Malnutrition in tuberculosis: value of fat-free mass and creatinine-height index

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Background The association between tuberculosis (TB) and undernutrition has long been known. TB worsens undernutrition and undernutrition weakens immunity, thereby increasing the likelihood that latent TB will develop into active disease.

Objective The aim of the study was to measure the fat-free mass, creatinine-height index (CHI) and other anthropometric measures, and serum albumin to assess the nutritional status of TB patients and to estimate the value of these indexes as prognostic factors of the disease.

Patients and methods The present prospective analytic case–control study was conducted in the Chest Department, Assiut University Hospital. The nutritional status of 61 TB patients and 68 controls was assessed. Anthropometric measures such as ideal body weight (IBW), BMI, triceps skin-fold thickness, arm muscle area (AMA), fat mass index, and fat-free mass index (FFMI) were recorded, as well as laboratory assessment of CHI and serum albumin.

Results There is significant decrease in BMI and IBW% ($P < 0.01$) in TB patients. The lean body mass using AMA and FFMI is significantly lower in TB patients than in controls (54.2 ± 6.9 vs. 61.9 ± 4.7 cm and 34.3 ± 5.0 vs. 35.8 ± 3.4 cm, respectively; $P < 0.01$). Loss of fat in TB patients is indicated by significant reduction in mid-arm circumference, skin-fold thickness, and fat mass index ($P < 0.01$ each). TB patients have significantly lower CHI and serum albumin compared with controls (76.5 ± 28.1 vs. 91.7 ± 24.2 and 37.4 ± 7.8 vs. 41.6 ± 4.2; $P < 0.01$). Using multiple regression, the significant determinants of malnutrition in TB patients are IBW, AMA, CHI, and serum albumin.

Conclusion Tuberculous patients have significantly decreased body weight with loss of both lean body mass and fat mass. The loss of CHI is a more significant marker than FFMI in this group of patients. These indexes as well as serum albumin may play an important role as prognostic markers in TB. *Egypt J Broncho* 2016 10:58–63

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Keywords: body composition, creatinine-height index, fat-free mass index, malnutrition, tuberculosis, wasting, weight loss

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Introduction

It has long been known that there is an association between tuberculosis (TB) and malnutrition. Malnutrition enhances the development of active TB, and active TB worsens malnutrition [1]. Most individuals with active TB are in catabolic state and experience weight loss, and some show signs of vitamin and mineral deficiencies at diagnosis. Low BMI (<18.5 kg/m^2) and lack of adequate weight gain with TB treatment are associated with an increased risk for death and TB relapse and can be an indication of severity of TB, poor treatment response, and/or the presence of other comorbid conditions [2]. Patients with active pulmonary TB usually have reductions in visceral proteins, anthropometric indexes, and micronutrient status [3].

As muscle usually forms between 60 and 80% of fat-free mass (FFM) or lean body mass, FFM can be used as a surrogate marker for muscle mass, and the creatinine-height index (CHI) is used to confirm that reduced FFM correlates with reduced muscle mass in these patients [4].

The urinary creatinine excretion is not only a biochemical reflection of total muscle mass but is also affected by several factors, such as strenuous exercise, diet, infection, fever, trauma, and renal function [5]. The CHI (expressed as a percentage) is defined as the individual 24-h urinary creatinine output of a patient divided by the ideal 24-h urinary creatinine excretion for a given height (in a reference population) multiplied by 100. A CHI of 60–80% of the standard (i.e. in comparison with the ideal) has been suggested to represent a moderate deficit in body muscle mass, whereas a value less than 60% indicates a severe deficit of body muscle mass [6]. The CHI has been recommended for evaluating the degree of protein depletion and repletion in potentially malnourished children [7]. Despite many limitations, many

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investigators have suggested that urinary creatinine output for a given height is a convenient measure for the assessment of somatic protein status because, on one hand, creatinine is a sufficiently reliable estimate of FFM and muscle mass and, on the other hand, height (as a major determinant of FFM and muscle mass) is not affected by fluid and adipose tissue imbalances [8].

Unfortunately, very few studies have been designed to examine the relationship between nutrition and the incidence of TB or its severity. It is very difficult to accurately determine the nutritional status of individuals with active TB before the onset of the disease, making it impossible to determine whether malnutrition leads to development of active TB or active TB leads to malnutrition. Furthermore, randomized trials, the gold standard in evidenced-based medicine, can be difficult to carry out in food-insecure regions because of ethical considerations [9].

The aim of the study was to:

(1) Assess the nutritional status and body compositions of tuberculous patients using anthropometric measures as ideal body weight (IBW), BMI, fat mass index (FMI), fat-free mass index (FFMI), and laboratory measures as serum albumin and urinary CHI; and
(2) Estimate the value of these indices as prognostic factors of the disease.

Patients and methods

Study design and ethics

The present prospective analytic case–control study was conducted in the Chest Department and Chest Outpatient Clinic, Faculty of Medicine, Assiut University Hospital, from January 2013 to February 2014. The study design was approved by the Scientific Ethics Committee of the Faculty of Medicine of Assiut University. After meeting the inclusion criteria, informed consent was obtained from the patients.

Patients and controls

The study included 61 newly diagnosed tuberculous patients (based on bacteriological, pathologic, and radiologic data) who were randomly selected (crossover 1 : 1) from the outpatient clinic, as well as 68 controls.

Exclusion criteria included the presence of chronic hepatic disease, renal failure, malignancy, pregnancy, and diabetes mellitus.

Baseline patient data

All patients underwent the following:

(1) Medical history, clinical examination, routine laboratory testing and investigations, and bacteriological examination of sputum for acid fast bacilli.
(2) Nutritional assessment:

Anthropometric variables

(1) Body weight (in kilograms).
(2) IBW: Body weight was expressed as a percentage of ideal weight [3]. The Devine formula was used for calculation of IBW [4].
(3) Height (in centimeters).
(4) BMI: BMI was identified using the following equation: BMI = weight (kg)/height (m^2).

The results of the equation were then classified as follows: underweight <18.5; normal ≥18.5 to >25; overweight ≥25 to >30; grade 1 obesity ≥30 to >35; grade 2 obesity ≥35 to >40; and grade 3 obesity ≥40.

Triceps skin-fold (TSF) and arm muscle area (AMA):

TSF was measured on the right arm at the midpoint between the acromion process of the scapula and the inferior margin of the olecranon process of the ulna. The arm should be bent at a 90° angle at the elbow to mark the midpoint. The arm hangs by the side with the palm facing anteriorly as a caliper is used to measure a pinch of skin-fold. The thumb and index finger of the left hand of the measurer grasp the skin-fold while the caliper is placed ~½ inch from the fingers. When the caliper is perpendicular to the skin-fold, the dial can be easily read [6].

AMA: The formula to calculate AMA is as follows:

$$\mathrm{AMA}=\frac{\left[\mathrm{MAC}(\mathrm{cm})-(\pi\times\mathrm{TSF\ cm})\right]^2 - 10\ \mathrm{cm}^2\ (\mathrm{males})\ \text{or}\ 6.5\ \mathrm{cm}^2\ (\mathrm{females})}{4\pi},$$

where MAC is mid-arm circumference and TSF is triceps skin-fold.

Fat mass index (FMI) and FFMI were ascertained by means of bioelectrical impedance analysis using an electronic scale, Korona (Korona Haushaltswaren GmbH & Co. KG, Germany). FFMI was defined as FFM (kg) divided by the square of height (m^2), and similarly for FMI [7].

Laboratory testing

CHI: The amount of creatinine excreted in the urine every 24 h reflects the skeletal muscle mass because the rate of creatinine formation in skeletal muscles is constant. Predicted values are based on sex and height, with reference value of ~18 mg/kg body weight/day for women and ~23 mg/kg body weight/day for men. Values of 60–80% of predicted indicate

a mild deficit of muscle mass, values 40–60% of predicted indicate a moderate deficit, and values less than 40% of predicted indicate a server depletion of muscle mass [10].

Expected creatinine = 23 mg/kg of IBW (in male patients).

Expected creatinine = 18 mg/kg of IBW (in female patients).

Serum albumin and C-reactive protein were also evaluated.

Statistical analysis of data

Data were analyzed using SPSS software, version 16. Descriptive statistics were assessed in the form of frequencies, mean and SD and analytic statistics were analyzed with the χ^2-test, the independent-sample *t*-test, correlations, and regression tests. The paired *t*-test was used to compare numerical parametric data before and after intervention. *P* values equal to or less than 0.05 were considered significant.

Results

In this study, 61 tuberculous patients and 68 controls were included.

Table 1 shows that TB patients have significantly lower body weight compared with controls (58.5 ± 12.3 vs. 64.3 ± 7.2; $P < 0.01$) and their BMI is significantly lower (20.6 ± 3.6 vs. 23.3 ± 2.5; $P < 0.01$).

In Table 2 body weight is expressed as a percentage of IBW. There was a statistically significant difference between TB patients and controls as regards their weight percentage of IBW ($P < 0.01$). The lean body mass using AMA was significantly lower in the TB group compared with the control group (54.2 ± 6.9 and 61.9 ± 4.7, respectively) and FFMI was also significantly lower than that in the control group (34.3 ± 5.0 and 35.8 ± 3.4, respectively). Loss of fat in TB patients is indicated by significant reduction in mid-arm circumference and skin-fold thickness ($P < 0.01$ each).

Table 3 shows that TB patients have significantly lower CHI compared with the control group (76.5 ± 28.1 vs. 91.7 ± 24.2; $P < 0.01$). In addition, serum albumin was significantly lower in TB patients (37.4 ± 7.8 vs. 41.6 ± 4.2; $P < 0.01$).

Table 4 shows that there was no statistically significant difference in BMI, weight (expressed as a percentage of IBW), and lean body mass using AMA, FFMI, and CHI between TB-positive and TB-negative patients.

Table 1 Demographic data of the studied groups

Parameters	Tuberculous patients	Controls	*P* value
Patients (*n*)	61	68	
Age (M ± SD) (years)	33.1 ± 15.6	39.0 ± 16.7	<0.040*
Sex [*n* (%)]			
Male	40 (65.6)	36 (52.9)	<0.145^{NS}
Female	21 (34.4)	32 (47.1)	
Weight (kg)	58.5 ± 12.3	64.3 ± 7.2	<0.01**
Height (cm)	168 ± 8.3	166 ± 6.6	0.130^{NS}
BMI (kg/m^2)	20.6 ± 3.6	23.3 ± 2.5	<0.01**

Categorical data are presented as frequency and percentage, Quantitative data are presented as mean ± SD (range), The χ^2-test and the *t*-test were used to test the significance between groups, NS, not significant ($P < 0.05$), *Significant ($P < 0.05$), **Significant ($P < 0.01$).

Table 2 Anthropometric parameters in the studied groups

Parameters	Tuberculous patients	Controls	*P* value
Patients (*n*)	61	68	
Ideal body weight	56.5 ± 8.8	61.9 ± 6.1	0.228^{NS}
% Weight (% of ideal body weight)	95.4 ± 16	108.3 ± 14	<0.01**
Mid-arm circumference. (cm)	25.2 ± 3.2	28.8 ± 2.2	<0.01**
Skin-fold thickness (ml)	7.47 ± 3.9	13.4 ± 8.9	<0.01**
Arm muscle area (cm)	54.2 ± 6.9	61.9 ± 4.7	<0.01**
Fat mass index	23.2 ± 6.6	23.4 ± 3.7	0.830^{NS}
Fat-free mass index	34.3 ± 5.0	35.8 ± 3.4	0.046*
Body water	53.8 ± 7.4	55.6 ± 5.8	0.124^{NS}

The *t*-test was used to test the significance between groups, NS, not significant ($P < 0.05$), *Significant ($P < 0.05$), **Significant ($P < 0.01$).

Table 3 Laboratory markers in the studied groups

Parameters	Tuberculous patients	Controls	*P* value
Patients (*n*)	61	68	
Creatinine height index %	76.5 ± 28.1	91.7 ± 24.2	<0.01**
C-reactive protein	2.66 ± 2.08	2.86 ± 3.57	0.702^{NS}
Albumin (g/dl)	37.4 ± 7.8	41.6 ± 4.2	<0.01**

The *t*-test was used to test the significance between groups, NS, not significant ($P < 0.05$), **Significant ($P < 0.01$).

Table 4 Anthropometric and laboratory parameters of malnutrition in patients with different degrees of tuberculosis reactivity

Parameters	TB (+)	TB (-)	*P* value
Patients (*n*)	28	33	
BMI (kg/m^2)	20.3 ± 4.1	21.0 ± 3.2	0.418^{NS}
Wt (% of ideal body weight)	92.8 ± 19.8	97.3 ± 14.5	0.367^{NS}
Arm muscle area (cm)	53.6 ± 7.4	54.7 ± 6.6	0.570^{NS}
Fat mass index	23.4 ± 6.3	23.1 ± 7.0	0.842^{NS}
Fat-free mass index	33.5 ± 5.1	35.0 ± 4.9	0.240^{NS}
Total body water	52.6 ± 7.8	55.1 ± 6.9	0.188^{NS}
Creatinine-height index %	74.1 ± 30.5	78.6 ± 26.2	0.526^{NS}
Albumin (g/dl)	34.9 ± 7.2	39.4 ± 7.7	0.025*

The *t*-test was used to test the significance between groups, NS, not significant, *Significant ($P < 0.05$).

Only serum albumin level was significantly lower in active TB patients ($P < 0.02$).

Table 5 shows that there was no statistically significant difference in BMI, weight (expressed as a percentage of IBW), lean BMI using FFMI and CHI, and albumin between TB patients with different degrees of disease severity, whereas lean body mass using AMA was significantly lower in TB patients with far advanced TB than in mild and moderately advanced patients ($P = 0.004$).

Table 6 shows that by multiple regression analysis the significant determinants of malnutrition in TB patients are IBW, MAC, CHI, and serum albumin.

Discussion

Undernutrition increases the risk for TB and in turn TB can lead to malnutrition. It is therefore highly prevalent among people with TB. Malnutrition has been demonstrated as a risk factor for progression from TB infection to active TB disease and undernutrition at the time of diagnosis of active TB is a predictor of increased risk of death and TB relapse [2].

Table 5 Anthropometric and laboratory parameters of malnutrition in different degrees of tuberculosis disease severity (based on radiological classification of tuberculosis)

Parameters	Minimal and moderately advanced TB	Far advanced TB	*P* value
Patients (*n*)	35	26	
BMI (kg/m^2)	20.7 ± 3.5	20.6 ± 3.9	0.883^{NS}
Wt (% of ideal body weight)	91.8 ± 14.9	99.5 ± 18.4	0.122^{NS}
Arm muscle area (cm)	56.4 ± 6.5	51.3 ± 6.6	0.004**
Fat mass index	23.9 ± 5.6	22.3 ± 7.8	0.344^{NS}
Fat-free mass index	33.5 ± 4.7	34.3 ± 4.2	0.451^{NS}
Total body water	52.1 ± 7.5	56.6 ± 6.5	0.016**
Creatinine height index %	76.1 ± 27.5	77.1 ± 29.1	0.888^{NS}
Albumin (g/dl)	38.5 ± 7.3	35.8 ± 8.2	0.181^{NS}

The *t*-test was used to test the significance between groups, NS, not significant, *= $P < 0.05$, **Significant ($P < 0.01$).

Table 6 Multiple regression analysis of determinants of malnutrition in tuberculous patients

Significant predictors	β	*P* value
Age	−0.14	0.063
Weight	−0.64	0.495
Height	−0.12	0.829
Ideal body weight	0.60	0.009**
Skin-fold thickness	0.01	0.921
Arm muscle area	−0.55	0.001**
BMI	0.49	0.576
Fat mass index	0.15	0.167
Body water	−0.17	0.103
Fat-free mass index	0.05	0.553
Creatinine-height index	−0.24	<0.01**
Serum albumin	−0.23	0.007**

Multiple regression analysis was used, *= ($P < 0.05$), **Significant ($P < 0.01$).

In this study, the simple assessment of body weight, BMI, and percentage of IBW showed that TB patients have significantly lower body weight and weight percentage of IBW as the majority of TB patients were underweight (95.4 ± 16% of ideal weight) at the time of diagnosis. Decreased body weight in TB patients has been established in many studies. The BMI in TB patients was reduced by up to 16% compared with controls, and body fat mass (percentage) by 45% [11–14]. The majority of TB patients were malnourished, as an overall 61% of patients had a BMI less than 19 in one study [15]. Another study of 30 patients with pulmonary TB in England revealed a reduction in BMI, as well as a decrease in triceps skin-fold, arm muscle circumference, and serum albumin [3]. The mean BMI of patients with active TB recently admitted for treatment was 20% lower than in controls (BMI of 18.5 ± 3.2 vs. 21.9 ± 2.8 in male, 17.8 ± 3.1 vs. 21.9 ± 3.5 in female patients vs. controls respectively, $P < 0.01$), and 66% of patients had a BMI less than 18.5 (six times more frequent than in controls [16].

This is important as many authors studied factors associated with early mortality and found that increasing degrees of malnutrition, age older than 35 years, and HIV seropositivity were the most important [11]. Over half of all TB patients in a rural district of Malawi were malnourished at the time of registration, and over one-third had moderate-to-severe malnutrition. Patients with moderate-to-severe malnutrition (BMI < 17.0 kg/m^2) had higher rates of early death compared with those whose nutritional status was normal or mildly impaired, and these differences were found regardless of age, HIV sero-status, and other factors [3]. Also, among adults with moderate-to-severe malnutrition, 10.9% died in the first 4 weeks of treatment as opposed to a 6.5% death rate in adults who were normal or had mild malnutrition [14].

Further assessment of anthropometric measures is needed in TB patients. In the current study, the lean body mass using AMA was significantly lower in the TB group than in the control group (54.2 ± 6.9 and 61.9 ± 4.7, respectively) and FFMI was also significantly lower than in the control group (34.3 ± 5.0 and 35.8 ± 3.4, respectively). Loss of fat in TB patients is shown as significant reduction in mid-arm circumference and skin-fold thickness ($P < 0.01$ each). This is an indication that wasting in TB involves both muscle and adipose tissue. In agreement, many authors showed that weight,

skin-fold thicknesses, mid-upper-arm circumference, fat mass, and FFM were all significantly lower in those with active TB [3,17,18].

Laboratory indexes as urinary CHI and serum albumin were significantly reduced in TB patients in the present study. They are simple early indicators of lean body mass loss in patients with active TB. As far as we know this study is the first to recommend the assessment of CHI as a surrogate marker of malnutrition in TB. The CHI was used to confirm that reduced FFM correlated with reduced muscle mass in malnourished patients [4]. The CHI has also been recommended for evaluating the degree of protein depletion and repletion in potentially malnourished children [7]. The urinary creatinine output for a given height is a convenient measure for the assessment of somatic protein status because, on one hand, creatinine is a sufficiently reliable estimate of FFM and muscle mass and, on the other hand, height (as a major determinant of FFM and muscle mass) is not affected by fluid and adipose tissue imbalances [8].

In this study, there was no statistically significant relation between reactivity of the disease and nutritional status, except that serum albumin was significantly lower in TB-positive patients than in TB-negative patients (34.9 ± 7.2 and 39.4 ± 7.7, respectively). The explanation may be that, during active TB, catabolic processes that cause wasting usually begin before the patient is diagnosed; therefore, more is known about nutritional status at the time of diagnosis than of the wasting process *per se*. As with HIV infection, at the time of diagnosis the metabolic rate or resting energy expenditure is increased, resulting in increased energy needs to meet the basic demands for body function. At the same time, energy intakes are likely to decline as a result of illness-associated anorexia. This combination of conditions results in weight loss with eventual wasting if energy intakes are not increased or energy expenditures decrease. Utilization of amino acids and protein synthesis may be further inhibited because of the presence of proinflammatory cytokines [19].

As regards the radiological classification, TB patients with far advanced, moderate, and mild TB did not show statistically significant difference in anthropometric parameters with the exception of the AMA, which was significantly lower in TB patients with far advanced disease than in those with mild or moderately advanced disease. Similar to the current study, Van Lettow and colleagues (2004) found that when compared with normal lung appearance far advanced lung disease was associated with lower BMI and fat mass. The same applied for minimal and moderately advanced lung disease, which were associated with lower fat mass and BMI, respectively [1].

It has been suggested that generalized malnutrition, by reducing the expression of g-interferon, tumor necrosis factor-a, and other mycobactericidal substances, may selectively compromise portions of the cell-mediated response that are important for containing and restricting TB [20]. Cell-mediated immunity is the most important defense against TB. An already malnourished individual is more likely to become infected with TB, and latent infection is more likely to become active TB when the cell-mediated immunity response is impaired. In fact, among individuals with latent TB, the occurrence of malnutrition may be an important trigger for active TB development [9]. This immune-deficiency represents a key factor in susceptibility to infections and has therefore been termed 'nutritionally acquired immunodeficiency syndrome'. In severely malnourished patients, both acquired immunity – that is, lymphocyte functions – as well as innate host defense mechanisms – that is, macrophages and granulocytes – are affected [20].

Although increases in body weight and lean tissue usually accompany treatment for TB, such recovery can be slow and may not be complete, even at the end of the course of TB therapy. It was explained by the fact that 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 TB can mount a protein anabolic response to feeding. 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 TB [21]. Paton *et al.* (2004) [16] performed the first known randomized controlled trial of nutritional supplementation in patients with TB and showed that in the initial stage there is a significant effect on lean mass and functional status.

This study has some limitations: first is the difference in age between the two groups, but this was corrected by measuring the IBW, which is corrected for age, sex and height. Second, the nutritional status before TB infection in the studied groups cannot be estimated, and the disease duration was not accurately defined by the patients. Third, the assessment of lung disease through chest radiographs, although done with a descriptive grading scheme, is subjective.

Taken together, it seems that undernutrition is a risk factor for TB infection rather than a consequence of the disease. It is important to assess the relative loss of lean and fat mass due to TB in order to know what should be gained during treatment. This is crucial because it is probably the gain of lean and not

fat mass that may have both survival and functional benefits. There are few published studies on deficits in weight and functional outcomes among TB patients starting treatment. Furthermore, most of these studies are small and do not include appropriate non-TB controls**.** Further research is needed to understand the role of such determinants on changes in body composition occurring during treatment in order to design interventions that might lead to improved TB treatment outcomes and long-term health**.**

Conclusion

Malnutrition is a common feature among TB patients. Tuberculous patients have substantially lower body weight with significant loss of lean body mass as demonstrated by decrease in CHI, AMA, and FFMI. The loss of CHI is a more significant risk factor than FFMI in this group of patients. These indexes as well as serum albumin may play an important role as prognostic markers in TB. However, it seems that malnutrition is the risk factor for progression from TB infection to active TB disease as well as a result of the disease regardless of the TB severity. Nutritional support to the vulnerable population is highly recommended to minimize the development of active disease.

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Conflicts of interest

There are no conflicts of interest.

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