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Central Obesity is a Contributor to Systemic Inflammation and Monocyte Activation in Virally Suppressed Adults with Chronic HIV in Kenya

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Abstract

Objectives: Heightened systemic inflammation is common in obese individuals and persons with HIV-infection (PWH) and is independently associated with an increased risk of cardiovascular diseases(CVD). We investigated the combined effect of central obesity, a surrogate measure of visceral fat, and HIV on circulating levels of inflammatory cytokines among Kenyan adults.

Design: Cross-sectional study.

Methods: We analyzed and compared data from 287 virally suppressed PWH and 277 non-infected Kenyan adults including biomarkers of gut epithelial dysfunction (intestinal fatty acid binding protein), monocyte activation (soluble CD163 and CD14), and inflammation (interleukin [IL]-1 β , IL-6, TNF- α , and hsCRP) by HIV/central obesity status (HIV+/obese, HIV-/obese, HIV+/-obese).

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non-obese, and HIV-/non-obese). Central obesity was defined as waist circumference >80 cm for women and >94 cm for men. We assessed the association of HIV/obesity status with elevated biomarkers (>75th percentile) using logistic regression.

Results: Median age for participants was 44 years and 37% were centrally obese. Levels of all biomarkers were higher among the HIV+/obese compared to the HIV-/non-obese ($p < 0.05$ for all comparisons). The HIV+/obese group had the greatest odds of having elevated inflammatory biomarkers compared to other groups even after adjustment of age, BMI, and other conventional CVD risk factors ($p < 0.05$ for all). Additional adjustment for sCD163 in the multivariate model substantially attenuated the association for HIV+/obesity with IL-1 β , IL-6, and TNF- α but not hsCRP. The contribution of HIV+/obesity to inflammation was independent of the degree of immunosuppression.

Conclusions: Central obesity is prevalent among virally suppressed African PWH and is associated with greater inflammation and monocyte activation independent of other comorbidities and HIV-specific factors.

Keywords

HIV; Africa; inflammation; obesity; monocyte activation; sCD163; microbial translocation.

Introduction

Antiretroviral therapy (ART) has greatly reduced mortality associated with HIV/AIDS in low-resource settings including Kenya^[1]. However, after ART, most persons with HIV (PWH) gain weight and while weight gain after ART initiation is associated with a survival advantage among normal weight individuals, it may exacerbate risk for cardiovascular disease (CVD) and other non-AIDS comorbidities^[2–8].

Elevated levels of pro-inflammatory cytokines (interleukin [IL]-1 β , IL -6, tumor necrosis factor [TNF]- α , and high sensitivity C-Reactive Protein [hsCRP]) and monocyte activation biomarkers (soluble CD163 [sCD163] and sCD14) are associated with increased risk of developing CVD^[9–17]. We have recently shown that African PWH and the obese adults exhibit high levels of these biomarkers even after ART compared to the non-infected adults^[10, 16]. The pathophysiology of HIV-associated immune activation and inflammation is still unclear and may be multifactorial, however hsCRP has been shown to correlate with visceral fat mass in PWH implying that visceral adiposity may be a risk factor^[18]. The heightened inflammatory state observed in obese individuals regardless of the HIV status is thought to be due to increased inflammatory cytokine production by the immune cells that have infiltrated the adipose tissue, adipocyte hypertrophy, and the direct effect of leptin on hepatocytes to induce hsCRP production^[12, 13].

To date, there is limited information on the combined effect of HIV and central obesity on biomarkers of inflammation after viral suppression especially from the low- and middle-income countries. Previous studies have reported high levels of circulating markers of inflammation among generally obese PWH but other studies have found modest effects^[19–21]. It is important to note that most of these studies did not include women

or HIV-negative adults for comparison and used body mass index (BMI) as a measure of adiposity. Waist circumference is a superior surrogate marker of visceral adipose tissues compared to BMI^[22] and while both subcutaneous and visceral adipose tissues have been associated with cardiometabolic diseases, high visceral adipose tissue is more strongly correlated with cardiometabolic diseases than its counterpart^[23, 24]. In fact, waist circumference is a superior predictor of health risks than BMI^[25–29].

In this present study, we sought to investigate the combined effects of central obesity and HIV on biomarkers of inflammation, monocyte activation, and gut enterocyte damage among Kenyan adults. We hypothesized that central obesity and HIV would both be associated with inflammation independent of each other, but their joint presence would be associated with greater levels of these biomarkers.

Methods

Study Setting and Participants

We analyzed data from 287 PWH and 277 HIV-negative participants enrolled between 2017–2018 in an observational cross-sectional study in western Kenya. The cohort was established to assess risk factors for CVD in PWH on long-term ART. Recruitment and study procedures have been described elsewhere^[10, 30, 31]. Briefly, the study is comprised of a convenience sample of PWH and HIV-negative men and women 30 years old enrolled from the Kisumu District Hospital HIV clinic and voluntary HIV testing centers. Data were collected through a standardized questionnaire and medical chart abstraction while anthropometric measurements and serum collection were performed as part of the study visit. Mid-waist circumference was measured in cm by a validated WHO STEPwise survey protocol^[32]. Central obesity was defined based on International Diabetes Federation (IDF) definition as waist circumference >0.80 m for women and greater than 0.94 m for men, considered as indicative of an increased risk of cardiometabolic diseases^[33]. Overweight referred to body mass index (BMI) greater than or equal to 25 kg/m² to 29.9 kg/m² and general obesity was BMI greater than or equal to 30 kg/m².

Laboratory testing consisted of CD4 cell counts, HIV viral load, inflammatory biomarkers, fasting glucose, and lipids (total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol. Individuals with a recorded history of CVD, neoplasia, active infection, or those who at the time of recruitment were on medications that could influence their immune status were excluded from this analysis.

Immunological biomarker analysis

Serum levels of IL-1 β , IL-6, and TNF- α were measured using multiplex enzyme-linked immunosorbent assay (Meso-Scale Discovery, Rockville, MD). Samples with a coefficient of variation greater than 30% were rerun and the duplicate and the lower coefficient of variation was averaged for the analyses. hsCRP testing was performed using an automated Beckman Coulter AU5812. Serum levels of intestinal fatty acid binding protein (I-FABP), sCD163 and sCD14 were measured using commercially available ELISA assays (Quantikine ELISA kit, R&D systems). The inter-assay coefficients of variation were <11%. All samples

were tested centrally at University of Washington (Seattle, WA). Assays were performed in duplicate and in accordance with manufacturers' protocols. These markers were selected because they have been shown to be associated with cardiometabolic diseases or death and were likely to be produced by adipose tissue-resident immune cells^[34–37].

Statistical analysis

We first compared demographic and clinical characteristics within and across groups (HIV+/obese, HIV-/obese, HIV+/non-obese, and HIV-/non-obese) using t-tests, Wilcoxon rank sum tests, or Kruskal-Wallis test for continuous variables and X^2 test or Fisher test for categorical variables. We used univariable and multivariable logistic regression to estimate the association between obesity/HIV-infection comorbidity and prevalence of elevated biomarkers (highest quartile [>75 th percentile] vs. lower three quartiles) before and after adjustment of clinical characteristics. We defined elevated biomarkers as levels $>75\%$ because with the exception of hsCRP it is still unclear what thresholds are associated with clinical events for these biomarkers. This is also consistent with other studies that have looked at the association between biomarkers with health risks using biomarker quartiles^[35, 38, 39]. hsCRP was categorized according to clinical risk, and the cut off of 2mg/L was used as previously described^[40]. Models were adjusted for demographic characteristics (age and sex), and traditional CVD risk factors (hypertension, hypercholesterolemia, and alcohol use status) and further adjusted for body mass index (BMI). These covariates were selected based on prior work suggesting an association between covariates and the biomarkers^[10, 16, 41]. Multivariable models were sequentially adjusted for each of the biomarkers; I-FABP, sCD14 and sCD163 respectively. In separate analyses among PWH, we further adjusted for potential HIV-specific confounding factors, such as current and nadir CD4+ T-cell count, duration of ART intake, ART regimen (efavirenz vs. nevirapine vs. protease inhibitor-based regimen). We also conducted multivariable linear regression analysis to evaluate the association between (log-transformed) biomarkers and HIV status in separate models for each biomarker, and adjusted for age, sex, hypertension, cholesterol, waist circumference, and alcohol use status. We report the exponentiated β -coefficients and their calculated 95% confidence intervals (CIs) representing the fold increase/decrease in biomarker level. An interaction term between sex and HIV status was introduced in the model to test the difference of these associations by sex. Finally, in a sensitivity analysis, we repeated models after excluding individuals with hsCRP greater than 10mg/L ($n=50$) as this could indicate the presence of an acute infection,^[42, 43] and the underweight individuals with BMI less than 18.5 kg/m² ($n=51$). Significance was set at a p value <0.05 . Analyses were performed using STATA[®] version 13 (San Antonio, Texas).

Ethics Statement

The Ethics and Research Committee of Kenyatta National Hospital and the Institutional Review Board at University of Washington approved the study. All participants provided written informed consent.

Results

Study participants characteristics

Socio-demographic and clinical characteristics are shown in Table 1, stratified by HIV and central obesity status. The median (IQR) age for all participants was 44 (35–54) years, half were female (82% of those with obesity were female). The prevalence of abdominal obesity was lower in PWH relative to the HIV negative participants (30% versus 40%; $p=0.001$; sup Table 1). PWH with central obesity were less likely to have an obese BMI ($BMI>30\text{kg/m}^2$) compared to their HIV-negative counterparts (22% vs. 44%; $p<0.0001$). Centrally obese participants were more likely to have hypertension and dyslipidemia, and less likely to report current alcohol and tobacco use compared to the non-obese (Table 1). The mean $CD4^+$ T-cell count for the PWH was 520 cells/ mm^3 and was not statistically different between the obese and non-obese groups ($p=0.07$). The majority (97%) of PWH were virally suppressed (HIV RNA <1000 copies/mL). All PWH were on co-trimoxazole prophylaxis and ART consisting of a non-nucleoside reverse transcriptase inhibitor (NNRTI) backbone of efavirenz (45%) or nevirapine (42%) with lamivudine plus tenofovir or zidovudine; only 13% were on protease inhibitors (PI), and none were on integrase inhibitors. The mean duration of ART across groups was 8 years.

Difference in biomarkers levels according to HIV status and sex.

Median levels of all biomarkers including sCD14, sCD163, I-FABP, IL-1 β , hsCRP, TNF- α , and IL-6 were significantly higher in PWH compared to the HIV-negative participants (Sup Table 2). When comparing biomarkers by sex and HIV status, men with HIV demonstrated significantly higher levels of IL-1 β , TNF- α , and IL-6 than the women with HIV and men and women without HIV (Sup Figure 1). In contrast levels of sCD163 was significantly higher among women with HIV compared to the men with HIV and persons without HIV. sCD14 and I-FABP levels did not differ significantly between HIV-positive men and women. After adjustment for age, sex, and traditional CVD risk factors, HIV infection remained associated with higher levels of all biomarkers in men with HIV compared to men without HIV ($p < 0.05$; Sup Table 3). However, women with HIV had higher adjusted levels of sCD14, sCD163, I-FABP, TNF- α , and IL-6 but not IL-1 β or hsCRP than the uninfected women ($p < 0.05$). There was evidence of an interaction between HIV and sex for sCD163 ($p = 0.03$) but not for other biomarkers (Sup Table 3).

Intestinal barrier dysfunction and monocyte/macrophage activation biomarkers

Median levels of sCD14, sCD163, and I-FABP biomarkers were significantly higher among the HIV+/obese compared to the HIV-/non-obese ($p<0.001$; Figure 1). After controlling for clinical factors including BMI, HIV+/obese status remained associated with higher odds of elevated sCD14 (Odds ratio [OR], 6.58; $p<0.001$), sCD163 (OR, 2.45; $p=0.04$), and there was a trend for I-FABP (OR 1.94, 95% CI: 0.99 – 4.21) compared with HIV-/non-obese (Table 2).

Inflammatory biomarkers

In unadjusted analysis, there was significant higher median levels of hsCRP, TNF- α , and IL-6 among HIV+/non-obese and the HIV+/obese groups relative to the HIV-/non-obese (Figure 1). Median levels of hsCRP were also significantly higher among the HIV+/obese compared to HIV+/non-obese participants. Levels of IL-1 β were comparable between HIV+/obese and the HIV-/non-obese group (Figure 1). When we adjusted for traditional CVD risk factors, such as age, sex, BMI, alcohol use, hypertension, triglycerides and HDL, HIV+/obese continued to have a significantly greater odds for elevated IL-6 (OR, 3.01; $p=0.004$), hsCRP (OR, 2.31; $p=0.001$), TNF- α (OR, 3.91; $p=0.01$), and IL-1 β (OR, 4.37; $p<0.001$) compared to the HIV-/non-obese (Table 2). There were no significant changes in the OR for the biomarkers among HIV+/obese individuals in analyses that stratified PWH by current CD4+ T-cell count (or > 200) or ART duration (or > 4 years; *data not shown*). Our analysis by (highest quartile [>75 th percentile] vs. lower three quartiles) mimicked the linear relationships of HIV/obese status with inflammatory cytokines (*data not presented*). We also found no meaningful differences in these relationships in a sensitivity analysis that excluded those with hsCRP of greater than 10mg/L or underweight individuals with BMI 18.5kg/m^2 (*data not shown*).

Given the findings above, we evaluated whether monocyte/macrophage activation (sCD163 and sCD14) or gut epithelial damage (I-FABP) were potential mediators of the association between HIV+/obesity and inflammation. Additional adjustment for sCD163, a monocyte activation biomarker, in the multivariable model used for Table 2 did change the association of HIV+/obese with IL-6 (OR, 1.19; $p=0.72$), TNF- α (OR, 1.11; $p=0.84$), and IL-1 β (OR, 1.07; $p=0.89$), but not hsCRP (OR, 2.43; $p=0.03$, Figure 2). By contrast, adjustment for sCD14 and I-FABP among those with HIV and obesity had minimal effect on the association with the inflammation biomarkers.

Discussion

We found a high prevalence of central obesity in our cohort of normal/overweight virally suppressed Kenyan PWH. Importantly, PWH with central obesity exhibited immune dysregulation as reflected by elevated biomarkers of inflammation and monocyte activation. The associations were robust to adjustment for age, sex, body mass index, and traditional CVD risk factors. sCD163 strongly attenuated the association of HIV+/obese with IL-6, TNF- α , and IL-1 β but not that of hsCRP. Our data imply that abdominal adiposity promotes HIV-associated immune activation, and this may in part be due macrophage activation. To our knowledge, this is the first study to assess the contribution of HIV and obesity to inflammation and immune activation in a virally suppressed African cohort of PWH.

We have previously shown that HIV was associated with greater inflammation and immune activation in our study cohort^[10, 16]. The present study expands on our data and those from prior studies in the US and Europe that found greater inflammation and monocyte/macrophage activation among obese PWH^[12, 19–21]. In the Fat Redistribution and Metabolic Change in HIV-Infection cohort, each 2-fold increase in visceral adipose tissue was associated with a 17% higher serum CRP level^[44], after adjustment for the Framingham Risk Score factors. Another study among veteran men reported that HIV/obese status

had positive associations with IL-6 elevation particularly among the PWH with detectable viremia^[45]. However, some differences between our data and these prior studies may be explained by the way central obesity was categorized (quartiles versus means), the referent group (HIV-/non-obese versus HIV+/non-obese), and the study population. Despite these differences, most of these previous studies reported increase in biomarkers of inflammation among obese PWH, which is consistent to the findings of the current study.

IL-1 β is one of the major inflammatory cytokines produced by macrophages and a key contributor to the pathogenesis of atherosclerosis^[46]. Recently, Hoel and et al. demonstrated that activation of IL-1 β was associated with an approximately 1.5-fold increased risk of myocardial infarction among PWH^[47]. Indeed, the Canakinumab Anti-inflammatory Thrombosis Outcome Study demonstrated a decrease in the risk of cardiovascular events in individuals with established CVD after IL-1 β inhibition with canakinumab^[48]. Thus, our findings of higher prevalence of elevated IL-1 β among obese adults in our cohort is of concern for this particularly healthy population of PWH. Our findings are novel as there is a lack of studies comparing IL-1 β by HIV/obesity status. Longitudinal studies are needed to further confirm these findings.

Intestinal fatty acid binding protein (I-FABP) is a cytosolic protein found in enterocytes of the gastrointestinal tract and is involved in the translocation of fatty acids from the apical membrane of enterocytes to the endoplasmic reticulum. It is highly expressed in disease conditions where the intestinal wall is injured by pathogens such as HIV and is currently used as a marker of intestinal damage in PWH^[49]. Higher circulating levels of I-FABP are associated with increased mortality in PWH^[50, 51]. On the other hand, CD14 is a glycoprotein and a co-receptor that mediates the interaction of lipopolysaccharide (LPS), a major constituent of bacterial endotoxin, with monocytes/macrophages. Our findings of lower levels of sCD14 and I-FABP among obese PWH compared to the non-obese PWH in our study may reflect improvement of malnutrition-associated enteropathy commonly observed in PWH in resource limited settings^[52]. Nonetheless, we still observed significantly higher rates of elevated I-FABP and sCD14 in the HIV+/obese and HIV+/non-obese compared to HIV-negative participants, suggesting that these markers do not fully normalize after ART. Our results are consistent with previous published data that reported similar associations between body mass index and sCD14 and I-FABP^[19–21, 53]. Our study and those previously published are unusual in that we observe a decrease in sCD14 and I-FABP while hsCRP increased among obese patients, whereas the SMART study reported a positive correlation between hsCRP and sCD14^[36]. The negative association between abdominal obesity with I-FABP and sCD14 levels in PWH needs to be further explored because unlike the previous studies, we included multiple markers of monocyte/macrophage and individuals from sub-Saharan Africa who are also at high risk of co-infections that could potentially induce inflammation. Notably, we did not establish a correlation between sCD14 with sCD163 in PWH suggesting that the differences we observe between sCD14 and sCD163 may correspond to different pathways leading to their activation in African PWH or perhaps the availability of sCD14 in the blood.

While the exact mechanism underlying the association between adiposity and inflammation is not fully understood, the fact that sCD163, a marker of macrophage activation, attenuated

the association between obesity and IL-1 β , IL-6, and TNF- α in PWH suggests that macrophages play an important role^[12, 13, 54, 55]. Indeed, in human or animal models, obesity results in an increase in macrophage infiltration and activation in the adipose tissues^[12, 56, 57], consistent with the increase in inflammatory cytokines produced by these cells. Our data also suggest that there may be more than one pathway that leads to inflammation in addition to macrophage activation and microbial translocation, possibly through greater expression of pro-inflammatory cytokines by stromal vascular cells and hypertrophied adipocytes and/or by leptin-induced CRP expression in hepatocytes. Additional adjustment with sCD14, a known receptor for LPS and an indirect marker of microbial translocation or I-FABP, marker of gut epithelial damage, did not attenuate the association between obese status with inflammatory cytokines. Furthermore, these associations between abdominal obesity and inflammatory cytokines were independent of HIV specific factors (ART regimen, duration of HIV treatment, or the level of immunosuppression) in our PWH, implying that factors other than HIV virus may also play an important role. Other potential sources of inflammation in obese PWH that require further study include non-measured co-infections highly endemic in this population such as tuberculosis and cytomegalovirus.

Our study has several strengths. It is the first study to assess the contribution of HIV and central obesity on markers of inflammation and monocyte activation in Sub-Saharan Africa. Our study included a large diverse panel of inflammatory biomarkers not previously reported, a relatively large sample size, and robust clinical data on comorbid diseases that likely modulate inflammation. We enrolled an equal number of men and women, making our study results more generalizable. The relatively sex-matched HIV-negative persons allowed for direct comparison between groups. We acknowledge certain limitations to our study. This was a cross-sectional study and therefore we cannot exclude the possibility of non-measured confounding factors. We also lack cell surface immune activation marker data for comparison with the plasma cytokine data. At the time of recruitment, none of the PWH were on Integrase Strand Transfer Inhibitor (INSTI) treatment, making our results less generalizable for PWH currently on INSTI.

Our data suggests that central obesity is common in African PWH especially among the normal and overweight individuals. Centrally obese PWH with well controlled HIV are at the highest risk for elevated inflammation and immune activation and could be targeted to reduce the risk of CVD. As the prevalence of obesity increase in Africa^[58], more prospective studies are needed to define health risks associated with elevated biomarkers among Africans with and those without HIV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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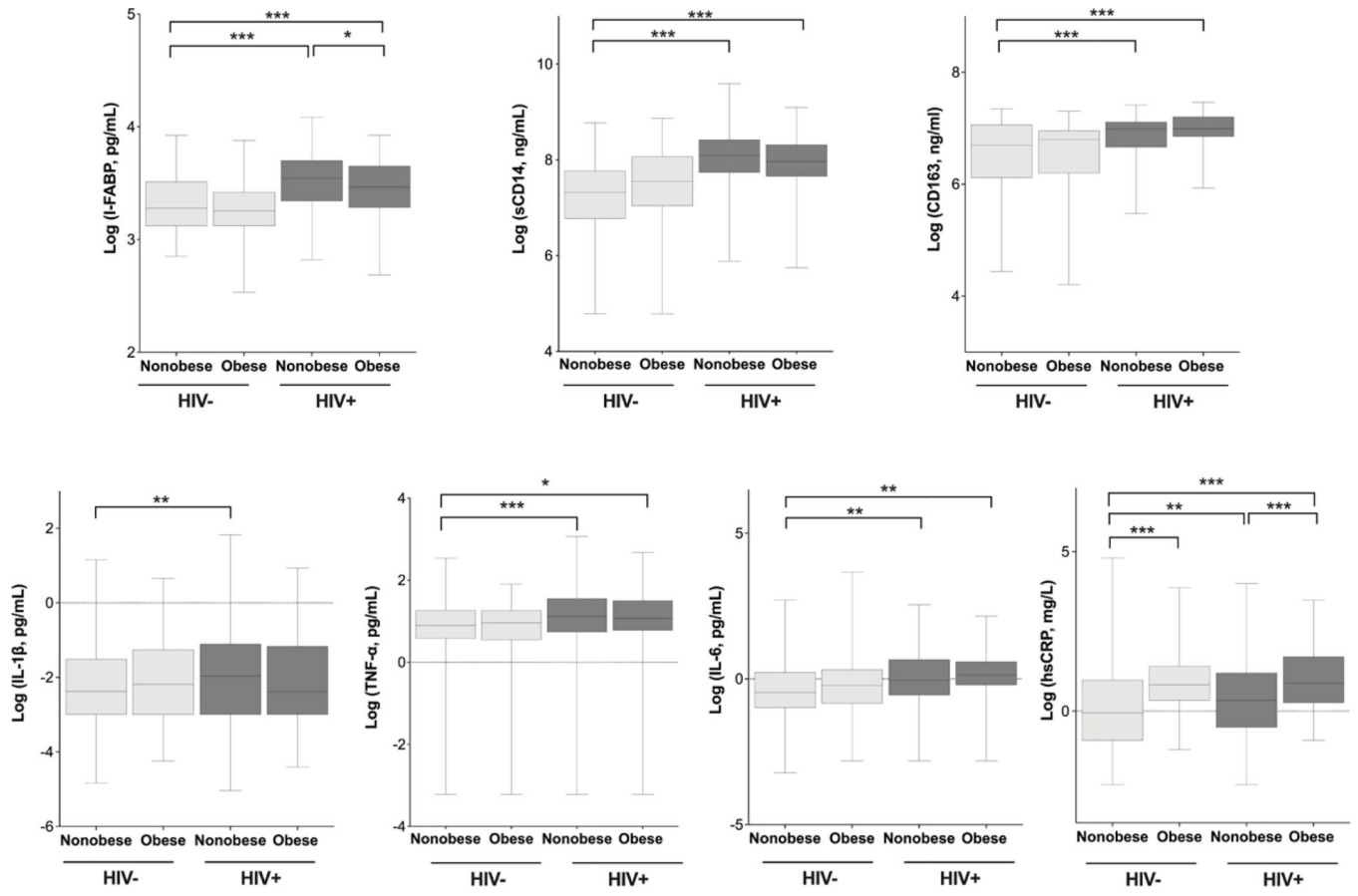


Figure 1. Serum levels of biomarkers by HIV serostatus and obesity status. All biomarkers were log transformed. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

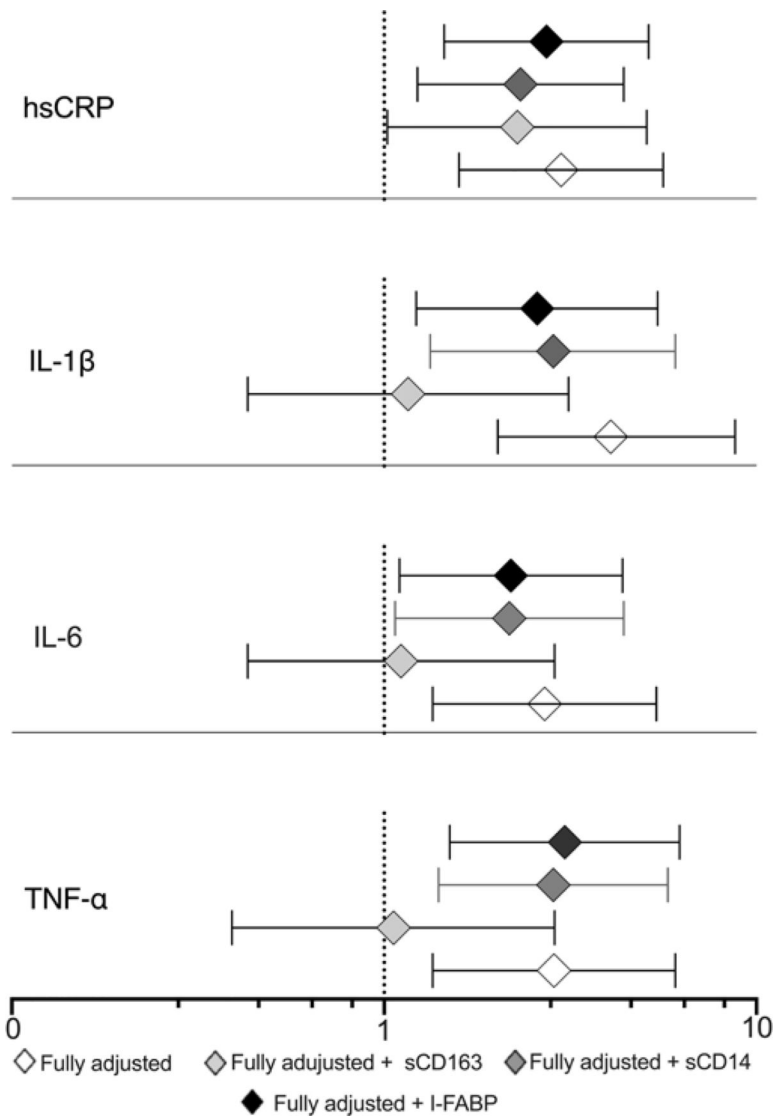


Figure 2: Association of central obesity with biomarkers among PWH adjusted for demographic, and CVD risk factors plus markers of intestinal barrier dysfunction and monocyte activation. Fully adjusted for age, sex, HDL, triglycerides, hypertension, BMI, and alcohol use status.

Table 1:

Characteristics of participants stratified by HIV and Obesity Status

	HIV-negative			HIV-positive		
	Centrally Obese (n=111)	Non-obese (n=166)	P value	Centrally Obese (n=85)	Non-obese (n=202)	P value
Demographics						
Age, years	44 (34, 55)	36 (31, 52)	0.01	45 (39,55)	45 (40,53)	0.44
Female	90 (81)	49 (30)	<0.001	72 (84)	71 (35)	<0.001
Cardiovascular Risk Factors						
Current Smoker	2 (2)	6 (4)	0.04	0 (0)	8 (4)	0.02
Current Alcohol use	17 (13)	14 (10)	0.008	9 (11)	42 (21)	0.06
Diabetes	5 (5)	4 (2)	0.33	2 (2)	1 (1)	0.16
Hypertension	37 (33)	23 (14)	<0.001	16 (19)	19 (9)	0.03
Other characteristics						
BMI, kg/m ²	29 (26, 34)	21 (20, 24)	<0.001	27 (25, 29)	21 (19, 23)	<0.001
BMI Category, kg/m ²			<0.001			<0.001
Underweight <18.5	0	19 (11)		0	32 (16)	
Normal weight (18.5 – 24.9)	21 (19)	121 (74)		21 (25)	156 (77)	
Overweight (25.0–29.9)	41 (37)	24 (14)		45 (53)	9 (5)	
General Obesity (>30)	49 (44)	2 (1)		19 (22)	5 (2)	
Waist Circumference, cm	93 ± 11	77 ± 7	<0.001	96 ± 11	77 ± 8	<0.001
Laboratory values						
HDL-Cholesterol, mg/dL	50 ± 10	51 ± 15	0.74	53 ± 14	55 ± 17	0.50
LDL- Cholesterol, mg/dL	106 ± 31	90 ± 30	<0.001	104 ± 35	91 ± 29	0.001
Triglycerides, mg/dL	74 (60, 101)	72 (55, 93)	0.003	86 (68, 121)	79 (60, 106)	0.09
Total cholesterol, mg/dL	172 ± 35	157 ± 37	<0.001	178 ± 44	165 ± 35	0.009
HIV related Characteristics						
Nadir CD4 T-cell count, cells/mm ³				458 ± 276	370 ± 225*	0.006
CD4 ⁺ T-cell count, cells/mm ³				556 ± 197	505 ± 235	0.08
Viral suppression RNA<1000 copies/mL				84 (97)	197 (97)	0.22
Total ART duration, years				9 (9,10)	8 (4,11)	0.43

Data reported as mean ± standard deviation, percentage, or median (interquartile range [IQR]).

Abbreviations: BP, Blood pressure; BMI, body mass index; PI, Protease Inhibitors; HDL, high density lipoprotein; LDL, low density lipoprotein. P value for comparisons between obese and non-obese participants (data were analyzed in HIV positive and HIV negative separately).

Table 2:

Association of HIV and obesity group with elevated biomarkers

	I-FABP [†] OR (95%CI)	sCD14 [†] OR (95%CI)	sCD163 [†] OR (95%CI)	TNF- α [‡] OR (95%CI)	IL-6 [‡] OR (95%CI)	IL-1 β [‡] OR (95%CI)	hsCRP [‡] OR (95%CI)
<i>Stratified by HIV and obesity status</i>							
<i>Unadjusted</i>							
HIV ⁻ , Non-obese		1.00	1.00	1.00	1.00	1.00	1.00
HIV ⁺ , Non-obese	2.90 (1.74 – 4.82)	7.73 (4.15 – 13.92)	1.73 (1.11 – 3.31)	1.96 (1.61 – 4.50)	1.87 (1.17 – 2.99)	1.62 (0.96 – 2.71)	1.44 (0.93 – 2.23)
xHIV ⁻ , Obese	0.40 (0.18 – 0.89)	0.76 (0.29 – 1.79)	0.77 (0.30 – 1.77)	0.74 (0.36 – 1.53)	0.94 (0.53 – 1.70)	1.50 (0.82 – 2.74)	3.37 (2.04 – 5.58)
HIV ⁺ , Obese	2.10 (1.14 – 3.88)	5.79 (2.86 – 11.06)	2.27 (1.08 – 4.76)	1.90 (0.97 – 3.51)	1.77 (0.99 – 3.18)	1.61 (0.85 – 3.06)	3.58 (2.07 – 6.19)
<i>Fully adjusted^a</i>							
HIV ⁻ , Non-obese	1.00	1.00	1.00	1.00	1.00	1.00	1.00
HIV ⁺ , Non-obese	2.58 (1.52 – 4.36)	7.57 (4.05 – 14.12)	1.93 (1.01 – 3.82)	2.45 (1.45 – 4.14)	1.95 (1.19 – 3.13)	1.98 (1.15 – 3.43)	1.26 (0.80 – 2.01)
HIV ⁻ , Obese	0.37 (0.15 – 0.84)	0.76 (0.30 – 1.92)	0.65 (0.26 – 1.63)	1.35 (0.64 – 2.82)	1.25 (0.63 – 2.46)	3.47 (1.71 – 7.08)	2.13 (1.58 – 5.07)
HIV ⁺ , Obese	1.80 (0.92 – 3.49)	5.73 (2.62 – 11.65)	2.18 (1.07 – 4.90)	2.86 (1.35 – 6.06)	2.70 (1.35 – 5.39)	4.06 (2.02 – 8.77)	2.99 (1.59 – 5.62)
<i>Fully adjusted + BMI</i>							
HIV ⁻ , Non-obese							
HIV ⁺ , Non-obese	2.51 (1.39 – 4.09)	7.43 (3.86 – 13.89)	1.81 (1.02 – 6.10)	2.66 (1.53 – 5.13)	2.24 (1.25 – 4.04)	1.89 (1.01 – 3.56)	1.61 (0.94 – 2.77)
HIV ⁻ , Obese	0.47 (0.19 – 1.16)	1.06 (0.38 – 2.97)	0.78 (0.27 – 2.22)	1.60 (0.65 – 3.95)	1.62 (0.67 – 3.44)	4.35 (1.83 – 9.84)	2.21 (1.11 – 4.40)
HIV ⁺ , Obese	1.94 (0.99 – 4.21)	6.58 (3.17 – 13.72)	2.45 (1.38 – 5.10)	3.91 (1.62 – 9.46)	3.01 (1.37 – 6.54)	4.37 (1.78 – 9.17)	2.31 (1.11 – 4.79)

I-FABP, intestinal fatty acid-binding protein; sCD14, cluster of differentiation 14; sCD163, cluster of differentiation 163; TNF- α , tumor necrosis factor alpha; IL-6, interleukin 6; IL-1 β , interleukin 1beta; hsCRP, high sensitivity C-reactive protein; BMI, body mass index. Obesity is defined as waist circumference of 80cm for women and 94cm for men.

^aFully adjusted for age, sex, HDL, triglycerides, LDL, hypertension, and alcohol use status.

[†]n=541

[‡]n=564