83–1.89)	0.29	0.95 (0.49–1.85)	0.88	0.88 (0.59–1.30)	0.51	0.93 (0.52–1.67)	0.81
Total plaque								
Model 1	1.32 (0.85–2.04)	0.23	1.18 (0.6–2.27)	0.64	1.34 (0.99–1.83)	0.06	1.29 (0.84–1.98)	0.24
Model 2	1.15 (0.69–1.89)	0.60	0.75 (0.33–1.67)	0.48	1.17 (0.74–1.86)	0.50	0.73 (0.37–1.44)	0.36
Stenosis > 50%								
Model 1	**1.82 (1.18–2.78)**	**0.007**	**3.23 (1.52–6.67)**	**0.002**	0.95 (0.68–1.32)	0.76	1.32 (0.86–2.01)	0.20
Model 2	**1.79 (1.11–2.86)***	**0.02**	**2.63 (1.12–6.25)**	**0.03**	1.06 (0.65–1.70)	0.83	0.67 (0.31–1.45)	0.32

Adiponectin values represent OR per 1 log decrease in adiponectin levels. Leptin values represent OR per 1 log increase in leptin levels. Separate logistic regression models Model 1: adjusted for age and race; Model 2: adjusted for age, race, and CV risk factors (Body mass index, tobacco pack years, systolic BP, antihypertensive medication use, diabetes medication use, fasting glucose, lipid medication use, total cholesterol, HDL) * After further adjustment for CD4+ T cell count, duration of HAART and undetectable HIV RNA level: OR per 1 log decrease in adiponectin levels 1.72 (1.05–2.86), p=0.03.

Table 5

Associations between adiponectin and leptin and the extent of coronary plaque among those with plaque present, by HIV serostatus after adjustment for age and race (Model 1) and adjustment for age, race, and cardiovascular risk factors (Model 2)

	ADIPONECTIN				LEPTIN			
	HIV+		HIV−		HIV+		HIV−	
NONCONTAST CT N= 398	**Estimate (S.E.)**	**P-value**	**Estimate (S.E.)**	**P- value**	**Estimate (S.E.)**	**P- value**	**Estimate (S.E.)**	**P- value**
Coronary artery calcium	N=262		N=136		N=262		N=136	
Model 1	0.17 (0.15)	0.25	0.23 (0.28)	0.41	0.06 (0.11)	0.59	0.05 (0.15)	0.77
Model 2	0.16 (0.16)	0.34	0.16 (0.32)	0.61	0.11 (0.14)	0.44	−0.05 (0.28)	0.86
CORONARY CT ANGIOGRAPHY N= 454								
Non-calcified plaque	N=250		N=120		N=250		N=120	
Model 1	0.13 (0.06)	0.06	**0.21 (0.10)**	**0.047**	−0.06 (0.05)	0.22	**0.14 (0.07)**	**0.049**
Model 2	0.12 (0.08)	0.13	0.11 (0.12)	0.38	−0.11 (0.07)	0.14	0.03 (0.12)	0.77
Calcified plaque	N=119		N=79		N=119		N=79	
Model 1	0.17 (0.12)	0.15	−0.01 (0.17)	0.94	0.06 (0.08)	0.45	−0.10 (0.09)	0.27
Model 2	0.22 (0.13)	0.10	0.06 (0.2)	0.77	0.06 (0.13)	0.63	−0.20 (0.18)	0.28
Mixed plaque	N=118		N=67		N=118		N=67	
Model 1	0.14 (0.10)	0.17	**0.53 (0.16)**	**0.002**	−0.007 (0.08)	0.93	**0.21 (0.10)**	**0.04**
Model 2	0.17 (0.11)	0.15	**0.46[a] (0.19)**	**0.02**	0.10 (0.11)	0.38	0.19 (0.20)	0.35
Total plaque	N=288		N=160		N=288		N=160	
Model 1	**0.23 (0.07)**	**0.002**	**0.31 (0.11)**	**0.007**	−0.07 (0.05)	0.22	0.09 (0.07)	0.19
Model 2	**0.21[b] (0.08)**	**0.008**	0.23 (0.13)	0.08	−0.12 (0.08)	0.10	−0.12 (0.12)	0.31

Separate linear regression models for each plaque outcome. Model 1: adjusted for age, race/ethnicity. Model 2: Model 1+ CV risk factors (BMI, tobacco pack years, systolic blood pressure, anti-hypertensive medication, fasting glucose, lipid medication use, total cholesterol, HDL). Adipokines and plaque outcomes log-transformed.

[a] After further adjustment for abdominal visceral and thigh subcutaneous fat, estimate 0.43, p=0.03.

[b] After further adjustment for HIV clinical variables estimate 0.20, p=0.02. After adjusting for abdominal visceral and thigh subcutaneous fat estimate 0.21, p=0.01