Randomized controlled trial of nutritional supplementation in patients with newly diagnosed tuberculosis and wasting

Nicholas I Paton, Yueh-Khim Chua, Arul Earnest, and Cynthia BE Chee

ABSTRACT

Background: Nutritional support is often recommended as part of the treatment of tuberculosis, but it has never been properly tested.

Objective: We assessed the effects of early nutritional intervention on lean mass and physical function in patients with tuberculosis and wasting.

Design: Patients who started antituberculous therapy within the previous 2 wk were randomly assigned to receive standard nutritional counseling (control group) or nutritional counseling to increase their intake through diet and high-energy supplements (nutritional supplement group) for 6 wk. Body composition was measured by dual-energy X-ray absorptiometry, and physical function was assessed by maximum grip strength.

Results: Patients in the nutritional supplement group (n = 19) had a significantly greater increase in body weight (2.57 ± 1.78 kg compared with 0.84 ± 0.89 kg, P = 0.001), total lean mass (1.17 ± 0.93 kg compared with 0.04 ± 1.26 kg, P = 0.006), and grip strength (2.79 ± 3.11 kg compared with −0.65 ± 4.48 kg, P = 0.016) than did the control subjects (n = 17) at week 6. During subsequent follow-up, the increase in body weight remained greater in the nutritional supplement group, but this increase was due mainly to a greater gain in fat mass in the nutritional supplement group than in the control group.

Conclusions: Early intervention to increase nutritional intake increases lean mass and physical function. This adjunct to tuberculosis therapy could confer socioeconomic and survival benefits that deserve investigation in large-scale trials. Nutritional intervention after the initial phase of treatment could be less beneficial because it mainly increases fat.


KEY WORDS Tuberculosis, wasting, nutritional supplements, body composition, physical function

INTRODUCTION

Tuberculosis remains one of the major infectious causes of morbidity and mortality worldwide. Effective drugs are available, but a long period of treatment and high levels of compliance are necessary to achieve a cure. Ancillary treatments that ameliorate morbidity and possibly decrease mortality are likely to have important economic and social benefits and, therefore, are an important area for investigation.

Wasting has long been recognized as a cardinal feature of tuberculosis. It is likely caused by a combination of reduction in appetite, leading to a decrease in energy intake, interacting with increased losses and altered metabolism as part of the inflammatory and immune responses (1–3). Wasting is associated with impaired physical function (4) as well as increased mortality in patients with tuberculosis (5–8). Although body weight usually increases during tuberculosis treatment, recovery can be slow, and significant wasting can persist for months after the start of effective tuberculosis therapy (1, 9). Optimizing nutritional intake is frequently advocated as part of the routine management of tuberculosis, but there has never been a properly conducted randomized controlled trial to assess the efficacy and practical benefits of nutritional supplementation (10).

Wasting usually comprises loss of fat and lean tissue, but any functional and survival benefits that result from nutritional intervention are likely to depend mainly on restoring lean tissue. However, in the face of ongoing inflammation it is possible that supplemental feeding could merely increase fat but not lean tissue, a change that is likely to be of little clinical benefit (11). We designed a randomized controlled trial to assess whether supplemental feeding would increase lean mass and improve physical function in patients with tuberculosis and wasting.

SUBJECTS AND METHODS

Patients

The study was conducted at the Tuberculosis Control Unit, Tan Tock Seng Hospital, Singapore, from November 2000 to July 2002. We recruited male or female patients aged between 18 and 69 y, who had evidence of active tuberculosis (defined as having symptoms of fever or cough and a sputum smear that showed acid-fast bacilli or a chest X-ray that showed changes compatible with a diagnosis of tuberculosis), had evidence of wasting [defined by a body mass index (BMI; in kg/m²) < 20 at the time of screening], and were started on combination antituberculosis chemotherapy within the previous 2 wk. We excluded patients who had diabetes mellitus or other severe underlying disease, were receiving concomitant corticosteroid or immunosuppressive...
therapy, had a positive HIV antibody test or were considered to be at risk of HIV infection but refused testing, had a past history of noncompliance to tuberculosis therapy, or were thought to be unable to tolerate a conventional treatment regimen or required inpatient treatment for their disease. All patients gave written informed consent, and the study protocol and patient information sheet were approved by the Tan Tock Seng Hospital Ethics Committee.

Study intervention
After completing the baseline assessments (described further in Study assessments) patients were randomly assigned to either the nutritional supplement group or the control group. The randomization was 1:1 for the 2 groups and was performed by randomly shuffling opaque envelopes containing study codes. Preparation of the randomization envelopes was performed by a member of the staff who was not directly involved in the study.

For patients in the nutritional supplement group, a target energy intake was calculated on the basis of 35 kcal·kg body weight \(^{-1}\) at baseline, and the importance of meeting this target intake was explained to the patient. An estimate of current dietary intake was made from a 24-h food recall, advice was provided about the intake in relation to the target intake, and patients were given a dietary plan to meet the target intake. The patients were also given a supply of high-energy oral nutritional supplements (Ensure Plus; Abbott Laboratories, Columbus, OH) with instructions to consume 2 packets of 200 mL/d (600 kcal/d), increasing to 3 packets/d (900 kcal/d) after 1 wk if tolerated. Patients were instructed to consume these supplements between meals in addition to the dietary intake required to meet the target. Patients were contacted by telephone after 1 wk to assess progress and to provide the necessary feedback. They were seen after 2 to 3 wk to conduct a further 24-h dietary recall and review compliance with diet and supplement intake. After 6 wk, patients who had reached a BMI of 20 or their usual body weight were encouraged to return to an ad libitum diet (containing \(\approx 35\) kcal/kg) and to discontinue supplements. In patients who had failed to achieve these body weight targets at week 6, the dietary plan was continued unchanged. Continued use of supplements was allowed, although patients were encouraged to decrease their reliance on supplements by substituting normal diet for the additional energy. Patients were reevaluated again with use of the same approach at week 12.

For patients randomly assigned to the control group, general advice was given to address any major dietary imbalance identified from the 24-h food recall at baseline. They were instructed to increase their food intake as they felt able but were not given a specific plan for dietary intake and were not provided with supplements. The dietary recall and advice were repeated at subsequent visits with the same frequency as for the nutritional supplement group.

All patients received combination antituberculous drug treatment and ancillary clinical care and follow-up for tuberculosis with use of the standard protocols operating in the Tuberculosis Control Unit. This standard protocol involved directly observed therapy of an initial daily regimen that contained rifampicin, isoniazid, and pyrazinamide plus, in some cases, either ethambutol or streptomycin for 2 mo followed by a continuation phase of 4 mo with rifampicin and isoniazid, usually given 3 times weekly.

Study assessments

Anthropometry and body composition
Body weight was measured to the nearest 0.1 kg with use of calibrated electronic scales at each study visit. Measurements were made in duplicate to ensure reproducibility. Height was measured to the nearest 0.1 cm with use of a portable stadiometer. BMI was calculated as weight (in kg)/height\(^2\) (in m).

Body composition was measured at baseline and at weeks 6, 12, and 24 by dual-energy X-ray absorptiometry (DXA) with the use of a Hologic QDR 2000+ scanner with software version 5.71 (Hologic Inc, Bedford, MA). Subjects wore light indoor clothing, and the measurement was made in the fed state. Total lean or fat mass was the sum of lean or fat tissue for the whole body. Limb lean or fat mass was the sum of lean or fat tissue in arms and legs. Trunk lean or fat mass was taken to be the remaining lean or fat tissue apart from the head region.

Functional status and quality of life
Functional status and quality of life were assessed at baseline and at weeks 6, 12, and 24 with use of the following methods.

Grip strength was measured with use of a Nicholas Manual Muscle Tester (CMS Weighing Equipment Ltd, London). Measurements were made with the patient seated and the arm flexed at 90 degrees. Three attempts were made with each hand, alternating hands between measurements to avoid fatigue, and the highest reading obtained with either hand was taken as the maximum grip strength.

A timed stands test was performed by recording the number of times that the subject was able to stand to full height and sit down over a period of 10 s. The movements were performed with the arms folded, and a chair of standard height was used for all tests.

Quality of life was measured with use of a 30-item questionnaire that was adapted from the Medical Outcome Study Short Form for use in patients with HIV infection. This questionnaire was successfully applied to measure quality of life in intervention studies for wasting associated with HIV disease and was also validated in the Singapore population (12, 13). English and Chinese translations of the questionnaire were available for the patient to select according to preference. The scores on individual questions were transformed to scores on 11 dimensions and also to a physical health summary score as previously described (13).

Nutritional intake, clinical aspects, and laboratory testing
Dietary intake was assessed at baseline and at weeks 6, 12, and 24 with use of a 24-h recall method performed and analyzed by an experienced dietitian. The total energy intake was calculated with reference to standard tables applicable to local foods (14).

Information on the clinical aspects of tuberculosis and the treatment was obtained from the clinic records and by discussion with the managing physician. A full blood count, erythrocyte sedimentation rate, glucose, liver function tests, albumin, total protein, and C-reactive protein were measured at baseline and at week 6 with use of standard laboratory methods.

Statistical analysis
The primary outcome indicator was the change from baseline to week 6 in total lean mass measured by DXA. We judged that a difference in total lean mass of 3 kg between the nutritional supplement and control groups would be clinically worthwhile.
and estimated the SD by using 2.2 kg for the SD of body weight change from a previous observational study of body weight recovery during treatment for tuberculosis (4). To detect such a difference with α (two-sided) 0.05 and power 90%, 11 patients would be needed in each group. To make an additional allowance for measurement errors of total lean mass by DXA and for study withdrawals, we aimed to recruit a total of 35 patients.

Differences in total lean mass, fat mass, body weight, grip strength, timed stands test, and quality of life between the nutritional supplement and control groups were compared with use of analysis of covariance, adjusting for baseline values. Analyses were performed on all available data for patients at each study time point. For change in body weight, an intention-to-treat analysis was performed for all enrolled patients with use of body weights obtained in the clinic at routine follow-up to replace missing values in those patients who had withdrawn from the study. We used the Bonferroni correction method to adjust for multiple comparisons, and the level of significance was thus set at a more stringent 0.05/3 = 0.017 for analyses of the secondary endpoints. Data analysis was conducted with STATA version 7.0 (Stata Corporation, College Station, TX).

RESULTS

Patients

From October 2000 to December 2001, 370 patients who attended the Tuberculosis Control Unit for newly diagnosed tuberculosis were screened for study entry. Of these patients, 109 were aged between 18 and 69 y, had received < 2 wk of tuberculosis chemotherapy, had symptoms of tuberculosis, and had a BMI < 20. Forty-seven patients were excluded, 29 because of diabetes; 16 because of malignancy, HIV infection, or other comorbid diseases; and 2 for defaulting previous tuberculosis treatment. Of the 62 patients who met all criteria, 26 declined to participate in the study. Thus, 36 eligible patients were enrolled into the study and were randomly assigned to the control group (17 patients) or the nutritional supplement group (19 patients). Two patients in the control group withdrew from the study before the week 6 visit, and a further 8 patients (4 from each group) withdrew after the week 6 visit. All study withdrawals were at the patients’ request. No clinical or laboratory adverse events were considered to be related to the use of nutritional supplements.

All patients had evidence of pulmonary tuberculosis on chest X-ray except one patient who had respiratory symptoms together with tuberculous lymphadenitis. *Mycobacterium tuberculosis* was grown in cultures from 22 patients, and in the remainder the diagnosis was confirmed by a clinical response to antimycobacterial therapy. The baseline demographic, nutritional, and laboratory characteristics of the study subjects are shown in Table 1.

At week 6, the energy intake from normal diet did not differ between the nutrition intervention (1757 ± 435 kcal/d) and control groups (1640 ± 440 kcal/d, P = 0.44), but the additional mean intake of 805 ± 175 kcal/d from supplements resulted in a significantly higher total energy intake in the nutrition intervention group (2562 ± 460 kcal/d) than in the control subjects (1640 ± 440 kcal/d, P < 0.001).

Changes in body composition and physical function are shown in Table 2. At week 6, patients in the nutritional supplement group had a significantly greater increase in body weight (2.57 ± 1.78 compared with 0.84 ± 0.89 kg, P = 0.001) and in total lean mass (1.17 ± 0.93 compared with 0.04 ± 1.26 kg, P = 0.006) than did control subjects. Total fat mass increased in both groups, with no significant difference between the groups. There was a significant increase in maximum grip strength in the nutritional supplement group (2.79 ± 3.11 kg) compared with control subjects at week 6 (−0.65 ± 4.48 kg, P = 0.016). Timed stands increased in both groups with no significant difference between the groups at week 6. Quality-of-life changes in the nutritional supplement group were equal to or more favorable than the control group on 9 of 11 subscales (except mental health and health transition) and on the physical health summary score at week 6, but there were no significant differences between groups on any of the individual measures (Table 3).

Total energy intake in the nutritional supplement group (2267 ± 528 kcal/d) remained significantly higher than for control subjects (1628 ± 370 kcal/d, P = 0.001) at week 12, although the magnitude of the difference reduced over time as supplement use decreased. There was no significant difference in energy intake between groups at week 24 (2085 ± 620 kcal/d compared with 1644 ± 307 kcal/d, P = 0.03).

The nutritional supplement group (4.14 ± 2.67 kg) had a greater increase in body weight than did the control group (1.92 ± 1.42 kg, P = 0.008) at week 12, but there was no significant difference at week 24 (4.44 ± 2.73 kg compared with 2.66 ± 2.51 kg, P = 0.073). Total lean mass increased more in the control subjects than in the nutritional supplement group after week 6, so that at week 24 there was no longer a significant difference between the 2 groups. Total fat mass increased more in the nutritional supplement group than in control subjects after week 6, and by week 24 there were trends toward greater increases from baseline in the nutritional supplement group than in control subjects for total fat (3.61 ± 2.30 compared with 1.92 ± 2.31 kg, P = 0.096) and limb fat mass (1.86 ± 1.01 compared with 0.89 ± 1.23 kg, P = 0.046). Grip strength increased more in the control group than in the nutritional supplement group after

| Table 1 | Baseline characteristics of the study participants
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<tr>
<td></td>
<td>Control group</td>
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<tr>
<td></td>
<td>(n = 17)</td>
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<tr>
<td>Age (y)</td>
<td>38.4 ± 19.3</td>
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<tr>
<td>Male sex</td>
<td>8 (47)</td>
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<tr>
<td>Height (m)</td>
<td>159.3 ± 7.9</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Total lean mass (kg)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>17.9 ± 1.9</td>
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<tr>
<td>Weight loss (kg)</td>
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<td>Energy intake (kcal/d)</td>
<td>1560 ± 439</td>
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<td>Hemoglobin (g/dL)</td>
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<td>White blood cell count (× 10³/L)</td>
<td>7.0 ± 2.6</td>
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<tr>
<td>Lymphocyte count (× 10³/L)</td>
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<td>Albumin (g/L)</td>
<td>40.5 ± 4.8</td>
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<td>Total protein (g/L)</td>
<td>79.1 ± 6.8</td>
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<tr>
<td>CRP (mg/L)</td>
<td>16.7 ± 25.2</td>
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<tr>
<td>ESR (mm/h)</td>
<td>33.5 ± 33.4</td>
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1 CRP, C-reactive protein; ESR, erythrocyte sedimentation rate. There were no significant differences between groups (Student’s t test or Fisher’s exact test).

2 ± SD (all such values).
Baseline values for body composition and physical function and changes during follow-up in the nutritional supplement and control groups

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Change at week 6</th>
<th>Change at week 12</th>
<th>Change at week 24</th>
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<tr>
<td><strong>Body weight (kg)</strong></td>
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<tr>
<td>Control group</td>
<td>45.61 ± 1.78</td>
<td>0.84 ± 0.89</td>
<td>1.92 ± 1.42</td>
<td>2.66 ± 2.51</td>
</tr>
<tr>
<td>Nutritional supplement group</td>
<td>42.6 ± 5.36</td>
<td>2.57 ± 1.78</td>
<td>4.14 ± 2.67</td>
<td>4.44 ± 2.73</td>
</tr>
<tr>
<td><strong>Total weight by DXA (kg)</strong></td>
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<tr>
<td>Control group</td>
<td>44.42 ± 6.90</td>
<td>0.87 ± 1.36</td>
<td>2.16 ± 1.39</td>
<td>2.95 ± 2.41</td>
</tr>
<tr>
<td>Nutritional supplement group</td>
<td>41.24 ± 5.16</td>
<td>2.67 ± 2.10</td>
<td>4.27 ± 2.60</td>
<td>5.02 ± 2.89</td>
</tr>
<tr>
<td><strong>Total lean mass (kg)</strong></td>
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<tr>
<td>Control group</td>
<td>33.85 ± 6.66</td>
<td>0.04 ± 1.26</td>
<td>0.65 ± 1.14</td>
<td>1.00 ± 1.66</td>
</tr>
<tr>
<td>Nutritional supplement group</td>
<td>31.63 ± 5.24</td>
<td>1.17 ± 0.93</td>
<td>1.37 ± 1.31</td>
<td>1.34 ± 1.52</td>
</tr>
<tr>
<td><strong>Limb lean mass (kg)</strong></td>
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<tr>
<td>Control group</td>
<td>12.94 ± 3.35</td>
<td>0.08 ± 0.60</td>
<td>0.39 ± 0.69</td>
<td>0.69 ± 0.87</td>
</tr>
<tr>
<td>Nutritional supplement group</td>
<td>12.16 ± 2.62</td>
<td>0.39 ± 0.62</td>
<td>0.77 ± 0.92</td>
<td>0.64 ± 1.14</td>
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<tr>
<td><strong>Trunk lean mass (kg)</strong></td>
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<tr>
<td>Control group</td>
<td>17.97 ± 3.27</td>
<td>-0.07 ± 0.72</td>
<td>0.18 ± 0.60</td>
<td>0.21 ± 0.82</td>
</tr>
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<td>Nutritional supplement group</td>
<td>16.64 ± 2.51</td>
<td>0.72 ± 0.49</td>
<td>0.51 ± 0.63</td>
<td>0.59 ± 0.69</td>
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<tr>
<td><strong>Total fat mass (kg)</strong></td>
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<tr>
<td>Control group</td>
<td>8.91 ± 4.95</td>
<td>0.81 ± 1.52</td>
<td>1.50 ± 1.81</td>
<td>1.92 ± 2.31</td>
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<tr>
<td>Nutritional supplement group</td>
<td>8.04 ± 3.94</td>
<td>1.47 ± 1.73</td>
<td>2.87 ± 2.07</td>
<td>3.61 ± 2.30</td>
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<tr>
<td><strong>Limb fat mass (kg)</strong></td>
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<tr>
<td>Control group</td>
<td>5.41 ± 3.11</td>
<td>0.23 ± 0.64</td>
<td>0.69 ± 0.88</td>
<td>0.89 ± 1.23</td>
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<tr>
<td>Nutritional supplement group</td>
<td>4.90 ± 2.51</td>
<td>0.66 ± 0.70</td>
<td>1.47 ± 1.05</td>
<td>1.86 ± 1.01</td>
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<tr>
<td><strong>Trunk fat mass (kg)</strong></td>
<td></td>
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<tr>
<td>Control group</td>
<td>2.79 ± 1.97</td>
<td>0.41 ± 0.73</td>
<td>0.79 ± 0.99</td>
<td>1.01 ± 1.15</td>
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<tr>
<td>Nutritional supplement group</td>
<td>2.46 ± 1.53</td>
<td>0.80 ± 1.0</td>
<td>1.38 ± 1.05</td>
<td>1.71 ± 1.32</td>
</tr>
<tr>
<td><strong>Maximum grip strength (kg)</strong></td>
<td></td>
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</tr>
<tr>
<td>Control group</td>
<td>25.86 ± 8.35</td>
<td>-0.65 ± 4.48</td>
<td>1.10 ± 4.03</td>
<td>2.83 ± 4.79</td>
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<tr>
<td>Nutritional supplement group</td>
<td>23.41 ± 8.05</td>
<td>2.79 ± 3.11</td>
<td>2.86 ± 3.95</td>
<td>3.22 ± 3.86</td>
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<td><strong>Timed stands test (s)</strong></td>
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<tr>
<td>Control group</td>
<td>6.18 ± 2.16</td>
<td>0.27 ± 1.44</td>
<td>0.62 ± 1.19</td>
<td>0.83 ± 1.27</td>
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<td>Nutritional supplement group</td>
<td>5.74 ± 2.00</td>
<td>0.66 ± 1.11</td>
<td>1.73 ± 1.83</td>
<td>2.00 ± 1.56</td>
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1 DXA, dual-energy X-ray absorptiometry.
2 Analysis of covariance with adjustment for the baseline value of each variable.
3 x ± SD (all such values).

DISCUSSION

We found that nutritional counseling to increase energy intake combined with provision of supplements, when started during the initial phase of tuberculosis treatment, produced a significant increase in body weight, total lean mass, and physical function after 6 wk. The increase in body weight in the supplement group was ⩾8% of body weight, a substantial amount in this relatively short period of time. A large proportion (46%) of the early weight gain comprised lean tissue, confirming the findings from nitrogen balance and protein metabolism studies that patients with tuberculosis can mount a protein anabolic response to feeding (2, 3, 15). The measured change in lean mass could be an underestimate of the actual improvement in nutritional status, given that feeding initially leads to a loss of the extracellular water that accumulates in malnourished individuals, including those with tuberculosis (1, 15). Although increases in body weight and lean tissue usually accompany treatment for tuberculosis, such recovery can be slow and may not be complete, even at the end of the course of tuberculosis therapy (4, 9, 16). Accelerating the recovery of lean tissue might help to restore physical function more rapidly. This relationship was observed in this study when the initial gain in lean tissue in the nutritional supplement was accompanied by a change in grip strength at week 6 that was only matched by the control group at week 24. Restoration of physical function might help to shorten the convalescent period and facilitate earlier return to productive work. The latter benefits could be particularly important because tuberculosis tends to affect the poor, especially those in underdeveloped countries. Poor people often depend on physically demanding resources to be able to take a prolonged period off work. Given that malnutrition is associated with decreased survival in tuberculosis, more rapid reversal of malnutrition could also confer some survival benefit. Although evidence for this benefit is limited, one study in patients with advanced HIV disease and severe wasting demonstrated that aggressive nutritional rehabilitation...
with use of total parenteral nutrition resulted in improved survival (17). Early restoration of nutritional status could also lead to immunologic changes that could enhance the clearance of mycobacteria and reduce infectiousness of patients. Large-scale randomized trials will be required to determine the potential socioeconomic, clinical, and survival benefits of early nutritional intervention in tuberculosis.

The patients in the nutritional supplementation group continued to show a greater increase in body weight than control subjects during later follow-up. However, the pattern changed toward deposition of predominantly fat mass, whereas in the control group the weight gain comprised fat and lean tissue in approximately equal proportions. These proportions are consistent with data from starvation-refeeding studies in healthy individuals that show that fat deposits tend to increase at a greater rate than lean tissue, especially when the energy intake is high (18, 19). This “catch-up” fat phenomenon, which might be mediated by maladaptive thermogenesis, could be a risk factor for later diabetes and cardiovascular disease (20, 21). Thus, although nutritional supplementation during the early stages of tuberculosis treatment could be beneficial in increasing total lean mass and restoring physical function, it is questionable whether continuing to encourage excess energy intake beyond this period is worthwhile given that the energy appears to be deposited mainly as fat. It is possible that the later follow-up results could be affected by the relatively high proportion of patients who dropped out after week 6. However, the dropout rate was the same in the 2 groups, and the intention-to-treat analysis of body weight change (in which weight data from dropouts was included) gave similar results to the DXA-measured weight changes in those patients who continued on follow-up. This finding suggests that a substantial bias is unlikely.

Several aspects of our study could affect the extent to which the findings can be generalized. The rates of drug resistance in Singapore are low (22), directly observed therapy is widely used, and cure rates are consequently high. It is uncertain whether the benefits of nutritional therapy on lean mass and physical function would occur in a group of patients in whom, because of drug resistance or poor adherence, the tuberculosis was not controlled adequately. However, one could argue that the benefits might be

<table>
<thead>
<tr>
<th>Quality-of-life scales</th>
<th>Baseline</th>
<th>Change at week 6</th>
<th>Change at week 12</th>
<th>Change at week 24</th>
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<td>Overall health</td>
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<tr>
<td>Control group</td>
<td>42.65 ± 21.22</td>
<td>6.67 ± 24.02</td>
<td>25.00 ± 27.00</td>
<td>29.17 ± 33.43</td>
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<td>Nutritional supplement group</td>
<td>27.63 ± 18.44</td>
<td>27.63 ± 21.88</td>
<td>30.00 ± 19.36</td>
<td>36.67 ± 18.58</td>
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<tr>
<td>Pain</td>
<td></td>
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<tr>
<td>Control group</td>
<td>69.41 ± 32.49</td>
<td>5.33 ± 35.83</td>
<td>15.38 ± 32.82</td>
<td>15.00 ± 25.76</td>
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<td>Nutritional supplement group</td>
<td>64.21 ± 29.50</td>
<td>16.84 ± 31.46</td>
<td>25.33 ± 25.60</td>
<td>22.67 ± 27.11</td>
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<tr>
<td>Physical function</td>
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</tr>
<tr>
<td>Control group</td>
<td>78.92 ± 20.65</td>
<td>1.67 ± 17.59</td>
<td>6.41 ± 16.37</td>
<td>12.00 ± 23.66</td>
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<td>Nutritional supplement group</td>
<td>67.54 ± 28.18</td>
<td>11.84 ± 30.21</td>
<td>24.44 ± 26.44</td>
<td>22.78 ± 32.80</td>
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<tr>
<td>Control group</td>
<td>83.82 ± 29.24</td>
<td>−5.00 ± 14.02</td>
<td>−5.77 ± 20.80</td>
<td>6.25 ± 33.92</td>
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<td>Nutritional supplement group</td>
<td>81.58 ± 29.86</td>
<td>5.26 ± 33.93</td>
<td>15.00 ± 26.39</td>
<td>16.67 ± 30.86</td>
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<td>−2.67 ± 39.90</td>
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<td>6.67 ± 34.47</td>
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<td>Nutritional supplement group</td>
<td>75.79 ± 29.50</td>
<td>10.53 ± 42.88</td>
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<tr>
<td>Control group</td>
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<td>10.67 ± 22.20</td>
<td>8.92 ± 20.08</td>
<td>11.00 ± 23.01</td>
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<td>Nutritional supplement group</td>
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<td>10.13 ± 26.74</td>
<td>11.20 ± 24.94</td>
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<td>10.67 ± 24.78</td>
<td>18.08 ± 21.27</td>
<td>14.58 ± 16.85</td>
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<tr>
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<td>15.00 ± 27.58</td>
<td>22.69 ± 23.06</td>
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<td>23.33 ± 30.80</td>
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<td>2.94 ± 9.98</td>
<td>5.61 ± 7.85</td>
<td>5.34 ± 9.75</td>
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1 Analysis of covariance with adjustment for the baseline value of each variable.
2 x ± SD (all such values).
greater in such a population, given that rapid reversal of malnutrition could enhance the immune response and help to produce more rapid clearance of sputum and improve overall cure rates. This is an important question that deserves further investigation. We did not study patients with concomitant HIV infection because this occurrence is uncommon among tuberculosis patients in Singapore. In contrast, in many parts of the world a high proportion of the patients with tuberculosis could be co-infected with HIV. Both are wasting diseases, and, when they occur together in the same patient, profound malnutrition can arise that, in turn, can contribute to mortality (1). Thus, in a setting in which HIV coinfection is common, there may be a particularly great need for nutritional supplementation as an adjunct for tuberculosis treatment. However, data from metabolic studies suggest that, when the 2 infections occur together, there could be a blunting of net protein anabolism so that the effect on lean mass could be reduced (2). In addition to use of supplements, the intervention group also received counseling to maintain a high-energy intake from normal diet. This counseling was intended to make sure that the supplements were used in addition to, rather than as a substitute for, normal diet. Although the counseling, therefore, differed between the 2 groups, the difference in energy intake between the groups was due to the additional energy from supplements. However, it might be possible to achieve the same results with counseling alone, or with alternative sources of supplemental intake that are derived from normal dietary components. This alternative could be important for patients in underdeveloped countries for whom the commercially produced nutritional supplements that we used might be too expensive. The cost-effectiveness of nutritional intervention for tuberculosis in underdeveloped countries is uncertain but merits further evaluation in large-scale studies.

In summary, we performed the first known randomized controlled trial of nutritional supplementation in patients with tuberculosis and showed that in the initial stage there is a significant effect on lean mass and functional status. Further studies are warranted to investigate the socioeconomic and survival benefits that these changes can confer as well as the efficacy of nutritional supplementation in patients with multidrug-resistant tuberculosis or concomitant HIV infection. Such studies should be of priority given the global magnitude of the morbidity and mortality associated with tuberculosis and the relative simplicity and inexpensive nature of adjunctive nutritional therapy.

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REFERENCES