



Original article

Macronutrient intake and body composition changes during anti-tuberculosis therapy in adults



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SUMMARY

Background: Malnutrition is common in patients with active tuberculosis (TB), yet little information is available on serial dietary intake or body composition in TB disease.

Objective: To evaluate macronutrient intake and body composition in individuals with newly diagnosed TB over time.

Design: Adults with active pulmonary TB ($n = 191$; 23 with multidrug resistant TB (MDR-TB) and 36 culture-negative household contacts (controls) enrolled in a clinical trial of high-dose cholecalciferol (vitamin D₃) were studied. Macronutrient intake was determined at baseline, 8 and 16 weeks. Serial body composition was assessed by body mass index (BMI; kg/m²) and bioelectrical impedance analysis (BIA) to estimate fat mass and fat-free mass. Descriptive statistics, repeated measures ANOVA for changes over time and linear regression were used.

Results: At baseline, mean daily energy, protein, fat and carbohydrate (CHO) intakes were significantly higher, and body weight, BMI, fat-free mass and fat mass were significantly lower, between TB subjects and controls. These remained significant after adjusting for age, gender, employment status and smoking. In all TB subjects, baseline mean daily intakes of energy, fat and protein were adequate when compared to the US Dietary Reference Intakes and protein significantly increased over time ($p < 0.0001$). Body weight, BMI, and fat and fat-free mass increased over time. MDR-TB patients exhibited lower body weight and fat-free mass over time, despite similar daily intake of kcal, protein, and fat.

Conclusions: Macronutrient intake was higher in TB patients than controls, but TB-induced wasting was evident. As macronutrient intake of TB subjects increased over time, there was a parallel increase in BMI, while body composition proportions were maintained. However, individuals with MDR-TB demonstrated concomitantly decreased body weight and fat-free mass over time versus drug-sensitive TB patients,

Abbreviations: AFB, acid-fast bacilli; BIA, bioelectrical impedance analysis; BMI, body mass index; CHO, carbohydrate; CRF, case report form; IU, International Units; kcal, kilocalories; *Mtb*, *Mycobacterium tuberculosis*; MDR-TB, multidrug resistant tuberculosis; NCTBLD, National Center for Tuberculosis and Lung Disease; NS, not significant; NRL, National Reference Laboratory; RCT, randomized controlled trial; TB, tuberculosis; Vit D, vitamin D₃.

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despite increased macronutrient intake. Thus, MDR-TB appears to blunt anabolism to macronutrient intake, likely reflecting the catabolic effects of TB.

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1. Introduction

Tuberculosis (TB) has long been associated with a decrease in body mass. The relationship between malnutrition and infection, especially in TB, is well established [1–5]. Evidence suggests that malnutrition, particularly low body mass index (BMI), can lead to secondary immune dysfunction that increases the host's susceptibility to infections [1,3,5,6]. Body weight changes during treatment have been explored as a simple biomarker for both disease severity and treatment outcomes [4,7]. Further, it has been shown that TB patients with low BMI (<18.5 kg/m²) are at increased risk for TB-related mortality and treatment failure [4,7,8]. Despite the abundance of cross-sectional data on the relationship between drug-sensitive TB and body composition, there are few serial studies of body composition in TB [9,10] or that combine dietary intake and body composition during anti-TB drug treatment. Also, the relationship between nutrient intake and body composition in individuals with multidrug resistant TB (MDR-TB) compared to those with drug-sensitive TB has not been reported.

Macronutrients, especially protein and energy intake, are critical factors involved in susceptibility to infection, but remain poorly studied in TB, a leading cause of infectious disease-related mortality worldwide [1]. Determination of accurate data regarding habitual dietary and nutrient intake has not been well characterized in patients with TB. The majority of studies in TB have measured body weight and BMI as a marker of nutrition status. While some studies suggest that nutritional supplementation may improve treatment outcomes in patients with active TB [11,12], a recent Cochrane review concluded there was insufficient evidence for specific nutritional supplementation recommendations in patients with active TB [13]. Given the limited and inconclusive data, we hypothesized that: 1) macronutrient intake would increase over time during anti-tuberculosis treatment in adults with TB and that this would be associated with concomitantly increased body weight and fat-free mass; and 2) high-dose vitamin D₃ (Vit D) would result in increased fat-free mass versus placebo-treated subjects. Our objectives were thus to determine changes in macronutrient intake and body composition in adults with newly diagnosed TB, without or with MDR-TB, in the context of a randomized controlled clinical trial (RCT) of high-dose Vit D.

2. Subjects and methods

2.1. Study subjects

Subjects were derived from a double blind, randomized, controlled intent-to-treat trial (RCT) of high-dose vitamin D₃ treatment of patients with active pulmonary TB disease (clinicaltrials.gov identifier NCT00918086). They were consecutively recruited between July 2009 and April 2012 from the Georgia National Center for Tuberculosis and Lung Diseases (NCTBLD) and an affiliated outpatient TB clinic in Tbilisi, Georgia.

Inclusion criteria were: 1) age ≥ 18 years; 2) newly diagnosed TB as determined by a positive AFB sputum smear and later confirmed by positive culture; 3) patient received ≤ 7 days of treatment with anti-TB drug therapy prior to entry; 4) subject has signed the informed consent. Exclusion criteria were: 1) patient had previous diagnosis of TB, known extra-pulmonary or MDR-TB at entry, or expected requirement for surgical resection of TB pulmonary

granuloma; 2) patient is currently pregnant or lactating or has a history of hypercalcemia, nephrolithiasis, hyperparathyroidism, sarcoidosis, organ transplant, hepatic cirrhosis, seizures, or cancer in the past 5 years; 3) patient has a serum creatinine concentration >250 mmol/L or requires renal replacement therapy; 4) patient required corticosteroid use in the past 30 days; 5) current use of cytotoxic or immunosuppressive drugs; and 7) current incarceration.

Acid-fast bacilli (AFB) sputum smear-positive subjects ($n = 784$) were assessed for eligibility. Of these, 345 did not meet inclusion/exclusion criteria and 240 additional subjects declined to participate (Supplemental Fig. 1). A total of 100 subjects were randomized to receive Vit D and 99 were randomized to receive placebo for a total of 16 weeks, during which the study measurements were performed. After randomization, 192 subjects (97 in the Vit D group and 95 in the placebo group) were determined to have sputum cultures positive for *Mycobacterium tuberculosis* (*Mtb*), confirming pulmonary TB, and were thus eligible for this analysis. In one subject randomized to placebo, study endpoints were not determined; thus, a total of 97 subjects randomized to Vit D and 94 assigned to placebo were eligible at baseline. A similar number of subjects in each study group were lost to follow-up (18 in the Vit D group and 15 in the placebo group; respectively) (Supplemental Fig. 1).

TB subjects receiving Vit D were given 50,000 IU of oral vitamin D₃ weekly for 8 consecutive weeks, followed by 50,000 IU of vitamin D₃ every two weeks for 8 consecutive weeks, for a total dose of 1.4 million IU vitamin D₃ during the 16-week period of study. The TB control group received an identical placebo capsule at the same time points as the Vit D group.

When a newly diagnosed TB patient presented to the clinical physician co-investigators, after informed consent, the subject's baseline data was obtained. We concomitantly attempted to enroll household contacts if these individuals accompanied the TB patient during the baseline visit day; thus, the 36 asymptomatic contacts enrolled were a convenience sample reference study group. These individuals were proven to be AFB sputum smear and culture negative and only baseline measurements were performed on these individuals.

2.2. Sputum culture and drug susceptibility testing

Two sputum specimens were obtained from all potential study subjects to confirm TB diagnosis. Direct sputum smears were examined by light microscopy. All sputum samples were sent to the NCTBLD National Reference Laboratory (NRL) for culture, using standard methodologies [14]. Drug susceptibility testing (DST) for first-line anti-TB drugs (isoniazid, rifampicin, ethambutol) and second-line drugs was done using absolute concentration method on solid media, as previously described [15].

2.3. Nutritional and body composition assessment

Dietary intakes were assessed for all study participants in the clinical trial at baseline, week 8 and week 16 of the clinical trial. A validated food/nutrient intake instrument which captures composition of specific foods and meal patterns common in Georgian culture was developed specifically for this RCT [16]. Trained study coordinators conducted one-on-one interviews using appropriate

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