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CD4/CD8 Ratio Predicts Peripheral Fat in HIV-infected Population

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Keywords

HIV; CD4/CD8 ratio; peripheral fat

Introduction

Loss of peripheral fat (lipoatrophy) was previously common among HIV-infected individuals and was associated with the use of older nucleoside reverse transcriptase inhibitors (NRTI) such as stavudine (d4T) and zidovudine (ZDV).¹⁻³ These older NRTIs are no longer in common use, but peripheral fat loss is still observed and could be from direct consequences of HIV per se and/or from HIV-induced immune activation/inflammation.^{4,5} Using dual energy absorptiometry (DXA), we compared peripheral fat content in older HIV-infected individuals who were virologically suppressed on potent antiretroviral therapy (ART) not including d4T or ZDV to HIV-negative individuals of similar age and socio-demographic characteristics, and assessed the relationship of T-cell immune parameters to peripheral fat content in HIV-infected individuals.

Methods

Patient Selection

Our study is a subgroup analysis utilizing baseline data from the Hawaii Aging with HIV-Cardiovascular Study (HAHC-CVD), a 5-year longitudinal cohort study of the pathogenesis of cardiovascular disease in HIV. Entry criteria included: documented HIV infection, 40

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years of age, and on suppressive ART for 3 months. HIV-negative subjects of similar age and health status were used as controls. The University of Hawaii Institutional Review Board approved this study and informed written consent was obtained from all study subjects. Details of the HAHC-CVD study has been previously published.⁶

Laboratory Evaluations

CD4⁺ T-cell nadir levels and past use of zidovudine (ZDV), stavudine (d4T) and didanosine (ddI) were provided by self-report and cross-referenced with medical records. Body composition including peripheral fat was measured by DXA using Lunar Prodigy scanner (GE Medical Systems, Inc., Milwaukee, WI). T-cell subset and plasma HIV RNA were performed at Diagnostic Laboratory Services, Inc., a CLIA-certified local commercial laboratory. CD8⁺ T-cell activation levels were derived by multiplying the total number of CD8⁺ T-cells by the percentage of CD8⁺ T-cells co-expressing CD38⁺ and HLA-DR as assessed by a separate flow cytometry assay in our laboratory (CD38⁺HLA-DR⁺CD8⁺ T-cell).

Statistical Analyses

Peripheral fat was quantified in grams, divided by height in meters squared (as described by J.E. Lake et al)⁷ and log₁₀-transformed to achieve normal distribution. Our analysis examined the effect of HIV status on height-normalized peripheral fat using multivariable linear regression analysis. Afterwards, we focused on the HIV-infected group and performed multivariable analyses to determine whether the outcome was associated with various T-cell immune parameters. Beta-estimates were back transformed to produce percentage estimates for all models. All models were adjusted for age, gender, and past use of ZDV, d4T or ddI, with all HIV-negative subjects classified as never using these ARTs. At all points of the analyses, tests were two-sided and p values < 0.05 were considered statistically significant. All statistical analyses were performed using commercially available software: SPSS version 22 (IBM corporation, Armonk, NY).

Results

Over-all, 207 subjects were included in the analysis (133 HIV-infected subjects and 74 HIV-negative subjects). Among the HIV-infected subjects: mean age 52.2 years, 88% male, 60.2% Caucasian, and mean BMI 26.4 kg/m². Among the HIV-negative subjects: mean age 54.3 years, 80% male, 66.2% Caucasian and mean BMI 27.3 kg/m². There was no statistically significant difference in age, gender, ethnicity and BMI between HIV-infected subjects and controls.

Among the HIV-infected subjects, mean CD4⁺ T-cell count was 535.2 cells/mm³. All had HIV RNA <50 copies/mL and 70.7% had previously been treated with ZDV, d4T, and/or ddI. There were 11 (8.3%) subjects currently receiving AZT and 3 (2.3%) subjects currently receiving DDI. The mean CD4⁺ T-cell nadir was 171 cells/mm³ and the mean CD8⁺ T-cell count was 787.6 cells/mm³. Mean CD38⁺HLA-DR⁺CD8⁺ T-cell count was 97.7. Mean CD4/CD8 ratio was 0.77.

HIV-infected subjects had 22% less peripheral fat normalized to height squared than the HIV-negative subjects, controlling for age, gender and past use of ZDV, d4T and/or ddI ($p = 0.02$). Multivariable linear regression models among the HIV-infected subgroup examining the association of T-cell immune parameters adjusting for the same covariates found that CD4/CD8 ratio was positively associated and CD8⁺ T-cell count and CD38⁺HLA-DR⁺CD8⁺ T-cell count were negatively associated with height-normalized peripheral body fat (see Table). Each 0.1 increase in CD4/CD8 ratio was associated with a 2.6% increase in peripheral fat. There was no statistically significant association between CD4⁺ T-cell count and CD4⁺ T-cell nadir with height-normalized peripheral fat.

Discussion

Our study found that HIV-infected subjects in the era of ART continue to have less peripheral fat than HIV-negative subjects of similar age. This difference was independent of past use of ZDV, d4T and/or ddI. These findings are consistent with previous studies which have suggested that peripheral fat loss is mainly affected by HIV immune dysregulation, specifically high levels of CD8⁺ T-cell activation.^{5,8}

Chronic inflammation has been described to play a major role in the development of lipodystrophy, as shown by increased circulating activated monocytes (CD16-expressing monocytes) and macrophages and high expression of TNF- α , IL-6 and IL-8 within subcutaneous adipose tissue of subjects with lipodystrophy.⁹ Our study found an association between peripheral fat loss and increased CD8⁺ T-cell immune dysregulation/activation, as well as with decreased CD4/CD8 ratio. A low CD4/CD8 ratio represents an imbalance in immune reconstitution and is associated with T cell activation, senescence and dysfunction, and with chronic inflammation.^{10,11} This increase in chronic inflammation has been hypothesized to explain the association between low CD4/CD8 ratio and non-AIDS related complications, such as cardiovascular disease, end-staged kidney disease, and non-AIDS malignancies.^{12,13} Very low CD4/CD8 ratios (< 0.3) independently predict the risk of serious non-AIDS events or deaths including cardio-metabolic disease.¹⁴ Our data suggests that low CD4/CD8 ratios are also a predictor of decreased subcutaneous fat loss.

Aging is also associated not only with increased inflammatory tendencies but also with body fat redistribution, including a relative loss of subcutaneous peripheral fat. These age-related changes in body fat have been linked to increased risk of metabolic complications including diabetes and cardiovascular disease.¹⁵ While much regarding its pathogenesis remains unknown, a recent study in a healthy older population showed an association between peripheral fat loss and a decline in adipogenesis which in turn was associated with higher plasma levels of soluble tumor necrosis factor receptor 2 (sTNFR2) and greater release of TNF- α from fat tissue.¹⁶

Our study has important limitations. First, our study is cross-sectional and causation or temporal effects of variables remains conjectural. Additionally, duration of ZDV, d4T, and ddI use was not available.

In conclusion, HIV-infected individuals in the era of potent ART continue to have lower peripheral fat compared to HIV-negative individuals. Similar to other non-infectious chronic complications of HIV, immune dysregulation and inflammation may serve to accentuate age-related peripheral fat loss. CD4/CD8 ratio, a commonly assessed clinical laboratory value, may be helpful in defining risk of peripheral fat loss and future cardio-metabolic disease risk in this population.

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Table
Multivariable linear regression analysis assessing association of each T-cell subset with peripheral fat in HIV infected subjects*

T-cell subset	% Effect [†]	95% CI [‡]	P-value
CD4/CD8 ratio	2.6	0.08, 57.7	0.049
CD4 ⁺ T-cell count	0.005	-0.03, 0.04	0.790
CD4 ⁺ T-cell nadir	-0.019	-0.08, 0.04	0.554
CD8 ⁺ T-cell count	-0.032	-0.06, -0.003	0.028
CD38 ⁺ HLA-DR ⁺ CD8 ⁺ T-cell count	-0.114	-0.21, -0.02	0.023

*Outcome is $\log_{10}(\text{peripheral fat (g)/height in meters}^2)$. Models were adjusted for age, gender and past use of ZDV, d4T, and ddI.

[†]Percent effect describes the estimate of the percentage differences in grams of peripheral fat normalized by height squared. Beta estimate was back transformed by $100 \times (10^{\beta} - 1)$

[‡]CI: Confidence Interval.

Statistically significant p-values are in bold