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Preliminary Report

Obesity and lymphocyte subsets in virologically suppressed HIV-infected patients

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1. Introduction

The prevalence of obesity is increasing among HIV-positive patients, with current estimates—20% to 30%—rivaling estimates for the general US population [1-3]. Obesity is associated with a chronic, systemic state of inflammation that may contribute to the development of many obesity-related comorbidities. Obesity increases the risk of hypertension, diabetes, myocardial infarction, heart failure, stroke, and some malignancies [4-6]. Because adipocytes are metabolically active, obesity also increases the production of a number of substances with proinflammatory or immune-modulating functions, which might mediate the adverse health effects: adipokines, such as leptin and adiponectin; C-reactive protein; interleukin (IL)-6; tumor necrosis factor–α; and IL-1-R agonist [4,7,8]. In a large cohort study of subjects without HIV, obesity was associated with higher CD3, CD4, and CD8 counts [9]. The treatment of morbid obesity with gastric bypass surgery in HIV-negative adults has also been reported in small studies to change cytokine levels and a number of immune markers [10,11]. In the first study, abnormal CD95 antigen expression on T cells was reversed with surgical weight loss [10]; and in the second study, C-reactive protein levels decreased significantly postsurgery as did lymphocyte subsets CD4 and CD8 [11]. Little is known about specific effects of obesity on the immune system in HIV-positive patients. The aim of our study was to explore the effects of obesity on lymphocyte subsets in HIV-positive patients with diabetes.

2. Methods

We conducted a cross-sectional study in a cohort of 216 HIV-positive patients with diabetes at the CORE Center in Chicago. The study was approved by the Cook County Bureau of Health Services institutional review board. Patients were eligible for study if they were taking highly active antiretroviral therapy (HAART) and had undetectable HIV RNA for at least 6 months. We chose to include only patients who had well-controlled HIV infection, as ongoing HIV viremia is known to cause elevations in CD8 levels.

The measure of obesity was based on body mass index (BMI), calculated as weight in kilograms divided by height in meters squared: normal weight, BMI 18.5 to 24.9; overweight, BMI 25 to 29.9; obese, BMI 30 to 34.9; and morbidly obese, BMI of at least 35. Our dependent variables were the white blood cell count and the following lymphocyte subgroups, defined by surface antigens: CD3 (T cells), CD4 (helper T cells), CD8 (cytotoxic or suppressor T cells), CD19 (B cells), and CD56 (natural killer cells).

We used linear regression models to test bivariate relationships between BMI and the concentrations of the different cell types, after visually inspecting locally weighted scatterplot smoother curves to ensure that linear models were appropriate. Because of consistently nonlinear relationships at BMI greater than 40, we restricted the analysis to patients with a BMI of 40 or less. We then used multivariable linear models to test the same relationships after adjusting for age, sex, ethnic group, renal function (inverse of serum creatinine), hemoglobin A_{1c} (HbA_{1c}) (measure of average glucose control), and the number of years since HIV diagnosis. To meet model distribution assumptions, we transformed dependent, predictor, and control variables to best approximate the normal distribution (square root transformations for HIV duration and CD3, CD4, CD8, and total lymphocyte counts; log transformations for BMI and

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CD56, CD19, and white blood cell counts). Data are presented as means ± SD. *P* values less than .05 were considered statistically significant. All analyses were conducted with Stata/IC 10.1 for Windows (StataCorp, College Station, TX).

3. Results

Among the cohort of 216 HIV-positive patients with diabetes, 135 (63%) had undetectable HIV RNA and thus were eligible for study. In our sample of 135 subjects, the mean age was 52 ± 9 years, 75% were men, 65% were African American, the mean HbA_{1c} was 7.1% ± 1.8%, and the duration since HIV diagnosis was 11 ± 5 years. All patients were on HAART with HIV RNA less than 75 copies per milliliter, and CD4 count was 560 ± 320. Body mass index was 27 ± 5 kg/m^2; 30% were obese.

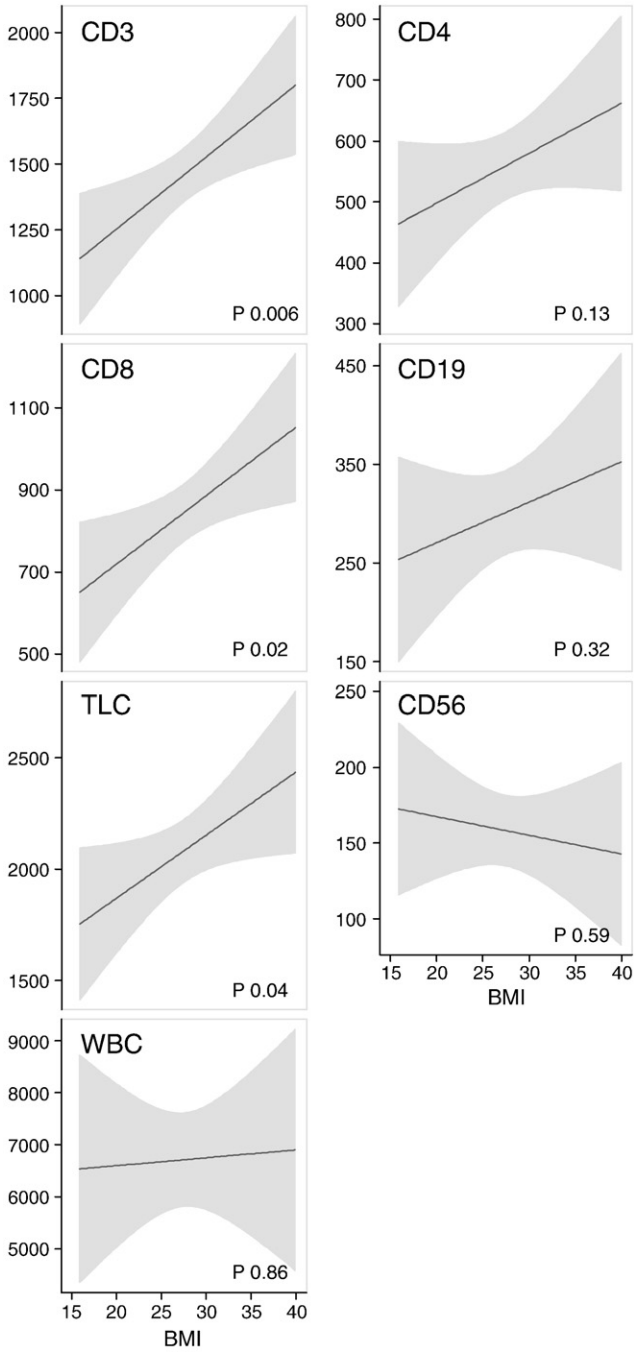

Fig. 1. Relationship between BMI and different cell types.

Table 1
Unadjusted and adjusted changes (*β*) in cell counts for every change in BMI of 1 kg/m^2

	Unadjusted		Adjusted[a]	
	β	*P* value	*β*	*P* value
CD3	28	.005	27	.004
CD8	17	.01	16	.01
TLC	0.03	.02	0.03	.04
CD4	–	.12	–	.13
CD19	–	.26	–	.19
CD56	–	.66	–	.55
WBC	–	.80	–	.32

The *P* values for unadjusted analyses in this table differ slightly from those in Fig. 1 because of the use of log-transformed BMI in this table and untransformed BMI in Fig. 1.

[a] Adjusted in a multivariable linear regression model for age, sex, ethnicity, renal function (1/Cr), glucose control (HbA_{1c}), and the square root transformation of duration since diagnosis of HIV disease. Because the predictor variable, BMI, was log-transformed, we calculated a change in cell count (*β*) for the equivalent of a change of 1 kg/m^2, which is the same as a 0.0155 change in log(BMI), near the sample mean value of BMI (27.5 kg/m^2).

Fig. 1 describes the relationship between BMI and the different cell counts. As BMI increased, there were significant increases in CD3, CD8, and total lymphocyte counts. For total white blood cell count and the other lymphocyte subgroups (CD4, CD19, and CD56), the relationship with BMI was not significant (Fig. 1). Relationships were unchanged after controlling for age, sex, ethnicity, renal function, glucose control (HbA_{1c}), and duration since diagnosis of HIV disease. Results also did not change in multivariable models after transforming all continuous variables (predictor, outcome, and control) to best approximate the normal distribution.

Obese patients had CD3 counts 26% higher than patients with normal weight (*P* = .004) and CD8 counts 28% higher (*P* = .01), controlling for age, sex, ethnicity, renal function, HbA_{1c}, and duration since HIV diagnosis. This is equivalent to an absolute increase in CD3 counts of 27 and absolute increase in CD8 of 16 for every increase of 1 kg/m^2 in BMI (Table 1). The higher number of CD3 and CD8 cells accounted for the 17% higher total lymphocyte count among obese patients, adjusting for the same covariates (*P* = .04).

In exploratory analyses, we tested the same relationships among patients with detectable HIV virus and found that the effect of BMI had the same direction and a similar magnitude for each of the dependent variables. However, except for total lymphocyte count, none of the relationships was statistically significant, probably because of the much smaller sample size (n = 49).

4. Discussion

Obesity was associated with higher CD3, CD8, and total lymphocyte counts in our cohort of HIV-positive patients. To our knowledge, this is the first study to show this association in treated HIV-positive patients with well-controlled HIV infection. This is important because obesity has been reported to be more common than wasting in HIV-positive patients in the era of HAART [1,2]. Although all subjects had diabetes, these findings are unlikely to be restricted to this metabolic subgroup because glucose control was not associated with any of the cell counts, except for CD3 (79 more CD3 cells per cubic millimeter for every 1 percentage point increase in HbA_{1c}). In addition, these findings are similar to results in studies of HIV-negative subjects [9,12]. Although there was an increase in CD4 cells with BMI, this was not statistically significant; and thus, we are unable to determine if this is due to a differential effect of weight on CD8 cells or a limitation of our small sample size.

The mechanism that accounts for these findings is unknown. Leptin, an important satiety factor, might play an important role. Obesity causes a dysregulation of leptin, which has pleiotropic effects on lymphocytes [13]. The high levels of leptin in obesity can increase T-cell proliferation and delay apoptosis, which could explain the higher CD3, CD8, and lymphocyte counts that were observed. In addition, leptin can block the inhibitory effects of IL-6, IL-11, and IL-12 on lymphocyte function and proliferation because of a structural homology between the leptin and cytokine receptors [13]. Leptin (not measured in the current study) may thus be the link between obesity and inflammation.

It is not known if these quantitative differences in lymphocyte subsets reflect qualitative differences in lymphocyte function or activation. If higher CD8 cell counts are associated with increased markers of immune activation and inflammation, this could explain some of the adverse effects of obesity on overall health. Additional research should be conducted to verify these findings among HIV-positive patients without diabetes and to determine if lymphocyte functional characteristics parallel the higher concentrations of CD3 and CD8 cells associated with obesity. It will be important to test whether the positive associations we identified are due to obesity causing alterations in lymphocyte subsets (perhaps through the action of leptin) or whether the cause-effect relationship is in the opposite direction—that is, a greater degree of immune reconstitution with the use of HAART (reflected by higher CD3) might reduce inflammation, increase appetite, improve gastrointestinal function, and, with other mechanisms, cause obesity. Only with rigorous longitudinal research will the meaning of our significant positive associations be clarified.

In addition to the relatively small sample size, other limitations of our study include the lack of information on pre-HAART CD4 and CD8 cell counts or pre-HAART BMI. Furthermore, all the study participants had diabetes mellitus, which is associated with impaired immune function. This limits the impact of our results. However, as stated earlier, our findings remained significant after adjusting for glycemic control.

In conclusion, we found a positive association between BMI and certain lymphocyte subsets in virologically suppressed HIV-positive patients. The mechanisms and implications of these findings should be explored in future studies.

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