Hidden Depletion of Fat-Free Mass and Bone Mineral Density in Adults With Cystic Fibrosis*

Alina A. Ionescu, MD; William D. Evans, PhD; Rebecca J. Pettit, BSc; Lisette S. Nixon, BSc; Michael D. Stone, MD; and Dennis J. Shale, MD

Background: Weight loss is associated with reduced survival in patients with cystic fibrosis (CF). Objective: We hypothesized that some adult patients with a normal body mass index (BMI) have evidence of hidden fat-free mass (FFM) and bone mineral density (BMD) depletion that is linked to more severe disease.

Design: Fat mass (FM), FFM, and BMD were determined by dual-energy x-ray absorptiometry (DXA) and by bioelectric impedance in 56 adults in clinically stable condition and 20 age-matched healthy subjects. FM index and FFM index (FFMI) [kilograms per meter squared] of the right arm, leg, and trunk (ratio to height squared) were calculated. Lung function, including the maximum inspiratory pressure (MIP) and sustained MIP (SMIP), physical activity, serum C-reactive protein (CRP) and the number of exacerbations in the previous year were recorded.

Results: Patients had a lower total FFM than healthy subjects (p < 0.01), while FM was similar. Of the 56 patients, 30 patients had a normal BMI, of which 12 patients had a low FFM (hidden loss) by DXA. The right arm, leg, and trunk FFMI and BMD at hip sites were less in these patients than in those with a normal BMI and normal FFM (all p < 0.01). This group had a lower FEV1, SMIP, more frequent exacerbations, and greater circulating CRP (all p < 0.05).

Conclusions: In adults with CF, apparent or hidden loss of FFM, rather than weight loss, was related to overall disease severity. Hidden depletion of FFM was associated with increased loss of BMD and systemic inflammatory activity.

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Key words: body composition; cystic fibrosis; hidden loss of fat-free mass

Abbreviations: BI = bioelectric impedance; BMD = bone mineral density; BMI = body mass index; CF = cystic fibrosis; CI = confidence interval; CRP = C-reactive protein; DXA = dual-energy x-ray absorptiometry; FFM = fat-free mass; FFMI = fat-free mass index; FM = fat mass; FMI = fat mass index; MET = metabolic equivalent; MIP = maximum inspiratory pressure; RV = residual volume; SMIP = sustained maximum inspiratory pressure; TLC = total lung capacity

Nutritional status is a predictor of survival in patients with cystic fibrosis (CF).1 Deficits in body composition appear early in life, with longitudi-
tions.5–7 We have previously reported that the response to antibiotic treatment is less in those adults with evident loss of fat-free mass (FFM).7 There is emerging evidence that body composition may be more important than body mass, with determination of FFM and bone thinning providing more information on systemic complications in CF.9–12 Preferential loss of FFM was reported in adults with CF compared with matched, healthy subjects without CF, with a lesser loss of fat mass (FM).13 Loss of FFM has also been shown to be associated with more severe lung disease, loss of inspiratory muscle function, and greater and more refractory systemic inflammation.5

We hypothesized that there should be a subgroup of adults with CF in whom FFM depletion may be hidden due to maintenance of body mass index (BMI) within normal limits and that FFM loss, either obvious or hidden, would be associated with a low bone mineral density (BMD), with the severity of lung disease and with greater systemic inflammation. To investigate this, we studied a group of unselected adults in clinically stable condition to determine the occurrence and distribution of hidden FFM loss and its relationship to indicators of disease severity.

Materials and Methods

Fifty-six patients (29 women) with proven CF and 20 age matched healthy subjects (10 women) were studied. Mean age of the patients was 23.0 years (95% confidence interval [CI], 20.8 to 25.3; age range, 17 to 38 years); mean age of the healthy subjects was 23.6 years (95% CI, 22.0 to 25.6; age range, 18 to 30 years). None of the patients had obvious signs of malabsorption; all had pancreatic insufficiency and were taking supplementary pancreatic enzyme products with meals. Patients with liver cirrhosis, cor pulmonale, or with exacerbation of the respiratory symptoms were excluded. Patients with CF from our department. The number of patients required in each group for a power of 85% and a significance level of 0.05 is 10. All subjects gave written informed consent, and the protocol was approved by the local research ethics committee.

Body Composition

Weight was determined with an electronic scale, height was measured barefoot with a stadiometer, and BMI was calculated.

Bioelectric Impedance

Leg-to-leg pressure contact bioelectric impedance (BI) measurements were obtained (Valhalla BIA; Valhalla Scientific; San Diego, CA) using a standard 50-kHz, 0.8-mA constant current. The subject stands barefoot on the scale, which has the electrodes incorporated at the level of the toes and heels. Individual FFM (kilograms) was derived from the linear equation relating the measured height squared/resistance to the reference FFM, while FM was calculated from the difference between weight and FFM.

Dual-Energy X-ray Absorptiometry

BMD, FM, and FFM were determined by dual-energy x-ray absorptiometry (DXA) using a QDR 2000+ absorptiometer (Hologic; Waltham, MA) with Enhanced Whole Body v5.70 software for body composition analysis. The measurements were recorded before a meal and after the subject emptied his or her bladder. Subjects were scanned in the supine position. The FFM of our healthy subjects was within the normal limits of the FFM of a healthy UK population of the same age and gender, though these data were generated from anthropometric measurements.14

Two groups of patients were defined according to FFM by DXA: (1) low FFM if less than the lower fifth percentile for the healthy subjects; (2) normal FFM if more than the lower fifth percentile for the healthy subjects. To determine preferential FFM loss, the FFM and FM were corrected for the height squared of the subject to give a FFM index (FFMI) and a FM index (FMI) [kilograms per meter squared] for the right arm, right leg, and trunk after subtraction of the bone mineral mass in each area.15,16

Lung Function

FEV1, FVC, and their ratio were determined by spirometry (Vitalograph Ltd; Alpha II; Buckingham, UK). The best of three recordings was reported. Total lung capacity (TLC), residual volume (RV), and RV/TLC were determined by helium dilution technique.15 Three groups of patients were defined according to the severity of the impairment of the lung function: severe impairment, FEV1 < 45% predicted; moderate impairment, FEV1 > 46% and < 65% predicted; and mild impairment, FEV1 > 65% predicted.18

Inspiratory Muscle Function

The maximum inspiratory pressure (MIP) and sustained MIP (SMIP) were measured with an electronic manometer and expressed in centimeters of water and pressure-time units, respectively.7

Physical Activity

Physical activity was assessed using a recall questionnaire for the month prior to the assessment when the patients were in clinically stable condition. An activity score was calculated and expressed in metabolic equivalents (METS) [1 MET = the energy expended by a person at rest].19

Exacerbations of Respiratory Symptoms and Circulating C-Reactive Protein

The number of exacerbations in the year prior to the assessment was obtained from the case notes. Serum concentration of C-reactive protein (CRP) was determined by in-house sandwich enzyme-linked immunosorbent assay with goat and rabbit anti-human CRP and anti-rabbit IgG-alkaline phosphatase conjugate.20

Statistics

Data are presented as arithmetic or geometric means (log 10 transformed nonnormally distributed data) and 95% CIs. Analysis
of variance and the post hoc Tukey test were used for comparison between groups to avoid multiple t tests. A Spearman rank correlation test and regression analysis were used to determine relationships between variables. Analysis of agreement between BI and DXA was made by determining the $\kappa$ coefficient and by calculation of the precision of the estimated limits of agreement.21

RESULTS

Body Composition: Patients Compared With Healthy Subjects

Patients had lower weight, height, BMI, and total FFM compared to the healthy subjects, but there was no difference in FMI between the two groups (Table 1). The FFMI of the right arm and right leg were less in patients than in the healthy subjects ($p < 0.01$ for both), while the FMI was not different at these sites (Fig 1). The BMD at all sites was less in patients than in healthy subjects (Table 2).

Body Composition: Within-Patient Comparison

There was a good agreement between DXA and BI for FFM ($\kappa = 0.75$) and FM ($\kappa = 0.82$). Seven patients were attributed to different body composition groups for FFM and three patients for FM by the two methods (Table 3). However, with the calculation of the precision of the estimated limits of agreement, we found a modest agreement between the two methods: the 95% CI for FFM was $-6.2$ to $-3.8$ kg for the lower limit of agreement and $5.6$ to $7.9$ kg for the upper limit of agreement. There was a good association between BMI and FFMI ($r^2 = 0.44$, $p < 0.001$) and between BMI and FMI ($r^2 = 0.36$, $p < 0.001$) for the whole patient group. Based on DXA assessment, 32 patients had a low FFM, 12 of whom had normal BMI (Table 4, Fig 2).

Patients with a low FFM were shorter than those with a normal FFM: mean height was 159.9 cm (95% CI, 157.4 to 163.2) and 169.6 cm (95% CI, 167.6 to 171.6) for the normal FFM group and the patient group, respectively ($p < 0.01$). Defining a low height as less than the lower fifth percentile for a healthy age- and gender-matched population,7 in the 32 patients with a low FFM, the BMI was less in patients than in healthy subjects (Table 2).

Table 1—Body Composition for Patients and Healthy Subjects*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n = 56)</th>
<th>Healthy (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>56.7 (53.8–59.5)</td>
<td>66.7 (63.4–69.9)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164.1 (161.7–166.4)</td>
<td>170.8 (167.0–174.7)</td>
</tr>
<tr>
<td>BMI</td>
<td>20.9 (20.1–21.7)</td>
<td>22.8 (22.1–23.5)</td>
</tr>
<tr>
<td>FFMI, kg/m²</td>
<td>15.8 (15.2–16.5)</td>
<td>17.0 (16.1–17.9)</td>
</tr>
<tr>
<td>FMI, kg/m²</td>
<td>4.7 (4.1–5.4)</td>
<td>5.4 (4.6–6.2)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (95% CI).

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and FM ($\kappa = 0.82$). Seven patients were attributed to different body composition groups for FFM and three patients for FM by the two methods (Table 3). However, with the calculation of the precision of the estimated limits of agreement, we found a modest agreement between the two methods: the 95% CI for FFM was $-6.2$ to $-3.8$ kg for the lower limit of agreement and $5.6$ to $7.9$ kg for the upper limit of agreement. There was a good association between BMI and FFMI ($r^2 = 0.44$, $p < 0.001$) and between BMI and FMI ($r^2 = 0.36$, $p < 0.001$) for the whole patient group. Based on DXA assessment, 32 patients had a low FFM, 12 of whom had normal BMI (Table 4, Fig 2).

Patients with a low FFM were shorter than those with a normal FFM: mean height was 159.9 cm (95% CI, 157.4 to 163.2) and 169.6 cm (95% CI, 167.6 to 172.5), respectively ($p < 0.01$). Defining a low height as less than the lower fifth percentile for a healthy age- and gender-matched population,147 of the 32 patients with a low FFM had a low height, while only 1 of the 24 patients with a normal FFM had a low height ($x^2 = 3.5$, $p = 0.06$).

The right arm, right leg, and trunk FFMI were significantly less in patients with a normal BMI and a low FFM compared with those with a normal BMI and normal FFM (Fig 3). Both groups had BMD less than the healthy subjects at most sites (Table 2). The mean total hip, trochanter, intertrochanteric and femoral neck BMDs were less in those with a normal BMI and a low FFM compared with the group with normal BMI and normal FFM (all $p < 0.01$), though there was no difference for the spine L1 through L4 site (Fig 4).

For the whole group of 56 patients, analysis of variance revealed that FFM had a greater effect on BMD at the trochanter and femoral neck sites ($p < 0.001$ for both) than BMI ($p = 0.045$ and 0.028, respectively). At the spinal site, FFM and BMI had a similar effect ($p < 0.001$). The two-way interaction between FFM and BMI in the analysis was not significant ($p = 0.6$).

Relationships Between Body Composition, Lung Function, and Inspiratory Muscle Function

Twenty-three patients had severe impairment, 11 patients had moderate impairment, and 22 patients had mild impairment of the lung function. The FEV$_1$ was related to the BMI ($r = 0.30$, $p = 0.02$) and FFM ($r = 0.44$, $p < 0.01$). The BMD was reduced at all sites ($p < 0.05$) in patients with severe impairment compared to those with mild impairment of lung function.

Patients with a low FFM had lower mean FEV$_1$ and SMIP values than those with a normal FFM, but there was no difference in the RV/TLC ratio or in MIP between the two groups (Table 5). Lung and inspiratory muscle function were not different between patients with a low BMI and those with normal BMI. In the 30 patients with a normal BMI, those with a low FFM (n = 12) had a lower FEV$_1$ and SMIP and greater RV/TLC than those with a normal FFM, though no difference in MIP was found (Table 6). This difference was maintained when FFM was corrected for height. For the whole group of patients, SMIP was related to FEV$_1$ ($r = 0.62$, $p < 0.001$), FFM ($r = 0.60$, $p < 0.001$), and regional FFMI of the trunk ($r = 0.64$, $p < 0.001$). MIP was related to FEV$_1$ ($r = 0.36$, $p < 0.05$), FFM ($r = 0.40$, $p < 0.01$), and FFMI ($r = 0.43$, $p < 0.01$) but not to BMI ($r = 0.30$, $p = 0.059$).

Levels of Physical Activity, Exacerbation Rates in the Previous Year, and Circulating CRP

The level of physical activity was lower in patients with a low FFM (Table 5). Those with severe
impairment of the lung function were less active than those with mild impairment: mean level of activity was 34.2 METs (95% CI, 30.2 to 38.2) vs 37.6 METs (95% CI, 33.6 to 41.5), respectively (p < 0.01); no difference in the level of activity was found between patients with moderate impairment (33.9 METs; 95% CI, 31.3 to 36.6) and severe impairment of the lung function. The level of physical activity was related to BMD ($r = 0.53$, $p < 0.01$) and FFM ($r = 0.37$, $p < 0.01$) for both.

In the year previous, the exacerbation rate was greater in the low FFM group than in the normal FFM group (Table 5). No difference in the number of exacerbations was found between the low and normal BMI groups: mean, 43 exacerbations (95% CI, 2.6 to 5.9) vs 4.1 exacerbations (95% CI, 2.6 to 5.5). Within the group of patients with a normal BMI, those with a low FFM had a greater number of exacerbations than those with a normal FFM (Table 6). The number of exacerbations was related to the FEV$_1$ ($r = -0.54$, $p < 0.01$) and to the concentration of CRP ($r = 0.44$, $p < 0.01$).

CRP concentrations were similar in patients with a low BMI and in those with a normal BMI: 7.6 μg/mL (95% CI, 3.2 to 15.9) vs 6.4 μg/mL (95% CI, 3.2 to 12.6), respectively. In the patients with a normal BMI, the CRP concentration was greater in patients with low FFM than in those with normal FFM (Table 6). A modest association was found between the level of CRP and FEV$_1$ ($r^2 = -0.30$, $p < 0.01$) and FFMI ($r^2 = 0.15$, $p < 0.01$).

**Discussion**

Overall, the BMI and the FFM were related in our patients. However, while 46% had a low BMI

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**Table 2—BMD in Patients and Healthy Subjects**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n = 56)</th>
<th>Patients Low FFM (n = 32)</th>
<th>Patients Normal FFM (n = 24)</th>
<th>Healthy (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip BMD, g/cm$^2$</td>
<td>1.09 (1.06–1.12)†</td>
<td>1.05 (1.02–1.07)†</td>
<td>1.17 (1.14–1.21)†</td>
<td>1.18 (1.12–1.24)</td>
</tr>
<tr>
<td>BMD trochanteric site</td>
<td>0.61 (0.57–0.65)†</td>
<td>0.57 (0.54–0.60)†</td>
<td>0.70 (0.67–0.74)†</td>
<td>0.76 (0.70–0.83)</td>
</tr>
<tr>
<td>BMD intertrochanteric site</td>
<td>0.96 (0.88–1.03)†</td>
<td>0.89 (0.84–0.94)†</td>
<td>1.10 (1.02–1.17)†</td>
<td>1.15 (1.06–1.24)</td>
</tr>
<tr>
<td>BMD femoral neck</td>
<td>0.72 (0.70–0.76)†</td>
<td>0.69 (0.65–0.72)†</td>
<td>0.83 (0.79–0.87)†</td>
<td>0.89 (0.80–0.97)</td>
</tr>
<tr>
<td>BMD lumbar spine</td>
<td>0.91 (0.86–0.96)†</td>
<td>0.85 (0.81–0.89)†</td>
<td>0.90 (0.74–1.06)</td>
<td>1.09 (1.03–1.17)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (95% CI).

†p < 0.01.

‡p < 0.05.
Data are presented as No. of patients. Coefficient of agreement (κ) = 0.75.

(< 19.9), 57% had a low FFM (less than the lower fifth percentile for the matched healthy subjects), and < 20% had a low FM using the same criterion. This separation between BMI and FFM led to our finding that 40% of patients with a normal BMI had hidden loss of FFM. We previously reported that patients with a low FFM have increased systemic inflammation, protein catabolism, and greater breakdown of bone tissue.7 Here we report that a proportion of patients have a hidden depletion of FFM, while BMI and FM are maintained. The importance of the hidden loss of FFM was indicated by the similarity of such patients to those with a low BMI and a low FFM and the significant separation from those with a normal BMI and FFM with an increased rate of exacerbations, greater circulating CRP, more impaired lung function and inspiratory muscle function. The association of hidden loss of FFM with an overall more severe disease status was emphasized by a low BMD compared with a normal BMD in patients with a normal BMI and FFM. The loss of FFM with relative preservation of FM, total body mass, and BMI in some patients indicates a preferential loss of FFM. The BMI is routinely assessed in many CF centers, but the dissociation between BMI and FFM in some patients makes it an unreliable measure of body composition changes and disease severity, as demonstrated by the failure of a low or normal BMI status to show significant differentiating relationships with the impairment of pulmonary function, inspiratory muscle function,22 the rate of exacerbations, and circulating CRP in the same way as FFM. This interpretation is supported by the loss of FFM being related to pulmonary function rather than steatorrhea.23 We report a good agreement between DXA and BI in identifying most patients with a low FFM. Therefore, despite the potential errors in measuring body composition by BI, due to the water distribution in patients with CF, this can be used as a simpler and less costly method than DXA to identify patients at risk of more severe disease and poorer outcome. However, because of the modest agreement with the estimated limits of agreement method and the wide CI, it is unlikely that BI could be used to assess changes in FFM over time in individual patients, which agrees with other studies.24,25 Additionally, once such patients have been identified, DXA scanning would still need to assess the BMD, which was related to the loss of FFM. Reduced BMD is associated with increased morbidity, in addition to the lung disease itself.9,10 Use of total FFM in disease states needs cautious interpretation, as our patients with a low FFM were shorter than those with a normal FFM, which may indicate impaired growth in childhood and adolescence. However, after correcting for height squared, the separation was maintained between those with a low or normal FFM, suggesting that preferential loss of FFM occurred in addition to possible earlier growth failure. Height squared standardization for body habitus allowed us to determine regional differences in body composition and to compare patients and healthy subjects. The FFMI for the arm and leg in patients was less than for healthy subjects, while there was a relative preservation of the FMI at these sites. These regional changes in body composition suggest a generalized distribution of loss of FFM.

Our patients with a low FFM were less active than those with a normal FFM, which was likely to be due to various factors including progressive decline in pulmonary function. Reduced levels of physical activity may enhance a reduction of skeletal muscle mass and, therefore, FFM.26 This possibility is supported by our finding that severe impairment of lung function is associated with loss of FFM, which may be contributed to by disuse. Patients with a low FFM had greater impairment of inspiratory muscle function as assessed by the SMIP, a measure of single-breath inspiratory muscle work capacity between RV and TLC. The MIP, a measure of inspiratory muscle force generation, was well preserved, confirming our earlier finding that only SMIP was related to severe impairment of the lung function and a low FFM.22 The reduced SMIP may be due to a low trunk FFM, which includes inspiratory and accessory inspiratory muscles, a relationship emphasized by similar findings in patients with a hidden loss of FFM, which determines inspiratory muscle work capacity and endurance during a SMIP maneuver.

### Table 3—Agreement Between DXA and BI for FFM and FM Categories*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low FFM/FM (DXA)</th>
<th>Normal FFM/FM (DXA)</th>
<th>Total FFM/FM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low FFM/FM (BI)</td>
<td>26/9</td>
<td>1/1</td>
<td>27/10</td>
</tr>
<tr>
<td>Normal FFM/FM (BI)</td>
<td>6/2</td>
<td>23/44</td>
<td>29/46</td>
</tr>
<tr>
<td>Total FFM/FM</td>
<td>32/11</td>
<td>24/45</td>
<td>56/56</td>
</tr>
</tbody>
</table>

*Data are presented as No. of patients.

### Table 4—Patients With a Low or Normal FFM in the Group With a Low or Normal BMI*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low BMI</th>
<th>Normal BMI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low FFM</td>
<td>20</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>Normal FFM</td>
<td>6</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>30</td>
<td>56</td>
</tr>
</tbody>
</table>

*Data are presented as No. of patients.
Loss of lung function is due to recurrent injury secondary to chronic infection and persistent local inflammation, which is accompanied by increased concentrations of circulating inflammatory mediators. The systemic inflammatory response in CF is essentially a persistent acute phase response and is associated with a continuous parallel catabolic response, which has its major effect on protein-rich tissues in the FFM compartment, such as skeletal muscle and bone connective tissue. These sys-
Systemic responses are related to an energy imbalance through their contribution to the increased resting energy expenditure, which is increased further during exacerbations of pulmonary symptoms. The systemic inflammatory response is maximal during such exacerbations and remains greater during clinical stability in patients with a low FFM compared with those with a normal FFM. This suggests that a greater and persistent inflammatory-catabolic stress occurs in patients with a low FFM, which may confound the reversal of changes in body composition because of frequent exacerbations and a poorer response to antibiotic treatment. A direct effect of interleukin-6 and tumor necrosis factor-α may be mediated through the nuclear factor-κB transcription factor leading to a proteolytic myopathy with a sustained increased protein breakdown, a response found in inflammatory diseases other than CF. Hidden depletion of FFM occurred in 10 to 30% of patients with COPD, and was associated with systemic inflammation. In particular, both apparent and hidden depletion of skeletal muscle mass was associated with greater concentrations of circulating interleukin-6 and tumor necrosis factor-α and their soluble receptors than in those with a normal skeletal muscle mass. This supports our findings and suggests common systemic processes may occur in both disorders where chronic pulmonary and systemic inflammation, lung destruction and in-

Table 5—Lung Function and Inspiratory Muscle Function in Patients With a Low or Normal FFM

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<th>Variables</th>
<th>Low FFM (n = 32)</th>
<th>Normal FFM (n = 24)</th>
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<tbody>
<tr>
<td>FEV1, % predicted</td>
<td>50.2 (40.9–61.5)</td>
<td>66.7 (56.8–78.9)</td>
</tr>
<tr>
<td>RV/TLC, % predicted</td>
<td>151.0 (131.5–172.6)</td>
<td>132.9 (106.7–152.5)</td>
</tr>
<tr>
<td>MIP, cm H2O</td>
<td>101.7 (89.7–126.6)</td>
<td>116.2 (100.4–142.2)</td>
</tr>
<tr>
<td>SMIP, PTU</td>
<td>486.1 (368.2–680.5)</td>
<td>719.1 (649.9–924.7)</td>
</tr>
<tr>
<td>Activity level, METs</td>
<td>33.7 (31.0–36.3)</td>
<td>37.6 (33.6–41.7)</td>
</tr>
<tr>
<td>Exacerbations, No.</td>
<td>4.8 (3.2–6.4)</td>
<td>2.8 (2.1–3.5)</td>
</tr>
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*Data are presented as mean (95% CI). See Table 5 for expansion of abbreviation. | 

Table 6—Characteristics of the Patients with a Normal BMI, According to FFM

<table>
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<th>Characteristics</th>
<th>Low FFM (n = 12)</th>
<th>Normal FFM (n = 18)</th>
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<tr>
<td>Weight, kg</td>
<td>56.6 (52.6–60.5)</td>
<td>68.3 (65.2–71.5)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>158.8 (153.8–163.7)</td>
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</tr>
<tr>
<td>FEV1, % predicted</td>
<td>47.4 (30.4–57.4)</td>
<td>67.4 (59.9–91.1)</td>
</tr>
<tr>
<td>RV/TLC, % predicted</td>
<td>159.7 (131.6–203.3)</td>
<td>125.5 (101.9–149.4)</td>
</tr>
<tr>
<td>MIP, cm H2O</td>
<td>105.4 (73.2–145.4)</td>
<td>118.8 (97.2–144.1)</td>
</tr>
<tr>
<td>SMIP, PTU</td>
<td>441.8 (271.8–680.1)</td>
<td>715.1 (648.1–950.6)</td>
</tr>
<tr>
<td>Exacerbations, No.</td>
<td>5.6 (2.5–8.7)</td>
<td>2.7 (1.9–3.5)</td>
</tr>
<tr>
<td>Serum CRP, μg/mL</td>
<td>19.9 (6.6–77.6)</td>
<td>2.0 (1.0–5.0)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (95% CI). See Table 5 for expansion of abbreviation.
paired lung function, and altered body composition are prominent features.\textsuperscript{35–38}

Our observations in patients in clinically stable condition indicate that changes in body composition including hidden depletion of FFM, rather than body mass, more closely relate to the overall severity of health impairment in adults with CF. This study shows that it is clinically relevant to determine body composition in adults with CF and to identify all patients with loss of FFM as an indicator of disease severity. It remains to be demonstrated if interventions such as segmental muscle training or anabolic treatment will maintain FFM, over long periods of time, improve skeletal muscle function at those sites and therefore maintain bone mass, and have an effect on other clinical indicators of disease severity.

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