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Serum Leptin Level Mediates the Association of Body Composition and Serum C-Reactive Protein in HIV-Infected Persons on Antiretroviral Therapy

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Abstract

Higher body mass index (BMI) is associated with increased serum C-reactive protein (CRP) levels in HIV-infected individuals on antiretroviral therapy (ART), but the relationship of adipose tissue mass to systemic inflammation is not well described in this population. We hypothesized that serum adipokine levels (i.e., hormones produced by adipocytes) are a superior predictor of CRP compared to anthropometric or radiographic measures of body composition in patients on effective, stable ART. We evaluated the relationship of serum leptin, adiponectin, and resistin, BMI, and dual energy x-ray absorptiometry (DEXA) measurements with serum highly sensitive CRP (hsCRP) in a cross-sectional cohort of 106 predominantly virologically suppressed, HIV-infected adults on ART for ≥ 24 weeks using multivariable linear regression and formal criteria to assess statistical mediation. Median BMI, hsCRP, and leptin values were 25.2 kg/m^2, 3.0 mg/liter, and 3.8 ng/ml, respectively. BMI and DEXA limb fat, body fat, and trunk fat measurements were significantly associated with both serum leptin and hsCRP levels (all $p \leq 0.02$). Leptin was also associated with hsCRP ($p < 0.01$). The regression coefficient for the effect of BMI or DEXA measurements on hsCRP was reduced, and the relationship was no longer statistically significant, after adjusting for leptin, indicating leptin functioned as a mediating variable within these relationships. Adiponectin and resistin levels did not demonstrate similar effects. Serum leptin was a superior predictor of hsCRP compared to BMI and DEXA body fat measurements, which may reflect alterations in body composition in treated HIV infection and the important contribution of adipose tissue to inflammation in this population.

Introduction

The introduction of effective combination antiretroviral therapy (ART) for HIV infection greatly reduced mortality from AIDS-related conditions, but this success is tempered by higher age-adjusted rates of several diseases more commonly associated with excess weight and a sedentary lifestyle, including myocardial infarction, type 2 diabetes mellitus, and the metabolic syndrome (i.e., the clustering of abdominal obesity, disorders of lipid and glucose metabolism, and hypertension).[1–4] HIV-infected men with normal body mass index (BMI; $< 25\,kg/m^2$) demonstrate roughly equivalent lipid profiles, insulin resistance, and serum inflammatory markers [e.g., C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α)] as obese (BMI $\geq 30\,kg/m^2$), HIV noninfected men.[5] The incidence of cardiovascular and metabolic diseases will likely rise as the proportion of overweight and obese HIV-infected individuals approaches parity with the general population, highlighting the need for aggressive management of cardiac and diabetes risk factors as a routine component of HIV care.[6,7]

Heightened systemic inflammation appears to be an important factor in the pathogenesis of several diseases associated with both HIV infection and obesity, and elevated serum CRP and other inflammatory markers are independently associated with increased risk of cardiovascular events, the development of diabetes mellitus, and all-cause mortality among HIV-infected individuals.[8–14] The adipocytes, stromal cells, and immune cells that constitute adipose tissue produce

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a range of proinflammatory cytokines, including several that increase hepatic CRP production [e.g., TNF-α, and IL-6, and interleukin-1 beta (IL-1β)], in addition to adipokine molecules with a variety of neuroendocrine and immune functions (primarily leptin, adiponectin, and resistin).[15–17] Prior studies found that BMI, visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) predict serum CRP levels in both HIV-infected and noninfected adults, suggesting adipose tissue is an important contributor to systemic inflammation.[18–21]

The clinical utility of both anthropometric and radiographic measurements of body composition may be reduced as a result of lipodystrophy, or fat redistribution, described in both primary HIV infection and ART treatment.[22,23] Since alterations in VAT, SAT, and lean tissue distribution affect circulating inflammatory molecule levels but may not be reflected by a change in BMI, we hypothesized that serum adipokines may be a superior indicator of adipose tissue mass in HIV-infected adults on ART.[18,23–25] A comparison of the relative correlation of anthropometric, radiographic, and biochemical markers of adiposity with circulating inflammatory molecules is relevant to clinical risk-stratification and our understanding of the role of adipose tissue in promoting inflammation in the setting of HIV. In this report, we describe the relationships between highly sensitive CRP (hsCRP) serum levels and BMI, waist-to-hip ratio, dual energy x-ray absorptiometry (DEXA) body fat measurements, and serum adipokine levels (leptin, adiponectin, and resistin) in a cohort of adults on ART.

Materials and Methods

Cross-sectional anthropometric measurements, DEXA measurements, and serum samples for laboratory assays were obtained from a prospective cohort of chronically HIV-infected adults enrolled at the Comprehensive Care Center in Nashville, Tennessee between June 2005 and July 2007. The cohort was established to assess markers of oxidant stress and metabolic and neurologic complications related to ART treatment and has been previously described.[19] Briefly, the inclusion criteria included age >18 years, ≥ 24 weeks of continuous ART treatment with a regimen containing ≥ 2 nucleoside reverse transcriptase inhibitors (NRTIs), and a plasma HIV-1 RNA $\leq 10{,}000$ within 180 days of enrollment. Patients with diabetes mellitus not controlled by diet or a history of myocardial infarction were excluded. The selection of participant ART regimens and routine medical care was at the discretion of clinic practitioners not directly affiliated with the study. The study was approved by the Vanderbilt University Institutional Review Board. All participants provided written informed consent and the investigators adhered to the human experimentation guidelines of the United States Department of Health and Human Services.

BMI and waist-to-hip ratio were measured using standard techniques. Current smoking status and self-reported use of routine nonsteroidal antiinflammatory drugs (NSAIDs) and aspirin were recorded due to potential effects on systemic inflammation. Serum samples were assayed for hsCRP (Laboratory Corporation of America, Birmingham, AL), and averaged duplicate measurements of plasma leptin, adiponectin, and resistin levels were performed using the Luminex multiplex immunoassay system (Millipore, Billerica, MA). The current ART regimen and most recent $CD4^+$ lymphocyte count and HIV-1 viral load (within 3 months of enrollment) were obtained from the medical record. Whole body DEXA measurements of total body fat, trunk fat, and limb fat were performed on a subset of participants (Lunar Prodigy bone densitometer, General Electric Healthcare).

Three sequential sets of multivariable linear regression models were used to assess the potential mediating effect of serum lepin, adiponectin, or resistin levels on the relationship between body composition and serum hsCRP level, following previously described statistical procedures.[26] First, the association between the potential mediator (adipokine) and the outcome variable (hsCRP) was assessed. Second, the association between the exposure (body composition variable) and the potential mediator (adipokine) was examined. Third, we evaluated the presence of attenuation in the effect of exposure (body composition) on the outcome (hsCRP) after adjustment for the potential mediator (adipokine). All regression models were adjusted for sex, age, race, $CD4^+$ lymphocyte count (in intervals of 100 cells/μl), current smoking status, routine NSAID and aspirin usage, and the inclusion of a protease inhibitor (PI) in the ART regimen as independent variables. To normalize the residuals, leptin, adiponectin, resistin, and hsCRP were natural logarithmically transformed. The variance inflation factor for all variables in the regression models before and after adjustment for leptin was less than 2.2, below the value of 5 to 10 frequently cited as an indicator of possible multicollinearity.[27] A two-sided p value <0.05 was considered as statistically significant. Analysis was performed using SPSS (SPSS Inc., Chicago, IL) and R 2.10.0 (http://www.r-project.org).

Results

The clinical and demographic characteristics of 106 study subjects, stratified by sex, are shown in Table 1. There were no statistically significant differences between sexes in age, the proportion from a nonwhite race, tobacco use, $CD4^+$ lymphocyte count, or plasma HIV-1 RNA. Fifty-eight participants were overweight (BMI $\geq 25\,kg/m^2$) and 16 (15%; 9 women and 7 men) were obese (BMI $\geq 30\,kg/m^2$). Median BMI was significantly higher among women compared to men (26.7 versus 24.8 kg/m^2), and the waist-to-hip ratio was lower (0.88 versus 0.92, respectively). Women had a significantly higher median serum leptin level compared to men (15.5 versus 3.5 ng/ml, respectively), and a higher adiponectin level (15.0 versus 12.0 μg/ml, respectively), but there was no difference in resistin level. Serum hsCRP was also higher among women (4.2 versus 2.4 mg/liter), but the difference was not statistically significant.

Eighty-seven (82%) participants had DEXA measurements performed; women had significantly higher total body fat, limb fat, and trunk fat compared to men. The median limb fat to trunk fat ratio was also higher among women compared to men (1.79 to 1.28), and higher among the obese compared to the nonobese (1.50 versus 1.37). The markedly higher median limb fat among women compared to men (10.2 versus 4.7 kg) may represent an important contributor to higher serum leptin levels among female subjects due to the increased expression of leptin by SAT (e.g., limb fat) compared to VAT (included in our measurement of trunk fat).[28–30]

While the cross-sectional design of our study did not permit longitudinal assessments of regional lipoatrophy or

Table 1. Demographic and Clinical Characteristics of the Study Subjects

Parameter[a]	*Males N = 80*	*Females N = 26*
Age, years	46 (43, 51)	48 (40, 52)
Nonwhite race, *n* (%)	32 (40%)	13 (50%)
Active tobacco use, *n* (%)	39 (49%)	17 (65%)
Routine NSAID use, *n* (%)	36 (45%)	14 (54%)
Daily aspirin use, *n* (%)	23 (29%)	3 (12%)
$CD4^+$ lymphocyte count, cells/μl	501 (345, 710)	507 (315, 870)
Plasma HIV-1 viral load, copies/ml	50 (50,102)	50 (50,50)
Protease inhibitor in treatment regimen, *n* (%)	46 (57%)	16 (62%)
Body mass index, kg/m^2	24.8 (22.7, 26.7)	26.7 (24.1, 30.6)†
Waist-to-hip ratio	0.92 (0.89, 0.92)	0.88 (0.84, 0.92)‡
Serum hsCRP, mg/liter	2.4 (0.7, 5.0)	4.2 (1.2, 7.5)
hsCRP <1.0, *n* (%)	25 (31%)	5 (19%)
hsCRP 1.0–3.0, *n* (%)	19 (24%)	4 (15%)
hsCRP >3.0, *n* (%)	36 (45%)	17 (65%)
Leptin, ng/ml	3.5 (1.5, 7.0)	15.5 (8.3, 29.9)‡
Resistin, ng/ml	9.9 (6.9 to 14.7)	10.6 (6.6, 15.7)
Adiponectin, μg/ml	12.0 (4.4, 18.0)	15.0 (8.5, 26.0)†
Dual-energy x-ray absorptiometry subgroup (67 males, 20 females)		
Age, years	47 (43, 52)	48 (40, 52)
Total body mass, kg	77 (66, 85)	74 (64, 88)
Body mass index, kg/m^2	24.3 (22.2, 26.5)	27.8 (24.8, 32.2)‡
Waist-to-hip ratio	0.92 (0.89, 0.98)	0.88 (0.86, 0.93)†
Limb fat, kg	4.7 (3.3, 8.5)	10.2 (8.7, 15.7)‡
Total body fat, kg	15 (11, 23)	27 (22, 36)‡
Total body % fat	22 (16, 28)	39 (36, 44)‡
Trunk fat, kg	9 (7, 14)	16 (12, 23)‡
Trunk % fat	27 (21, 35)	42 (38, 47)‡

[a]Data are presented as *N* (%) or median (interquartile range).
$^\dagger p < 0.05$, $^\ddagger p < 0.01$.
hsCRP, highly sensitive C-reactive protein; NSAID, nonsteroidal antiinflammatory drug.

lipohypertrophy, we examined the concordance between limb and trunk fat mass as surrogate measure of disproportionate fat gain or loss. Eighty-four percent of subjects with below-median limb fat values also had below-median trunk fat values, and 84% of those with above-median limb fat also had above-median trunk fat. Overall, only 16% of subjects had discordance in these above/below median values. Of note, the Spearman's correlation between leptin and hsCRP was highest among those with above-median limb fat and below-median trunk fat (rho = 0.41, $n = 7$), while it was negative among the subjects with below-median limb fat and above-median trunk fat (rho = −0.21, $n = 7$), which supports the hypothesis that limb fat is an important determinant of both leptin and hsCRP levels (data not shown). Finally, among the 16 obese subjects, the correlation between leptin and hsCRP was weaker compared to the nonobese (Spearman's rho = 0.043 versus 0.312, respectively), but the sample was too small to adjust for other covariates.

To assess for a mediating effect of serum adipokines on the relationship between BMI or DEXA measurements and hsCRP, we first examined whether each adipokine was significantly associated with both the predictor variable (BMI or DEXA value) and the outcome variable (hsCRP). Serum leptin concentrations were significantly associated with hsCRP after adjustment for age, sex, $CD4^+$ lymphocyte count, smoking status, and NSAID, aspirin, and protease inhibitor use [$\beta = 1.95$ (95% confidence interval: 1.36 to 2.80; $p < 0.001$)], but no significant associations were observed for adiponectin or resistin (Table 2). One IQR increase in leptin was associated with approximately a 2-fold increase in hsCRP.

Table 2. Relationship of Serum Adipokine Levels and Highly Sensitive C-Reactive Protein Level

	β (95% CI)[a]	*p* value
Leptin	1.95 (1.36, 2.80)	<0.001
Adiponectin	0.74 (0.45, 1.21)	0.23
Resistin	1.27 (0.90, 1.80)	0.18

[a]Regression coefficients (β) are derived from the exponential of the β-coefficient of the model and represent the fold-change in highly sensitive C-reactive protein (hsCRP) accompanying a one interquartile increase in the adipokine level. Models are adjusted for age, sex, $CD4^+$ lymphocyte count (in 100 cell/μl strata), smoking status, and nonsteroidal antiinflammatory drug, aspirin, and protease inhibitor use.

Given the observed association between serum leptin and hsCRP levels, we then assessed the relationship between anthropometrics or DEXA measurements and leptin (data not shown). BMI was significantly associated with serum leptin after adjustment for covariates ($p < 0.01$). Similar results were found for waist-to-hip ratio and DEXA measurements after adjustment for covariates (all $p < 0.01$).

Because serum leptin was associated with both the outcome variable (hsCRP) and the predictor variables (BMI, waist-to-hip ratio, and DEXA measurements), we then compared the strength of association between each body composition variable and hsCRP with and without adjusting for leptin (Table 3). A reduction in the regression coefficient ($\beta 1$ to $\beta 2$) and statistical nonsignificance in the relationship between body composition and hsCRP after adjustment for serum leptin indicates that leptin is a mediator, or effect modifier, of the body composition–hsCRP relationship. The regression coefficient for the effect of BMI on hsCRP was reduced from 1.57 ($\beta 1$) to 1.22 ($\beta 2$), and the relationship was no longer significant ($p = 0.02$ without adjustment for leptin versus 0.54 with adjustment for leptin), indicating leptin was a mediating variable and a superior predictor of hsCRP values. One IQR increase in leptin (2.3 to 11.0 ng/ml) was associated with a 1.7-fold increase in hsCRP after controlling for BMI and other confounders (95% confidence interval: 1.1 to 2.6, $p = 0.02$; data not shown).

Similarly, the relationships between limb fat, total and percent body fat, total and percent trunk fat, and hsCRP were attenuated after adjustment for leptin. For waist-to-hip ratio and hsCRP, attenuation was present as the beta coefficient decreased from 1.58 ($\beta 1$) to 1.22 ($\beta 2$), but the persistent statistically significant association after adjustment for leptin may indicate partial mediation ($p < 0.01$ to $p = 0.03$).

Discussion

In a cross-sectional analysis of a cohort of predominantly virologically suppressed HIV-infected adults on ART, serum

Table 3. Relationship of Body Composition to Serum Highly Sensitive C-Reactive Protein with and without Adjustment for Leptin

	Without adjustment for leptin		*With adjustment for leptin*	
Body composition variable	$\beta 1$ (95% CI)[a]	p value[b]	$\beta 2$ (95% CI)[a]	p value[c]
Body mass index	1.57 (1.11, 2.20)	0.02	1.22 (0.82, 1.80)	0.54
Waist-to-hip ratio	1.58 (1.06, 2.35)	< 0.01	1.22 (0.81, 1.84)	0.03
Limb fat	1.82 (1.09, 3.02)	0.05	1.10 (0.60, 2.04)	0.85
Total body fat	2.16 (1.20, 3.88)	< 0.01	1.41 (0.68, 2.92)	0.50
Total body % fat	2.45 (1.45, 4.14)	< 0.01	1.62 (0.82, 3.19)	0.31
Trunk fat	2.55 (1.53, 4.25)	< 0.01	1.83 (0.93, 3.59)	0.21
Trunk % fat	2.88 (1.70, 4.88)	< 0.01	2.04 (1.01, 4.09)	0.12

[a] $\beta 1$ and $\beta 2$: Regression coefficients represent the fold-change in hsCRP accompanying a one interquartile increase in each body composition variable.

[b] p values from multivariable linear regression with log hsCRP as the outcome variable, adjusting for age, sex, $CD4^+$ lymphocyte count (in 100 cell/μl strata), smoking status, and nonsteroidal antiinflammatory drug, aspirin, and protease inhibitor use.

[c] p values from multivariable linear regression with log hsCRP as the outcome variable, adjusting for leptin and the other covariates.

A reduction in the regression coefficient ($\beta 1$ to $\beta 2$) and statistical nonsignificance in the relationship between body composition (the independent variable) and hsCRP (the dependent variable) after adjustment for serum leptin indicate that leptin is a mediator, or effect modifier, of the body composition–hsCRP relationship.

leptin was a stronger correlate of hsCRP compared to BMI or DEXA-derived measurements of adipose tissue. These findings confirm prior observations that BMI can be an unreliable indicator of relative adiposity in the setting of HIV infection and ART exposure.[23,25] The median hsCRP value in our cohort was approximately 50% higher than the median value reported from the National Health and Nutrition Examination Survey.[31] Fat redistribution and relative changes in body composition may not be clinically apparent on examination, but increases in overall fat mass may have important consequences for systemic inflammation and, by extension, cardiovascular and metabolic disease risk.[8,10,32,33] Given the association of elevated inflammatory markers with a range of cardiovascular and metabolic diseases, the significant correlation of leptin and hsCRP in our study suggests weight control may represent an important risk reduction strategy among HIV-infected adults on ART.

A similar study by Shamsuzzaman *et al.* of healthy volunteers found a strong correlation between leptin and hsCRP (rho = 0.64; $p < 0.01$), which remained significant after controlling for sex, age, BMI, and smoking, among other factors.[34] The median BMI and leptin levels among these HIV-seronegative men and women [26 and 25 kg/m^2 (BMI), and 4.7 and 12.5 ng/ml (leptin), respectively] were similar to participants in our study (25 and 27 kg/m^2, and 3.5 and 15.5 ng/ml, respectively). However, the median hsCRP levels in our cohort among men (2.4 mg/liter) and women (4.2 mg/liter) were 2- to 3-fold higher compared to Shamsuzzaman *et al.* (0.8 and 1.8 mg/liter, respectively), suggesting that at any given BMI or serum leptin level, hsCRP is higher in HIV-infected individuals compared to uninfected individuals.

Our findings do not demonstrate a causal link between circulating leptin levels and CRP production. The primary stimuli for higher CRP production in the obese is hypothesized to be IL-6, TNF-α, and IL-1β production by hypertrophied adipocytes and adipose-resident macrophages (particularly surrounding necrotic fat cells), and it is unclear from our data whether serum leptin serves as a more accurate indicator of total adipose tissue compared to anthropometrics and DEXA, or if higher leptin levels are a marker of more "active" adipose tissue with higher cytokine expression per unit of tissue mass.[17,35,36]

The relationship between leptin and CRP is further complicated by differential production of leptin and proinflammatory cytokines by adipose tissue type. While SAT mass is a stronger determinant of serum leptin level compared to VAT mass, the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study found a greater rise in serum CRP for each incremental increase in VAT compared to SAT.[18,28–30] Furthermore, increased peripheral lipoatrophy, and a failure to regain SAT on treatment, observed among men compared to women in FRAM might exaggerate sex-differences in serum leptin levels.[37–39] Finally, central obesity may promote increased expression of IL-6 and other proinflammatory cytokine production by individual adipocytes and stromal-vascular cells, which may alter the linearity of the leptin-CRP relationship among heavier patients or those with greater treatment-related central lipohypertrophy.[40] Indeed, we observed a stronger correlation between leptin and hsCRP among the nonobese compared to the obese. While our analyses adjusted for sex and analyzed the relationships between leptin, CRP, and limb, trunk, and total fat separately, tissue-specific differences in adipokine and cytokine expression profiles may have confounded the results.

The major limitations of our study were the cross-sectional sampling method, which could not assess temporal changes in fat distribution or the effect of changing adipokine levels on systemic inflammation, and the lack of CT or MRI imaging to differentiate between abdominal VAT and SAT. Our results may not be generalizable to other populations; a majority of our cohort was male (75%), had a suppressed viral load (65%), and were receiving a PI-based regimen (58%). We did not have a HIV-seronegative control group, though we compare our findings with similar, published reports from seronegative cohorts. We also could not ascertain the presence and degree of hepatic steatosis, a condition associated with higher serum CRP.[41] However, DEXA trunk fat measurements (which we measured) predicted steatosis in a prior study.[42] Seventeen patients had a diagnosis of hepatitis C infection,

which is associated with lower CRP levels; however, the mediating effect of leptin was unchanged for all body composition variables when we further adjusted the models for coinfection.[18] Lastly, 11% of our patients were receiving a statin, which may have important antiinflammatory effects, but in an earlier analysis of the same cohort (prior to full enrollment) the inclusion of lipid-lowering therapy in multivariate models did not affect the independent association of hsCRP with other factors.[19]

HIV infection and treatment with ART are associated with a range of metabolic and inflammatory abnormalities, and concomitant obesity may represent a significant added risk for cardiometabolic diseases. Fat redistribution and relative changes in body composition may not be reflected by BMI, but may have profound effects on metabolism and disease risk. Further studies are needed to characterize the metabolic and inflammatory phenotype of obese HIV-infected individuals, and the impact of HIV on the adipocyte–macrophage interactions thought to be a prime contributor to inflammation in these patients. Finally, the potential benefit of weight loss or the use of antiinflammatory agents, such as high-dose statins or angiotensin receptor blockers, warrants investigation. As the proportion of overweight and obese HIV-infected adults continues to increase, the prevention of metabolic and cardiovascular complications will remain a challenge to HIV care providers.

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Author Disclosure Statement

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