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Body Mass Index and CD4+ T-Lymphocyte Recovery in HIV-Infected Men with Viral Suppression on Antiretroviral Therapy

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Abstract

Purpose—To better characterize the relationship between body mass index (BMI) and CD4+ T-lymphocyte recovery in HIV disease.

Methods—We analyzed the association between baseline BMI and CD4+ T-lymphocyte increases, as well as the association between BMI and immune activation (CD38 and HLA-DR co-expression on CD4+ and CD8+ T-lymphocytes), in male HIV-infected patients who achieved viral suppression on antiretroviral therapy (ART).

Results—Baseline BMI predicted change in CD4+ T-lymphocyte count at weeks 96 ($P = .03$, $n = 461$) and 144 ($P = .005$, $n = 357$) but not at week 48 ($P = .38$, $n = 558$). Relative to men with a normal BMI, overweight and obese men had increases at week 144 that were 35 and 113 cells/mm³ higher, respectively, while underweight men had CD4+ T-lymphocyte increases that were 94 cells/mm³ lower. No significant correlations between baseline BMI and cellular immune activation were seen.

Conclusions—BMI predicts CD4+ T-lymphocyte gains in men started on ART.

Keywords

body mass index; CD4 cell count; HIV infection; immune activation; obesity

Obesity is relatively common among HIV-infected individuals, with one study in an urban HIV-infected population demonstrating that 45% were obese or overweight.¹ Adipose tissue is immunologically active, but there have been few studies of the immune consequences of obesity in HIV infection.^{2,3}

After the initiation of antiretroviral therapy (ART), higher CD8+ T-lymphocyte activation is associated with lower CD4+ T-lymphocyte gains.⁴ Given that obesity is a chronic inflammatory condition characterized by abnormal cytokine production and upregulation of proinflammatory signaling pathways,² one might expect to observe less CD4+ T-lymphocyte recovery in individuals with higher body mass index (BMI). However, higher BMI has been found to predict higher CD4 T-lymphocyte counts and slower HIV disease progression in patients not on ART,^{5,6} whereas a recent study showed no positive effect of higher BMI on CD4 T-lymphocyte counts after ART.⁷ In an AIDS Clinical Trials Group

(ACTG) analysis of men initiating HAART, a higher pretreatment BMI was one factor independently associated with greater 3-year CD4 T-lymphocyte increases⁸; this association was not seen in women, although the number of women enrolled was small. The relationship between BMI and CD4 T-lymphocyte changes warrants more detailed evaluation.

METHODS

Subjects were ART-naïve HIV-infected men enrolled in ACTG Protocol A5001 (ACTG Longitudinal Linked Randomized Trial [ALLRT]). ALLRT is a prospective, longitudinal cohort of subjects enrolled in randomized parent ACTG clinical trials for long-term evaluation of clinical, virologic, immunologic, and pharmacologic outcomes associated with antiretroviral treatment.⁹ Subjects in 4 parent studies (ACTG 384, 388, A5014, A5095) who received randomized antiretroviral therapies and had baseline immune activation data (as measured by CD38 and HLA-DR co-expression on CD4+ and CD8+ T-lymphocytes) were analyzed. CD4+ T-lymphocyte activation was not uniformly measured together with CD8+ T-lymphocyte activation in the contributing studies, so fewer subjects are included in the CD4+ T-lymphocyte activation analyses. Women were not analyzed because an analysis of the small number of women enrolled would be unlikely to contribute meaningful results.

Utilizing the ALLRT protocol, we examined the relationship between baseline BMI and CD4+ T-lymphocyte recovery at several time points. We also examined the association between baseline BMI and immune activation at baseline and during follow-up. Flow cytometric analysis was performed on fresh cells; activated T-lymphocytes were defined as CD3+ lymphocytes that stained positive for CD38 and HLA-DR. BMI at baseline was calculated using the formula $\text{weight (kg)}/[\text{height(m)}]^2$ and categorized as underweight ($<18.5 \text{ kg/m}^2$), normal ($18.5\text{--}24.9 \text{ kg/m}^2$), overweight ($25\text{--}29.9 \text{ kg/m}^2$), and obese ($\geq 30 \text{ kg/m}^2$). CD38 and HLA-DR expression, as well as CD4+ T-lymphocyte count and HIV RNA level, measured by the Roche ultrasensitive assay (Amplicor HIV-1 Monitor; Roche Diagnostic Systems, Branchburg, New Jersey, USA), were analyzed at baseline and at weeks 16, 48, 96, and 144.

Regression models were used to evaluate the relationship between baseline BMI category and CD4 T-lymphocyte change from baseline, restricted to those with HIV RNA <400 copies/mL. Spearman rank correlations were used to analyze the association between baseline BMI and immune activation at baseline and weeks 16, 48, 96, and 144, similarly restricted to those subjects with HIV RNA <400 copies/mL during follow-up. For consistency between the analyses relating baseline BMI to CD4 T-lymphocyte changes and to T-lymphocyte activation, analyses at each time point examined those subjects who had available data on CD8+ T-lymphocyte activation. We estimated that baseline (pretreatment) CD8+ T-lymphocyte activation and BMI would be available for >800 antiretroviral-naïve men, which would provide 80% power to detect a correlation of 0.10 in magnitude.

RESULTS

Baseline Characteristics

Table 1 summarizes the baseline (pretreatment) characteristics of 808 male subjects. The median age was 37 years; 419 (52%) were white/non-Hispanic, 220 (27%) were black/non-Hispanic, and 169 (21%) were Hispanic or “other” race/ethnicity. The median baseline CD4 T-cell count was 254 cells/mL and HIV RNA was $4.94 \log_{10}$ copies/mL.

Baseline BMI Category and CD4+ T-Lymphocyte Increases

We analyzed subjects with HIV RNA <400 copies/mL and with activation data enrolled in ACTG A5001. To account for missing data, the week 48 CD4 change was based on an

average of week 32 and week 48 CD4 cell counts; the week 96 CD4 change was based on an average of weeks 80 and 96; and the week 144 CD4 change was an average of weeks 112, 128, and 144.

Table 2 summarizes the relationship between baseline BMI category and CD4 change from baseline. For the 357 subjects with week 144 follow-up, baseline BMI did predict change in CD4+ T-lymphocyte count to week 144 ($P = .005$). In this model, after adjusting for baseline plasma HIV RNA, CD4+ T-lymphocyte count, age, and race, relative to men with a normal BMI (18.5–25 kg/m²), underweight men had CD4 increases that were 94 cells/mm³ lower and overweight and obese men had increases that were 35 and 113 cells/mm³ higher, respectively.

Similarly, among the 461 subjects with week 96 data (one subject was missing weeks 80 and 96 CD4+ T-lymphocyte count data), BMI predicted change in CD4+ T-lymphocyte count to week 96 ($P = .03$), with larger baseline BMI associated with greater CD4 increases. Among the 558 subjects with week 48 data, baseline BMI did not significantly predict change in CD4+ T-lymphocyte count at week 48 ($P = .38$). To explore the week 48 result, we conducted a post hoc analysis among the 327 subjects also in the week 96 analysis; in this analysis, BMI was significant ($P = .02$) and showed a similar positive association with change in CD4+ T-lymphocyte count as seen at week 96. Again, these models adjusted for baseline plasma HIV RNA, CD4+ lymphocyte count, age, and race.

Baseline BMI Category and Activated CD4+ and CD8+ T-Lymphocytes

Table 3 summarizes unadjusted correlations between baseline BMI and CD8+CD38+DR+% and correlations adjusted for baseline CD4+ T-cell count and baseline plasma RNA. Similar correlations are presented for baseline BMI and CD4+CD38+DR+%. No significant correlations between BMI and immune activation were seen after adjustment for baseline CD4+ and RNA.

DISCUSSION

Immunologic reconstitution is highly variable, and a number of factors are known to predict CD4 T-lymphocyte increases in patients initiating ART. Age,^{8,10,11} CD4+ T-lymphocyte nadir,^{12,13} co-infection with hepatitis C virus,¹⁴ residual HIV viral replication,¹⁵ persistent immune activation,⁴ and thymic size¹⁶ have all been reported as possible factors that affect CD4 lymphocyte restoration in patients on ART.

Our study confirmed the preliminary ACTG-ALLRT analysis that higher baseline BMI predicts greater gains in CD4+ T-lymphocyte count at weeks 96 and 144 in ART-naïve men after starting ART. This finding is in contrast to the results in the Crum-Cianflone et al study,⁷ which showed that obese patients have smaller CD4 T-lymphocyte gains. Crum-Cianflone et al did not address posttreatment HIV RNA levels, however, whereas the present analysis was restricted to subjects with HIV RNA <400 copies/mL. In addition, it is challenging to interpret the associative findings between BMI and CD4 count in Crum-Cianflone et al,⁷ since only time-updated BMI was examined. In contrast, we evaluated the effect of pretreatment BMI on subsequent CD4 changes.

In our analyses, baseline BMI did not significantly predict CD4 changes to week 48; estimated CD4 changes from the model, however, did increase with BMI but were smaller in magnitude than at weeks 96 and 144. This may be due to different underlying mechanisms behind early versus later CD4 increases, or it may reflect a temporal relationship. The rate of increase of CD4+ T-lymphocytes is greatest during the first 3 years, followed by a general flattening of the slope.¹⁷ The week 96 and 144 time points may

provide a better window to fully appreciate the magnitude of CD4 lymphocyte recovery likely to be seen, whereas the week 48 time point may be too soon.

Possible explanations for the relationship between higher BMI and higher CD4+ T-lymphocyte gains include the effects of adipokines such as leptin, differences in thymic size, differences in lymphocyte population dynamics in the gastrointestinal tract and other mucosal sites, and differences in T-lymphocyte apoptosis. On the other hand, several studies have demonstrated that increasing BMI positively correlated with higher CD4+ T-lymphocyte counts in HIV-seronegative women^{18,19} and children.²⁰ Therefore, persons with higher BMI may naturally have higher CD4+ T-lymphocyte counts, and the greater CD4+ T-lymphocyte recovery on ART in HIV-infected patients with higher BMI could be explained simply by a “return to health” phenomenon.

Adipose tissue is an active endocrine and paracrine organ that regulates energy storage, inflammation, and immunity.²¹ Adipocytes produce cytokines and adipokines, including leptin and adiponectin. Serum leptin levels are higher in obese patients and are positively correlated with percentage of adipose tissue.²² Leptin is a cytokine-like hormone in both structure and function.² The leptin-deficient state in mice is associated with reduced thymic development and peripheral lymphocyte counts and function.²³ In humans, there are reduced lymphocyte numbers and function; leptin replacement therapy reverses these defects.^{24, 25} Future studies should explore the relationship between leptin and other adipokines with lymphocyte production and function in HIV disease and its role in CD4 T-lymphocyte recovery with ART.

An important limitation of our study was that the analysis was restricted to men. The ALLRT cohort did not have a large enough cohort of women to perform a meaningful analysis, and prior finding of an association of CD4+ T-cell increases with pretreatment BMI was only seen in men.⁸ Even though underlying mechanisms of CD4+ cell recovery might be similar regardless of sex, the results of this study cannot be generalized to include women. Another limitation is the potential for informative dropout (or exclusion from the analysis due to viral failure or due to missing data), as analyses were based on virally suppressed subjects with available data at the various time points. Furthermore, the measurement of BMI does not distinguish between fat and lean mass.

In summary, we have shown that BMI predicts CD4+ T-lymphocyte gains in HIV-infected men receiving antiretroviral therapy and that there is no association between BMI and cellular immune activation. Improving our understanding of the impact of BMI—specifically the effects of adipose tissue—on HIV immunopathogenesis may inform future strategies to improve immune function.

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Table 1

Baseline characteristics and body mass index (BMI) of 808 male subjects

Baseline characteristics	BMI (kg/m ²)			
	<18.5 (n = 23)	18.5–24.9 (n = 453)	25–29.9 (n = 248)	30 (n = 84)
Age, years ^a	37 (22–45)	36 (31–42)	38 (33–44)	36 (31–40)
White/non-Hispanic, n(%)	8 (35%)	251 (55%)	117 (47%)	43 (51%)
Black/non-Hispanic	8 (35%)	121 (27%)	68 (27%)	23 (27%)
Hispanic	6 (26%)	68 (15%)	61 (25%)	17 (20%)
Other race/ethnicity	1 (4%)	13 (3%)	2 (1%)	1 (1%)
Baseline CD4, cells/mL ^a	128 (35–289)	234 (68–370)	285 (125–460)	327 (164–452)
Baseline HIV RNA, log ₁₀ copies/mL ^a	5.1 (4.7–5.5)	5.1 (4.5–5.6)	4.8 (4.3–5.3)	4.7 (4.3–5.3)
Baseline activated CD8% ^a	51 (44–60)	54 (39–63)	51 (36–64)	48 (36–57)
Baseline activated CD4% ^a	20 (12–32) (n = 8)	18 (11–31) (n = 250)	15 (9–33) (n = 142)	13 (7–21) (n = 36)

^aMedian (25th – 75th percentiles)

CD4+ T-cell count increases (to week 48, 96, and 144) by baseline body mass index (BMI) in subjects with HIV RNA < 400 copies/mL

Table 2

	Baseline BMI (kg/m ²)					P
	<18.5	18.5–24.9	25–29.9	30	n	
Week 48^a(n = 558)	n = 14	n = 3 04	n = 183	n = 57		
Mean CD4+ T-cell count increase (SD) cells/mm ³	150 (95)	178 (115)	165 (138)	199 (143)		
CD4 increase relative to BMI 18.5–24.9 (95% CI) ^b	–23 (–88, 43)	-	–2 (–25, 20)	26 (–9, 61)		.38
Week 96^a(n = 461)	n = 13	n = 263	n = 146	n = 39		
Mean CD4+ T-cell count increase (SD) cells/mm ³	218 (114)	259 (159)	251 (167)	318 (190)		
CD4 increase relative to BMI 18.5–24.9 (95% CI) ^b	–52 (–141, 36)	-	8 (–25, 41)	72 (18, 125)		.03
Week 144^a(n = 357)	n = 10	n = 199	n = 121	n = 27		
Mean CD4+ T-cell count increase (SD) cells/mm ³	232 (108)	299 (164)	307 (232)	392 (248)		
CD4 increase relative to BMI 18.5–24.9 (95% CI) ^b	–94 (–214, 26)	-	35 (–8, 78)	113 (38, 189)		.005

^aThe week 48 CD4 change is based on the average of week 32 and week 48 CD4 cell counts; the week 96 CD4 change is based on the average of weeks 80 and 96; and the week 144 change is based on the average of weeks 112, 128, and 144. Most subjects (>97%) had CD4 measurements at each of the weeks that were averaged. At week 48, HIV RNA<400 copies/mL at weeks 32 and 48; at week 96, HIV RNA<400 at weeks 32, 48, 80, and 96; at week 144, HIV RNA<400 at weeks 32, 48, 64, 80, 96, 112, 128, and 144.

^bBased on linear regression models that additionally adjusted for baseline log10 HIV RNA (as continuous predictor), baseline CD4+ T-cell count (as continuous predictor), age (as continuous predictor), race (as white/non-Hispanic vs black/non-Hispanic vs Hispanic/other), and relative to men with a normal BMI (18.5–25 kg/m²). The P value is testing for differences in CD4 increases across the 4 BMI categories in the adjusted model.

Table 3

Baseline body mass index (BMI) category and activated CD4+ and CD8+ T-lymphocytes

Week	Baseline BMI vs activated CD8%: correlation	Baseline BMI vs activated CD4%: correlation	Activated CD8%: median (Q1,Q3)	Activated CD4%: median (Q1,Q3)
Baseline				
Unadjusted	-0.03 ($P = .37$, $n = 808$)	-0.10 ($P = .05$, $n = 418$)	52 (37,63)	17 (10,31)
Adjusted ^a	-0.003 ($P = 0.93$, $n = 808$)	0.05 ($P = 0.31$, $n = 418$)		
Week 16 (VL <400) ^b				
Unadjusted	-0.05 ($P = .31$, $n = 465$)	-0.07 ($P = .35$, $n = 193$)	31 (21,45)	10 (6,20)
Adjusted ^a	-0.009 ($P = .84$, $n = 465$)	0.04 ($P = .63$, $n = 193$)		
Week 48 (VL <400) ^b				
Unadjusted	-0.05 ($P = .26$, $n = 558$)	-0.08 ($P = .15$, $n = 323$)	24 (15,35)	7 (4,11)
Adjusted ^a	0.01 ($P = .76$, $n = 558$)	0.02 ($P = .68$, $n = 323$)		
Week 96 (VL <400) ^b				
Unadjusted	-0.02 ($P = .59$, $n = 462$)	-0.13 ($P = .04$, $n = 244$)	18 (12,27)	6 (4,8)
Adjusted ^a	0.01 ($P = .80$, $n = 462$)	-0.05 ($P = .46$, $n = 244$)		
Week 144 (VL <400) ^b				
Unadjusted	-0.07 ($P = .20$, $n = 357$)	-0.11 ($P = .17$, $n = 162$)	16 (10,26)	6 (3,9)
Adjusted ^a	-0.07 ($P = .22$, $n = 357$)	-0.04 ($P = .62$, $n = 162$)		

Note: VL = HIV RNA viral load.

^aPartial correlations adjusted for baseline CD4 and baseline log₁₀ HIV RNA.

^bAt week 16, viral load <400 copies/mL; at week 48, VL <400 at weeks 32 and 48; at week 96, VL <400 at weeks 32, 48, 64, 80, and 96; at week 144, VL <400 at weeks 32, 48, 64, 80, 96, 112, 128, and 144.