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Obesity and immune cell counts in women

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Abstract

Obesity is common in women and is associated with a number of adverse health outcomes including cardiovascular disease, infectious diseases, and cancer. We explore the relationship between obesity and immune cell counts in women in a longitudinal study of 322 women from 1999 through 2003 enrolled as HIV-negative comparators in the Women's Interagency HIV Study. Body mass index (BMI, kg/m^2) was categorized as normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9), obese (BMI 30-34.9), and morbidly obese (BMI ≥35). CD4 and CD8 counts and percents and total lymphocyte and white blood cell (WBC) counts were measured annually using standardized techniques. A mixed model repeated measures analysis was performed using an autoregressive correlation matrix. At the index visit, 61% of women were African American; mean age was 35 years, and median BMI was 29 kg/m^2. Immunologic parameters were in the reference range (median CD4 count, 995 cells/mm^3; CD8 count, 488 cells/mm^3; total lymphocyte count, 206 cells/mm^3; median WBC, 6×10^3 cells/mm^3). In multivariate analyses, being overweight, obese, or morbidly obese were independently associated with higher CD4, total lymphocyte, and WBC counts than being normal weight; morbid obesity was associated with a higher CD8 count. The strongest associations between body weight and immune cell counts were demonstrated in the morbidly obese. Increasing body weight is associated with higher CD4, CD8, total lymphocyte, and WBC counts in women. Investigation into the impact of obesity on immune function and long-term adverse outcomes is needed.

1. Introduction

The prevalence of obesity has increased markedly in the last two decades in the United States [1,2]. Recent data suggest that 65% of adults in the United States are overweight, with 30% of these being obese and 5% extremely obese [1]. Disparities in the prevalence of obesity exist by gender, race, and ethnicity. Women are more likely to be obese than men, and Mexican Americans and non-Hispanic Blacks are more likely to be obese than non-Hispanic Whites [1,2].

These trends are of particular concern as obesity is associated with many adverse health conditions including type 2 diabetes mellitus (DM), cardiovascular disease, hypertension, dyslipidemia, asthma, arthritis, and poor health in general [2-7]. Obesity has also been associated with a higher incidence of infections in acutely ill [8] and postsurgical populations [9,10] as well as with an excess incidence of cancer [6], which raises the possibility that altered immune cell count or function may be one of the links between obesity and disease.

Research into the effect of obesity on lymphocytes and T-lymphocyte subsets has produced conflicting results. Potential reasons for these inconsistencies include the cross-sectional nature of these studies as well as small sample size. One small study [11] found reduced CD4$^+$ and

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$CD8^+$ T-lymphocyte subsets in 34 obese subjects compared with 50 nonobese subjects, whereas another found elevations in $CD4^+$ T lymphocytes and no change in $CD8^+$ T lymphocytes in 116 obese women compared with 41 nonobese women [12]. Others have demonstrated an increase in $CD4^+$ T cells and a decrease in $CD8^+$ T cells in morbidly obese women compared with healthy, normal-weight controls [13], whereas still others demonstrate no difference between either $CD4^+$ or $CD8^+$ T-cell counts in obese and normal-weight patients [14].

We investigate the longitudinal relationship between body mass index (BMI) and white blood cell (WBC) count, total lymphocyte count, and T-cell subsets including $CD4^+$ and $CD8^+$ cell counts and percents, as well as CD4/CD8 ratio, in a large, ethnically diverse cohort of women.

2. Methods

2.1. Participants and study design

HIV-uninfected women enrolled in the Women's Interagency HIV Study (WIHS), an ongoing multicenter longitudinal cohort study of the characteristics and progression of HIV infection in women, were studied in this analysis. The WIHS enrolled 2059 HIV-infected and 569 HIV-uninfected women from 6 sites across the United States: New York (Bronx/Manhattan), Washington, DC, Chicago, Los Angeles, and the San Francisco Bay Area from October 1994 through November 1995. At baseline, the HIV-uninfected women had sociodemographic and HIV risk factors similar to the HIV-infected women. The recruitment methods and baseline characteristics of enrollees have been reported elsewhere [15,16]. Women were studied at semiannual visits, which include a structured interview, a physical examination, including measures of height and weight, and the collection of blood, urine, and cervicovaginal fluid samples.

2.2. Measurement of BMI

Weight was measured at baseline and at semiannual visits, whereas height was measured at the baseline visit only. BMI was calculated using the formula: (body weight in kilograms)/(height in meters)^2.

2.3. Measurement of white blood cells, lymphocytes, CD4, and CD8

$CD4^+$ and $CD8^+$ T-cell counts and percents were measured annually in HIV-uninfected women using standard flow cytometry performed in laboratories certified by the National Institute of Allergies and Infectious Diseases (NIAID) Flow Cytometry Quality Assessment Program. In keeping with the NIAID guidelines, 3-color immunophenotyping is used. The monoclonal antibody combinations used include CD3/CD4/CD45 as well as CD3/CD8/CD45 to determine $CD4^+$ T cells and $CD8^+$ T cells, respectively. Using low side scatter and gating on "bright" CD45 for each tube helped ensure inclusion of only lymphocytes and eliminated the need to correct for gate purity [17]. A complete blood count, including WBC count, with automated differential was measured annually at these same visits. The total lymphocyte count was calculated by multiplying the WBC count by the automated percent lymphocytes.

2.4. Covariates

Covariates that have an independent effect on immune cell function and number were selected through a review of the literature and included: age, race/ethnicity, hepatitis C virus (HCV) seropositivity, and self-report measures of current injection drug use (IDU), current smoking, diabetes, menopausal status and use of postmenopausal hormone replacement therapy (HRT), and use of hormonal birth control. The HCV 2.0 enzyme-linked immunoassay (Abbott Laboratories, Abbott Park, IL) and the recombinant immunoblot assay determined HCV status. Use of postmenopausal HRT was evaluated, but as data were available only from April 2002 on, those women who self-reported using HRT were removed from the analysis, and only postmenopausal women not on hormone replacement were evaluated.

2.5. Statistical analysis

Data on the covariates of interest were routinely collected at the beginning of the 10th semiannual WIHS visit in April 1999. At this time, of the 569 HIV-uninfected women enrolled in the original cohort, 322 had complete BMI data and were thus included in the analysis and followed between April 1999 and March 2003. Compared with those women not included in this study at the index visit, the women included had similar CD4, WBC, and lymphocyte counts, but higher BMI and lower CD8 count and CD8 percent (data not shown). The differences observed in BMI, CD8 count, and CD8 percent did not appear to be clinically significant. No other differences in the outcome variables were found between the 2 groups.

Univariate analyses indicated nonnormal distribution for some of the variables. Appropriate transformations were performed and used in the model analyses. However, as the transformed variables did not lead to any differences in the final models, the results from the original variables are reported here.

Bivariate analyses on index visit data were conducted to identify potentially confounding relationships between the covariates and the dependent and independent variables. These analyses demonstrated a nonlinear relationship between BMI and all of the immunologic variables. Therefore, BMI (in kg/m^2) was categorized by using National Heart, Lung, and Blood Institute guidelines: underweight, BMI less than 18.5; normal weight, BMI 18.5 to 24.9; overweight, BMI 25 to 29.9; obese, BMI 30 to 34.9; morbidly obese (classes II and III obesity), BMI of 35 or greater . For the purposes of the multivariate analyses, dummy variables

were created for each of the BMI categories. The normal-weight group served as the reference group.

Mixed model analyses using an autoregressive correlation matrix were performed for the multivariate, longitudinal analyses. Initial analyses demonstrated that the assumption of compound symmetry was violated in all models; thus, the autoregressive correlation matrix was used. To select the best predictive model of the immunologic outcomes, BMI, along with all covariates and interaction terms, were entered into the model. Through backward selection using null model likelihood, the best, most parsimonious model was selected. In cases where the best fit model included nonsignificant covariates, multicollinearity, defined conservatively as Pearson correlation coefficient between predictor variables of greater than 0.60, was evaluated, but did not play a role in these models. An α of 0.05 was used to determine significance. Least squares means were used to compare the impact of BMI, body composition, and the covariates on the immunologic outcomes. Analyses were carried out in SAS 9.1 (SAS, Cary, NC), using proc GLM and proc Mixed.

3. Results

Of the 322 women included in the analyses, 61% were Black. The mean age was 35 ± 8 years (Table 1). More than two thirds had an annual income of less than $18 000 and two thirds had completed 12 or fewer years of education. A history of IDU was reported in one quarter of women, but only 5% reported current IDU. More than one quarter of the women were HCV seropositive. Most of the women reported currently smoking. A diagnosis of diabetes was reported by 3% of women at or before the index visit. Table 2 shows the body composition and immunologic parameters. The median BMI fell into the overweight category. Four percent of the sample was underweight, 27% normal weight, 26% overweight, 18% obese, and 24% morbidly obese. Median immunologic indices were within laboratory-defined reference ranges at the index visit.

Table 1
Sociodemographic characteristics of the 322 women at the index visit

Characteristic	Number (%) *
Race [a]	
Non-Hispanic White	37 (11)
Hispanic White	6 (2)
Black	196 (61)
Native American	76 (24)
Other	7 (2)
Age [b] (y), mean ± SD	35 ± 8
Marital status [b]	
Living with partner	100 (31)
Separated/divorced/widowed	86 (27)
Never married	114 (35)
Other	2 (1)
Income per year [b]	
≤$18,000	216 (67)
>$18,000	85 (26)
Education [b]	
High school or less	216 (67)
College or greater	106 (33)
Employed [b]	147 (46)
Current alcohol consumption [b]	
Abstain or <3 drinks/wk	236 (73)
>3 drinks/wk	86 (27)
Current intravenous drug use	17 (5)
Current smoking	194 (60)
HCV seropositive	88 (27)
Self-reported diabetes	11 (3)
Menopausal	52 (16)
Use hormonal birth control	22 (7)

[a] Data from baseline.
[b] Data from visit 10.
* Percents may not sum to 100 because of missing data and rounding.

Table 2
Median weight and immunologic parameters at the index visit

Characteristic	Median (interquartile range)
BMI (kg/m^2)	29.2 (24.7-35.1)
CD4 count (cells/mm^3)	995.0 (792.0-1264.5)
CD4 %	48.0 (43.0-53.0)
CD8 count (cells/mm^3)	487.5 (383.0-653.0)
CD8 %	23.5 (19.2-28.3)
CD4/CD8 ratio	2.0 (1.6-2.6)
Total lymphocyte count (cells/mm^3)	206.4 (168.8-255.4)
WBC count (× 10^3 cells/mm^3)	6.1 (4.9-7.5)

Bivariate analyses demonstrated that BMI was a significant predictor of WBC count, total lymphocyte count, CD8 count, and CD4 count, but did not predict CD4 and CD8 percent or CD4/CD8 ratio. None of the models demonstrated a significant interaction between BMI and time.

In the unadjusted model, overweight, obese, and morbidly obese women had significantly higher CD4 counts than normal-weight women (Table 3). CD4 counts in underweight women did not differ significantly from those of normal-weight women. The association between weight and CD4 count was strengthened by the addition of current smoking, current IDU, and self-reported DM into the model, although neither current IDU nor self-reported DM were significantly associated. Current smokers had a higher CD4 count than those not reporting current smoking (1240 vs 1145 cells/mm^3, respectively; $P = .0006$). Those who reported IDU had a trend toward a lower CD4 count than those who did not (1136 vs 1250 cells/mm^3, respectively; $P = .07$). Those who self-reported DM appeared to have a higher CD4 count than those who did not (1224 vs 1162 cells/mm^3, respectively; $P = .22$). A significant interaction between morbid obesity and self-reported DM was noted, where in morbidly obese women, the CD4 count was higher in those who self-reported DM than in those who did not. The mean CD4 count in each BMI category at each visit after adjustment is shown in Fig. 1.

As noted earlier, the model with the best fit included covariates that were not significantly associated with CD4 count (eg, current IDU and self-reported DM). When we included only the significant covariates in the model, the associations between weight and CD4 count remained the same.

Table 3
Unadjusted and adjusted models for the association between BMI category and CD4 count and CD8 count

Variables	CD4 count				CD8 count			
	Unadjusted model		Adjusted model		Unadjusted model		Adjusted model	
	F	*P*	F	*P*	F	*P*	F	*P*
Visit	2.48	.04	2.43	.04	1.82	.12	1.81	.12
Underweight	2.10	.19	2.21	.18	2.53	.15	2.56	.15
Normal weight	Ref	–	Ref	–	Ref	–	Ref	–
Overweight	7.18	.009	8.20	.005	1.91	.17	2.01	.16
Obese	11.26	.001	12.40	<.001	2.20	.14	2.29	.13
Morbid obesity	22.69	<.001	26.63	<.001	12.18	.001	12.75	<.001
Current smoking			12.92	<.001			0.96	.33 [a]
Current IDU			3.88	.07 [a]				– [b]
Self-reported DM			1.58	.22 [a]				– [b]
Self-reported DM × morbid obesity			10.06	.002				– [b]

Ref indicates reference.
[a] Variable is not significant, but removal significantly changes fit of the model.
[b] Covariate does not contribute significantly to the adjusted model and therefore is not included.

When we studied the association between BMI category and CD8 count, only morbidly obese women had significantly higher CD8 counts than normal-weight women (Table 3). CD8 counts in underweight, overweight, and obese women did not differ significantly from those of normal-weight women. The addition of current smoking into the model strengthened the association between morbid obesity and CD8 count. As with the adjusted CD4 model, the association remained the same when only significant covariates were included in the model. Current smokers had CD8 counts similar to nonsmokers (609 vs 594 cells/mm^3, respectively; $P = .33$).

Table 4 shows that overweight, obese, and morbidly obese women had a total lymphocyte count that was significantly higher than that found in normal-weight women. The addition of current smoking, self-reported menopause, and self-reported DM into the model strengthened the association, although the latter 2 covariates and the

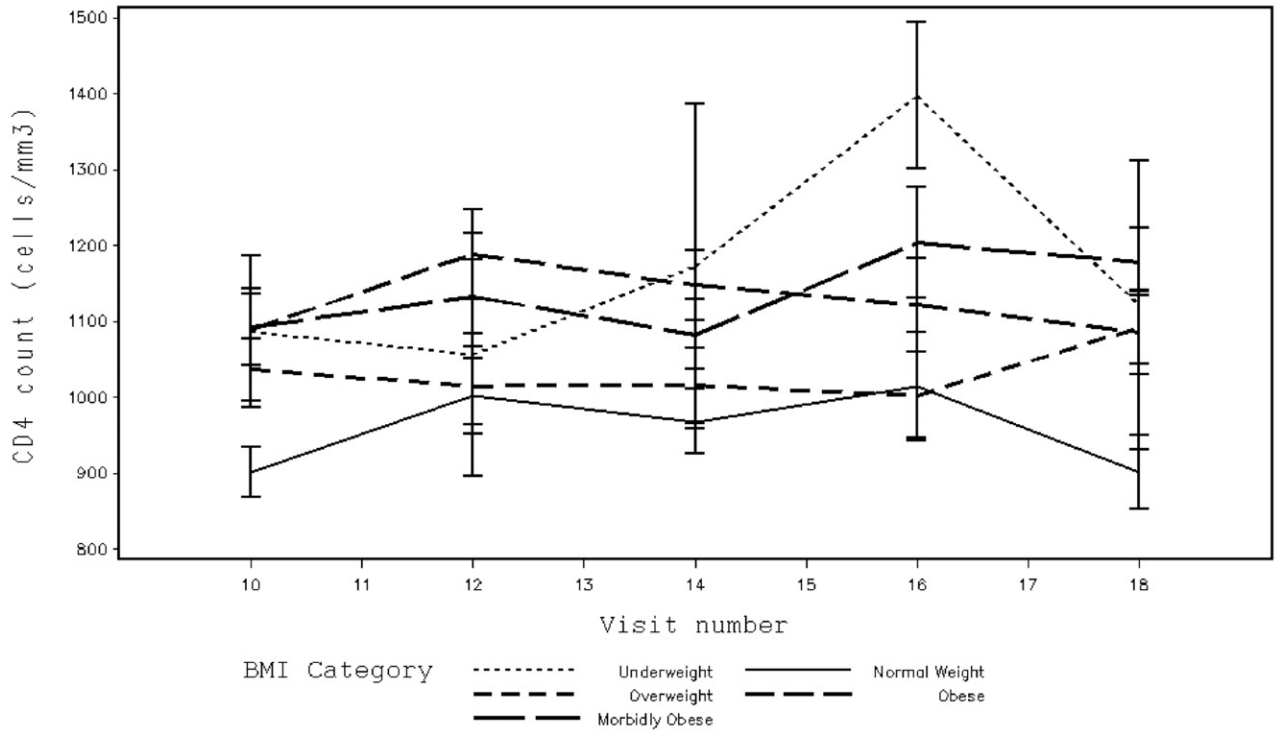

Fig. 1. Adjusted mean CD4 counts with standard errors by BMI category at semiannual WIHS visits from April 1999 (index visit corresponds to WIHS visit 10) through March 2003 (visit 18) for the 322 study participants. Women who are overweight, obese, or morbidly obese have significantly higher CD4 counts (in cells per cubic millimeter) than do normal-weight women (overweight women [1169] vs normal-weight women [1079], $P = .006$; obese women [1190] vs normal-weight women [1058], $P = .001$; morbidly obese women [1215] vs normal-weight women [1034], $P < .001$).

Table 4
Unadjusted and adjusted models for the association between BMI category and total lymphocyte count and WBC count

Variables	Total lymphocyte count				WBC count			
	Unadjusted model		Adjusted model		Unadjusted model		Adjusted model	
	F	*P*	F	*P*	F	*P*	F	*P*
Visit	1.75	.14	3.03	.02	1.05	.38	0.84	.50
Underweight	4.41	.07	4.43	.07	1.92	.20	1.97	.20
Normal weight	Ref	–	Ref	–	Ref	–	Ref	–
Overweight	7.03	.01	7.88	.006	4.39	.04	4.53	.04
Obese	15.11	<.001	16.53	<.001	9.30	.003	10.65	.002
Morbid obesity	27.16	<.001	23.70	<.001	22.71	<.001	29.59	<.001
Current smoking			4.35	.04			9.42	.003
Menopause			2.63	.11 [a]			4.45	.04
Self-reported DM			0.00	.99				– [b]
Self-reported DM × visit			3.88	.004				– [b]
Self-reported DM × morbid obesity			6.42	.01				– [b]
Race				– [b]			3.31	.01
HCV				– [b]			15.27	<.001

[a] Variable is not significant, but removal significantly changes fit of the model.
[b] Covariate does not contribute significantly to the adjusted model and therefore is not included.

outcome were not significantly associated. We observed an interaction between morbid obesity and self-reported DM that was similar to that observed in the CD4 model and an interaction between time and self-reported DM. We found that over time, those who reported DM had a rise in lymphocyte counts 2 years after the index visit followed by a decline back to baseline in the last year of the study, whereas in women who did not report DM, the lymphocyte count remained constant over the duration of the study. Current smokers had a higher mean total lymphocyte count than those not reporting current smoking (263 vs 252 cells/mm^3, respectively; $P < .04$). Women who reported being menopausal had a total lymphocyte count similar to those who did not (252 vs 262 cells/mm^3, respectively; $P = .12$). Those who self-reported DM had a total lymphocyte count similar to those who did not (268 vs 247 cells/mm^3, respectively; $P = .99$).

Similarly, overweight, obese, and morbidly obese women had significantly higher WBC counts than normal-weight women (Table 4). The addition of self-reported menopause, race, and HCV seropositivity into the model strengthened the association. Non-Hispanic Whites had the highest WBC count, and Blacks the lowest (6.99×10^3 vs 6.09×10^3 cells/mm^3, respectively; $P = .01$). Those who were HCV seropositive had a higher WBC count than those who were seronegative (7.26×10^3 vs 6.52×10^3 cells/mm^3, respectively; $P < .01$). Current smokers had a higher WBC count than nonsmokers (7.11×10^3 vs 6.67×10^3 cells/mm^3, respectively; $P = .003$), and those who self-reported menopause had a lower WBC count that those who did not (6.71×10^3 vs 7.07×10^3 cells/mm^3, respectively; $P = .04$).

Because the underweight group comprised only 3% of all of the BMI observations (N = 11 at the index visit), the small sample size may be insufficient to provide a reliable analysis. Therefore, all BMI analyses were repeated without this group. No differences in the results were observed.

4. Discussion

In our large cohort of ethnically diverse women, we found that being overweight or obese was associated with higher CD4, total lymphocyte, and WBC counts. Being morbidly obese was associated with these outcomes, as well as with a higher CD8 count. The associations between weight and immune cell counts became stronger with each successive increase to the next weight category. It is noteworthy that cigarette smoking was associated with increases in immune cell number across cell types, which is consistent with previous findings in the WIHS cohort [18] as well as in the wider literature [19,20]. When we adjusted for cigarette smoking, the association between obesity and immune cell number was further strengthened.

A potential mechanism for the association between body weight and immune cell count may be via the production of the adipokine leptin from adipose tissue. Obesity in humans is characterized by high circulating levels of leptin, consistent with a leptin-resistant state [21,22]. Immunologically, leptin supports proliferation and prevents apoptosis in a variety of immune cell types, especially T_H1 CD4 subsets [23,24]. It also stimulates the production of proinflammatory cytokines [25]. The role of leptin in the association between body weight and immune cell counts needs to be explored in our cohort.

The relationship between weight and CD8 count invites additional consideration. Our data demonstrated a relationship between morbid obesity and CD8 count, but not overweight and obesity when compared with normal weight. These results are consistent with findings from other studies [14,26]. It may be that fat has a more direct effect on CD4 count, total lymphocyte count, and WBC count than on CD8 count. Naïve $CD8^+$ T cells require more costimulatory activity than do naive $CD4^+$ T cells [27], possibly because $CD8^+$ T cells are more destructive once activated. CD4

subtypes are directly stimulated by various cytokines including tumor necrosis factor α, which is responsible for differentiation of $CD4^+$ T cells into the T_H1 subset [28-31], and leptin. Whereas cytokines produced by fat are not central to CD8 activation, an increase in $CD4^+$ T-cell count is. Therefore, whereas fat, via the action of various adipokines, directly influences CD4 count, it may influence CD8 counts only via its ability to activate $CD4^+$ T cells, and thus, its influence on CD8 counts may only be seen in the most extreme comparisons.

The strengths of our study include a large sample size compared with previous investigations, along with a longitudinal study design. We have also included several measures of body fat, as well as CD4 percent, CD8 percent, and CD4/CD8 ratio, which may provide a better estimation of immune system function than cell counts alone. The depth and breadth of the database used also allowed for an evaluation of these various measures of weight/fat and immune function in the context of a variety of covariates that have a documented impact on immune cell counts.

The primary limitation of our study was that our current analysis did not include an evaluation of $CD4^+$ and $CD8^+$ T-cell activity, and therefore we are unable to comment on the impact of fat on CD4 subsets and activation and on $CD8^+$ T-cell activation. In general, functional analyses of the cell types included in this study would provide important additional information, as cell counts do not necessarily reflect function.

Our data should be interpreted with caution because the women studied were enrolled into the WIHS based on behaviors that put them at risk for HIV. These women were also impressively obese, more than is reported in the general population. Nevertheless our findings of an association between obesity and a higher CD4 count correspond closely to those found by Nieman and colleagues [26] who studied a community-based sample of generally healthy obese White women (mean BMI 33 kg/m^2) compared with normal-weight White women. Our results differed from those found in other groups [11,13,14], possibly because those studies were smaller and included both men and women.

In conclusion, we found strong evidence of an association between obesity and increased CD4 counts, total lymphocyte counts, and WBC counts in a population of women at risk for HIV infection. The increased number of immune cells associated with obesity may be the result of a chronic inflammatory state due to increased cytokine production by adipose tissue. Future research is needed to understand the association among obesity, immune function, and long-term morbidity and mortality outcomes in women.

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