Randomised controlled trial of food supplements in patients with newly diagnosed tuberculosis and wasting

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ABSTRACT

Introduction: Wasting is the cardinal feature of tuberculosis, but not much documentary evidence supporting food supplements exists. This study was done to assess the effects of food supplements on body weight, physical function, quality of life and treatment outcomes in patients with tuberculosis and wasting.

Methods: The study was conducted in 30 Anganwadi centres of 16 villages in the catchment area of Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation and the Gannavaram Directly Observed Treatment Short Course chemotherapy centre from August 2005 to December 2005. A total of 100 patients participated in the study. Patients who were started on anti-tubercular therapy within the previous two weeks were randomly assigned to either the control or the food supplement group. At the end of three months, their body weight was measured and physical function and quality of life were assessed. Treatment outcomes were assessed at the one-year follow-up for both groups.

Results: Patients who received supplements had a significant increase in body weight (8.6 percent versus 2.6 percent, p-value less than 0.001) and maximum grip strength (p-value less than 0.001), a higher sputum conversion rate (p-value is 0.039), a higher treatment completion rate (p-value is 0.031) and improvements in the quality of life scores.

Conclusion: Intake of food supplements resulted in a definitive increase in body weight and physical function in our study sample. Improvements can be observed in all areas, including psychologically, physiologically, socially and in the treatment outcomes.

Keywords: body weight, food supplements, tuberculosis, wasting disease

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INTRODUCTION

According to the World Bank's estimated global burden of tuberculosis in terms of disability-adjusted life years, tuberculosis stands seventh among the ten leading causes of global disability-adjusted life years lost, and it is expected to maintain its position even up to the year 2020.[1] It is estimated that approximately one-third of the world's population (more than two billion people) is infected with tuberculosis. India accounts for nearly one-third of the global tuberculosis burden. Every year, around two million people are detected with tuberculosis and half a million die of the disease; around 20,000 people become infected every day, out of whom more than 5,000 develop tuberculosis disease and more than 1,000 die every day, which is about one tuberculosis death every minute.[2]

The World Health Organization recommends the Directly Observed Treatment Short Course (DOTS) strategy, comprising the five elements: (a) case detection with the help of microscopy and a system of multi-tier cross-checking and quality assurance of sputum smear; (b) regular and uninterrupted supply of drugs; (c) direct observation of the patient during chemotherapy by the health worker or community volunteers; (d) systematic evaluation and monitoring; and (e) political will. Although this strategy is employed in India, its effectiveness often depends on the individual's nutritional status. Wasting, one of the important signs of tuberculosis, is attributed to loss of appetite that leads to low daily food intake, and altered metabolism as part of the inflammatory and immune response.[3-5] Wasting is associated with impaired physical function[6] as well as increased mortality in tuberculosis patients.[7-10] Body weight generally increases during treatment, but the recovery process is slow and wasting persists for months after the start of anti-tuberculosis therapy.[3,11] Energy needs are also increased due to the disease (35–40 kcal/kg body weight), and thus a protein intake of about 1.2–1.5 g/kg body weight, and

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good multivitamin and mineral supplements are required.[12] It is empirically believed that food supplementation is a part of tuberculosis management, but very few studies have confirmed its practical benefits.[13]

This study was conducted to assess whether food supplements would increase body weight as well as improve the physical function and quality of life in patients with tuberculosis and wasting. The treatment outcomes, such as sputum conversion, death and treatment completion rates, were incorporated in the study during the follow-up of the patients.

Table I. Baseline characteristics of the study groups.

	Mean ± SD	
	Group I (n = 50)	Group II (n = 50)
Age (yrs)	39.5 ± 14.3	41.0 ± 14.2
Male†	38 (76)	36 (72)
Height (m)	1.6 ± 0.9	1.6 ± 0.7
Weight (kg)	44.2 ± 6.8	43.0 ± 8.2
BMI (kg/m^2)	17.9 ± 2.1	17.1 ± 2.8

Group I: Control group; Group II: Nutritional supplement group
† Data is presented as number of patients (%).
No significant differences were noted between the two groups (student's *t*-test).
SD: standard deviation; BMI: body mass index

METHODS

The study was conducted in 30 Anganwadis (community-based government-sponsored childcare centres) of 16 villages in the catchment area of Pinnamaneni Siddhartha Institute of Medical Sciences and Research Foundation and Gannavaram DOTS centre from August 2005 to December 2005. In India, the workers at the village level who deliver services are called Anganwadi workers. There is an Anganwadi worker for a population of 1,000 under the Integrated Child Development Services Scheme, which was started in India in 1975 in pursuance of National Policy for Children. The Anganwadi worker is a woman who is selected from the community she is expected to serve and undergoes training in various aspects of health, nutrition and child development for a period of four months. She is a part-time worker who is paid an honorarium of Rupees 1,200 per month. She is selected to both motivate and give out supplements to patients mainly because she belongs to the same village and thus, has a strong association with the patients.

Patients recruited for the study were male and female subjects aged 18–65 years who had evidence of active tuberculosis (defined as having symptoms of fever or cough and a sputum smear that showed acid-fast bacilli, or one culture positive specimen from an extrapulmonary site) and wasting (defined by a body mass index [BMI] < 20 kg/m^2 at the time of screening), and who were started on DOTS within the past two weeks. Patients with diabetes mellitus, a positive human immunodeficiency virus (HIV) antibody test or other severe underlying diseases were excluded from the study. The incidence of drug-resistant tuberculosis was not known. Consent was obtained from all the patients. The study protocol and the patient information forms were approved by our institution.

After completing the baseline assessments (Table I), the patients were randomly assigned to either the food supplement group or the control group. The randomisation was 1:1 for the two groups and was performed by randomly shuffling the envelopes that contained the study codes. For patients in the food supplement group, a target intake was calculated on the basis of 35 kcal/day/kg body weight[12] at baseline, and the importance of meeting this target was explained to the patient. An estimate of the current dietary intake was made from a 24-hour food recall. Advice was provided about the dietary intake in relation to the target intake, and patients were provided a dietary plan with the locally available foods in order to meet the target intake. The patients were also given food supplements (sweet balls made from wheat flour, caramel, groundnuts and vegetable ghee, providing 6 g protein and 600 kcal energy, as well 100 g of sprouted grams and nuts for vitamins and minerals) everyday. The Anganwadi worker ensured that these supplements were collected and distributed to the patients, who had to consume the supplements in the presence of the Anganwadi worker. The patients were evaluated at the end of three months. Patients who were randomly assigned to the control group were not given any dietary plan, nor were they provided with supplements. They were only given general advice and instructed to increase their food intake.

The Revised National Tuberculosis Control Programme in India has categorised tuberculosis patients into three categories. Category I consists of new sputum smear-positive cases, seriously ill sputum smear-negative and seriously ill extrapulmonary cases. Category II includes smear-positive relapses, smear-positive failure cases and smear-positive patients being treated by default. Category III patients are new cases of smear-negative pulmonary and extrapulmonary patients who are not seriously ill. All the patients received DOTS chemotherapy.[2] Ancillary clinical care and the follow-up of the two groups of patients were done in their respective DOTS centres.

Table II. Values for body weight and physical function at baseline and during follow-up in the two study groups.

	Mean ± SD	
	Baseline	Change at 3 months
Body weight (kg)		
Group I	44.2 ± 6.8	1.1 ± 2.3
Group II	43.0 ± 8.2	3.7 ± 2.1
Maximum grip strength (kg)		
Group I	20.0 ± 1.5	2.4 ± 0.9
Group II	19.9 ± 1.8	3.9 ± 1.2
Timed-stands test (no.)		
Group I	5.7 ± 1.3	1.9 ± 0.4
Group II	5.6 ± 1.1	2.0 ± 0.8

Group I: Control group; Group II: Nutritional supplement group
Body weight ($t = 5.9$, $p < 0.01$); Maximum grip strength ($t = 6.13$, $p < 0.001$).
SD: standard deviation

Table III. Values for quality of life at baseline and during follow-up in the two study groups.

Quality of life-scales	Mean ± SD	
	Baseline	Change at 3 months
Physical function		
Group I	41.50 ± 30.47	6.70 ± 31.27
Group II	40.00 ± 31.87	23.34 ± 33.87
Role limitation due to physical problems		
Group I	24.50 ± 42.98	5.67 ± 41.67
Group II	26.50 ± 43.54	14.00 ± 44.39
Role limitation due to emotional problems		
Group I	24.00 ± 43.00	4.67 ± 40.08
Group II	25.30 ± 43.84	15.67 ± 41.24
Energy/fatigue		
Group I	30.00 ± 20.00	8.92 ± 19.00
Group II	27.00 ± 21.00	16.00 ± 20.00
Emotional well-being		
Group I	31.76 ± 18.65	2.56 ± 21.45
Group II	27.12 ± 20.49	22.32 ± 22.69
Social functioning		
Group I	29.25 ± 23.10	1.65 ± 21.80
Group II	26.25 ± 22.80	20.45 ± 26.10
Pain		
Group I	35.90 ± 21.20	5.80 ± 22.20
Group II	29.80 ± 21.24	30.90 ± 25.46
General health		
Group I	23.50 ± 18.92	6.50 ± 19.42
Group II	18.50 ± 17.37	32.50 ± 22.17

Group I: Control group; Group II: Nutritional supplement group
Analysis of co-variance with adjustment for the baseline value of each variable was used.
SD: standard deviation

Body weight was measured to the nearest 100 g using calibrated electronic scales (Essae-Teroka Ltd Indo, Bangalore, Karnataka, India) at baseline and at the end of three months. The mean percentage of weight change in the two groups was calculated as the mean difference in weights divided by the mean weight at baseline, multiplied by 100. Height was measured to the nearest 1 mm using a portable Seca 242 stadiometer (Itin Scale Co Inc, Brooklyn, NY, USA). BMI was calculated as weight in kg/height in m^2.

Functional status and quality of life were assessed at baseline and at the end of three months. Grip strength was measured using Nicholas Manual Muscle Tester (Lafayette Instruments, Lafayette, IN, USA) The measurements were carried out with the patient seated down and the arm flexed at 90°. Three attempts were made with each hand, alternating hands between measurements so as 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 the subject was able to stand to full height and sit down over a period of ten seconds. The movements were performed with the arms folded, and a chair of standard height was used for all the tests.

Quality of life was measured using a 36-item questionnaire adapted from the Medical Outcome Study Short Form for use in patients with HIV infection. The questionnaire comprised questions on general health, performance of vigorous and moderate activities, lifting of groceries, climbing of stairs, bending or stooping, walking, bathing, problems with work, daily activities and emotion, body pain as well as pain interfering with normal work. Scores were given for each response and then recoded. The average of the recoded values was translated into the physical health summary score. An average of ten questions was taken to assess physical functioning, four questions for role limitations due to physical health, three for role limitations due to emotional problems, four for energy or fatigue, five for emotional well-being, two for social functioning, two for pain and six for general health. This questionnaire was successfully applied to measure quality of life in intervention studies for wasting associated with HIV disease and has also been validated in the Singapore population.[14,15]

In order to assess the bacteriological conversion, two sputum specimens were taken each time for follow-up sputum smear examinations at specified intervals; at the end of the intensive phase, two months into the continuation phase and at the end of treatment. A patient was considered smear-positive if one of the two specimens tested positive. When a patient was smear positive after the intensive phase, the intensive phase was repeated for an additional month (extended

Table IV. Comparison of treatment outcomes in the two study groups.

	No. (%)		
	Sputum conversion rate	Death rate	Treatment completion rate
Group I	29/36 (80.6%)	2/50 (4.0%)	41/50 (82.0%)
Group II	35/36 (97.2%)	0/50 (0%)	49/50 (98.0%)
p-value†	0.039		0.031

Group I: Control group (2.8% weight gain); Group II: Nutritional supplement group (8.6% weight gain)
† Chi-square test

intensive phase). At the end of the extended intensive phase, two sputum smears were examined, and regardless of the sputum smear status, the continuation phase was started. Sputum conversion rate was measured at the end of the intensive phase of treatment. There were 36 sputum smear-positive patients in each group and these were compared. "Cured" was defined as when an initially smear-positive patient who completed treatment had negative smear results on at least two occasions. "Treatment completed" was defined as when an initially smear-negative patient received the full course of treatment, or when a smear-positive patient who completed treatment had a negative-smear at the end of the initial phase but one or more negative smear during the continuation phase and none at the end of treatment. "Died" was defined as patients who died during the course of the treatment regardless of the cause. The baseline to three months changes in body weight, grip strength, timed-stands test and quality of life between the two groups were compared using the student's *t*-test and analysis of co-variance. The treatment outcomes of the patients in the two groups were compared after the completion of treatment and during the one-year follow-up. Data analysis was conducted with the Statistical Package for the Social Sciences version 11.5 (SPSS Inc, Chicago, IL, USA).

RESULTS

From August 2005 to December 2005, 142 patients who attended the DOTS centres and Anganwadi centres for newly diagnosed tuberculosis were screened for study entry. Of these patients, 126 were aged 18–65 years, had received less than two weeks of anti-tuberculosis chemotherapy, had symptoms of tuberculosis and had a BMI < 20. Of these, 26 patients were excluded; 16 due to diabetes mellitus and ten due to HIV infection or malignancy. Thus, 100 patients, consisting of 52 in Category I, 20 in Category II and 28 in Category III, were enrolled into the study. These patients were randomly assigned to the control group (n = 50) or the food supplement group (n = 50).

The baseline demographic characteristics are shown in Table I. Changes in body weight and physical functions are shown in Table II. At the end of three months, patients in the food supplement group had a significantly greater increase in body weight ($t = 5.9$, $p < 0.01$). The mean weight gain in the control group was 2.8% compared to 8.6% in the food supplement group. Patients in the food supplement group had a significant increase in maximum grip strength ($t = 6.13$, $p < 0.001$) compared to the control group. The result of the timed-stands test improved in both groups of patients, with no significant difference between the two groups. Quality of life changes in the nutritional supplement group were more favourable than those in the control group (Table III), although the difference was not statistically significant (p-value > 0.05) for all the subscales of quality of life. The treatment outcomes are shown in Table IV. The sputum conversion rate was 80.6% and 97.2% in the control and food supplement groups, respectively. The death rate was 4% in the control group. Treatment completion rate was 82% in the control group as compared to 98% in the food supplement group. All the outcomes were statistically significant based on chi-square test.

DISCUSSION

Weight loss and nutritional depletion are often seen in patients with tuberculosis at the time of tuberculosis diagnosis.[16] Most patients face difficulties regaining their usual body weight during the six months of treatment. Although an increase in body weight was observed in both our study groups, only the food supplement group had a significant increase in body weight after three months of treatment. In our study, a significant increase in the maximum grip strength and an objective increase in the timed-stands test were also noted, indicating an improvement in the physical function of the food supplement group. Regaining of physical function shortens the convalescent period and enables patients to resume work.[17] This is beneficial in our country, where tuberculosis generally affects the poor who depend on their physical strength as manual workers. Tuberculosis breaks the poor not only physically but also financially, as they are usually unable to perform physically demanding jobs. The benefit of food supplements was observed in our study since these patients could resume work earlier compared to those in the control group.

Diseases in resolution or interventions that prolong

life aim to improve the quality of life of patients. However, it has been shown that the quality of life, as the patient assesses it, may deteriorate despite an "objectively" successful treatment.[18] It was observed that changes in the quality of life subscales in the food supplement group were more favourable than those in the control group. Subjective improvement was noted in the quality of life of patients in the food supplement group in that their social life was not hampered. They were also emotionally stronger and could perform their daily activities without depending on other family members. Psychologically, they could cope well with the disease without feeling depressed.

Sputum conversion rate was assessed in this study. During the routine follow-up of patients at the end of the two months of intensive phase, all the patients in the supplement group were sputum-negative for acid-fast bacilli and thus the continuation phase of treatment was started. However, in the control group, seven patients remained positive, and an additional month of intensive phase of treatment was administered. Sputum conversion rate at the end of the intensive phase of treatment was 80.6% in the control group compared to 97.2% in the supplement group, which was statistically significant ($p = 0.039$). Whether this benefit was due to the supplements given to the patients remains uncertain. However, the rapid reversal of malnutrition could have enhanced the immune response and helped to bring about a more rapid clearance of sputum and reduce the infectiousness of the patients. This warrants a large-scale investigation. The major benefit of a faster sputum conversion would be seen at the community level due to the reduced risk of tuberculosis transmission; a person with active tuberculosis will infect an average of 20–28 persons before recovering from the disease or dying.[19]

The patients in both groups had a BMI < 20 at the time of diagnosis. The patients in the food supplement group were able to regain an average of about 8.6% of their weight during the first three months of treatment, while the average weight gain was about 2.8% in the control group. The relapse risk could not be observed in our study because the patients have not completed two years of follow-up. A recent study by Khan et al found that among patients who were underweight at diagnosis, a weight gain of 5% or less during the first two months of therapy is associated with an increased risk of relapse.[20] It is still unclear whether patients have an increased risk of relapse due to the lack of weight gain during the initial months of treatment. Efforts could be made to increase the body weight of patients who are underweight at diagnosis by prescribing food supplements.

Malnutrition is associated with increased mortality in tuberculosis. Thus, rapid correction of malnutrition could prevent deaths due to tuberculosis. A study conducted by Melchior et al in patients with advanced HIV disease and severe wasting has demonstrated the benefits of aggressive nutritional rehabilitation with the use of total parenteral nutrition, which resulted in improved survival.[21] In our study, two deaths occurred in the control group during treatment, but none in the food supplement group. Treatment completion rate was observed to be 82% in the control group compared to 98% in the supplement group, which was statistically significant ($p = 0.031$). Further studies are warranted in our country in order to investigate the impact of nutritional intervention in tuberculosis on socioeconomic and clinical areas, survival, relapse risk, sputum conversion rates, cure rates and death rates. The Government of India should provide nutritional supplements under the DOTS programme to tuberculosis patients with wasting in the intensive phase of treatment.

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