Body composition in HIV-infected children: relations with disease progression and survival

Massimo Fontana, Giovanna Zuin, Anna Plebani, Ketty Bastoni, Giovanna Visconti, and Nicola Principi

ABSTRACT

Background: Malnutrition is common in HIV-infected children, but the body compartment that is most affected has been ill defined. Objectives: Our objectives were to 1) compare the fat-free mass (FFM) of children with HIV infection with that of control children, 2) assess the contribution of FFM to body weight in HIV-infected children compared with that of control children, and 3) study the relations between body weight, FFM, and mortality.

Design: A cross-sectional study was performed in 86 HIV-infected and 113 uninfected children (mean ages: 6.9 and 7.7 y, respectively). FFM was estimated from single-frequency bioelectrical impedance analysis by using 3 different published equations; a further estimate was obtained from triceps-skinfold-thickness measurements.

Results: All 4 estimates of body composition showed that FFM in HIV-infected children was significantly less than in control children of similar age. However, FFM as a percentage of body weight was not significantly different between groups. In the whole group of infected children, an age-specific z score < -2 for weight and for FFM was significantly associated with an increased risk of death [relative risk (95% CI) = 11.4 (3.1, 41.0) and 5.1 (1.5, 18.2), respectively]; when only children with more severe disease were considered, only z score for weight was significantly associated with an increased risk [4.6 (1.4, 14.9)].

Conclusions: These findings suggest that no preferential catabolism of FFM occurs in HIV-infected children and that body weight for age is a better prognostic indicator than is FFM estimated by bioelectrical impedance analysis.


KEY WORDS HIV, human immunodeficiency virus, acquired immune deficiency syndrome, AIDS, body composition, bioelectrical impedance analysis, children, malnutrition, prognosis, survival, cachexia, wasting syndrome, fat-free mass, lean body mass

INTRODUCTION

Malnutrition is a frequent finding in HIV-infected children and wasting syndrome is among the criteria for including these children in clinical category C (severely symptomatic) according to the Centers for Disease Control and Prevention (CDC) 1994 classification system (1, 2). At present, the pathogenesis of weight loss or growth failure in HIV infection is largely speculative; many factors, including poor oral intake, malabsorption, and hypermetabolism, may be involved. Loss of fat and fat-free mass (FFM) could both contribute to body weight loss, but studies of their relative contribution have yielded conflicting results. Body cell mass (the metabolically active component of FFM) was found to be lower than normal in 193 HIV-infected adult patients studied by bioelectrical impedance analysis (BIA) (3) and in otherwise asymptomatic patients. Very young HIV-infected children were found to have significantly less lean body mass (as assessed by midarm circumference and triceps skinfold thickness) than control children of similar age (4). These observations suggest that a preferential loss of FFM occurs early in the disease progression and that cachexia, rather than protein-energy malnutrition, is the most important mechanism of weight loss.

On the contrary, Sharpstone et al (5), using whole-body dual-energy X-ray absorptiometry in adult, HIV-infected asymptomatic men, found that fat mass was the most severely affected body compartment, FFM being apparently increased. More recently, Paton et al (6), using 4 different techniques, found that the weight loss of a group of adult patients with symptomatic HIV infection was not due to excessive FFM catabolism, but was compatible with undernutrition.

Assessment of FFM in HIV-infected patients might prove useful in predicting survival (7), in clinical staging (8), and in evaluating responses to both nutritional and pharmacologic interventions (9, 10). BIA is a safe, noninvasive, and inexpensive technique for estimating FFM in children. Its ability to predict FFM has been confirmed in adults with AIDS (11). The aim of this work was to study FFM in a large group of HIV-infected children and its correlation with the different stages of illness and with survival.

SUBJECTS AND METHODS

Eighty-six prepubertal children with vertically transmitted HIV infection, as defined by the CDC criteria (2), were recruited...
TABLE 1
Characteristics of the HIV-infected and control children

<table>
<thead>
<tr>
<th>Control children (n = 113)</th>
<th>HIV-infected children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CDC clinical category</td>
</tr>
<tr>
<td></td>
<td>N (n = 11)</td>
</tr>
<tr>
<td></td>
<td>(0.8–14.2)</td>
</tr>
<tr>
<td></td>
<td>7.7 ± 3.3</td>
</tr>
<tr>
<td></td>
<td>(0.6–14.3)</td>
</tr>
<tr>
<td>Males/females</td>
<td>50:63</td>
</tr>
<tr>
<td>CDC category of immunologic suppression</td>
<td></td>
</tr>
<tr>
<td>1, none</td>
<td>—</td>
</tr>
<tr>
<td>2, moderate</td>
<td>—</td>
</tr>
<tr>
<td>3, severe</td>
<td>—</td>
</tr>
</tbody>
</table>

There were no significant differences between either HIV-infected and control children or between children in different clinical categories and control children (Student’s t test, ANOVA, and multiple-range test for age; chi-square test for the proportions of males and females). CDC, Centers for Disease Control and Prevention; N, asymptomatic; A–C, mildly, moderately, and severely symptomatic, respectively.

x ± SD: range in parentheses.

between January 1995 and December 1996 from the First and the Fourth Pediatric Departments of the University of Milan. They were compared with 113 children attending the department clinics for well visits or for scheduled minor surgery; these children were normally nourished at clinical assessment and free from acute or chronic medical conditions that could potentially affect their nutritional status. Informed consent was obtained from the legal guardians of the children, and the study was approved by the local ethics committee. All procedures were performed only after they had been clearly described and explained to the children.

The characteristics of the children studied according to CDC classification criteria are given in Table 1. The clinical categories are as follows: N, asymptomatic; A, B, and C, mildly, moderately, and severely symptomatic, respectively.

The HIV-infected children were studied the first time they attended the departments after the beginning of the study if they were free from acute complications. Four children (3 in category C and 1 in category B) with acute febrile diseases (2 with otitis media and 2 with pneumonia) were studied 3 mo later, after they had recovered. Four children with chronic cytomegalovirus infection, 3 were colonized with Cryptosporidium, 2 had mild-to-moderate chronic diarrhea, 3 had pulmonary tuberculosis, and 2 were infected with Mycobacterium avium complex. Ten children in category A, all children in category B, and 25 children in category C were taking zidovudine (600 mg·m⁻²·d⁻¹). Didanosine (270 mg·m⁻²·d⁻¹) was also given to 4 children in category B and to the remaining 5 children in category C. Standard dietary advice was offered to the parents or guardians of all HIV-infected children and most children in category C were consuming lactose-free diets; no child was being given enteral or parenteral nutritional support.

All measurements were performed in the morning after the children fasted overnight. Weight (to the nearest 0.1 kg), standing height (0.1 cm), nondominant upper arm circumference (0.1 cm), and triceps skinfold thickness (0.1 mm) were measured by the same operator using standard techniques (12, 13). BIA was performed with a tetrapolar bioelectrical analyzer (model Human HI-Scan; Dietosystem, Milan, Italy) after the children voided and rested in bed for 15 min; electrodes were placed as recommended by the manufacturer and a standard, 800-µA, 50-kHz oscillating current was applied.

Upper arm area and upper arm muscle area were derived from measurements of arm circumference and triceps skinfold thickness as described by Frisancho (13). To predict FFM (in kg) from BIA measurements, the following published equations for children were selected:

Goran et al (14):

\[
FFM = \frac{0.59(RI) + 0.065(wt) + 0.04}{0.769 - 0.0025(A) - 0.019(G)}
\]

Houtkooper et al (15):

\[
FFM = 0.61(RI) + 0.25(wt) + 1.31
\]

Arpadi et al (16):

\[
FFM = 0.68(RI) + 0.70(A) + 1.34
\]

where RI is resistance index [height (cm)²/resistance (ω)], wt is weight (kg), A is age (y), and G is sex (0 for females and 1 for males).

To allow comparison of patients of different age groups because body composition is known to change with age (though these differences were not statistically significant), standardized differences from the age-specific means were calculated (z score = (patient’s value – age-specific mean)/age-specific SD). The EPI-INFO software package (CDC, Atlanta) was used to calculate weight-for-age and height-for-age z scores (WAZ and HAZ, respectively). To calculate z scores of FFM, control children were divided in 3-y age groups (0–3, 3–6, 6–9, 9–12, and 12–15 y), the mean and SD of the appropriate age group was then used to calculate the FFM z score of an individual patient. To test for accuracy, this procedure was also applied to 37 children with nonorganic recurrent abdominal pain (age range: 3.4–12.8 y); mean values between 0.08 and −0.03 were obtained for the z scores of different estimates of FFM, and the corresponding SDs ranged between 0.97 and 1.12.

All statistical analyses were performed by using the STAT-GRAPHICS software package (version 6.0; Manugistics, Inc, Rockville, MD). Categorical variables were compared by using the chi-square test. Continuous variables were compared with one-way analysis of variance (ANOVA) after confirming their normal distribution by standardized coefficients of skewness and kurtosis within the range of −2 to 2. When the ANOVA F ratio was statistically significant, a post hoc multiple range analysis was performed by using Tukey’s test to compare infected children in different clinical categories and control children.

The American Journal of Clinical Nutrition
TABLE 2
Anthropometric and body-composition measures of the HIV-infected and control children

<table>
<thead>
<tr>
<th>HIV-infected children</th>
<th>Control children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 113)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>27.8 ± 12.3*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>124.5 ± 21.5*a</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td></td>
</tr>
<tr>
<td>Goran et al (14)</td>
<td></td>
</tr>
<tr>
<td>Houtkooper et al (15)</td>
<td></td>
</tr>
<tr>
<td>Arpadi et al (16)</td>
<td></td>
</tr>
<tr>
<td>Upper arm area (cm²)</td>
<td>2157 ± 663a*</td>
</tr>
</tbody>
</table>

* ± SD. Means with different superscript letters are significantly different, P < 0.05 (Tukey’s test after ANOVA on 5 groups). CDC, Centers for Disease Control and Prevention. FFM, fat-free mass. N, asymptomatic; A–C, mildly, moderately, and severely symptomatic, respectively.

RESULTS

The anthropometric and body-composition data of the children are shown in Table 2. HIV-infected children were significantly lighter and shorter than control children; all prediction equations showed significantly lower FFM and upper arm muscle area for HIV-infected children. The different groups of HIV-infected children differed significantly for all variables studied, except for height, for which only children belonging to categories B and C had mean values significantly lower than those of the control children.

The z scores of body weight, FFM, and upper arm muscle area in the different groups of children studied are shown in Figure 1. Scores for children in clinical categories B and C, but not N or A, were significantly different from those of control children. This analysis confirmed that both FFM and WAZ are compromised in children with more severe disease. Moreover, it showed that the different estimations of lean body mass are highly consistent within each group of children and that their changes parallel body weight changes.

When FFM and upper arm muscle area were given as percentages of body weight and upper arm area, respectively (Table 3), no statistically significant differences were observed between HIV-infected children and control children or between children in the different HIV categories.

Eleven HIV-infected children had a WAZ < –2 (3 in category B and 8 in C) and 14 had an FFM z score < –2 according to the Houtkooper equation (1, 4, and 9 in categories A, B, and C, respectively). Eight children, in category C3 (the children in clinical category C with the most severe immunologic suppression), died before the end of the study, 1–17 mo after the evaluation (median: 3.9 mo). The WAZ was < –2 in 5 of them and between –1 and –2 in 3; the FFM z score was < –2 in 4 children, between –1 and –2 in 3, and > –1 in 1 child. In the whole group of HIV-infected children, a WAZ or an FFM z score < –2 was associated with an increased risk of death; when only children in clinical category C were considered, only WAZ was (Table 4). This figure did not change when FFM and WAZ were estimated by the equations of Goran et al or Arpadi et al were used (data not shown).

DISCUSSION

Several equations have been published predicting FFM from BIA. However, most of them have been developed in healthy individuals, and the assumption of linearity, which seems to be valid for FFM and other lean body mass measures, may not be consistent in the clinical situation. The WHO guidelines for fat-free body mass, excluding HIV-infected children, were based on the Linear Regression method (16). The slope of the regression line between FFM and BIA body fat mass was significantly lower for HIV-infected children than for control children (P < 0.01). The slope of the regression line between FFM and BIA body fat mass for control children was 0.84 ± 0.17 (n = 86), while for HIV-infected children it was 0.69 ± 0.16 (n = 86). A similar difference was observed comparing the FFM values calculated by different formulas: the Houtkooper equation (15) was significantly lower than the Arpadi et al (16) in control children, and the Goran et al (14) was significantly lower than the Houtkooper equation in control children. All these results were confirmed using ANOVA and Scheffe’s method.

The comparison of FFM and WAZ values between control children and HIV-infected children confirmed that HIV-infected children had significant differences compared with control children, except for height. Significant differences were observed for all variables studied, except for height, for which only children belonging to categories B and C had mean values significantly lower than those of the control children.

The z scores of body weight, FFM, and upper arm muscle area in the different groups of children studied are shown in Figure 1. Scores for children in clinical categories B and C, but not N or A, were significantly different from those of control children. This analysis confirmed that both FFM and WAZ are compromised in children with more severe disease. Moreover, it showed that the different estimations of lean body mass are highly consistent within each group of children and that their changes parallel body weight changes.

When FFM and upper arm muscle area were given as percentages of body weight and upper arm area, respectively (Table 3), no statistically significant differences were observed between HIV-infected children and control children or between children in the different HIV categories.

Eleven HIV-infected children had a WAZ < –2 (3 in category B and 8 in C) and 14 had an FFM z score < –2 according to the Houtkooper equation (1, 4, and 9 in categories A, B, and C, respectively). Eight children, in category C3 (the children in clinical category C with the most severe immunologic suppression), died before the end of the study, 1–17 mo after the evaluation (median: 3.9 mo). The WAZ was < –2 in 5 of them and between –1 and –2 in 3; the FFM z score was < –2 in 4 children, between –1 and –2 in 3, and > –1 in 1 child. In the whole group of HIV-infected children, a WAZ or an FFM z score < –2 was associated with an increased risk of death; when only children in clinical category C were considered, only WAZ was (Table 4). This figure did not change when FFM and WAZ were estimated by the equations of Goran et al or Arpadi et al were used (data not shown).
All HIV-infected children

Only children in category C

Mortality of HIV-infected children according to their age-specific weight and fat-free mass (FFM)

TABLE 4

<table>
<thead>
<tr>
<th></th>
<th>CDC-infected children</th>
<th>HIV-infected children</th>
<th>All (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (n = 22)</td>
<td>A (n = 23)</td>
<td>B (n = 22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C (n = 30)</td>
</tr>
<tr>
<td>Number of deaths (%)</td>
<td>3/75 (4.0)</td>
<td>5/11 (45.4)</td>
<td>4/72 (5.6)</td>
</tr>
<tr>
<td>Survival time (mo)</td>
<td>32.4 ± 0.8</td>
<td>20.2 ± 4.1</td>
<td>31.9 ± 0.9</td>
</tr>
<tr>
<td>Frequency of death (deaths/100 child-months)</td>
<td>0.17</td>
<td>2.80*</td>
<td>0.24</td>
</tr>
<tr>
<td>Relative risk of death (95% CI)</td>
<td>—</td>
<td>11.36 (3.15, 41.03)</td>
<td>1.41*</td>
</tr>
</tbody>
</table>

Only children in category C

Number of deaths (%)      | 3/22 (13.6)            | 5/8 (62.5)*           | 4/22 (18.2)  |
| Survival time (mo)       | 28.9 ± 2.7             | 15.7 ± 4.3*           | 27.6 ± 2.8   |
| Frequency of death (deaths/100 child-months) | 0.63                  | 4.45*                 | 0.87         |
| Relative risk of death (95% CI) | —                    | 4.58 (1.41, 14.93)    | 3.11         |

1Significantly different from children with z scores > -2.
could advocate for vigorous nutritional support, either enteral or their weight loss or growth faltering. If confirmed, these results This suggests that poor energy intake could be the main cause of potential reduction in FFM in HIV-infected children by the age of 7 y. body data from our study show that there is no apparent, prefer-
tion changes in HIV-infected children. Nevertheless, the whole-
data from our study nor these observations support the hypothesis of dis-
proportionate catabolism of FFM. Obviously, all cross-sectional studies are potentially biased by early mortality. Because 26% of HIV-infected children are estimated to die before the age of 6 y and an estimated 21% of children die within 1 mo of developing a category C illness (21), underrepresentation of children with both asymptomatic and early-onset symptomatic disease is likely to occur in cross-sectional studies. The question of whether the body-composition changes of these children are similar to those of other HIV-infected children who are in other cross-sectional studies is still unanswered.

Further studies, mainly longitudinal cohort studies, are needed to precisely describe the time course of body-composition changes in HIV-infected children. Nevertheless, the whole-body data from our study show that there is no apparent, prefer-
ential reduction in FFM in HIV-infected children by the age of 7 y. This suggests that poor energy intake could be the main cause of their weight loss or growth faltering. If confirmed, these results could advocate for vigorous nutritional support, either enteral or parenteral, early in the course of the disease.

John J Reilly, at the Department of Human Nutrition of the University of Glasgow, United Kingdom, kindly commented on an earlier version of the manuscript.

REFERENCES