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Adiponectin and Interleukin-6, But Not Adipose Tissue, Are Associated with Worse Neurocognitive Function in HIV-Infected Men

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Abstract

Background—Generalized obesity has been associated with cognitive decline, a process potentially mediated by adipocytokines. The effects of regional adipose tissue (AT) on cognition, however, are not well understood. We explored cross-sectional relationships between regional AT, adipocytokines, inflammatory markers and neuropsychological (NP) test scores among HIV+ and HIV− men enrolled in the Multicenter AIDS Cohort Study.

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Methods—Visceral, subcutaneous abdominal and subcutaneous thigh AT areas were quantified by computed tomography (CT). NP tests (Trail Making Test parts A and B and Symbol Digit Modalities) obtained within two years of CT screened for psychomotor speed and executive function. Adiponectin, leptin, interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) were measured.

Results—Of 509 HIV+ and 271 HIV− participants, HIV+ men (98% on ART, 81% HIV-1 RNA <50copies/mL) had lower median subcutaneous AT and adiponectin levels and higher hs-CRP levels, but visceral AT, BMI, IL-6 and NP scores did not vary by HIV serostatus. In multivariable analysis, older age, ≤high school education and African American race, but not AT area or site, were associated with worse NP test scores among all participants. In HIV+ only, higher adiponectin and IL-6 were associated with worse cognitive function independent of AT area. No HIV-specific factors were associated with NP test scores.

Conclusions—Demographic factors were associated with NP test performance, but regional adiposity was not. In HIV+ only, higher adiponectin and IL-6 were associated with worse NP test scores, supporting a role for chronic inflammation and adipocytokine imbalance in neurocognitive decline in HIV+ persons.

INTRODUCTION

HIV-infected (HIV+) patients on antiretroviral therapy (ART) may experience regional adipose tissue changes ranging from peripheral lipoatrophy to central lipohypertrophy (including visceral fat accumulation). While visceral adiposity has been associated with multiple metabolic perturbations (including changes in insulin glucose homeostasis, dyslipidemia and cardiovascular disease) in both HIV+ and HIV−uninfected (HIV−) subjects,[1–7] other regional adipose tissue depots have recently been shown to confer disparate risk profiles by HIV serostatus. For example, in the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) Study, greater cardiovascular disease risk correlated with greater thigh subcutaneous adipose tissue in HIV− subjects, but less thigh adipose tissue in HIV+ subjects.[4] Whether regional fat redistribution imparts other differential health risks by HIV infection status is still unclear.

In HIV− persons, generalized obesity and visceral adipose tissue (VAT) accumulation have been associated with declines in cognitive function.[8, 9] In the Health ABC study of elderly subjects, higher levels of total [8] and subcutaneous adipose tissue (SAT) were associated with greater declines in Modified Mini Mental State Examination scores in men only, after adjustment for confounding factors. A similar but not statistically significant trend was seen for VAT in men.[8] Associations between isolated increased waist circumference (a commonly used surrogate for VAT volume) and the risk of dementia or other measurable cognitive impairment was also reported in the SALSA cohort of Latino men and women over the age of 60.[9]

In HIV+ persons, an association between increased waist circumference and neurocognitive impairment has been described,[10] and the presence of clinical lipodystrophy (whether lipoatrophy or lipohypertrophy) has been associated with decreased grip strength (an index of physical function),[11] but relationships between regional adipose tissue accumulation or

atrophy and cognitive decline are not well defined.[12, 13] However, chronic inflammation has been associated with cognitive decline in the general population,[14, 15] and both lipoatrophy and lipohypertrophy in HIV have been associated with pro-inflammatory cytokine profiles.[16, 17] Similarly, adipocytokines may be a link between regional adipose tissue and cognitive function in the general population. Higher leptin levels have been associated with lower incident dementia and Alzheimer's disease rates,[18] and higher adiponectin levels have been associated with protection against neural toxicity[19, 20] and mild cognitive impairment.[12] Leptin is preferentially produced by SAT,[21] whereas VAT is the main physiologic source of adiponectin. Adiponectin production is suppressed in the setting of VAT accumulation, and both adiponectin and leptin production may be suppressed in the setting of HIV lipodystrophy.[17, 22] As such, perturbations of adiponectin and/or leptin homeostasis might contribute to associations between lipodystrophy, visceral adiposity and cognitive decline among HIV+ persons.

To help clarify these issues, we assessed cross-sectional relationships between regional adipose tissue depots, adipocytokines, inflammatory biomarkers and neurocognitive test scores in Multicenter AIDS Cohort Study (MACS) participants. We hypothesized that greater abdominal (visceral and subcutaneous) and less thigh adipose tissue would be associated with worse neurocognitive test scores in HIV+ participants, whereas greater adipose tissue in all depots would be associated with worse test scores in HIV− participants. Similarly, we hypothesized that higher interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) levels and lower adiponectin and leptin levels would be associated with worse neurocognitive performance in all participants.

METHODS

Study Population

The MACS began in 1984 to study the natural history of AIDS among men who have sex with men, identify risk factors for the occurrence and clinical expression of HIV infection, and establish a repository of biologic specimens for future study.[23] The MACS is an on-going, multicenter (Pittsburgh, PA; Baltimore, MD/Washington, DC; Chicago, IL; and Los Angeles, CA), prospective, observational cohort study in which participants return semi-annually for a standardized interview, clinical evaluations, laboratory tests and storage of specimens.

The MACS initiated longitudinal neuropsychological (NP) test assessment of participants in 1986 to study the effects of HIV on the brain and central nervous system.[24] Additionally, the MACS Cardiovascular Disease 2 (CVD2) sub-study was designed to assess metabolic, inflammatory, immunologic and HIV-specific contributors to cardiovascular disease. Full methodological details of the CVD2 sub-study have been previously reported.[25, 26] Briefly, of the 1006 men enrolled in the CVD2 sub-study, 791 men (516 HIV+ and 275 HIV −) were eligible and recruited from the parent MACS study between January 2010 and December 2012, when this analysis began. Subjects were eligible if they: were 40–70 years of age, did not have a history of heart surgery (coronary artery bypass grafting or valve surgery) or coronary angioplasty, weighed ≤ 300 pounds and were able and willing to

provide informed consent.[25, 26] Of note, men enrolled in CVD2 have characteristics that are generally similar to the larger MACS cohort.

We conducted a nested cohort study of MACS participants who 1) participated in the CVD2 sub-study and 2) completed NP tests within two years of a computed tomography (CT) scan to measure adipose tissue area. All participants provided informed consent, and both the parent and sub-study protocols were approved by the Institutional Review Boards of the participating sites.

Clinical Assessments

Neuropsychological Testing—The Trail Making Test parts A (TA) and B (TB) and Symbol-Digit Modalities (SymD) tests are administered to MACS participants every six months as screens of psychomotor speed and executive function. Specifically, TA and Sym D predominately assessed psychomotor speed, and TB predominately assessed executive function. NP tests performed ± two years from CVD2 abdominal and thigh CT scans were used for association with adipose tissue areas. This interval was based upon acceptable rates of change of these tests in the population. Higher TA/TB and lower SymD scores indicate worse performance.

Adipose Tissue Quantification—Non-contrast CT was performed to assess VAT and abdominal and thigh subcutaneous adipose tissue (aSAT and tSAT, respectively) areas. Following a centralized training, scans were performed locally (Los Angeles and Pittsburgh: 64-detector LightSpeed Volume CT scanner, GE Medical Systems, Milwaukee, Wisconsin, USA; Chicago: 64-detector SOMATOM Definition Dual Source scanner, Siemens Medical Solutions, Forchheim, Germany; Baltimore: 320-detector row AquilionONE, Toshiba Medical Systems, Tokyo, Japan) and read centrally by an experienced reader at Los Angeles Biomed (Harbor-University of California, Los Angeles, Torrance, CA), who also assessed scan quality and consistency.

Adipose tissue areas were measured in cm^2. Total abdominal fat was measured at the L4-L5 level using single slice CT. VAT was defined as adipose tissue (CT tissue density between −190 and −35 Hounsfield units) between the internal-most abdominal and oblique muscle walls and the posterior aspect of the L4-L5 vertebral body. Abdominal SAT was defined as total fat minus VAT. Thigh SAT was measured from a mid-thigh single slice (CT tissue density of −150 to −50 Hounsfield units).

Biomarker Assessments—Adipokines were measured under the direction of Dr. Russell Tracy at the University of Vermont Laboratory for Clinical Biochemistry Research (Burlington, Vermont, USA). Stored (−70° Celsius) fasting serum and plasma obtained at the time of CT scan) were analyzed for adiponectin, leptin, hs-CRP and IL-6. Total adiponectin, leptin and IL-6 were measured by enzyme-linked immunosorbent assays (R & D Systems, Minneapolis, Minnesota, USA). The lower limit of detection for adiponectin was 390 ng/mL, with an inter-assay coefficient of variation of 5.3–10.8%. For leptin, the lower limit of detection was 1300 pg/mL, with an inter-assay coefficient of variation range of 5.9–6.8%. For IL-6, the lower limit of detection was 0.5 pg/mL, with an inter-assay

coefficient of variation range of 6.6–12.5%. hs-CRP was measured by nephelometry (lower limit of detection 0.2 μg/mL; interassay coefficient of variation range 3.0%–6.2%).

Fasting insulin and glucose levels were measured on serum, collected under standardized protocols and stored at −70° Celsius by the Heinz Laboratory (Pittsburgh, Pennsylvania, USA). Insulin was measured using a radioimmunoassay technique (Linco Research, St. Charles, Missouri, USA) with a lower limit of detection of 0.2 microunits/mL and a coefficient of variation of 2.6%. Fasting glucose levels were measured using a combined hexokinase/glucose-6-phosphate dehydrogenase method[27] (coefficient of variation 1.8%).

Other Measurements—Age, race, level of education, smoking history, medication use and diagnosis history were assessed by self-report unless otherwise defined. AIDS and other clinical events were confirmed via medical record review. Depression was defined as Center for Epidemiologic Studies Depression Scale Score >16 or diagnosis of or treatment for depression. Chronic Hepatitis C Virus (HCV) infection was defined as HCV RNA positivity. Chronic Hepatitis B Virus (HBV) infection was defined as positive HBV surface antigen or diagnosis of chronic HBV infection. Height and weight were measured using standardized procedures and used to calculate the body mass index (BMI) in kg/m^2. Fasting glucose and insulin levels were used to calculate homeostasis model assessment of insulin resistance (HOMA-IR) values according to the formula HOMA-IR = fasting glucose (mmol/L) × fasting insulin (μU/mL)/22.5. Mid-waist and hip circumferences (cm) were measured using a standardized protocol, and used to calculate waist-to-hip ratios. All socio-demographic and medical data were obtained using the visit closest (and immediately prior) to the CT scan date. CD4+ T lymphocyte subsets were enumerated using standardized flow cytometry [28] and CD4+ T-cell count nadir was defined as the lowest count prior to and including the CT scan date.

Data Analysis Techniques

Wilcoxon rank sum non-parametric tests were performed to compare distributions of continuous demographic, anthropometric, body composition, biomarker and NP test outcome variables between HIV+ and HIV− participants. Univariate and nonparametric tests of correlation were performed to examine the distribution and associations of all continuous variables by HIV status. Categorical demographic and clinical variables were compared between the two groups using χ^2 testing (data not shown).

Multivariable linear regression analyses were performed to determine factors associated with NP function. The analyses used all person-visits for three primary outcomes: (1) TA, (2) TB and (3) SymD raw score. With exception of the SymD test, all NP tests outcomes, body composition and biomarker measures were log10-transformed and centered on the mean to stabilize the variance and better approximate a normal distribution for our linear regression models. Continuous covariates in our models included adipose tissue areas (VAT, aSAT or tSAT in cm^2), leptin (pg/mL), adiponectin (ng/mL), IL-6 (pg/mL), hs-CRP (μg/mL), waist circumference (in cm, centered on mean of 96cm), hip circumference (in cm, centered on mean of 98cm), waist-to-hip ratio, BMI (in kg/m^2, centered on mean of 26 kg/m^2), HOMA-IR, years on ART, age (in years, centered on mean of 54 years) and both

current and nadir CD4+ T lymphocyte counts (cells/μL). Categorical predictors of NP test scores included education (≤high school, ≤college, >college), current CD4+ T lymphocyte count (<200, 200–500, or >500 cells/μL), race (African American or Caucasian/Other), self-report of lipodystrophy (any lipodystrophy, lipoatrophy only or lipohypertrophy only), and the interaction between CD4+ T lymphocyte count and age.

Models were developed in succession and stratified by HIV status. First, log-transformed TA and TB and raw SymD score outcomes were assessed using models that included variables significant in the univariate analysis. Then, adipose tissue areas were added (one adipose tissue area per model). Finally, biomarkers were individually added to models controlling for demographics and adipose tissue depot, so that each model contained a maximum of one adipose tissue depot and one biomarker. Interactions between adipose tissue depots (between VAT and tSAT, for example) were explored.

Next, models for HIV+ participants only were developed to assess the role of HIV/ART-specific covariates and included ART duration, current CD4+ T lymphocyte count and nadir CD4+ T lymphocyte count, HIV-1 viral load (measured by Roche ultrasensitive assay with 50 copies/mL limit of detection), history of an AIDS diagnosis and/or a diagnosis of lipodystrophy (in addition to age, race, education, adipose tissue area and/or biomarker).

In a secondary analysis, HOMA-IR was added to the multivariate models to determine whether insulin resistance could potentially mediate any observed effects of adipose tissue depots or adipocytokines. Additionally, sensitivity analyses were performed to determine whether a potential practice effect of repeat NP testing could bias our results. Based on the mean number of previous tests per group (≥15), practice effects were estimated to be equivalent for HIV+ and HIV− participants. Additionally, number of previous tests was not significant in univariate analysis and was not included in the final models. Missing data were minimal, and values were not imputed.

RESULTS

Participant Characteristics

Complete demographic and clinical characteristics are provided in Table 1. Of the 791 CVD2 participants who were eligible and enrolled prior to December 2012, eleven did not have complete NP test data and were excluded; therefore, 780 men (509 HIV+, 271 HIV−) met inclusion criteria. Briefly, HIV+ men were younger ($p<0.001$), less likely to have college-level education ($p<0.0001$), more likely to be African American ($p=0.02$) and current smokers ($p<0.001$), and more likely to have concomitant hepatitis C virus co-infection ($p<0.01$), metabolic syndrome ($p=0.03$) and depression ($p<0.001$). BMI values and VAT areas were similar between HIV+ and HIV− participants; however, HIV+ men had significantly less aSAT and tSAT (both $p<0.0001$). Adiponectin was lower in HIV+ participants ($p<0.01$), as was leptin, although the latter was not statistically significant ($p=0.10$). hs-CRP and HOMA-IR were higher in HIV+ participants (hs-CRP: $p=0.04$, HOMA-IR: $p<0.01$), but IL-6 did not differ by HIV serostatus ($p=0.11$). Overall NP test scores were similar between the two groups, although somewhat lower SymD scores were

observed among HIV+ participants (p=0.07). Of note, the median time between CT scan and NP testing was less than six months, with 87% of participants included in this window.

Among HIV+ participants, the median nadir CD4+ T lymphocyte count was 244 cells/μL, and the median current CD4+ T lymphocyte count was 583 cells/μL, with 96% of men having >200 cells/μL. Only 14% of men had a history of AIDS. Ninety-eight percent were on ART for a median of 9.5 years, and 81% had HIV-1 viral loads <50 copies/mL. Current ART regimens most commonly included nucleoside reverse transcriptase inhibitors (NRTI, 91%), followed by protease inhibitors (PI, 51%) and non-nucleoside reverse transcriptase inhibitors (NNRTI, 48%).

Correlations Between NP Test Scores and Adipose Tissue Depots and Biomarkers

In HIV+ only, VAT and tSAT areas correlated significantly with all three NP test scores. Interestingly, an inverse correlation was seen between VAT and TA ($r=-0.12$, $p<0.01$) and TB scores ($r=-0.16$, $p<0.001$), and a positive correlation was seen between VAT and SymD score ($r=0.18$, $p<0.0001$). Because lower TA and TB and higher SymD scores represent better performance, these findings indicate that greater VAT correlated with better NP test scores in HIV+ participants. Greater tSAT, however, correlated with worse test scores (TA: $r=0.11$, $p=0.01$; TB: $r=0.19$, $p<0.0001$; SymD: $r=-0.18$, $p<0.0001$).

Also in HIV+ only, IL-6 consistently correlated with NP test score and correlated more strongly than adipose tissue area (TA: $r=0.18$, $p<0.001$; TB: $r=0.22$, $p<0.0001$; SymD: $r=-0.22$, $p<0.0001$). Adiponectin levels correlated positively with TA and SymD scores (higher adiponectin=worse performance; TA: $r=0.15$, $p<0.01$; SymD: $r=-0.17$, $p<0.01$), with a minimal correlation for TB ($r=0.09$, $p=0.09$). In HIV− participants, neither adipose tissue areas nor inflammatory biomarker levels correlated with NP test score.

Correlations Between Adipose Tissue Depots and Inflammatory Biomarkers

In HIV+ participants, VAT correlated negatively with adiponectin ($r=-0.37$, $p<0.0001$) and positively with leptin ($r=0.57$, $p<0.0001$). Neither IL-6 nor hs-CRP correlated with VAT area in HIV+ men. aSAT correlated positively with both IL-6 ($r=0.13$, $p=0.02$) and leptin ($r=0.79$, $p<0.0001$) in HIV+ participants, and tSAT correlated positively with both adiponectin ($r=0.19$, $p<0.001$) and leptin levels ($r=0.56$, $p<0.0001$). Additionally, a trend was observed between tSAT and IL-6 ($r=0.10$, $p=0.07$). hs-CRP did not correlate with any adipose tissue depot in HIV+ participants.

In HIV− participants, adiponectin, leptin, IL-6 and hs-CRP significantly correlated with each adipose tissue depot, with directionality supporting higher levels of inflammation in participants with greater adipose tissue areas (data not shown).

Univariate Analysis

Age, African American race and <high school education were significantly ($p<0.05$) associated with NP test scores for all participants in univariate analysis. BMI, HCV co-infection, history of depression smoking history, study site and anthropometric

measurements were also explored, but had no significant associations with NP outcomes and were not preserved in later models (data not shown).

Multivariate Analysis

Models were stratified by HIV serostatus. For all participants, only older age, African American race and <high school education were consistently associated with poorer NP test performance (Table 2). In models controlling for socio-demographic factors, individual adipose tissue depots were not associated with NP performance in HIV+ or HIV− participants, and no interactions between adipose tissue depots were observed (Table 3). When adiponectin, leptin, IL-6 and hs-CRP were individually added to models controlling for demographics and adipose tissue, higher adiponectin ($p<0.01$) and IL-6 ($p=0.04$) levels were consistently associated with worse SymD scores in HIV+ only, and leptin was negatively associated with SymD scores in HIV+ when controlling for VAT and aSAT but not tSAT (Table 3). The addition of HOMA-IR to the models did not significantly modify these observed relationships.

Consistent with the findings above, in an HIV-specific model controlling for demographics in addition to current ART and current and nadir CD4+ T lymphocyte count, higher adiponectin ($p<0.01$) and IL-6 ($p=0.07$, borderline statistical significance) levels were associated with poorer SymD scores (Table 4). No other inflammatory biomarker or adipose tissue depot was associated with NP score. Additionally, outcomes were not affected when current CD4+ T lymphocyte count was categorized as <200, 200–500, or >500 cells/μL (vs. continuous). The addition of years on ART, HIV-1 viral load, history of an AIDS diagnosis and/or a diagnosis of lipodystrophy did not improve model fit. No CD4+ T lymphocyte count-by-age interaction was observed.

DISCUSSION

This analysis demonstrates associations between NP test score and traditional risk factors for neurocognitive decline that did not vary by HIV serostatus, without observed associations between NP score and adipose tissue area or site. Additionally, no associations between HIV-specific risk factors and NP scores were observed in this cross-sectional analysis. While these findings underscore the importance of traditional risk factor modification in preservation of cognitive function, the unexpected association between higher adiponectin and IL-6 levels and lower SymD scores in HIV+ participants only is of significant importance. The Sym D test assesses psychomotor speed and, to a lesser degree, executive function suggesting that IL-6 and adiponectin could preferentially affect these domains. While TA and TB also assess psychomotor speed and executive function, respectively, TA is less sensitive than SymD, and TB has a significantly larger standard deviation than Sym D, which likely contribute to the fact that we did not observe an association between TA or TB and IL-6 or adiponectin. Of note, in older adults, IL-6 has been associated with poorer executive function,[29–31] but similar associations have not yet been reported for adiponectin.

HIV infection is characterized by a state of persistent immune activation, and inflammatory biomarkers such as IL-6 have been associated with both comorbid disease and all-cause

mortality in HIV infection.[32–35] Higher adiponectin levels have been associated with improved insulin sensitivity, decreased risk of diabetes mellitus and >50% coronary artery stenosis and lower coronary artery plaque burden;[36–38] however, adiponectin has a less clear role in the development of other comorbid diseases, and may variably serve pro- and anti-inflammatory roles.[39, 40] Additionally, while higher adiponectin levels are associated with neuroprotection in vitro[41, 42] and in men following the development of neurocognitive impairment,[43] its role prior to the onset of neurocognitive decline is less clear. IL-6 has been associated with anemia in HIV infection, which has in turn been associated with AIDS dementia;[44] however, in this analysis of participants with primarily treated HIV infection and higher CD4+ T lymphocyte counts, anemia was not associated with NP test score, suggesting the possibility of other links between IL-6 and neurocognitive function.

In this analysis, higher IL-6 and adiponectin levels correlated with worse NP test scores in HIV+ participants, and in physiologically expected directions with adipose tissue areas in all participants, suggesting that adiponectin excess may contribute to cognitive decline in HIV+ men. Supporting this hypothesis are the observations that adiponectin and leptin, but not IL-6 or hs-CRP, correlated strongly with VAT and tSAT area in HIV+ participants, suggesting potential uncoupling or disequilibrium of traditional relationships between adipose tissue, adipocytokines and inflammatory biomarkers in the setting of HIV infection. Similarly, the fact that strong associations between adipocytokines, inflammatory markers and NP scores were not observed among HIV− men in our primarily non-obese cohort may highlight the presence of adipose tissue dysfunction in normal weight HIV+ participants.

Although we did not observe an association between regional adipose tissue or anthropometric measurements and NP test scores in our analysis, the CHARTER study did find an association between central obesity (as defined by waist circumference) and neurocognitive impairment in HIV+ persons (defined according to the Frascati criteria for HIV-associated neurocognitive disorder). The CHARTER and MACS populations differ in that CHARTER participants were: younger (median age 46 vs. 53 years); only 87% male; less commonly Caucasian (57% vs. 64%); more likely to have an AIDS diagnosis (91% vs. 14%), a lower CD4+ T lymphocyte nadir (120 vs. 244 cells/mm^3) and a detectable HIV-1 viral load (40% vs. 19%); and less likely to be on ART (82% vs. 98%). Additionally, the CHARTER analysis was smaller (n=130), did not include an HIV− control group and used a more extensive NP test battery (which improved sensitivity).[10] Similarly, Grima and colleagues reported an association between high-grade hepatic steatosis and cognitive impairment (also via Frascati criteria) in their cross-sectional analysis of HIV+ adults. Again, their cohort was smaller (n=129), younger in age (median 45 years) and lacked a control group.[45] Additionally, the CHARTER and Grima cohorts did not formally quantify adipose tissue areas or report data on adiponectin or IL-6. The combination of cohort differences and the use of different screening tools for neurocognitive function may have contributed to discrepancies between our findings and other available data. Thus, additional study is needed to clarify the role of regional adiposity, inflammation and neurocognitive function in the setting of HIV infection.

Limitations

First, our data are cross-sectional, and cannot define the mechanism by which adiponectin and IL-6 may affect cognitive function in HIV+ men. However, traditional correlations between biomarkers and adipose tissue depots were not consistently seen in HIV+ men in our cohort, suggesting possible disruption or uncoupling of these relationships in the setting of (primarily treated) HIV infection. Second, specific ART agents may have differential effects on adiponectin and IL-6 secretion,[46–50] and teasing out such differences is beyond the scope of this analysis. Third, correlation coefficients were small, and, although p values indicated high levels of statistical significance, this was in part a function of our large sample size. Fourth, the MACS cohort is limited to men, and it is unknown whether our findings can be generalized to women living with or at risk for HIV. Fifth, adipose tissue quantification and biomarker measurement is not available for all MACS participants, limiting our sample size to men meeting criteria for inclusion into the CVD2 sub-study, which could also limit generalizability. Lastly, the TA, TB and SymD scores are screening tests that may be less sensitive to HIV-associated neurocognitive impairment. Despite these limitations, 1) our cohort is large, well characterized and has an internal control group of HIV− participants, and 2) our results are internally consistent, lending validity to our observations. Additionally, our results are not surprising given the known associations between chronic immune activation/inflammation and comorbid disease.

Conclusions

In this subset of MACS participants, relationships between regional adipose tissue, inflammatory biomarkers and NP test scores differed by HIV serostatus. While demographic factors but not adiposity were associated with NP test performance in all participants, higher adiponectin and IL-6 were associated with worse cognitive function in HIV+ participants only, supporting a role for chronic inflammation and adipocytokine imbalance in neurocognitive decline in HIV+ persons. Whether these findings can be replicated in other studies remains to be determined. Longitudinal analysis of this cohort will provide additional insight into the relationships between regional adipose tissue, inflammatory biomarkers and cognitive function.

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Table 1

Baseline Demographic and Clinical Characteristics of Participants

	(N=780)				
	HIV−		HIV+		
	N	% or median/IQR	N	% or median/IQR	P value
Number	271	35%	509	65%	
Age in years	271	55 (51, 62)	509	53 (48, 58)	p<0.001
Race					
African American	75/265	28%	186/509	37%	
Caucasian/Other	190/265	72%	323/509	64%	p=0.02
Education					
≤High school	40/271	15%	121/509	24%	
≤College	111/271	41%	243/509	48%	
>College	120/271	44%	145/509	29%	p<.0001
Smoking History					
Current	55/267	21%	159/501	32%	
Former	145/267	54%	213/501	43%	
Never	67/267	25%	129/501	26%	p<0.001
Dementia	0/271	--	3/509	0.6%	--
Diabetes mellitus	29/232	13%	72/438	16%	p=0.18
Metabolic Syndrome	66/271	24%	162/509	32%	p=0.03
Dyslipidemia	197/271	73%	392/509	77%	p=0.32
Depression[1]	98/268	37%	252/505	50%	p<0.001
Chronic HCV[2]	11/191	6%	52/405	13%	p<0.01
Chronic HBV[3]	1/191	0.5%	11/405	3%	p=0.08
BMI (kg/m^2)	271	26.3 (23.9, 29.9)	509	25.5 (23, 28.8)	p=0.18

	(N=780)				
	HIV−		HIV+		
	N	% or median/IQR	N	% or median/IQR	P value
Hip circumference (cm)	233	99.5 (94.5, 106.1)	430	95.5 (91, 102.4)	p<0.0001
Waist circumference (cm)	232	95.5 (88.0, 106.2)	431	94.3 (87.2, 104.5)	p=0.01
Waist to Hip Ratio	231	1.0 (0.9, 1.0)	426	1 (0.9, 1.0)	p<0.01
HOMA-IR	224	2.8 (2.1, 4.2)	409	3.2 (2.4, 4.9)	p<0.01
VAT (cm^2)	270	143.5 (85.5, 212.4)	508	148.5 (87.1, 216.4)	p=0.65
aSAT (cm^2)	270	232.2 (155.5, 319.3)	508	185.1 (104.8, 278.2)	p<0.0001
tSAT (cm^2)	271	48.8 (35.1, 68.5)	508	25.7 (12.6,46)	p<0.0001
Adiponectin (ng/mL)	234	6900 (4799,10673)	453	5910 (3791, 9756)	p<0.01
Leptin (pg/mL)	234	6133 (3021, 11791)	453	5324 (2302.7, 10672.9)	p=0.10
IL-6 (pg/mL)	234	1.3 (0.9, 2.3)	453	1.5 (1.0, 2.5)	p=0.11
CRP (μg/mL)	234	0.9 (0.5, 1.8)	454	1.2 (0.6, 2.7)	p=0.04
Neuropsychological Tests					
Trail A (seconds)	271	20 (15, 25)	509	20 (16, 26)	p=0.15
Trail B (seconds)	271	42 (32, 57)	509	45 (34, 62)	p=0.12
Symbol-Digit (raw score)	271	53 (46, 63)	509	51 (42, 61)	p=0.07
Any lipodystrophy	29/271	11%	83/509	16%	p=0.03
Lipoatrophy only	3/271	1%	27/509	5%	P<0.01
Lipohypertrophy only	24/271	9%	29/509	6%	p=0.10
Years since HIV diagnosis	--		509	10 (8, 25)	
Current CD4+ T cell count (cells/μL)	--		507	583 (410, 747)	
CD4+ T cell count nadir (cells/μL)	--		509	244 (133,331)	

	(N=780)				
	HIV−		HIV+		
	N	% or median/IQR	N	% or median/IQR	P value
HIV-1 RNA <50 copies/mL	--		411/509	81%	
History of AIDS diagnosis	--		72/509	14%	
On ART since last visit			480/491	98%	
PI	--		250/490	51%	
NRTI	--		445/490	91%	
NNRTI	--		237/490	48%	
Years on ART	--		493	9.5 (8.0, 14.5)	

IQR=interquartile range, HCV=hepatitis C virus, HBV=hepatitis B virus, BMI=body mass index, VAT=visceral adipose tissue, aSAT=abdominal subcutaneous adipose tissue, tSAT=thigh subcutaneous adipose tissue, IL-6=interleukin-6, CRP=C-reactive protein, AIDS=Acquired Immunodeficiency Syndrome, ART=antiretroviral therapy, PI=protease inhibitor, NRTI=nucleoside reverse transcriptase inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor

[1]Defined as Center for Epidemiologic Studies Depression Scale Score >16 or diagnosis of or treatment for depression

[2]Defined as HCV RNA positivity

[3]Defined as positive HBV surface antigen or diagnosis of chronic HBV infection

Table 2

Associations Between Demographics and Neuropsychiatric Test Scores

	Age	Black Race	<High School Education		Age	Black Race	<High School Education
HIV+	β (p)			**HIV−**	β (p)		
TA	**1.009 (<0.0001)**	**1.164 (<0.0001)**	**1.268 (<0.0001)**	TA	**1.014 (<0.0001)**	**1.312 (<0.0001)**	**1.194 (<0.01)**
TB	**1.009 (<0.01)**	**1.023 (<0.0001)**	**1.469 (<0.0001)**	TB	**1.014 (<0.001)**	**1.469 (<0.0001)**	**1.374 (<0.0001)**
SymD	**−0.248 (<0.01)**	**−5.744 (<0.0001)**	**−9.543 (0.02)**	SymD	**−0.462 (<0.001)**	**−9.984 (<0.0001)**	**−6.620 (0.02)**

Note: For TA and TB, beta estimates <1 indicate better performance. For SymD, beta estimates >1 indicate better performance. TA=Trails A, TB=Trails B, SymD=symbol-digit

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Table 3

Associations Between Regional Adipose Tissue, Adipocytokines and Neuropsychiatric Test Scores

Controlled for demographics*	VAT	aSAT	tSAT	Controlled for demographics* and:	Adiponectin	Leptin	IL-6	hs-CRP
HIV+	β (p)				β (p)			
TA	0.95 (0.47)	0.98 (0.78)	1.00 (0.84)	VAT	1.10 (0.08)	1.07 (0.14)	1.10 (0.07)	1.02 (0.57)
				aSAT	1.10 (0.07)	1.10 (0.15)	1.10 (0.07)	1.02 (0.58)
				tSAT	1.10 (0.06)	1.05 (0.41)	1.10 (0.08)	1.02 (0.59)
TB	1.00 (0.94)	1.10 (0.08)	1.07 (0.11)	VAT	1.10 (0.19)	**1.15 (0.01)**	1.10 (0.10)	1.00 (0.96)
				aSAT	1.10 (0.18)	1.10 (0.17)	1.10 (0.11)	1.00 (0.99)
				tSAT	1.07 (0.30)	1.10 (0.10)	1.10 (0.10)	1.00 (0.96)
SymD	1.48 (0.42)	−0.86 (0.62)	−2.03 (0.13)	VAT	**−5.73 (<0.01)**	**−5.38 (<0.01)**	**−3.60 (0.04)**	−2.24 (0.09)
				aSAT	**−5.54 (<0.01)**	**−5.23 (0.02)**	**−3.56 (0.04)**	−2.19 (0.10)
				tSAT	**−5.27 (<0.01)**	−2.07 (0.23)	**−3.55 (0.04)**	−2.20 (0.10)
HIV−	β (p)				β (p)			
TA	0.03 (0.26)	0.04 (0.27)	0.05 (0.19)	VAT	0.98 (0.91)	0.93 (0.36)	1.15 (0.08)	1.10 (0.10)
				aSAT	0.98 (0.91)	0.89 (0.23)	1.15 (0.09)	1.10 (0.11)
				tSAT	1.00 (0.95)	0.91 (0.23)	1.12 (0.12)	1.10 (0.15)
TB	0.06 (0.06)	0.04 (0.25)	0.04 (0.30)	VAT	1.15 (0.24)	0.95 (0.68)	1.07 (0.33)	1.12 (0.08)
				aSAT	1.10 (0.41)	1.00 (0.98)	1.10 (0.29)	1.12 (0.06)
				tSAT	1.10 (0.35)	1.00 (1.00)	1.05 (0.51)	1.10 (0.15)
SymD	−2.42 (0.40)	1.60 (0.61)	0.08 (0.98)	VAT	0.98 (0.81)	0.45 (0.89)	4.01 (0.17)	1.34 (0.54)
				aSAT	2.52 (0.52)	−3.16 (0.36)	3.42 (0.25)	0.80 (0.71)
				tSAT	1.69 (0.65)	−1.34 (0.66)	3.96 (0.19)	1.11 (0.60)

* Includes age, race, and education

Note 1: For TA and TB, beta estimates <1 indicate better performance. For SymD, beta estimates >1 indicate better performance. For each NP test outcome, models include one adipose tissue depot and one biomarker.

Note 2: No interaction was observed between adipose tissue depots.

TA=Trails A, TB=Trails B, SymD=symbol-digit, VAT=visceral adipose tissue, aSAT=abdominal subcutaneous adipose tissue, tSAT=thigh subcutaneous adipose tissue, IL-6=interleukin-6, hs-CRP=high-sensitivity C-reactive protein

Table 4

Associations Between Regional Adipose Tissue, Adipocytokines and Neuropsychiatric Test Scores After Controlling for HIV-Specific Factors

Controlled for demographics* and HIV-specific factors:**	**VAT**	**aSAT**	**tSAT**	**adiponectin**	**leptin**	**IL-6**	**hs-CRP**
TA	0.98 (0.55)	0.98 (0.67)	0.98 (0.73)	1.10 (0.13)	1.02 (0.37)	1.07 (0.09)	1.02 (0.65)
TB	1.00 (0.94)	1.10 (0.13)	1.07 (0.19)	1.10 (0.20)	1.07 (0.11)	1.07 (0.17)	1.00 (0.82)
SymD	1.74 (0.37)	−0.54 (0.77)	−1.91 (0.18)	**−5.59 (<0.01)**	−2.00 (0.18)	−3.33 (0.07)	−1.81 (0.19)

Note 1: For TA and TB, beta estimates <1 indicate better performance. For SymD, beta estimates >1 indicate better performance.

Note 2: No interaction was observed between adipose tissue depots.

** Includes age, race, and education

** HIV-specific factors=Current antiretroviral therapy (ART), current CD4 T cell count and nadir CD4 T cell count. Inclusion of years on ART, HIV-1 viral load, and/or history of AIDS diagnosis did not improve model fit. When CD4 count stratified by <200, <500, or >500 cells/μL, significant effect of CD4<500 cells/μL found for Trails A only. CD4-by-age interaction existed for current CD4<200 cells/μL.

TA=Trails A, TB=Trails B, SymD=symbol-digit, VAT=visceral adipose tissue, aSAT=abdominal subcutaneous adipose tissue, tSAT=thigh subcutaneous adipose tissue, IL-6=interleukin-6, hs-CRP=high-sensitivity C-reactive protein