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Predictors of Nutritional Status in Patients Treated for Multidrug-Resistant Tuberculosis at a Referral Hospital in Tanzania

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Abstract

Tuberculosis (TB) and malnutrition co-exist. Malnutrition predisposes to development of TB, and may further predict treatment outcomes. Given the paucity of data regarding malnutrition in specific populations with multidrug-resistant (MDR)-TB, we aimed to determine the pre-treatment and post-treatment change in nutrition status, as measured by body mass index (BMI), in patients from Tanzania initiating MDR-TB treatment, as well as potentially modifiable determinants of BMI in this population at high-risk for treatment failure.

Design: A retrospective cohort was followed consisting of patients admitted for MDRTB treatment at Kibong'oto National MDR-TB Center of Excellence, the national referral hospital for all cases in Tanzania.

Results: Of 104 MDR-TB cases admitted from November 2013 through June 2014, 96 (92%) cases were assessed for nutrition status. Fifty-one (53%) were malnourished, of which 15 (30%), 15 (30%) and 21 (45%) were classified as mild (BMI <18.5 - 17), moderate (BMI <17 ≥ 16) and severe (BMI <16) respectively. Gender, HIV status, and pre-treatment CD4 count among those HIV infected did not influence pre-treatment nutrition status. Thirty-seven (39%) of MDR-TB patients improved grades (e.g. from severe to moderate malnutrition) and gained a mean BMI of 2 kg/m^2 (95% CI: 1-3), yet 9 (9%) deteriorated grades and thus developed acute adult malnutrition during treatment. In those that developed acute malnutrition during treatment, the mean lost BMI was 3 kg/m^2 (95% CI; 0.3-8). Categorical change in BMI grade trended toward association with the duration of inpatient admission (p=0.05).

Conclusion: Malnutrition is a common comorbidity in MDR-TB patients receiving treatment in Tanzania. Importantly, some MDR-TB patients while on treatment developed acute malnutrition. Given the lack of predictors of developing malnutrition, these findings suggest the need for frequent assessment of nutrition status during the course of MDR-TB treatment, to identify patients that may require additional therapeutic supplements.

Keywords: Multidrug resistant tuberculosis (MDR-TB); Malnutrition; Body Mass Index (BMI); HIV coinfection; Kibong'oto; Therapeutic nutrition; Intravenous nutrition

Introduction

Tuberculosis (TB) is a public health disease, causing significant morbidity and mortality in resource-limited settings [1]. Malnutrition is also common in resource-limited settings particularly in sub-Saharan Africa [2]. TB and malnutrition have been associated since the first published report of consumption which we now attribute to *Mycobacterium tuberculosis* disease [3,4]. More recent reports explain how not only malnutrition predisposes to development of active TB disease but also in predicting poor outcomes in TB cases [5-12]. Essentially in some studies, moderate or severe malnutrition was independently associated with early mortality during TB treatment [13,14].

As untreated TB disease progress, malnutrition can worsen. The possible explanations rely partly on immunopathophysiology and hormonal mechanisms, and include increased cytokine release, such as TNF- ∝ and production of gut hormone such as plasma peptin YY (PYY) [15,16]. Proper TB treatment may result in improvement of nutritional status [17-19]. A Cochrane review showed that both macro and micronutrient supplements during TB treatment had low to modest benefits in-terms of outcomes. The results were inconclusive as trials were too small to provide sufficient evidence for clinical benefit [20].

Multidrug-resistant (MDR)-TB treatment includes second-line drugs such as flouroquinolones, ethionamide and para-aminosalicylic acid, which can produce remarkable gastrointestinal intolerance [11,17]. Furthermore, patients with MDR-TB have often undergone prior treatment for TB without success and have consequently suffered from a more prolonged illness, which predisposes to malnutrition [17]. In contrast to drug-susceptible TB, the relationship of malnutrition

and MDR-TB has not been as thoroughly studied. Therefore this study seeks to describe the pre-treatment nutrition status of patients admitted for MDR-TB treatment at the national referral hospital in Tanzania, a TB endemic and resource limited country. Furthermore, the study examines if the severity of malnutrition or the change in nutrition status during treatment correlated with modifiable clinical factors or duration of stay in the hospital.

Methods

Study design

Hospital staff reviewed consecutive medical charts of all MDR-TB patients admitted at Kibong'oto National MDR-TB Centre of Excellence from November 2013 to June 2014. Patients were considered eligible for inclusion if they were on MDR-TB treatment and had measurements for their weight and height taken. Pregnant women and children were excluded. The Kilimanjaro Christian Medical College Research Ethics and Review Committee (CRERC) and the Institutional Review Board and the University of Virginia approved this study.

Study site

Kibong'oto National MDR-TB Centre of Excellence is a public hospital and was a formerly used as a TB sanatorium. Currently, it is the country's only referral hospital for MDR-TB management [17]. The inpatient MDR-TB service has a 100- bed capacity. MDR-TB referred cases were diagnosed by molecular diagnostics (Xpert MTB/RIF or GenotypeMTBDRplus) or conventional drug-resistance surveillance performed programmatically at the Central TB Reference Laboratory in Dar es Salaam. MDR-TB drug treatment was first available in November 2009 [17], and has consisted of a standardized WHO approved drug regimen of one injectable agent (kanamycin or capreomycin), levofloxacin, ethionamide, cycloserine and pyrazinamide. HIV seropositive patients were also given antiretroviral therapy (ART) and cotrimoxazole prophylaxis therapy. The ART used were either a regimen with emtricitabine, tenofovir and efavirenz or zidovudine, lamivudine and efavirenz or nevirapine [21].

Definitions and outcome measures

For the purpose of analysis, the nutrition status was defined by body mass index (BMI) as the ratio of weight (kg)/height^2 (m^2). Low BMI or malnutrition (<18.5) was further classified into three categories. BMI of (17.00-18.49), (16.00-16.99) and (<16) were considered as mild, moderate and severe malnutrition according to WHO criteria [22]. While BMI >18.5 kg/m^2 was classified as normal nutrition and BMI ≥ 25 kg/m^2 was defined as over nutrition. Clinical variables included were age, gender, alcohol consumption, cigarrete smoking, HIV status and pretreatment CD4+ T lymphocytes in those HIV infected.

Results were expressed in simple proportion (%), mean (standard deviation or 95% confidence interval) or median (interquartile range) when appropriate. Statistical tests were two-tailed. Measures of associations were determined by chi-square of trend, for instance in nutrition status (normal, mild, moderate and severe malnutrition) with clinical variables such as age, gender, HIV status and CD_4 count. The Kruskal- Wallis test was used to identify if there was a significant difference between the median duration of admission for cases with BMI change (improvement or worsening) or no change.

Results

Demographics and clinical characteristics

A total of 104 MDR-TB patients were admitted from November 2013 to June 2014. Ninety-six cases were eligible for analysis while 8 cases were excluded. Reasons for exclusion included age (children), pregnancy, and bedridden state (unable to calculate BMI) in 6 (6%), 1 (1%) and 2 (2%) respectively. Sixty-five (68%) of patients were male and the age distribution of 90 (86%) cases was in the category of 20-59 years while above 60 years was only 3 (3%). Thirty-eight (40%) were from Dar es Salaam and others were from 17 different regions in the country (Table 1). MDR-TB patients with history of cigarrete smoking were 5 (5%) and alcohol drinking were 19 (18%). HIV seropositive patients were 35 (37%), with median CD4 T lymphocytes count of 232 cells/µl (IQR 20-691). All MDR-TB/HIV positive patients were on ART (Table 1). The overall prevalence of malnutrition (BMI<18.5 kg/m^2) among MDR-TB patients prior to treatment was 51 (53%) while over nutrition (BMI>24.9 kg/m^2) was 5 (5%). MDR-TB pretreatment malnutrition graded as mild, moderate and severe was present in 15 (30%), 15 (30%) and 21 (40%), respectively.

Characteristic	Sub category	Measure
Gender (%n)	Male	62 (65)
	Female	34 (35)
HIV status (%n)	Positive	35 (37)
	Negative	59 (61)
	Unknown	2 (2)
CD4 Count (Median. IQR)	-	232 (20-691) cells/µl
Age Category years (%n)	<20	2 (2)

	20 – 39	52 (54)
	40 -59	39 (41)
	>60	3 (3)
Regional of referral/Domicile (%n)	Dar es Salaam	38 (40)
	Mwanza	8 (8)
	Kilimanjaro	7 (7)
	Mara	7 (7)
	Mtwara	6 (6)
	Arusha	6 (6)
	Others (Mbeya, Tanga, Lindi, Manyara, Kigoma, Morogoro, Musoma, Zanzibar, Bukoba, Dodoma, Ruvuma, Rukwa)	24 (25)
Cigarette smoking (%n)	Yes	5 (5)
	No	91 (95)
Alcohol drinking (%n)	Yes	19 (20)
	No	77 (80)

Table 1: Baseline characteristics of MDR-TB evaluated for nutrition status (N=96).

Possible demographic and clinical risk factors associated with malnutrition

In a univariate analysis (Table 2), BMI grades were similar between male and female (p=0.97). Males with severe and moderate malnutrition were 13 (21%) and 11 (18%) while females were 8 (24%) and 4 (12%) respectively. Likewise BMI grades were similarly across different age groups (p=0.58). Among cases with severe malnutrition, 12 (57%) and 8 (38%) were clustered in the age group of 20-39 and 40-59 years respectively while rarely 1 (5%) above 60 years. Similarly all cases of moderate malnutrition, 10 (67%) and 5 (33%) were between the age group of 20-39 and 40-59 years correspondingly. Even though Dar es Salaam contributed 38 (40%) of MDR-TB patients, distribution of different BMI grades was not predicted by the domicile region (p=0.46). Importantly, HIV status also did not predict the distribution of BMI grades (p=0.7). Unexpectedly, a higher number of patients with MDR-TB but without HIV co-infection had more advanced malnutrition than HIV co-infected cases. MDR-TB/HIV-coinfection among severe malnutrition was 5 (24%) compared with 16 (76%) without HIV-coinfection. Similarly, among cases with moderate malnutrition and MDR-TB/HIV-coinfection was 6 (40%) while without HIV coinfection was 9 (60%). Stratification of HIV-infected patients by CD4 count also did not reveal any further association with degree of malnutrition (p=0.41). BMI grades were not predicted by previous alcohol consumption (p=0.12). Among MDR-TB cases with severe and moderate malnutrition 6 (29%) and 6 (40%) respectively reported to consume alcohol prior to start of treatment. Untypically, 20 (95%) and 11 (73%) among those with severe and moderate malnutrition respectively did not smoke cigarrete previously and were more prone to malnutrition (p=0.004).

Trends of nutrition status during treatment of MDR-TB measured by BMI

Further analysis stratified MDR-TB patients with a BMI increase or decrease at different time points following treatment initiation. Thirty-seven (39%) of MDR-TB patients had improved grades (e.g. Improving from moderate to mild malnutrition) and gained a mean BMI of 2 kg/m^2 (95%; 1-3) while 9 (9%) deteriorated grades and thus developed acute adult malnutrition during treatment. In those with deteriorating grades, the mean lost BMI was 3 kg/m^2 (95%; 0.3 - 8). Fifty (52%) patients had no change in nutrition grade.

Patients with no change in BMI grades had a mean duration of admission of 68 days (95%; 56-80). While those with BMI grades that improved or worsened, the mean duration of admission was 87 days (95%; 73-101) and 94 days (95%; 55-134) respectively. BMI grades improve or no improve including worsening was predicted by duration of admission thus days of treatment (p=0.05).

Of interest, MDR-TB cases that received treatment for at least 4 months, 9 (9%) had malnutrition while those treated for 2-4 months 18 (19%) were malnourished. Analogously, malnutrition was distributed throughout regardless of the duration of stay at the hospital (p=0.08) (Table 2). However, gender (p=0.41), age (p=0.45), HIV status (p=0.84), CD4+ T lymphocytes count among HIV positive (p=0.15), previous alcohol consumption (p=0.12) or cigarette smoking (p=0.15) did not influence change of BMI grades during treatment.

Characteristics		Classification of nutrition status according to the body mass index (BMI)				
		Normal nutrition/Overweight (Normal BMI)	Under Nutrition (Low BMI)			p –value
			Mild Malnutrition	Moderate Malnutrition	Severe Malnutrition	
Gender	Male	28 (45)	10 (16)	11 (18)	13 (21)	0.97 (χ^2=0.87)
	Female	17 (50)	5 (14)	4 (12)	8 (24)	
HIV status*	Positive	19 (55)	5 (14)	6 (17)	5 (14)	0.71 (χ^2=7.2)
	Negative	25 (42)	9 (15)	9 (15)	16 (28)	
CD4 Count (cells/ul)**	<100	4 (100)	0 (0)	0 (0)	0 (0)	0.37 (χ^2=8.7)
	100 – 200	3 (37)	1 (13)	2 (25)	2 (25)	
	>200	9 (50)	4 (22)	2 (11)	3 (17)	
Days of hospital stay	2 months or less	27 (57)	10 (21)	6 (13)	4 (9)	0.08 (χ^2=10.5)
	>2-4 months	14 (44)	11 (34)	7 (22)	0 (0)	
	>4 months	8(47)	5 (29)	2(12)	2(12)	

*2 MDR-TB patients had unknown HIV status

**8 of MDR-TB patients had missing CD4 count results

Table 2: Comparison of BMI according to different characteristics.

Discussion

In this study, we found that half of cases receiving MDR-TB treatment at a referral hospital in Tanzania had malnutrition, of which 22% had severe forms of malnutrition (BMI<16 kg/m^2). This is a major finding, often neglected in TB programs, but is remarkably similar with the other few reports from MDR-TB treatment settings [11,23]. Unexpectedly, approximately 9% of MDR-TB developed acute malnutrition during treatment. The development of malnutrition appeared to relate to duration of stay in the hospital, however did not related with other pretreatment modifiable characteristics. Hence, a special consideration to increased frequency of monitoring for nutrition status and interventions for dietary support may be needed in this vulnerable population.

The same prepared food was given to MDR-TB patients with both normal nutrition and malnutrition status. Whether alteration of diet to include prescribed nutrition supplement could impact treatment outcome remains to be rigorously studied. Yet our findings support such study particularly in light of another report that found MDR-TB patients with malnutrition had more adverse drug reactions [11]. Others have reported TB patients to have a lower intestinal area of absorption compared to healthy controls and malabsorption was more pronounced for cases with MDR-TB [24]. Such malabsorption may explain poor concentrations of anti-TB drugs, a situation we have described in MDR-TB patients in Tanzania [25], and may be partially responsible for earlier increased mortality in MDR-TB patients with severe malnutrition [26].

Demographic or clinical factors like gender, age, alcohol consumption and HIV sero-status did not influence the pre-treatment nutrition status of patients or change of nutrition status during treatment. While HIV alone can be a major cause of wasting, we suspect the use of ART in all patients studied had a protective influence. This explanation is supported by the observation that none of the HIV positive MDR-TB patients with CD4 T lymphocytes>200 cells/μl had severe malnutrition. Limiting the interpretation of this lack of association with clinical characteristics, daily quantification of the food intake per patient was not performed and thus we are not sure if all patients ate what they were provided.

Loss of appetite due to prolonged exposure to second-line anti-TB medication might have also predisposed to persistence of severe malnutrition in cases that stayed for>4 month of treatment or development of acute malnutrition in others [17]. However, MDR-TB cases not gaining weight during the course of treatment could also signify MDR-TB treatment failure. Further evaluation of second-line anti-TB drug susceptibility testing could have also been performed to exclude bacteriological failures [27].

Monitoring of weight at least monthly has been proposed as the standard of care for MDR-TB programmes [28]. As BMI monitoring can be used to guide a nutritional management plan and make weight-based medication dose adjustments, we promote at least this monthly BMI assessment, but our data suggest the need for an even more intensive frequency in our setting.

For those cases with baseline moderate and severe malnutrition or without weight gain during treatment, a specialized diet must be considered and is currently inaccessible for national TB programmes such as in Tanzania. Recommended special food products include homemade F 75 (mixture of 300 ml full cream of cows milk, 100 g of

sugar, 20 g of oil, vitamin and mineral supplements with water to achieve 1000 ml). Another option, "plumpy nut," is patented French mixture of 500 Kcal containing peanut paste, vegetable oil, powdered milk, powdered sugar, mineral and vitamins.

For those cases with moderate and severe malnutrition but also significant vomiting or diarrhea, intravenous supplements of electrolytes, fluids, amino acid and fatty acid may be needed [29]. The latter two ingredients are limited in supply in many TB endemic settings. Food support strategies have been advocated to enhance adherence to TB treatment and to improve overall treatment outcomes [30]. We support such an approach but acknowledge the necessity to involve other stakeholders from government and non-governmental organizations.

Despite the degree of malnutrition observed, we suspect the food provided by the hospital, though not consistently balanced, may have contributed to the improvement of nutrition status in some patients. Therefore, comprehensive strategies to optimize MDR-TB treatment must be evaluated carefully, and in a prospective manner. Such an approach is increasingly important given the current plan to scale up ambulatory MDR-TB treatment in Tanzania, which undoubtedly will mean a wider variation in food availability and access.

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