Low body weight and loss of bone mass are major problems in adults with cystic fibrosis (CF) and chronic pulmonary infection. Although these complications probably have a multifactorial origin, we hypothesized that the continuous acute-phase inflammatory and catabolic state may contribute. We determined body composition, bone turnover, physical activity, and circulating interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and their soluble receptors in 22 adults with CF and 22 age- and sex-matched healthy subjects. Comparisons were also made within patients before and after treatment of an exacerbation of respiratory symptoms. The patients had a lower mean (95% confidence interval [CI]) fat-free mass (FFM) 39.9 (36.3, 43.6) kg than healthy subjects, 49.4 (45.1, 53.7) kg, p < 0.05. The patients were in negative nitrogen balance and had 20 had bone mineral density (BMD) Z scores < 2.5 SD (n = 13) or ≤ 1 SD (n = 7) at least at one site. They had increased bone collagen breakdown, greatest in those with a reduced FFM. BMD was related to FEV₁ (r = 0.44), IL-6 (r = -0.60), and TNF-α-soluble receptors (r = -0.42, r = -0.50). Patients with a low FFM had greater concentrations of IL-6, which suppressed less after antibiotic treatment than in those with a normal FFM. Those with a low FFM were more catabolic and less active than those with a normal FFM. The association between altered body composition, catabolic status, and circulating inflammatory mediators suggests that chronic pulmonary infection in adults with CF may be a contributory factor in the long-term complications of low weight and bone disease.

Attainment of adulthood is now common in cystic fibrosis (CF) and survival continues to increase. Such patients experience chronic pulmonary infection from very early in life, which is a major determinant of survival because of its association with lung destruction (1). Additionally, failure to maintain body weight is an indicator of a poor prognosis. The major complications emerging with longer survival are failure to maintain body mass, osteoporosis, and diabetes mellitus (1–10). These metabolic complications have an impact on morbidity as well as mortality. Loss of fat-free mass (FFM) impairs skeletal muscle function including the inspiratory muscles and adds to the severity of pulmonary compromise (11, 12). Reduction in both bone mineral density (BMD) and FFM may be linked by physical inactivity, possible malabsorption, corticosteroid therapy, reduced sex hormone levels, increased resting energy expenditure (REE), and hypoinsulinemia associated with diabetes mellitus. An additional metabolic possibility is a generalized loss of body protein secondary to an association between chronic lung disease and a catabolic intermediary metabolism.

Chronic pulmonary infection with associated continuous inflammatory and catabolic responses present in patients even when clinically stable may affect body composition (13). This catabolic state as part of the stress response to infection and inflammation could be mediated by the combined effects of catecholamines, proinflammatory cytokines such as interleukins 1β and 6 (IL-1β, IL-6) and tumor necrosis factor-α (TNF-α), and stress-response hormones such as cortisol, and induce protein breakdown in muscle and bone (13, 14). Supporting a link between the lung disease in CF and body composition is the effect of antibiotic treatment of an exacerbation of respiratory symptoms, which partially reduces the inflammatory response with a modest weight gain (15, 16).

We hypothesized that the normally host-protective, acute-phase inflammatory and catabolic responses are sustained in patients with CF and chronic pulmonary infection, and add to other mechanisms of weight loss and bone demineralization. Such links have been suggested to occur in human immunodeficiency virus (HIV) infection, cancer, and cardiac failure where cachexia is associated with excess procatabolic hormones and increased circulating inflammatory mediators (17–20). To test these ideas, we studied adult patients with CF and chronic pulmonary infection during an exacerbation of respiratory symptoms and its treatment to determine relationships between the host inflammatory response, body composition, bone protein turnover, and catabolic status.

METHODS

Subjects

Twenty-two patients (11 males, mean [95% confidence interval [CI]) age 23.6 (21.4, 24.7) yr, with proven CF based on clinical findings, sweat Na⁺ and Cl⁻ > 70 mmol/L, and genotype (16, ΔF508/ΔF508; 2, ΔF508/G542X; 2 ΔF508/R1283M, and 1 each ΔF508/1717+G-A and ΔF508/ΔF508; G-A and ΔF508/621+1G-T) were studied. All had Pseudomonas aeruginosa isolated from sputum more than three times in the 6 mo preceding the study. Patients were studied at the start and end of 2 wk intravenous antibiotic treatment for an exacerbation of respiratory symptoms. This was defined as a combination of increased cough, sputum production, sputum purulence, shortness of breath, systemic symptoms such as fever or weight loss, and a decrease in FEV₁ > 10% compared with values when clinically stable in the preceding year.

Patients with diabetes mellitus, liver cirrhosis, chronic respiratory failure with cor pulmonale, or failure to give informed consent were excluded, otherwise consecutive patients were studied. None of the patients were receiving long-term treatment with oral corticosteroids or had received a short course of oral corticosteroids in the 3 mo before the study. Six patients received treatment for over 1 yr before the study with inhaled corticosteroids. Five received budesonide 800 μg twice a day by turbohaler and one fluticasone propionate 500 μg twice a day by pressurized aerosol. Three of these patients had a low FFM and three a normal FFM. Four patients received chronic treatment with nebulized corticosteroids, budesonide 1 mg twice a day; three had a low FFM and one a normal FFM. The remaining 12 patients...
were not receiving inhaled or nebulized treatment with corticosteroids; six had a low FFM and six a normal FFM. Four patients, one with a low FFM, received treatment for at least 1 yr before the study with nebulized antibiotic (Colomycin 1 mega U twice a day).

Twenty-two age-matched [23.8 (22.5, 25.1) yr] and sex-matched healthy subjects were also studied; subjects were matched as closely as possible. None of these subjects had a restricted diet or was involved in intense physical training. All subjects gave written informed consent and the study was approved by the local research ethics committee.

Protocol
At each assessment venous blood was obtained, spirometry performed, a 24-h urine collected, and a 3-d food intake diary completed. The healthy subjects provided venous blood on one occasion, a 24-h urine sample and a food diary on two occasions.

Body Composition
Weight and height were determined. Fat mass, FFM, and BMD of the lumbar spine, femur, and whole body were measured when clinically stable (no exacerbation in the preceding 2 mo), but before the exacerbation studied here, by dual energy X-ray absorptiometry (DXA) using a QDR 2000+ absorptiometer (Hologic Inc., Waltham, MA). Our healthy subjects had a fat mass and FFM within the reported age- and sex-adjusted reference ranges for the healthy U.K. population, which are based on anthropometric measures (21). Two groups of patients were defined as having a FFM either more or less than the lower fifth percentile for the matched healthy subjects. The group with FFM less than the lower fifth percentile was chosen to give a clearly defined group with a low FFM. The coefficient of variation for the BMD measures at all sites and the body composition measurements using the Hologic QDR 2000 device was less than 1%. The BMD of the healthy subjects at all sites studied were not different from that for the healthy age- and sex-adjusted values quoted for this equipment. Using the BMD values for our healthy subjects as a standard we derived BMD Z scores (SD scores) for our patients at each bone site studied.

Estimated nitrogen (N₂) balance was determined as protein intake (g) / 6.25 – [urinary urea N₂ (g) + 4] where 4 is the estimated fecal loss of N₂. Protein and calcium intake were determined as the mean of 3 d intake. Circling cortisol was determined by radioimmunoassay (Coat-a-count; Diagnostic Products Corporation, Los Angeles, CA) with intra- and interassay coefficients of variation of 6%. Serum insulin-like growth factor-1 (IGF-1) was determined by ELISA with intra- and interassay variation for the aforementioned assays was less than 10%. The 24-h urinary calcium excretion was measured photometrically (Olympus Optical, Southall, UK).

Spirometry and Inspiratory Muscle Function
FEV₁, FVC, and their ratio were determined by spirometry (Vitalograph Ltd). Maximal inspiratory pressure (Pmax) and the sustained Pmax were measured with an electronic manometer and expressed in cm H₂O and as pressure–time units respectively (12).

Physical Activity
Activity was assessed by recall questionnaire for the month before the assessment when patients were clinically stable. An activity score was calculated in METs (1 MET = the energy expended by a person at rest) (22). The number of exacerbations of respiratory symptoms in the year before the study was obtained from case records.

Inflammatory Mediators
Circulating immunoreactive TNF-α, IL-6, and their soluble receptors were determined by ELISA (R&D Systems, Europe Ltd, Abingdon, Oxford, UK) (16). Intra- and interassay variation was less than 10% in all assays, and no samples were below the sensitivity for each assay.

Statistics
Data are presented as either arithmetic mean, or geometric mean, and 95% CI. Non-normally distributed data were log₅ transformed before analysis. Student’s t test was used for comparisons between groups. Spearman’s rank correlation test was used to determine relationships between variables.

RESULTS
Comparisons between CF and Non-CF Subjects

**Body composition.** The mean (95% CI) FFM for the patients was 39.9 (36.3, 43.6) kg compared with 49.4 (45.1, 53.7) kg for the healthy subjects, p < 0.05. The lower fifth percentile FFM for the female healthy subjects was 36.4 kg and for the male healthy subjects was 49.6 kg. Only 10 of the 22 patients had a normal FFM. The mean (95% CI) FFM of the low FFM group was 34.3 (30.6, 38.2) kg compared with 45.6 (40.6, 50.5) kg for those with a normal FFM (p < 0.05). The mean (95% CI) fat mass for the healthy subjects was 15.6 (13.6, 17.7) kg compared with 12.6 (10.4, 14.8) kg for the patients, p = 0.05. The fat mass of the patients with a low FFM was 11.7 (8.4, 14.9) kg, p < 0.05 compared with the healthy subjects, and 13.4 (10.0, 16.9) kg for the patients with a normal FFM, p > 0.05 compared with healthy subjects. The mean weight gain after treatment was 1.24 (0.50, 2.0) kg, although six patients had no weight change.

The mean negative N₂ balance in the patients was unchanged by antibiotic treatment and was significantly greater

| TABLE 1 | NITROGEN BALANCE AND BONE METABOLISM IN SUBJECTS WITH AND WITHOUT CF* |
|---------|----------|----------|----------|
|         | Before Treatment (n = 22) | After Treatment (n = 22) | Controls (n = 22) |
| Nitrogen balance | −2.61 (−3.6, 1.9)†‡ | −1.54 (−4.7, 0.79)† | 3.8 (−1.1, 8.6)† |
| NTx, nmol/mmol creatinine | 139.3 (95.7, 202.3)§ | 89.1 (56.8, 139.6)§ | 35.5 (29.5, 41.7) § |
| Osteocalcin, ng/ml | 4.70 (0.99, 7.14) | 3.74 (1.39, 6.08) | 3.70 (1.0, 6.55) |
| Bone alkaline phosphatase, U/L | 20.9 (18.7, 23.2) | 21.6 (19.3, 23.9) | 16.8 (14.1, 19.6) |
| Parathormone, pg/ml | 22.0 (15.8, 28.3) | 21.6 (15.1, 28.2) | 16.8 (12.6, 19.6) |
| Calcium intake, mg/d | 702.0 (200.1, 698.5)§ | 699.4 (212.1, 745.5)§ | 1,435.5 (757.2, 1,655.1) |
| Urinary calcium, mmol/d | 2.46 (1.7, 3.21) | 3.05 (1.95, 4.15) | 2.74 (1.58, 3.91) |

* All values are geometric means (95% CI). 
† p < 0.05 compared with controls at each time point. 
‡ p < 0.05 patients compared before and after treatment. 
§ Mean of two determinations.
The patients had a mean (95% CI) BMD deficit of 15.6 (9.7, 21.4)% when compared with the healthy subjects. Total body BMD and total and individual site Z scores were significantly reduced in the patients (Table 1). Twenty patients had an abnormal Z score at least at one site assessed, < 2.5 in 13 patients, of whom nine had a low FFM, and ≤ 1 in seven patients of whom one had a low FFM. Total body BMD in patients was related to FEV1 (r = 0.44, p < 0.05) and inversely to circulating IL-6 (r = −0.60, p < 0.01) and TNF-α receptors 1 and 2 (r = −0.42, p < 0.05; r = −0.50, p < 0.05) at the end of 14-d antibiotic treatment.

**TABLE 2**

**PATIENTS’ BONE Z SCORES AT VARIOUS SITES COMPARED WITH 22 HEALTHY AGE- AND SEX-MATCHED SUBJECTS**

<table>
<thead>
<tr>
<th>Site</th>
<th>Mean Z Score</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>−2.09</td>
<td>−2.81, −1.36</td>
</tr>
<tr>
<td>Trochanter</td>
<td>−1.80</td>
<td>−2.24, −1.37</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>−1.53</td>
<td>−1.89, −1.17</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>−1.55</td>
<td>−2.14, −0.96</td>
</tr>
<tr>
<td>Intertrochanteric</td>
<td>−1.84</td>
<td>−2.29, −1.39</td>
</tr>
</tbody>
</table>

Bone metabolism. Calcium intake at the start and end of antibiotic treatment was less in the patients than healthy subjects (p < 0.05 and p < 0.05 respectively) (Table 1). Urinary 24-h calcium excretion was the same in patients at the beginning and end of antibiotic treatment and was similar in non-CF subjects. Urinary NTx was greater in patients at the start (p < 0.05) and end (p < 0.05) of antibiotic treatment compared with non-CF subjects, although it fell after antibiotic treatment (p < 0.05) (Table 1, Figure 1). Circulating osteocalcin, bone alkaline phosphatase, and PTH were not different between patients and non-CF subjects (Table 1). The mean (95% CI) plasma vitamin D was 18.8 (14.2, 23.6) ng/ml, reference range 8 to 50 ng/ml. Two patients had vitamin D values less than 8 ng/ml and eight had values lower than the 25th percentile of the healthy population reference range. Urinary NTx concentrations were related to circulating IL-6 (p < 0.01), IL-6-soluble receptor (p < 0.05), and TNF-α-soluble receptors 1 and 2 (p < 0.05 and p < 0.01). FEV1 was inversely related to NTx (r = −0.51, p < 0.05) and IL-6 (r = −0.65, p = 0.001). The BMD at the femoral neck, but not at other sites, was related to physical activity (r = 0.47, p = 0.02). No relationship was found between BMD and vitamin D, PTH, calcium intake, or other markers of bone metabolism.

**TABLE 3**

**CIRCULATING PROINFLAMMATORY CYTOKINES, THEIR RECEPTORS, AND ANABOLIC AND CATABOLIC HORMONES IN SUBJECTS WITH AND WITHOUT CF**

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment (n = 22)</th>
<th>After Treatment (n = 22)</th>
<th>Controls (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6, pg/ml</td>
<td>6.37 (3.46, 8.71)</td>
<td>3.31 (2.04, 4.27)</td>
<td>0.56 (0.39, 0.74)</td>
</tr>
<tr>
<td>IL-6 receptor, pg/ml</td>
<td>43,651 (37,153, 46,773)</td>
<td>44,668 (38,018, 48,977)</td>
<td>33,100 (28,200, 38,900)</td>
</tr>
<tr>
<td>TNF-α, pg/ml</td>
<td>4.17 (2.95, 4.68)</td>
<td>3.01 (2.5, 3.8)</td>
<td>1.51 (0.87, 2.69)</td>
</tr>
<tr>
<td>TNF-α receptor 1, pg/ml</td>
<td>1,297 (1,000, 1,479)</td>
<td>1,069 (871, 1,175)</td>
<td>645 (501, 794)</td>
</tr>
<tr>
<td>TNF-α receptor 2, pg/ml</td>
<td>3,890 (3,388, 4,466)</td>
<td>3,147 (2,818, 3,467)</td>
<td>1,819 (1,584, 2,041)</td>
</tr>
<tr>
<td>Cortisol, nmol/L</td>
<td>453.0 (333.7, 571.4)</td>
<td>347.0 (244.3, 450.1)</td>
<td>361.7 (280.6, 442.9)</td>
</tr>
<tr>
<td>IGF-1, ng/ml</td>
<td>126.0 (101.4, 150.2)</td>
<td>150.0 (130.6, 169.4)</td>
<td>145.3 (117.9, 172.7)</td>
</tr>
<tr>
<td>Cortisol:IGF-1 ratio</td>
<td>4.8 (2.2, 7.3)</td>
<td>2.6 (1.6, 3.7)</td>
<td>2.4 (1.8, 3.1)</td>
</tr>
</tbody>
</table>

*All values are geometric means (95% CI).

p < 0.05 compared with controls at each time point.

p < 0.05 patients compared before and after treatment.

p < 0.01.
rheic. The males had evidence of normal sexual development for their age, and sex hormone levels were not determined.

**Bone metabolism.** The NTx:FFM ratio was greater in the low-FFM group before treatment 6.44 (1.75, 11.1) nmol/mmol creatinine/kg FFM and after treatment 4.39 (1.68, 7.1) compared with the normal-FFM group, 3.17 (1.88, 4.47) before and 2.37 (0.99, 3.76) after treatment.

**Inflammatory status.** The mean circulating IL-6 concentration was greater in the patients with a low FFM compared with a normal FFM both before and after the antibiotic treatment; before 10.7 (5.1, 22.9) pg/ml and 4.3 (2.4, 7.4) pg/ml, p < 0.05 and after treatment 5.7 (2.1, 14.8) pg/ml and 2.2 (1.7, 2.9) pg/ml, respectively. No difference occurred between the two groups at any assessment for IL-6 receptor, TNF-α, and its receptors.

**Clinical status.** The FEV₁ and sustained P_{max} were less in the low-FFM group compared with the normal-FFM patients, both at the start and end of antibiotic treatment, whereas P_{max} was well preserved (Table 4). Physical activity in the low-FFM group was less than in the normal-FFM group, p < 0.01 (Table 4). There was no difference in activity levels between males and females. The low-FFM subjects had more exacerbations of respiratory symptoms in the year before the study, 4.8 (3.2, 6.3), compared with the normal-FFM subjects, 2.3 (2.0, 3.4), p > 0.01.

**Catabolic status.** Circulating cortisol levels were greater (p = 0.04), IGF-1 lower (p = 0.02), and the cortisol:IGF-1 ratio greater (p = 0.02) in the patients with a low FFM when starting antibiotics compared with those with a normal FFM and the non-CF subjects, but were not different at other times (Table 4).

**DISCUSSION**

Our findings of an association between greater concentrations of circulating inflammatory mediators, a negative N\textsubscript{2} balance and increased bone collagen breakdown, and an imbalance between anabolic and catabolic hormones favoring a catabolic state support our view that chronic pulmonary infection and its associated inflammation is a potential factor in the development of the nutritional complications of CF. The finding that such changes were greater in patients with loss of FFM, who also had the greatest impairment of lung function and more frequent exacerbations of respiratory symptoms and a lesser response to antibiotic treatment, strengthens this interpretation and suggests this may be a continuous process in such patients. Our suggestion of a continuous inflammatory-catabolic process is supported by the reported increased REE, raised catecholamines, TNF-α, and inappropriate lipolysis, present in similar patients with CF and chronic pulmonary infection (13). The greater concentrations of circulating IL-6, TNF-α, and their soluble receptors in our patients support and extend observations of a sustained acute-phase response that is only partially responsive to antibiotic treatment, particularly in the low-FFM patients (15, 16).

Most of our patients had reduced BMD Z scores confirming reports in children and adults with CF of a high prevalence of undermineralization (2–10). Multiple factors may interact to contribute to the low BMD and high fracture rate reported in CF (2–10). Bone strength and mass depend partly on the voluntary load imposed by skeletal muscle contraction (23, 24). The combined reduction of skeletal muscle mass, a component of the FFM, and physical activity, secondary to progressive impairment of pulmonary function, probably reduced muscle loading on our patient’s bones, adding to other mechanisms impairing mineralization (23, 24). In adults with CF, severity of pulmonary disease and BMI were independent predictors of a low bone mass (8), whereas in our patients BMD was related to FEV₁ and FFM, and inversely to IL-6- and TNFα-soluble receptors. The relationship with FFM supports the potential importance of skeletal muscle mass and BMD. Our findings are supported by earlier reports of a relationship between nutritional status and BMD, both in children and adolescents with a normal nutritional status (10) and in a mixed group of children and adults (7). In 40 patients (age range, 5.7 to 20.3 yr) Henderson and Madsen (10) reported a strong correlation between total BMD and FFM. Their reported mean 19.1% deficit of total BMD compared with matched healthy subjects was similar to our finding of a mean deficit of 15.6%.

In both studies there was a wide range in BMD deficit, which in our patients could be explained by the effect of the significantly lower BMD in those with a low FFM. In these studies in children and young adults (7, 10), 25-hydroxy-vitamin D, PTH, osteocalcin, and bone alkaline phosphatase were essentially normal, as in our patients, and no relationship was found in either study between vitamin D, bone formation markers, and BMD, which suggests that bone disease in CF is not caused by a primary abnormality of bone metabolism.

In addition to the significantly lower BMD, bone resorption was greater in patients with a low FFM as shown by the greater excretion of NTx/kg FFM. This confirms the report of Baroncelli and coworkers (25) in 59 patients of increased markers of bone resorption (NTx and cross-linked carboxy-terminal telopeptide of type I collagen) in prepubertal, pubertal, and young adults. The reduced BMD of our patients was not a result of hyperparathyroidism, although low normal vitamin D concentrations may have been a minor contributory factor, but would not have caused the other changes in body composition we noted (8). Similar levels of calcium excretion in patients and healthy subjects, though potentially influenced by many factors, indicate no excess loss of calcium in our patients. The lack of difference between patients and healthy subjects for the circulating markers of bone formation, osteocalcin, and bone-specific alkaline phosphatase suggests that in CF bone formation is normal but out of balance with resorption, as indicated by NTx excretion, an index of bone protein breakdown. In contrast to our finding, Baroncelli and coworkers (25) found decreased bone formation markers in their patients. The difference may be methodological or due to age differences, with our patients being older.

The association of both low FFM and low bone mass with circulating IL-6, TNF-α, and their soluble receptors may be fortuitous, but viewed in the context of the proposed role of IL-6 and TNF-α in bone and muscle homeostasis and in other disorders with altered body composition it suggests a possible mechanism linking chronic pulmonary infection and the metabolic

**TABLE 4**

<table>
<thead>
<tr>
<th></th>
<th>Low FFM</th>
<th>Normal FFM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ %predicted, start iv</td>
<td>36.1 (28.7, 43.3)</td>
<td>64.5 (46.6, 82.3)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>FEV₁ %predicted, end iv</td>
<td>43.8 (32.1, 55.4)</td>
<td>65.1 (47.8, 76.8)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>P_{max} start iv, cmH\textsubscript{2}O</td>
<td>88.8 (60.9, 117.4)</td>
<td>120.1 (94.5, 145.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>P_{max} end iv, cmH\textsubscript{2}O</td>
<td>95.2 (63.5, 126.8)</td>
<td>135.1 (110.5, 159.7)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Sustained P_{max} start iv, ptu</td>
<td>402.1 (254.4, 603.9)</td>
<td>706.7 (525.7, 887.7)</td>
<td><strong>&lt; 0.01</strong></td>
</tr>
<tr>
<td>Sustained P_{max} end iv, ptu</td>
<td>503.6 (316.7, 690.5)</td>
<td>791.2 (650.3, 932.2)</td>
<td><strong>&lt; 0.01</strong></td>
</tr>
<tr>
<td>Level of activity, MET</td>
<td>32.3 (26.4, 38.0)</td>
<td>40.2 (36.1, 44.2)</td>
<td><strong>&lt; 0.01</strong></td>
</tr>
<tr>
<td>Cortisol, nmol/L</td>
<td>549.8 (351.8, 747.7)</td>
<td>361.7 (280.6, 442.9)</td>
<td><strong>&lt; 0.04</strong></td>
</tr>
<tr>
<td>IGF-1, ng/ml</td>
<td>102.9 (68.7, 137.0)</td>
<td>145.3 (117.9, 172.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Cortisol:IGF-1</td>
<td>6.89 (2.50, 11.28)</td>
<td>2.73 (1.96, 3.49)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Definition of abbreviations: iv = intravenous infusion; MET = energy expenditure at rest; ptu = pressure time units.

匍 At the commencement of antibiotic treatment.
complications of CF (26–28). The IL-6 transgenic mouse constitutively secretes IL-6 which is associated with a proteolytic based muscle atrophy reversed by blockade of the IL-6 receptor (29). TNF-α, IL-1α, and IL-6 decrease bone collagen synthesis, and promote muscle catabolism and the redistribution of protein to viscera with associated loss of muscle mass and the symptoms of anorexia and lethargy (26–28). Soluble receptors were determined as they may indicate the biological relevance of the measured immunoreactive cytokine (30). Additionally, the IL-6-soluble receptor level may represent the potential for wider biological action through gp 130 subunit activation in cells not expressing the IL-6 receptor (31). IL-6 may have a role in the physiological response to stress and a pivotal position in the linkage between the inflammatory response and catabolism as it is secreted in response to TNF-α, IL-1, and catecholamines, and is itself a potent stimulus of cortisol secretion (32–34). IL-6 and TNF-α are related to bone resorption in primary hyperparathyroidism, with IL-6 predicting resorption (28). The relationship between NTx and serum IL-6 and its soluble receptor, and the inverse relationship between IL-6 and FEV1 in our patients suggests that more severe pulmonary disease and greater bone resorption are linked, possibly through continuous inflammation. This mechanism has been proposed for osteoporosis in other disorders with a chronic inflammatory component, such as cardiac failure and rheumatoid arthritis (20, 35).

The association of a reduced FFM with impaired inspiratory muscle function, particularly endurance as determined by sustained Pmax, confirms our earlier observations (12). Associated with a low FFM and impaired inspiratory muscle function was a significantly greater number of exacerbations of respiratory symptoms. As we have shown, antibiotic treatment only partially suppresses the inflammatory-catabolic state, particularly in those with a low FFM. Hence, such patients experience many years of a continuous vicious cycle of pulmonary inflammation and catabolic intermediary metabolism, which could be a factor in the metabolic outcomes for adults with CF. Additionally, the loss of FFM feeds back negatively on inspiratory muscle function, adding to the problems of pulmonary impairment and symptomatic decline. This suggested interaction is supported by the increased cortisol, decreased IGF-1, and increased cortisol:IGF-1 ratio we found in the group with a low FFM when in exacerbation, which was not present in patients with a normal FFM. We cannot prove a causal linkage between the inflammatory response and the metabolic consequences of CF, but the strong association of proinflammatory cytokines with a low FFM and a catabolic state is similar to findings in patients with HIV, heart failure, and cancer (17–20). Options available to confirm the links that we are suggesting include anti-inflammatory agents to suppress the inflammatory response, use of proanabolic therapies, and blockade of target tissue cytokine receptors.

Adults with CF and chronic pulmonary infection have a low BMD and increased bone resorption related to a general reduction of FFM in the presence of a largely continuous inflammatory and protein catabolic state. These data suggest that the emerging clinical problems of adults with CF are mediated by multiple factors, but that the long-term consequences of continuous pulmonary infection may be an important factor worthy of further study to define its role.

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References


