LIPODYSTROPHY IS AN IMPORTANT DETERMINANT OF MARKERS OF ARTERIAL INFLAMMATION IN HIV

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Background

•Individuals living with HIV well-treated on antiretroviral therapies remain at risk for ensuing arterial inflammation.

•The exact mechanism for inflammatory-mediated cardiovascular disease (CVD) in HIV remains unclear.

•HIV lipodystrophy has been associated with advanced metabolic disease. In this regard, visceral adipose tissue (VAT) accumulation and subcutaneous adipose tissue (SAT) loss may contribute to a unique and highly inflamed phenotype that contributes to CVD.

Objectives

We sought to investigate the relationship between adipose depots and specific markers of arterial inflammation to gain insight into the potential link between lipodystrophy and CVD risk. We took advantage of a previously recruited study of 155 HIV-infected and 70 non-HIV-infected individuals without known CVD who were well-phenotyped for body composition.

We hypothesized that markers of arterial inflammation would be increased in relation to excess VAT and loss of SAT in the HIV population, a metabolic phenotype and pattern of fat redistribution that has been associated with pronounced inflammation.

Methods

Study Participants and Design

•Inclusion criteria for all individuals: age ≥ 18 and ≤ 60 years.
•Inclusion criteria for HIV-infected individuals: stable ART regimen ≥ 3 months.
•Major exclusion criteria for all subjects: history of CVD or symptoms suggestive of CVD; contraindications to CT abdomen; creatinine level >1.5 mg/dL or creatinine clearance <60 mL/min

Body Composition Phenotyping

The iliac crest served as the anatomic reference to standardize waist circumference. Body mass index (BMI) was calculated using height and weight. Body adiposity index (BAI) was calculated as [hip circumference taken at the broadest location/(height)$^{1.5}$]-18. VAT and SAT were quantified on an axial non-contrast CT slice through the abdomen at the level of the L4 pedicle. Abdominal visceral and subcutaneous fat areas were determined based on offline analysis of tracings obtained utilizing commercial software (Vitrak, Merge e/Film).

Laboratory Assessment

Biomarkers were obtained after individuals underwent a 12 hour fast:
•Serum lipoprotein-associated phospholipase A2 (LpPLA2) was quantified with activity assay reagents (Diadexus, San Francisco, CA) on a Vista Dimension 1500 system (Siemens Healthcare Diagnostics, Glasgow, DE). Measurement range was 10-400 nmol/min/mL and inter-assay CVs were 1.7% and 3.2% at values between 97 and 304 nmol/min/mL.

•Serum high sensitivity troponin T (hs-cTnT) was measured using specific reagents for the Cobas e 601 instrument system (Roche Diagnostics, Indianapolis, IN). Measurement range was 3.0 -10,000 ng/L and inter-assay CVs ranged from 3.6% and 2.3% at values between 28 and 4962 ng/L.

•Serum oxidized LDL (oxLDL) was assayed using ELISA with a measurement range of 8-150 U/L. Inter-assay CVs ranged from 8.3% to 7.4% at values between 8.5 and 32 U/L.

•Plasma high sensitivity C-reactive protein (hsCRP) were quantified by ELISA (Labcorp).

Statistical Analysis

Normality of distribution was assessed using the Shapiro-Wilks test. Data are presented as mean ± SEM if normally distributed or median [IQR] if not normally distributed. Categorical variables are reported as proportions. Between group comparisons (HIV or non-HIV) were made using the Student's t-test for normally distributed variables or Wilcoxon Rank Sums test for non-normally distributed variables. Spearman's correlation coefficient was used to perform linear regression to relate body composition to markers of arterial inflammation by HIV status. Multivariate regression was performed among the HIV group to assess independent effects of HIV-related parameters and body composition on markers of arterial inflammation. Statistical significance was defined as P≤0.05. All statistical analyses were performed using SAS JMP (version 12.0).

Results

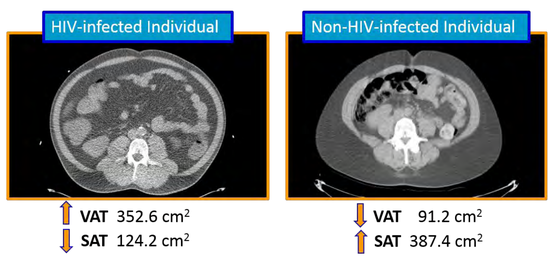
Table 1. Baseline Demographics and Clinical Characteristics of HIV and Non-HIV-infected Individuals

	HIV-Infected (n=155)	Non-HIV-Infected (n=70)	P Value
Demographics			
Age (years)	47±1	46±1	0.17
Race (%)			0.38
Caucasian	53	51	
African American	40	37	
Male Sex (%)	61	59	0.70
Current Tobacco Use (%)	44	40	0.56
Current Dyslipidemia (%)	34	23	0.08
Current Statin Use (%)	14	4	0.03
Current Diabetes Mellitus (%)	10	7	0.43
Current Hypertension (%)	24	16	0.18
HIV Parameters			
CD4$^+$ T cell count (cells/μL)	552±24	N/A	--
CD4$^+$ T cell nadir (cells/μL)	193±15	N/A	--
CD8$^+$ T cell count (cells/μL)	912±40	N/A	--
Log HIV RNA Viral Load (copies/mL)	1.82±0.04	N/A	--
Duration HIV (years)	14±1	N/A	--
Duration ART use (years)	8±0	N/A	--
Current PI use (%)	55	N/A	--
Current NRTI use (%)	95	N/A	--
Current NNRTI use (%)	37	N/A	--
History of HCV infection (%)	27	9	0.0008
Body Composition and Metabolic Parameters			
Iliac Waist Circumference (cm)	97±1	97±2	0.90
Waist to Hip Ratio	0.94±0.01	0.92±0.01	0.19
BMI(kg/m^2)	27±1	27±0	0.31
BAI (%fat)	50±1	50±1	0.99
VAT (cm^2)	109 [54,174]	103 [54,174]	0.35
SAT (cm^2)	199 [126,288]	239 [148,358]	0.04
VAT/SAT	0.54 [0.30,1.13]	0.42 [0.23, 0.79]	0.03
Adiponectin (ng/mL)	5401 [2532,10200]	4362 [3326,7106]	0.50
Total Cholesterol (mg/dL)	183±4	180±4	0.53
Triglycerides (mg/dL)	97 [77,172]	84 [62,121]	0.001
HDL (mg/dL)	50 [41,62]	49 [42,64]	0.81
LDL (mg/dL)	98 [78,124]	105 [89,127]	0.25
ALT (U/dl)	35±2	25±2	0.0006
AST (U/dL)	39±2	28±2	0.001
Systolic BP (mmHg)	119±1	117±2	0.16
Diastolic BP (mmHg)	76±1	76±1	0.62

Table 2. Markers of Arterial Inflammation among HIV and Non-HIV-Infected Individuals

	HIV-Infected (n=155)	Non-HIV-Infected (n=70)	P Value
Markers of Arterial Inflammation			
LpPLA2 Activity (nmol/min/mL)	184.2[152.6,229.7]	173.0[146.7,216.6]	0.12
Oxidized LDL (U/L)	43.9[33,54]	44.4[35.8,56.4]	0.48
hs-cTnT (ng/L)	3.09[2.99,6.44]	2.99[2.99,3.99]	0.03
hsCRP (mg/L)	1.4[0.5,3.9]	1.3[0.5,3.5]	0.67

Figure 1.
Sample comparison of an HIV-infected individual vs. a non-HIV-infected individual participating in the study. Single slice of the CT abdomen taken at the level of the L4 body demonstrating relatively increased VAT and decreased SAT in HIV vs. non-HIV. In parallel to changes in fat redistribution, markers of arterial inflammation are relatively increased in HIV vs. non-HIV.



LpPLA2 Activity (nmol/min/mL)	217.136	109.295
Oxidized LDL (U/L)	47.7	42.4
hs-cTnT (ng/L)	7.35	2.99
hsCRP (mg/L)	3.3	0.2

Results (cont.)

Table 3. Markers of Arterial Inflammation among HIV and Non-HIV-Infected Individuals

	LpPLA2 Activity (nmol/min/mL)		Oxidized LDL (U/L)		hs-cTnT (ng/L)		hsCRP (mg/L)	
	ρ	P Value	ρ	P Value	ρ	P Value	ρ	P Value
HIV-Infected Subjects (n=155)								
Waist Circumference (cm)	0.001	0.99	0.20	0.02	0.08	0.33	0.39	<0.0001
Waist to Hip Ratio	0.16	0.06	0.21	0.02	0.240	0.007	0.28	0.002
BMI (kg/m^2)	-0.05	0.50	0.22	0.007	-0.02	0.83	0.36	<0.0001
BAI (%fat)	-0.03	0.75	0.19	0.03	0.02	0.83	0.39	<0.0001
SAT (cm^2)	-0.19	0.02	0.12	0.16	-0.24	0.004	0.17	0.04
VAT (cm^2)	0.25	0.003	0.28	0.005	0.28	0.0007	0.32	<0.0001
VAT/SAT	0.38	<0.0001	0.16	0.06	0.40	<0.0001	0.16	0.06
Adiponectin (μg/mL)	-0.23	0.02	-0.18	0.07	-0.16	0.12	-0.13	0.22
Non-HIV-Infected Subjects (n=70)								
Waist Circumference (cm)	0.10	0.45	0.13	0.31	0.06	0.62	0.20	0.11
Waist to Hip Ratio	0.32	0.01	0.31	0.01	0.18	0.17	0.24	0.06
BMI (kg/m^2)	0.03	0.84	0.05	0.71	0.04	0.73	0.18	0.14
BAI (%fat)	0.02	0.87	0.12	0.36	-0.03	0.84	0.21	0.10
SAT (cm^2)	-0.24	0.05	-0.07	0.58	-0.19	0.12	0.15	0.24
VAT (cm^2)	0.37	0.002	0.24	0.05	0.10	0.42	0.29	0.02
VAT/SAT	0.49	<0.0001	0.19	0.12	0.30	0.01	0.20	0.11
Adiponectin (μg/mL)	-0.31	0.05	-0.16	0.32	-0.10	0.53	0.03	0.84

Table 4. Model to Assess Determinants of Markers of Arterial Inflammation among HIV-Infected Individuals

	LpPLA2 Activity (nmol/min/mL)		Oxidized LDL (U/L)		hs-cTnT (ng/L)		hsCRP (mg/L)	
Overall Model	(R^2=0.13; P=0.005)		(R^2=0.10; P=0.03)		(R^2=0.08; P=0.08)		(R^2=0.07; P=0.12)	
	β Estimate	P Value	β Estimate	P Value	β Estimate	P Value	β Estimate	P Value
HIV-Infected Subjects								
Age (years)	0.3094	0.66	0.1204	0.54	0.1212	0.24	-0.0067	0.90
CD4+ count (cells/μL)	-0.0148	0.36	-0.0020	0.66	0.0014	0.56	-0.0005	0.68
Log HIV viral load (copies/mL)	-10.4531	0.34	-1.5876	0.60	1.0740	0.50	0.7988	0.34
SAT (cm^2)	-0.0994	0.006	0.0093	0.34	-0.0120	0.02	0.0043	0.12
VAT (cm^2)	0.1248	0.007	0.0371	0.004	0.0091	0.17	0.0068	0.05

Summary

•Despite similar BMI and VAT, HIV-infected individuals (199[126,288] vs. 239[148,358]cm^2, P=.04) had significantly lower SAT compared to non-HIV-infected indviduals. (Table 1)

•Reduced SAT was inversely correlated with LpPLA2 (ρ=-0.19, P=.02) and hsTNT (ρ=-0.24, P=.004) among HIV-infected individuals. (Table 3)

•Furthermore, increased VAT was significantly and positively related to LpPLA2 (ρ=0.25, P=.003), oxLDL (ρ=0.28, P=.005), hsTNT (ρ=0.28, P=.0007), and hsCRP (ρ=0.32, P=<.0001) among the HIV group (Table 3)

•Similar analyses among the non-HIV group revealed significant relationships between SAT and LpPLA2 (ρ=-0.24, P=.05), as well as VAT and LpPLA2 (ρ=0.37, P=.002), oxLDL (ρ=0.24, P=.05), and hsCRP (ρ=0.29, P=.002). (Table 3)

•In separate models simultaneously controlling for VAT, SAT, age, CD4+ count, and viral load among HIV-infected individuals, reduced SAT was an independent predictor of LpPLA2 (P=.006) and increased VAT was an independent predictor of LpPLA2 (P=.007) and oxLDL (P=.004). (Table 4)

Conclusions

Highly inflamed adipose tissue, in the context of SAT loss and/or VAT accumulation (Figure 1), may be linked to arterial inflammation. Strategies to reduce lipodystrophy and restore normal adipose biology may have therapeutic benefit to dampen arterial inflammation in the HIV population among whom traditional risk factor modification does not completely mitigate CVD risk.

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