Protein Intake Is Positively Associated with Body Cell Mass in Weight-Stable HIV-Infected Men¹,²

ABSTRACT Depletion of body cell mass (BCM) in human immunodeficiency virus (HIV)-infected patients is strongly associated with disease progression and death. Although whole-body protein turnover is increased in HIV infection, it is not known whether protein intake is independently associated with BCM. The purpose of this study was to determine the associations, if any, between protein intake and several body composition variables in 467 weight-stable, HIV-infected men with CD4 <200 cells/mm³ enrolled in a multicenter nutritional supplementation trial. Baseline BCM, total body fat and extracellular mass as measured by bioelectrical impedance analysis, dietary intake (24 h food recall) and muscle building activity assessed by structured interview were analyzed to determine association(s) between body composition variables and macronutrient intake. Multiple regression analysis showed that BCM was positively associated with body weight (P = 0.001), height (P < 0.001), protein intake (P < 0.001), muscle-building activity (P < 0.001) and African-American ethnicity (P < 0.05) and negatively associated with carbohydrate intake (P < 0.05), age (P < 0.001) and number of prior AIDS-related diagnoses (P < 0.001). We conclude that protein intake is associated with increased BCM, whereas carbohydrate intake is negatively associated with BCM in HIV-infected men, independently of muscle building activity.


KEY WORDS: • protein • body composition • human immunodeficiency virus

Wasting has been a common feature of the human immunodeficiency virus (HIV)³ epidemic since its appearance in the early 1980s and is associated with increased morbidity and mortality (1,2). Although all body compartments are affected, (3,4) loss of body cell mass (BCM) is strongly associated with disease progression and predicts mortality (2,5).

Because protein is the principal component of BCM, fluctuations in its metabolism may contribute to clinically important wasting. Studies of whole-body protein turnover in HIV patients suggest that it is correlated with BCM (6) and protein intake (7). This is consistent with findings reported from studies in animals (8), elderly women (9–11) and burn patients (12). A previous cross-sectional study in HIV-infected patients found that, in fact, protein intake was highly correlated with lean body mass (13).

In animals and in normal, untrained male volunteers, protein intake in the absence of resistance exercise does not result in enhanced protein synthesis in skeletal muscle (14,15). It is not known, however, whether this is the case in malnourished or chronically ill individuals, such as those with HIV disease, because relevant studies have yet to be conducted.

The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) conducted a randomized, controlled trial comparing the ability of three oral dietary regimens to maintain or increase body weight and BCM in HIV-infected patients with stable (nondecreasing) weight and CD4⁺ cell counts <200 cells/mm³ (16). Baseline data collected afford the opportunity to ask whether protein intake is independently associated with BCM in clinically weight-stable HIV-infected patients.

SUBJECTS AND METHODS

Subjects. Baseline data from CPCRA 039, a multicenter, randomized, open-label nutritional supplementation study conducted among HIV-infected patients between July 31, 1996 and November 30, 1997 were analyzed for this paper. Entry criteria and study procedures are described elsewhere (16). Of the 536 randomized patients, 467 were men with baseline dietary recall data available and provide the basis of this paper. The number of women participating in the trial was insufficient to draw statistically valid conclusions concerning the question posed here.

Body composition. Height and weight were measured following a standard procedure. Body composition was measured according to a written protocol using a single-frequency bioelectrical impedance analysis (BIA)-101Q analyzer (RJL Systems, Clinton Township, MI). Formulas for computing BCM, total body fat (TBF) and extracellular mass (ECM) were provided by the manufacturer as published (17).

Dietary recall. Macronutrient intake was assessed from a single 24-h dietary recall using the Minnesota Nutrition Data System NDS-93, Food Database version 11A, Nutrient Database version 26, de-


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TABLE 1
Demographic, human immunodeficiency virus (HIV) disease, therapeutic, body composition, and macronutrient intake characteristics of HIV-infected men1,2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>40.4 ± 8.2</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
</tr>
<tr>
<td>Latino/Hispanic</td>
<td>14.8</td>
</tr>
<tr>
<td>African American</td>
<td>36.4</td>
</tr>
<tr>
<td>White</td>
<td>45.4</td>
</tr>
<tr>
<td>Other</td>
<td>3.4</td>
</tr>
<tr>
<td>History of injection drug use, %</td>
<td>19.5</td>
</tr>
</tbody>
</table>

1 Values are means ± sd, n = 467.
2 Abbreviations: AIDS, acquired immunodeficiency syndrome; ARD, AIDS-related diagnosis.
3 Not treated with a protease inhibitor.

RESULTS

Subject characteristics. Among the 467 HIV-infected males included in the study, the mean age was 40 y and there was a diverse ethnic representation. The cohort exhibited relatively advanced HIV disease with a mean CD4+ cell count of 104 cells/mm³ and 54.8% having had at least one ARD. Body composition and macronutrient intake variables included a mean BCM of 28.2 kg and mean daily energy, protein and carbohydrate intakes of 13.97 MJ, 117.9 g and 432.4 g, respectively. Other characteristics of the cohort are listed in Table 1.

MBA. Eighty-four (18%) participants reported regularly participating in a weight training program. One hundred thirty-five (28%) reported regularly performing some strength-building exercises, whereas 248 (53%) reported not regularly participating in any program.

Backward stepwise regression analysis of variables associated with body composition parameters. For BCM and ECM, the backward stepwise regression resulted in the selection of weight, height, MBA, age, African American, number of ARD events, total daily protein intake and daily carbohydrate intake in the final models (Table 2). When “total protein” (g) was replaced by two terms, i.e., “animal protein” (g) and “vegetable protein” (g), “animal protein” was retained in the model and “vegetable protein” was the last eliminated. When “animal protein” was expressed as a percentage of total protein intake, it was the first variable eliminated in the backward elimination process. We therefore concluded that animal and vegetable protein intakes were nearly equivalent in their associations with BCM. Given this equivalence, total protein (g) was used in the present analysis.

Body weight, height, MBA level, African American race and protein intake were all positively associated with BCM (Table 2), whereas age, number of ARD events and carbohydrate intake were negatively associated. For TBF, the backward stepwise regression selected only weight, height and MBA. The MBA level was negatively associated (P < 0.001) with TBF. CD4 cell count did not remain in any model tested and was not included as a variable in the multiple regression analysis.

DISCUSSION

In this cross-sectional study of men with advanced, asymptomatic HIV disease, an association between total protein intake and BCM, controlling for other confounding variables, was identified, consistent with findings in animals and other human populations.

The significant, positive association between protein intake and BCM independent of MBA observed here most likely represents a clinically meaningful relationship. In asymptomatic HIV-infected patients, protein intake is greater than that of uninfected individuals (21). In chronic HIV infection, increased whole-body protein turnover may require greater

TABLE 2
Regression coefficients from the multiple regression of body cell mass, total body fat and extracellular mass on variables in the final model of backward stepwise regression analysis1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Body cell mass</th>
<th>Total body fat</th>
<th>Extracellular mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>0.28†</td>
<td>0.45†</td>
<td>0.27†</td>
</tr>
<tr>
<td>Height, m</td>
<td>4.53†</td>
<td>−14.19†</td>
<td>9.78†</td>
</tr>
<tr>
<td>MBA level (1 = lowest, 7 = highest)</td>
<td>0.28‡</td>
<td>−0.23‡</td>
<td>−0.07‡</td>
</tr>
<tr>
<td>Age, 10 y</td>
<td>−0.42‡</td>
<td>0.46‡</td>
<td></td>
</tr>
<tr>
<td>African American (1 = yes, 0 = else)</td>
<td>0.37*</td>
<td>−0.51†</td>
<td></td>
</tr>
<tr>
<td>Prior ARD events, n</td>
<td>−0.34‡</td>
<td>0.25‡</td>
<td></td>
</tr>
<tr>
<td>Protein intake, 100 g</td>
<td>0.68‡</td>
<td>−0.44‡</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate intake, 100 g</td>
<td>−0.12*</td>
<td></td>
<td>0.11†</td>
</tr>
</tbody>
</table>

1 Abbreviations: MBA, muscle-building activity; ARD, AIDS-related diagnosis.
* P < 0.05; † P < 0.01; ‡ P < 0.001.
intake to provide adequate substrate to maintain BCM homeostasis (6), possibly to compensate for a subclinical protein-wasting enteropathy, whereas MBA is required for anabolism beyond baseline. Because a controlled, biochemical analysis of protein turnover was not conducted in this study, its relationship to the association between protein intake and BCM observed here cannot be determined.

In this study, the sources of dietary protein contributed equally to the observed association of protein intake with BCM. Whether this would hold true in a prospective trial randomized on the basis of protein source is not known. Assuming a similar daily protein intake and availability of a comprehensive complement of amino acids, however, there is no reason to assume the superiority of one component over the other with regard to an association with BCM.

Carbohydrate intake was negatively associated with BCM. The reasons for this are unclear although it is possible that patients whose diets include a greater proportion of carbohydrates consume a proportionately lower amount of protein. This would be consistent with the main finding that greater protein intake is positively associated with BCM.

CD4 cell count was not associated with any body composition variables in this cohort. This most likely is explained by the fact that all patients were asymptomatic and weight stable at study entry. In this context, CD4 cell counts may offer only a long-term prognosis concerning disease progression, which does not reliably reflect body composition in the absence of decreased intake or active opportunistic disease.

In the present study, a negative correlation between BCM and the number of prior ARD events was observed, whereas no association between ARD and TBF was noted. Whether this is because fat repletion occurs preferentially after the resolution of opportunistic infections, whereas BCM repletion occurs more slowly or incompletely, was not evaluated in this study, although this mechanism is supported by others (22,23). Because it is not known whether a "threshold of benefit" of dietary protein intake exists, a prospective protein supplementation trial comparing symptomatic and asymptomatic populations may be warranted.

The use of highly active antiretroviral regimens (HAART), particularly those including protease inhibitors, has been associated with significant changes in body composition (24,25). In this study, all patients were following antiretroviral regimens, 74% of which included a protease inhibitor. No differences in BCM or protein intake between those taking protease inhibitors and those not taking them were observed. Because the duration, content and virologic efficacy of protease inhibitor–containing HAART regimens were not controlled in this study, it is not possible to identify a relationship with BCM.

African-American ethnicity was independently associated with BCM in this study. None of the measures considered here, including MBA and protein intake, altered this association when controlling for age, weight and height. This cannot be explained on the basis of the data measured here and may simply reflect genetic differences. It is unlikely that it is an artifact of BIA measurement because the equations used are not affected by race (17). Further research is required to determine whether other factors are present and could be useful in specifying therapeutic recommendations for this group.

When the data were analyzed in a stepwise backward elimination regression, no association between a history of IDU and any variable associated with body mass was found. In particular, a history of IDU was not independently associated with BCM (P = 0.72). Previous studies of body composition among IDU have been inconclusive but in general are consistent with this finding (26–28).

Several limitations of this study point to the need for additional clinical trials. The utility of the 24-h dietary recall in accurately characterizing nutritional intake has been questioned (29). The accuracy of self-reporting and short duration of recall may not reliably capture longer-term dietary trends. Prospective food logs, 72-h recalls or even direct observation may improve the accuracy and precision of macronutrient intake estimates (30). Although it is reassuring that the mean protein intake observed here is consistent with previous estimates of daily requirements in HIV patients (21,31), a more intensive, long-term prospective evaluation of an outpatient population would be helpful.

An additional limitation of this study was that only one method was available to assess BCM, i.e., single-frequency BIA, a method that has been validated for HIV patients using total body potassium scanning and isotopic dilution techniques as criterion methods (22). Although this validation study included HIV patients studied before the widespread use of HAART, single-frequency BIA has been widely used in recent clinical studies in patients receiving HAART (32,33) and is common in clinical practice today (34). The method therefore has external validity for studies such as this one.

The results reported here for men, although suggestive, cannot be validly extrapolated to women. Body composition changes associated with the variables tested here should be explored in HIV-infected women in future trials.

As a cross-sectional study, the associations identified here suggest, but do not prove, an independent relationship between protein intake and BCM in HIV-infected men. Con founding variables not identified here, particularly those associated with improved viral suppression and disease prophylaxis, may be present. A longitudinal, randomized, prospective trial examining the role of protein intake in maintaining BCM in weight-stable HIV-infected patients conducted within the context of careful scrutiny of antiretroviral and opportunistic infection prophylactic therapy is required to confirm these results.

Although this study supports an independent association between protein intake and BCM, we cannot conclude from the present data that increasing protein intake will lead to clinically important increases in BCM. In the non-HIV-infected elderly, age-related skeletal muscle mass loss is not prevented by either protein intake or exercise above a minimum level (35). A prospective comparison evaluating dietary intake and MBA in asymptomatic HIV-infected patients and HIV-negative controls would be helpful in determining whether protein intake is more important in maintaining BCM in chronic HIV disease than in an infected state.

LITERATURE CITED


