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Association between HIV replication and serum leptin levels: an observational study of a cohort of HIV-1-infected South African women

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Abstract

Background: Advanced HIV infection can result in lipoatrophy and wasting, even in the absence of ongoing opportunistic infections, suggesting that HIV may directly affect adipose tissue amount and distribution.

Methods: We assessed the relationship of fat (measured using anthropometry, DEXA, MRI scans) or markers related to glucose and lipid metabolism with viral load in a cross-sectional sample of 83 antiretroviral-naïve HIV-1-infected South African women. A multivariable linear model was fitted to $\log_{10}VL$ to assess the combined effect of these variables.

Results: In addition to higher T cell activation, women with viral load greater than the population median had lower waist circumference, body mass index and subcutaneous abdominal fat, as well as lower serum leptin. We demonstrate that leptin serum levels are inversely associated with viral replication, independent of the amount of adipose tissue. This association is maintained after adjusting for multiple variables associated with disease progression (i.e., cellular activation and innate immunity effector levels).

Conclusions: Our results demonstrate that serum leptin levels are inversely associated with viral replication, independent of disease progression: we postulate that leptin may affect viral replication.

Background

Progressive HIV infection [1,2] leads to loss of body fat, altering subjects' appearance and resulting in social stigma and negative body image, particularly in women [3]. Caloric intake and adiposity are regulated by adipokines, neurotransmitters, hormones and their receptors that modulate appetite, fat metabolism and energy homeostasis [4]. Leptin is produced by adipocytes, and contributes to appetite reduction via a negative hypothalamic feedback [5], as well as exerting immunomodulatory activity (e.g., inhibition of cell proliferation and promotion of type 1 adaptive responses [6-8]).

A correlation between adipose tissue and leptin is maintained in antiretroviral-treated HIV-infected individuals, independent of viremic status or disease stage

[9-12], even though leptin receptor expression and phosphorylation are increased in peripheral blood mononuclear cells [13]. A number of factors (chronic fever, increased TNF- α and IL-6 levels, opportunistic infections and other secondary causes [1,14,15]) have been considered to contribute to fat loss in advanced disease; however, a direct link to viral replication has not been established.

Women account for more than 50% of HIV-1 prevalence worldwide [16]. Here, we explore the relationship between viral load, cellular activation, innate immunity effector levels and adipose tissue-related measures in a cohort of antiretroviral therapy (ART)-naïve South African women.

Methods

Study subjects

A cross-sectional convenience sample of 83 ART-naïve, HIV-1 infected women without evidence of prior or

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ongoing opportunistic infection was enrolled at the Clinical Research HIV-1 Unit, Themba Lethu Clinic (University of the Witwatersrand, Johannesburg, South Africa). Screening CD4+ T cell count was 200-350 cells/mm³. Medical history was obtained from the clinic record and by interview. Informed consent was obtained from all participants as per University of the Witwatersrand Ethics Committee and Wistar Institute IRB-approved study protocol.

Flow cytometry

CD4+ T cell counts were assessed using the single platform method described by Scott and Glencross [17]. Expression of lineage, differentiation and activation markers on CD3+ T cells (CD4, CD8, CD38, CD95, HLA-DR, CD28), CD3- NK cells (CD16, CD56, HLA-DR) and Lin-1⁻ Dendritic cells (Lin-1, HLA-DR, CD123, CD11c) was assessed on whole peripheral blood using lyophilized mAb panels (BD Biosciences, Palo Alto, CA). Samples were tested using a Faxcalibur Analyzer, followed by analysis using CellQuest software (BD Biosciences).

Adipose tissue measurements

Body mass index (BMI) was calculated as weight (kg)/height (m)². Dual Energy X-ray Absorptiometry (DEXA) scans were performed using a Hologic QDR-2000 scanner, assessing limb and trunk fat and lean mass. Bone mineral density (g/cm²) was also measured.

Magnetic resonance imaging (MRI) scans were performed using a Toshiba Flexart 0.5 T; a single L4-L5 axial section was analyzed. Variables collected were sagittal diameter, visceral, subcutaneous abdominal and perirenal fat. The analysis was conducted using V3.51*R553 software.

Clinical laboratory testing

Serum from fasting blood draws was tested for:

- *Leptin*: ELISA, BioVendor Laboratory Medicine, Inc, Czech Republic
- *High density lipoprotein (HDL)- and low density lipoprotein (LDL)-associated cholesterol, triglycerides, glucose*: Roche Integra analyzer 400, Roche Diagnostics, Mannheim, Germany
- *Insulin*: Immulite 1000 analyzer Diagnostics Corp, Los Angeles, CA
- *Proinsulin*: ELISA, Dako-Cytomation Ltd (UK)
- *Free fatty acids (FFA)*: half-micro test, Roche Diagnostics, Mannheim, Germany
- *HIV-1 infection (confirmation)*: rapid antibody testing and/or Ultra-sensitive (US) PCR, (Roche COBAS Ampliprep/COBAS Amplicor v1.5 methods)
- *Homeostatic Model Assessment for insulin resistance (HOMA2-IR)* was determined using the

HOMA2 calculator, v. 2.2, from the Diabetes Trials Unit, University of Oxford, GB <http://www.dtu.ox.ac.uk/homa>.

Statistical analysis

Study subjects were divided into two groups: Group 1 (low viral load, LVL): 41 subjects, viral load (VL) < sample median; and Group 2 (high viral load, HVL): 42 subjects, VL ≥ sample median. Differences in means between groups for each of the variables listed in Table 1 were tested using two-sample t-tests. Corresponding p-values and q-values based on the positive false discovery rate (FDR) are reported; q-values of less than 0.2 were considered meaningful. Pairwise correlations were tested by determining the Pearson correlation coefficient (r).

The effect of selected variables on log₁₀VL (univariate analysis) was assessed by fitting a linear model using the least square method. Additionally, a multivariable linear model was fitted to log₁₀VL using a step-wise approach based on likelihood ratio tests [18]. For the final model, Wald test statistics with p-values < 0.1 were considered relevant. Goodness-of-fit was evaluated based on the adjusted coefficient of determination (R²): briefly, variables were added individually to the model, and those variables that did not lead to an increase of R² were rejected. All statistical tests were performed using r vers. 2.10.0 ("the r Foundation for Statistical Computing", <http://www.r-project.org/>).

Results

Cohort clinical and immunological characterization

Eighty-three HIV-1-infected, ART-naïve women, aged 19 to 55 (mean age 34.5 years, see Table 1), and of black (n = 81) or mixed race (n = 2) were studied. The cohort median serum HIV RNA (VL) was 60,400 copies of HIV RNA/ml (log₁₀VL = 4.78; IQR = 1.21). Based on BMI, our cohort was composed of three underweight (BMI < 18.5 kg/m²), 33 normal weight (BMI 18.5-24.9 kg/m²), 26 overweight subjects (BMI 25-29.9 kg/m²) and 20 obese subjects (BMI > 30 kg/m²), in keeping with prior reports on similar South African cohorts [19]. The cohort mean CD4+ T cell count was 260 cells/mm³, indicative of moderately advanced disease. Due to enrolment restrictions of 200-350 CD4+ T cell count/mm³, entry CD4+ T cell counts were only slightly lower in HVL (Table 1) than LVL subjects. However, confirming previous reports [20,21], cellular activation was higher in HVL subjects, as assessed by the expression of CD38 on CD4+ and CD8+ T cells, and of HLA-DR on CD4+ T cells (Table 1). Likewise, we did not detect significant differences in the levels of mature or activated NK cells, or of plasmacytoid (PDC) or myeloid (MDC) dendritic cells.

Table 1 Expression of metabolic, anthropometric and immunologic markers in high and low viral load subjects

Variables	Units	All subjects (n = 83)			VL ≥ median (n = 42)			VL < median (n = 41)			unadjusted p *	FDR q**
		N	Mean	SD	N	Mean	SD	N	Mean	SD		
Age	years	83	34.5	8.2	42	34.7	8.4	41	34.3	8.2	0.85	0.86
log ₁₀ VL	c/ml	83	4.5	0.8	42	5.2	0.3	41	3.9	0.6	n/a	n/a
Immunology markers:												
CD4+ T cell count	cells/mm ³	83	260.8	53.9	42	249.0	50.7	41	272.9	54.9	0.04	0.14
CD8+ T cell count	cells/mm ³	59	814.0	484.0	29	874.6	560.8	30	755.4	397.1	0.35	0.51
% CD38+ CD4+ T cells	% of CD4	60	75.5	11.3	30	79.0	9.0	30	72.0	12.3	0.02	0.1
% CD38+ CD8+ T cells	% of CD8	60	87.0	11.2	30	91.1	7.8	30	82.8	12.6	0.0034	0.1
% HLA-DR+ CD4+ T cells	% of CD4	60	26.25	9.71	30	29.5	10.04	30	23.0	8.3	0.0090	0.1
% HLA-DR+ CD8+ T cells	% of CD8	60	56.4	14.3	30	59.6	14.6	30	53.2	13.4	0.08	0.1
% CD95+ CD4+ T cells	% of CD4	60	78.5	10.9	30	80.6	10.9	30	76.4	10.6	0.13	0.28
% CD95+ CD8+ T cells	% of CD8	60	60.6	7.2	30	60.4	6.1	30	60.8	8.3	0.84	0.86
% CD28+ CD4+ T cells	% of CD4	60	80.7	11.1	30	80.1	10.7	30	81.2	11.7	0.70	0.82
% CD28+ CD8+ T cells	% of CD8	60	30.8	9.3	30	30.3	9.7	30	31.3	9.1	0.68	0.82
Total NK cells	cells/mm ³	59	12.9	10.2	29	14.4	12.9	30	11.5	6.6	0.28	0.46
% CD56+/CD16+ cells	% of NK	60	54.9	20.1	30	50.4	18.8	30	59.4	20.6	0.08	0.1
% CD56+/CD16- NK cells	% of NK	60	22.1	16.2	30	23.4	17.6	30	20.9	14.9	0.55	0.74
% HLA-DR+ total NK cells	% of NK	60	19.9	16.8	30	22.2	17.9	30	17.6	15.6	0.29	0.46
% HLA-DR+ CD56+/CD16+ NK cells	% of NK	60	23.0	20.8	30	26.2	22.7	30	19.7	18.6	0.23	0.4
Plasmacytoid dendritic cells	cells/mm ³	58	0.2	0.1	28	0.1	0.1	30	0.2	0.1	0.18	0.37
Myeloid dendritic cells	cells/mm ³	59	0.5	0.8	29	0.5	0.6	30	0.5	1.0	0.86	0.86
Adipose tissue-associated variables:												
Body mass index (BMI)	kg/m ²	82	27.4	7.1	41	25.6	6.4	41	29.2	7.4	0.02	0.1
Waist circumference	cm	83	83.9	14.9	42	80.2	13.4	41	87.6	15.5	0.02	0.1
Subcutaneous abdominal fat (MRI)	cm ²	81	338.8	195.9	42	294.2	185.9	39	386.9	197.3	0.03	0.12
Visceral abdominal fat (MRI)	cm ²	81	51.5	30.4	42	47.3	28.8	39	56.1	31.9	0.20	0.37
Perirenal hilar fat (MRI)	cm ²	81	5.7	3.1	42	5.5	3.4	39	6.0	2.8	0.40	0.56
Total fat mass (DEXA)	kg	80	26.2	12.2	41	24.1	11.9	39	28.5	12.2	0.11	0.28
Total lean mass (DEXA)	kg	80	40.9	5.9	41	39.8	54.4	39	42.1	6.1	0.09	0.26
Leg fat mass (DEXA)	kg	80	11.6	5.6	41	10.8	4.5	39	12.5	6.5	0.20	0.37
Trunk fat mass (DEXA)	kg	80	10.4	6.1	41	9.4	6	39	11.5	6	0.03	0.12
Weight	kg	83	70.2	17.9	42	67.2	17.1	41	73.2	18.3	0.12	0.28
Reported weight loss	% true	83	38	n/a	42	40	n/a	41	36.7	n/a	0.86***	0.86
Leptin	ng/ml	66	28.3	17.6	33	23.4	17.7	33	33.3	16.3	0.02	0.1
Triglycerides	mmol/l	77	0.9	0.4	38	0.9	0.3	39	0.9	0.4	0.57	0.74
LDL-associated cholesterol	mmol/l	77	2.3	0.8	38	2.2	0.6	39	2.3	0.9	0.62	0.78
Free fatty acids	mmol/l	66	0.5	0.2	33	0.5	0.2	33	0.4	0.3	0.31	0.47
Glucose	mmol/l	74	4.3	0.4	37	4.3	0.4	37	4.3	0.4	0.75	0.85
HOMA2-IR	n/a	67	0.9	0.5	32	0.8	0.4	35	1.0	0.6	0.10	0.27

* based on two-sample t-test

** false discovery rate. q values < 0.2 were considered significant

*** Chi square test

Association of viral load with adipose tissue

HVL women had lower BMI and waist circumference than LVL women (Table 1). Direct MRI assessments of abdominal fat content confirmed that HVL subjects had considerably less subcutaneous abdominal fat than LVL women, but similar amounts of visceral and perirenal fat (Table 1). HVL women also had slightly lower DEXA scan-based fat and lean mass measurements than LVL

women, but only trunk fat mass reached the level of significance, confirming that the difference in adipose tissue between HVL and LVL women is due to differential representation of central fat. Bone density was similar in the two groups (not shown).

We tested a number of markers associated with fat and glucose regulation (Table 1); of all the indicators assessed, only leptin levels were significantly lower in HVL subjects.

As expected, leptin levels were directly correlated with BMI ($r = 0.6991$; $p < 0.0001$), MRI-measured subcutaneous (Figure 1) or visceral abdominal fat ($r = 0.7755$ and 0.5417 , respectively, both $p < 0.0001$) or DEXA-based total fat mass, ($r = 0.7637$; $p < 0.0001$).

Unlike direct measures of adiposity, serum lipids and glucose were similar in HVL and LVL women.

Visceral fat was positively associated with levels of insulin ($r = 0.3861$, $p = 0.0010$), C-peptide ($r = 0.5331$, $p < 0.0001$) and HOMA2-IR ($r = 0.2774$, $p = 0.0241$), but not proinsulin/insulin ratio; similar results were obtained for subcutaneous abdominal fat. Reported recent weight loss rates and free fatty acids (FFA) levels were similar in both groups (Table 1), and FFA showed no association with the amount of adipose tissue ($r = 0.1084$, $p = 0.3868$).

Modelling of leptin levels as a predictor of viral load, independent of fat accumulation

To determine the relationship between metabolic parameters and viral replication, we first assessed the relationship of all individual variables (see Table 1) with

\log_{10} VL by fitting a linear model using all available data points (i.e., no censoring of subjects missing individual variable measurements). As illustrated in Table 2 and Figure 2, of the 35 variables tested, only eight had a significant ($p < 0.05$) effect on \log_{10} VL based on univariate analysis. As expected, the direction of this effect was positive for parameters associated with activation (CD4+ T cells expressing CD38 or HLA-DR, CD8+ T cells expressing CD38), indicating that subjects with higher viral load also have higher cellular activation. Conversely, a negative effect was observed for PDC counts, mature NK cell frequency, as well as BMI, subcutaneous abdominal fat and leptin (Figure 2), supporting the observations of differences between HVL and LVL women, as we have described. Importantly, the negative association between leptin serum levels and \log_{10} VL was maintained ($n = 65$; effect estimate = -0.0186653 ; $p = 0.0289$), even after adjusting for subcutaneous abdominal fat area in multivariate analysis, supporting a direct association between leptin levels and viral replication, independent of the amount of adipose tissue.

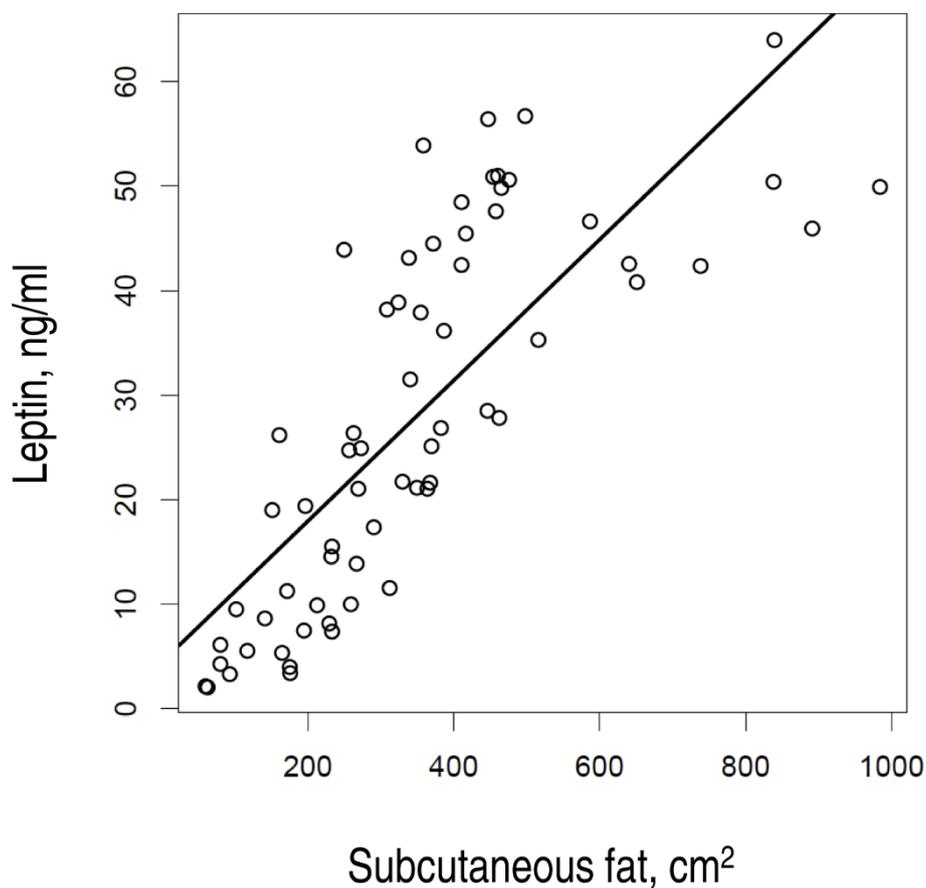


Figure 1 Association of serum leptin levels with subcutaneous fat. Linear regression modelling of the association between observed serum leptin levels and MRI-assessed subcutaneous fat area. Circles represent individual observations. $P < 0.0001$; adjusted $R^2 = 0.5983$.

Table 2 Variable association with log₁₀VL, univariate analysis*

Predictor	n	Effect estimate	SE	Pr(> t)	Adjusted R ²
% CD56+/CD16+ NK cells	60	-0.005	0.005	0.0048	0.1140
% HLA-DR+ CD4+ T cells	60	0.020	0.009	0.0358	0.0092
% CD38+ CD4+ T cells	60	0.020	0.009	0.0358	0.0578
% CD38+ CD8+ T cells	60	0.025	0.009	0.0091	0.0964
Plasmacytoid dendritic cells	58	-1.718	0.814	0.0392	0.0572
Leptin	66	-0.003	0.005	0.0130	0.0784
Subcutaneous abdominal fat (MRI)	81	-0.001	0.0004	0.0400	0.0403
Body mass index (BMI)	82	-0.025	0.012	0.0403	0.0397

* linear model fitting, least squares method

The eight variables with univariate association to log₁₀VL were further tested in a subset of subjects with complete datasets (no missing variable measurements; n = 45). Based on their ability to improve the model predictivity (as assessed by testing the model likelihood

ratio), five significant variables were selected to build the additive model: the estimate terms for the model and corresponding test statistics are provided in Table 3. Leptin levels, mature NK frequency and PDC count have a negative effect on log₁₀VL that were significant

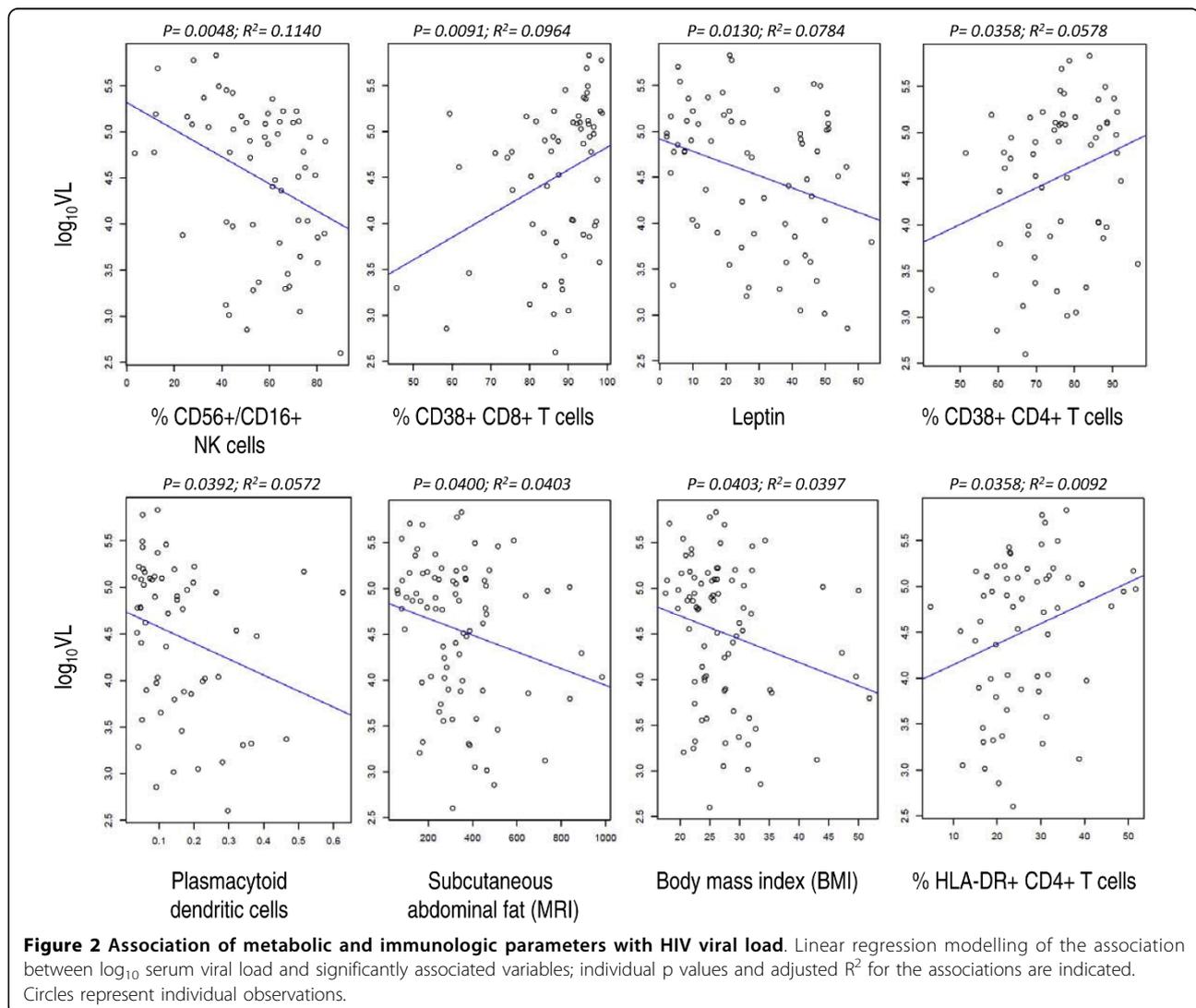


Table 3 Effect* of selected variables on viral load: multivariate analysis

Predictor	Effect estimate	SE	T value	Pr (> t)
Intercept	3.896921	0.839040	4.644	<0.0001
% CD56+/CD16+ NK cells	-0.009494	0.005328	-1.782	0.0826
Leptin	-0.011514	0.005597	-2.057	0.0464
Plasmacytoid dendritic cells	-2.801874	1.147009	-2.443	0.0192
% HLA-DR+ CD4+ T cells	0.017391	0.010856	1.602	0.1172
% CD38+ CD8+ T cells	0.016283	0.009788	1.664	0.1042

Residual standard error: 0.6274 on 39 degrees of freedom

Multiple R-squared: 0.4301, Adjusted R-squared: 0.357

F-statistic: 5.877 on 5 and 39 DF, p-value: 0.0003816

* The final model is an additive model with main effects for each of the terms

at the 10% level, whereas the positive effect of the expression of CD38 on CD8+ T and HLA-DR on CD4+ T cells was not significant. Taken together, our analysis indicates that leptin levels, together with mature NK and PDC frequency, remain negatively associated with \log_{10} VL after adjustment for multiple metabolic and activation parameters, suggesting an independent association.

Discussion

We show for the first time that leptin levels are associated with viral load after adjusting for fat measurements. Body fat changes in HIV-infected individuals have been the subject of a number of studies, many of which have focused on ART-associated lipodystrophy [22-26]. Yet to our knowledge, no study has directly sought to determine the relationship between fat, leptin and HIV replication. Importantly, since opportunistic infections (OIs), in association with lower CD4+ T cell count, might also contribute to low adiposity in chronic HIV infection (via LPS-induced TNF, limited food intake, malabsorption, etc.), we chose to study OI-free, ART-naïve women within a narrow CD4+ T cell count range (200-350 CD4+ T cell count/mm³ at screening); however, a contribution of prior or subclinical OIs and other potential confounding factors cannot be categorically excluded.

The narrowness of the cohort's CD4+ T cell count range (which limits the confounding effects of this variable) might explain the observed lack of a significant effect of CD4+ T cell count levels on VL, which has been consistently reported in larger, unrestricted cohorts [27]. However, as expected, in our cohort, viral load was positively associated with immune activation (CD38 and HLA-DR expression) and negatively associated with the frequency of innate immunity effectors (PDC and mature NK cells) in peripheral blood, confirming prior observations [28-32].

HVL women showed lower BMI, waist circumference and subcutaneous abdominal fat than LVL women, with a significant negative association between VL and several measures of central fat. Leptin levels observed in LVL women were similar to those observed in a cohort of 50 healthy women with similar age, ethnicity and provenance (median BMI 27 kg/m², IQR 10.85; median serum leptin 36.15 pg/ml, IQR = 38.95, N Crowther, unpublished results).

As predicted by the fact that leptin is mainly produced by subcutaneous fat adipocytes [33], this adipokine was also lower in HVL women, and its levels are inversely correlated to viral replication. Interestingly, however, HOMA2-IR, another marker usually highly correlated with adiposity, presented no association with VL in our cohort, and was only weakly associated with leptin levels ($p = 0.0751$). Taken together, these results indicate that: (a) adipose tissue is associated with both leptin levels and insulin resistance; and (b) only leptin levels are inversely associated with viral replication, suggesting the hypothesis that the inverse relationship between viral replication and leptin levels may be independent of the amount of adipose tissue. Formal testing of this hypothesis in a multivariate model demonstrated that the effect of leptin is in fact independent of direct measures of fat (e.g., subcutaneous fat area).

With the exception of leptin, serum molecules associated with adipose tissue and obesity (e.g., total or LDL cholesterol, triglycerides, glucose, insulin) did not independently correlate with VL in our cohort, in contrast with prior reports that VL could predict BMI in HIV-infected women [2], and correlate negatively with LDL and HDL cholesterol and positively with triglycerides, but not with insulin or glucose levels [34,35]. Indeed, we confirmed the selection of leptin over any other adipose tissue measure that appeared to be individually correlated with \log_{10} VL by introducing BMI or subcutaneous abdominal fat in a multivariate model with leptin: neither carried a significant independent association ($p = 0.3667$ and 0.884 , respectively), and both actually resulted in making our model less accurate by reducing the adjusted R² (0.063 and 0.05, as compared to 0.066 for leptin alone).

Therefore, among measures and correlates of adipose tissue, leptin remained the variable best associated with viral replication, suggesting the possibility that leptin may play a role in the observed significant association between fat and viral replication. Interestingly, prior studies (FRAM cohort [36]) testing whether viral replication was associated with serum adipokines did not evidence a significant association between adiponectin and leptin levels and HIV viral load: the fact that our cohort is composed only of ART-naïve women with a narrow CD4 range, and possibly the high levels of

adiposity in our cohort, might contribute to this discordance.

Based on leptin's known immunomodulatory activity [6-8,13,37,38], it is interesting to speculate that in HVL women, lower leptin levels may contribute to chronic immune activation, in keeping with the observed increased expression of CD38 and HLA-DR in T cell subsets. Obesity is associated with chronic low-level inflammation and high levels of TNF- α [39], which is produced by subcutaneous adipocytes [40]. This condition would be expected to promote viral replication since TNF- α promotes HIV replication via NF- κ B activation [41].

The negative association between leptin and viral replication that we report here suggests that leptin, which is produced by adipocytes in response to exposure to TNF- α [42], may be part of a negative regulatory feedback that attenuates the pro-inflammatory and pro-replicative effects of TNF- α . Interestingly, this effect is likely lost in chronic inflammatory conditions where a negative association between TNF- α and leptin production has been observed [43,44]. Conversely, increased body fat may attenuate viral load via the effects of other mediators (e.g., MIP-1 α) known to suppress HIV infection [45]). Another potential mechanism could be that high viral replication and cellular activation may result in chronic inflammation, affecting adipocytes and causing lipoatrophy and lower leptin levels.

The interpretation of these results should be qualified in light of the cross-sectional design of the study, which does not allow the interpretation of cause-effect relationships in the variables studied. Further longitudinal studies focusing on these factors will be required to determine whether fat changes directly contribute to alterations in viral replication via adipocyte-mediated leptin secretion.

Conclusions

Our data provide the first demonstration of a relationship between VL and leptin in African women and suggest that lower leptin levels associated with the loss of adipose tissue may contribute to disease progression.

Abbreviations

ART: antiretroviral therapy; BMI: body mass index; DEXA: dual energy X-ray absorptiometry; FDR: false discovery rate; FFA: free fatty acids; HDL: high density lipoprotein; HOMA2-IR: homeostatic assessment for insulin resistance; HVL: high viral load; LDL: low density lipoprotein; LVL: low viral load; MDC: myeloid dendritic cells; MRI: magnetic resonance imaging; OI: opportunistic infection; PDC: plasmacytoid dendritic cells; VL: viral load;

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Authors' contributions

LA was responsible for study design, data management, critical analysis, manuscript and illustration preparation. NJC undertook leptin and lipid assessment, critical analysis, data discussion and manuscript preparation. CF undertook clinical coordination, patient interaction, data discussion and manuscript preparation. ASF undertook statistical analysis, data discussion and manuscript preparation. XY undertook statistical analysis, data discussion and manuscript revision. DG undertook flow cytometry analysis, CD4+ T cell count assessment, data discussion and manuscript preparation. RG undertook statistical and epidemiology analysis, data discussion and manuscript preparation. MDK undertook DEXA scan and MRI performance, DEXA data analysis, data discussion and manuscript preparation. EP undertook data discussion and manuscript revision. DS undertook database management, data discussion and manuscript revision. WS undertook clinical laboratory test performance, data discussion and manuscript preparation. TvdM undertook MRI data analysis, data discussion and manuscript revision. RW undertook leptin and lipid assessment, critical analysis, data discussion and manuscript revision. IS undertook clinical site supervision, clinical coordination, patient interaction, data discussion and manuscript preparation. LJM undertook study design, immunology laboratory supervision, critical analysis and manuscript preparation. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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