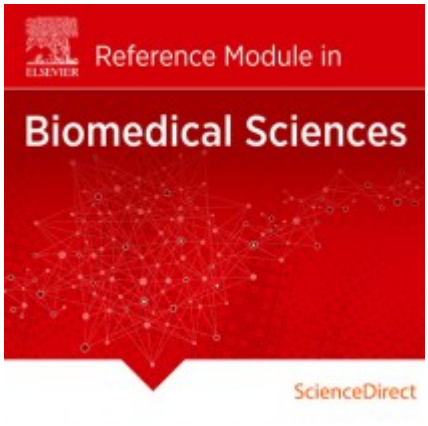

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Tuberculosis: Nutritional Management☆

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Glossary

Antimicrobial drug resistance The inability of a drug to kill or slow the growth of a microbe due to genetic mutations in the microbe.

Bacillary load The amount of disease causing bacteria found within a medium (i.e. sputum) usually associated with severity of disease.

Multi-drug resistant (MDR) TB Drug resistant TB that is resistant to at least rifampin and isoniazid.

Protein-energy malnutrition (PEM) A potentially fatal body-depletion disorder of which there is inadequate protein intake.

Tuberculosis (TB) An infectious disease caused by *Mycobacterium tuberculosis* which usually affects the lungs, but can be found elsewhere (extrapulmonary disease).

Globally, an estimated 2 million tuberculosis (TB) deaths and 9 million new TB cases occur each year, while an estimated 16 million people are living with TB. One-third of the world's population may be latently infected with *Mycobacterium tuberculosis* and at risk for reactivation TB. Before the advent of specific anti-TB drugs, nutritional support was a mainstay of the treatment of TB. Highly effective anti-TB drugs were first developed in the 1940s and 1950s. In the 1970s, the combination of isoniazid, rifampin, and pyrazinamide enabled the duration of treatment to be shortened to 6–9 months. However, TB staged a dramatic comeback in the late 20th century in both affluent and developing countries, especially in countries of the former Soviet Bloc and in countries with a high prevalence of HIV infection in sub-Saharan Africa and parts of Southeast Asia. Today, TB is the leading cause of death among persons with HIV infection, one of the top five leading infectious cause of death, and one of the leading causes of maternal mortality worldwide.

TB patients may be difficult to cure for many reasons, including antimicrobial drug resistance, drug toxicity and intolerance, advanced TB disease, and comorbidities such as HIV infection. Therefore, there is renewed interest in nutritional support in the management of TB.

Nutritional Status of Tuberculosis Patients

Undernutrition is an important risk factor for developing TB, and TB causes anorexia, weight loss and cachexia. Weight loss can be severe. Compared to healthy individuals, TB patients have significantly lower body mass index (BMI), skin fold thickness, limb circumference, and overall proportion of body fat. In the United States, weight loss was present at diagnosis in 45% of patients. In Tanzania, among 200 consecutive adults with sputum smear-positive pulmonary TB, 77% of males and 58% of females had a BMI < 18.5 kg m^{-2}, while 20% had a BMI < 16 kg m^{-2}. In Malawi, TB patients were substantially weaker than controls as measured by hand-grip dynamometry, suggesting loss of skeletal muscle protein. In addition, these patients had 35% lower fat mass and 19% lower lean body mass than the control group. More extensive TB disease and longer duration of symptoms were associated with lower BMI. BMI among Asian TB patients living in the United Kingdom (UK) (19.3 kg m^{-2}) was lower than controls (22.2 kg m^{-2}), skin fold thickness was 13% lower, and arm muscle circumference was 20% lower. Patients with concurrent HIV infection tend to be even more malnourished.

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Weight loss and wasting in TB may result from the production of tumor necrosis factor-alpha (TNF-α) and other pro-inflammatory cytokines that play a critical in protection against TB. In experimental mycobacterial infections, TNF-α is required for the control of bacillary growth and the protective granulomatous response. Patients receiving anti-TNF-α monoclonal antibodies for the treatment of rheumatoid arthritis and other autoimmune diseases develop reactivation TB at much higher rates than comparable patients not receiving TNF blockers.

Protein utilization may be altered by the cytokine milieu. Studies in the UK documented that TB patients had significantly lower serum albumin levels than controls (mean, 37 g L^{-1} vs. 46 g L^{-1}), suggesting protein undernutrition and/or a systemic inflammatory response. Anabolic pathways may be functionally blocked due to preferential oxidation of ingested amino acids for energy rather than for protein synthesis, contributing to wasting despite nutritional support.

At the same time, protein–energy malnutrition (PEM) rarely occurs without micronutrient deficiencies as well. TB patients have been found to be deficient in vitamins A, B6, and D as well as zinc, copper, iron, and selenium, although serum levels of fat soluble vitamins A, carotene, and D,and certain micronutrients like zinc, iron, and selenium also fall while serum copper levels rise with systemic inflammation. In Ecuador, Koyanagi et al. observed that TB patients had significantly lower serum concentrations of zinc, retinol and selenium. More than 800 TB patients in Malawi demonstrated deficiencies in circulating selenium, carotenoids and vitamin A. These deficiencies were exacerbated in the most severely wasted group (BMI < 16). There were no significant differences between the HIV-infected and HIV-uninfected TB patients. Low plasma selenium levels were associated with anemia.

In a study of 155 Ethiopian TB patients, HIV co-infection was associated with lower serum zinc and selenium concentrations and an elevated copper/zinc ratio compared with HIV-negative TB patients. After the intensive phase of antibiotic therapy, serum levels of both selenium and zinc improved in both patient groups. Another study in Ethiopia reported serum concentrations of vitamins C, E and A were significantly lower in TB patients than in healthy controls. High malondialdehyde concentrations, an indicator of overall oxidant stress, were associated with increased clinical severity of TB, and these parameters were exacerbated in HIV co-infected individuals.

Wiid and coworkers observed significantly lower total antioxidant status (TAS) in TB patients compared with community controls, and TAS values increased during anti-mycobacterial chemotherapy. Similar results were seen with vitamin A and zinc levels, but not with vitamin E. The vitamin A status of 100 TB patients was studied in Tanzania before and after the intensive phase of anti-TB therapy. Vitamin A levels were low in TB patients and improved with therapy in HIV-negative, but not in HIV infected patients. HIV infection was also associated with low vitamin A status in otherwise asymptomatic controls.

Ramachandran et al. observed low serum vitamin A levels in 47 newly-diagnosed TB patients compared with household contacts and healthy controls. Their vitamin A status improved significantly following anti-TB therapy without the need for vitamin A supplementation. Pediatric TB patients in India had markedly reduced levels of plasma zinc, irrespective of their general nutritional status, and there was significant improvement after six months of anti-TB therapy. Turkish investigators also observed a significant improvement in serum zinc (which increased) and copper/zinc ratios (which decreased) after two months of anti-TB therapy in adult patients.

Vitamin D is linked with TB because of its importance as a macrophage-activating hormone. Vitamin D receptor genetic polymorphisms are associated with vitamin D deficiency and increased incidence of TB. TB patients of Asian and African origin in the UK were significantly vitamin D deficient. Studies in India and Africa also found vitamin D deficiency associated with receptor polymorphisms in TB patients. Recently, in vitro studies of human macrophages have revealed mechanisms that may explain the link between vitamin D deficiency and TB. Vitamin D is critical for induction of innate macrophage functions via Toll-like receptor ligation of mycobacterial cell surface molecules, mycobacteria-specific activation of T lymphocytes by infected macrophages, and fusion of phagosomes containing mycobacteria with lysosomes within infected macrophages.

Effect of Nutritional Factors on the Course of TB

In one study of nearly 1200 TB patients followed prospectively, 10.9% of patients with moderate to severe malnutrition died in the first 4 weeks compared with 6.5% of the patients with normal nutritional status or mild malnutrition. Another study found that TB patients with a body mass index <17.0 kg m^{-2} were at increased risk of early death. In children, weight for age is an important indicator of prognosis. In other words, malnutrition correlates strongly with disease severity. The severity of malnutrition is an important indicator of the progress of the disease, and normalization of body weight in response to treatment is a positive sign.

Among patients with multi-drug resistant (MDR) TB in Latvia, Leimane and colleagues reported worse outcomes of chemotherapy if patients had a BMI < 18.5 kg m^{-2}, independent of other factors. Although low BMI may be a sign of worse disease, these authors controlled for disease severity by multivariable logistic regression. Chemotherapy is less effective in MDR-TB, and the impact of nutritional deficits may be more pronounced.

Low serum albumin, anemia, weight loss, and lack of weight gain were associated with the severity and clinical course of TB. Among 373 patients hospitalized for TB in Ecuador, hypoalbuminemia increased the odds of in-hospital death >3-fold, controlling for HIV infection and other co-morbidities. In the U.S., Khan and coworkers demonstrated that TB patients who were underweight at diagnosis had a fourfold increased risk of relapse within two years after completing treatment, and patients who did not gain weight had a twofold increase in risk of relapse.

Controlled Intervention Studies of Nutritional Supplements in the Management of TB

Historically, the use of cod-liver oil for the treatment of TB was the taproot from which grew the broader field of nutritional management of TB. In 18th and 19th century Europe, TB was responsible for 25% of adult deaths. Survival after diagnosis was approximately two years. Treatment for TB was revolutionized by the use of cod-liver oil which had been used for its medicinal properties. Treating TB patients with cod-liver oil in the 18th century resulted in weight gain and increased survival rates from 2 to 8 years. In the early 20th Century, one U.S. study reported that TB patients treated with cod-liver oil gained weight and only 10% died in contrast with weight loss and 70% mortality in the comparison group during approximately 1 year of observation. Cod-liver oil contains vitamins A and D which are important in host defense against TB.

With the advent of highly effective anti-TB drugs in the 1940s and 1950s, interest in cod-liver oil and other nutritional interventions waned. An influential clinical trial was carried out in Madras, India, in the 1950s to compare sanatorium treatment with outpatient treatment with regard to nutritional influences on treatment outcome. Patients treated in the sanatorium had substantially better diets and gained more weight than home-treated patients. Improvement was slightly faster in the sanatorium treated group, but the outcomes were nearly the same in the two groups after 12 months after controlling for baseline differences in disease severity. Chemotherapy was so effective that any modest effects of nutritional support apparently were overshadowed.

Chemotherapy is less effective in MDR TB and HIV-associated TB, renewing interest in nutritional interventions. In the past decade, trials of nutritional intervention during chemotherapy of TB patients have shown modest to no benefits. Eighty Indonesian TB patients with low BMI, low plasma retinol, and low plasma zinc were treated with a retinol and zinc supplement versus placebo in addition to standard anti-TB drugs. Sputum conversion, radiographic improvement, and increased plasma retinol levels were observed in the treated group after six months of therapy. Two weeks post-therapy, the percentage of patients with negative sputum smears was significantly higher ($p < 0.01$) in the micronutrient-treated group (23%) compared with the placebo group (13%). Lesion area was significantly reduced in the treated group after two months of therapy ($p < 0.01$). Plasma retinol concentrations were correlated inversely with reduction in mean lesion size at six months ($r = -0.367$; $p = 0.02$).

A much larger randomized control trial (RCT) in Tanzania examined the effect on treatment of supplemental zinc alone, multiple micronutrients (MMN: vitamins A, B, C, D, E and minerals Se, Cu), MMN + zinc, or a placebo. Approximately 43% of each group was HIV-infected, and all received standard anti-TB chemotherapy. After eight weeks of therapy, neither supplement had a significant effect on sputum culture positivity; however, patients receiving the MMN experienced a significant improvement in body weight. HIV status had no influence on the outcome. On the other hand, after eight months of therapy, the MMN + zinc group had significantly reduced mortality (RR = 0.29; 95% confidence interval 0.10–0.80), but only in the TB-HIV co-infected patients.

Several RCTs have examined the impact of supplemental zinc, iron or vitamin D on the outcome of chemotherapy in TB patients. 66 HIV-infected TB patients in Singapore who were receiving antiretroviral and anti-TB therapies were assigned to 28 days of oral zinc sulfate supplements or placebo. Zinc supplements had no effects on PPD-stimulated IFNγ production; however, nearly all (94%) of the subjects had normal plasma zinc levels at baseline. In the second study, 117 anemic, adult male TB patients in India were enrolled in an RCT of iron supplementation during the first two months of conventional anti-TB therapy. During six months of follow up, hematological status improved as the TB disease improved, but supplemental iron had no additional benefit as determined by the extent of radiographic abnormalities. In Egypt, 24 newly diagnosed pediatric TB patients were enrolled in an RCT to examine the effect of vitamin D supplementation (1000 IU/day for eight weeks) on the outcome of anti-TB therapy. Most of the children were vitamin D-deficient at baseline and serum levels of 1,25 (OH)2D3 improved in both groups during chemotherapy, but, supplementation did not affect this parameter. The supplemented group showed significant radiological and clinical improvement at follow-up with significantly increased body weights (3.3 kg) compared with the placebo group (2.2 kg) ($p < 0.05$). Two recent randomized placebo-controlled trails have examined the effect of vitamin D supplementation on TB treatment outcomes, one in India and one in the Republic of Georgia. The primary outcome measured was the rate of Mtb clearance from sputum samples. Although the serum 25(OH)D levels increased to normal among those with baseline vitamin D deficiency, sustained throughout the study, there were no significant difference in the mean to sputum culture conversion between the placebo and vitamin D groups in both studies.

Hanekom et al. conducted a RCT of vitamin A supplementation in 85 South African children with TB who were not co-infected with HIV. Children were given either 200,000 IU of retinyl palmitate or placebo on day 0 and day 1 and then followed up during three months of conventional anti-TB therapy. Nearly two-thirds of the patients were vitamin A-deficient at the beginning of the study, and the deficiency was more pronounced in children with extra-pulmonary disease. Vitamin A status improved in both groups, but supplementation had no significant effect on treatment outcome. Vitamin A supplementation was associated with significant decreases in a plasma protein biomarker of a Th2-type cytokine response which may indicate that vitamin A supplementation promoted a protective Th1-type 1 cytokine profile.

Inducible nitric oxide (NO) is a critical proximal mediator of anti-mycobacterial resistance in rodent models of TB, while its role in human TB remains controversial. Arginine is the substrate for inducible nitric oxide synthase, the enzyme that produces NO in macrophages. An RCT of oral arginine supplementation (1 g/day) was conducted in 120 HIV-infected and HIV–uninfected Ethiopian TB patients for four weeks along with standard anti-TB therapy. At eight weeks, arginine supplementation resulted in significant improvement in serum arginine levels, weight gain, sputum conversion, and reduction of symptoms compared with the placebo group, but these benefits were observed only in HIV-negative patients. No treatment effect was observed in HIV co-infected patients.

In a small RCT in Mexico City, investigators compared the clinical responses of 10 TB patients who received a cholesterol-rich diet (800 mg/day) with 11 TB patients who consumed a control diet (250 mg/day) during the first 8 weeks of standard anti-TB chemotherapy. Respiratory symptoms improved in both groups: however, culture-negative sputum at two weeks was more frequent in patients consuming a high-cholesterol diet (91%) compared to the placebo group (20%) ($p < 0.002$). The bacillary load in sputum was much lower in the cholesterol-supplemented patients (0.05 colony forming units [cfu]) than in the placebo patients (3.4 cfu) ($p < 0.0002$). The cholesterol content of macrophage vesicle membranes (i.e. phagosomes, lysosomes) has been shown to affect the ability of the phagocytes to suppress intracellular growth of mycobacteria.

Nutritional Management of TB

The goal of nutritional interventions is to (1) compensate for the elevated resting energy expenditure and catabolic state associated with TB, (2) support the extensive cellular proliferation and protein production associated with anti-mycobacterial immune responses, (3) allow repair of diseased tissues, and (4) replenish somatic reserves. Supplementation with specific nutrients (e.g. vitamin A, vitamin D, zinc) may be required to correct specific deficiencies. The research reviewed above provides limited support for the use of dietary supplementation with specific macro- and micronutrients for their beneficial impact on both nutritional status and treatment outcomes in TB.

While this article is not intended to offer specific recommendations for medical practice, some general guidelines are discussed. The expertise of clinical nutritionists and dieticians should be sought in managing TB patients with complex nutritional requirements. In the absence of such expertise, reference works focusing on the nutritional management of patients with infectious diseases should be consulted.

Careful assessment of nutritional status is the starting point, including the medical history and physical examination, anthropometric data, dietary information, as well as laboratory tests. Nutritional interventions to correct specific nutrient deficiencies can be based on this assessment.

The medical history and physical examination should include questions to identify unintentional weight loss which is associated with poorer treatment outcomes, higher risk of relapse, and increased mortality. Anorexia, abdominal discomfort, nausea, vomiting, and diarrhea will affect nutritional status and nutritional support. Co-morbidities that have nutritional implications such as diabetes mellitus, hepatitis, alcohol abuse, and HIV infection should be identified. Fever affects resting energy expenditure and caloric requirements. The expert clinician's subjective global assessment is one of the critical aspects of evaluating nutritional status. The clinical manifestations of specific nutrient deficiencies have been described in many other reference works to which the interested reader is referred. Peripheral neuropathy deserves special mention because it is a common side effect of isoniazid, one of the primary anti-TB drugs (see below), and vitamin B6 supplements are routinely prescribed with anti-TB treatment to prevent peripheral neuropathy.

Anthropometric data should include weight and height in relation to age, sex, and reference standards. BMI can be calculated to determine the overall macronutrient deficit. Skin fold thicknesses, linear and circumferential measurements of specific body parts, and bioelectric impedance may help categorize the nutritional deficit as involving energy, protein, or essential fats.

A dietary survey should include questions regarding recent patterns and quantities of food consumption pre- and post-illness (e.g., food availability and intake, dietary restrictions, preferences). Standardized tools include 24 h diet recall, 72 h food diaries, and food frequency questionnaires used in clinical and epidemiological research, but they also may be useful in patient care. The information is translated into nutrient intakes based on the known composition of foods and estimates of the quantities consumed. Dietary information should include specific requirements and restrictions based on age, co-existing medical conditions, cultural and religious practices, personal preferences, food allergies, and intolerance of certain foods. Dietary assessment will set specific boundaries around possible dietary recommendations and, the availability and cost of foods and nutritional supplements will affect these boundaries.

Basic hematology and biochemistry laboratory tests can be supplemented as indicated by the history, clinical examination, and abnormalities identified in these basic tests. Anemia is common in inflammatory conditions such as TB. However, anemia may also result from deficiencies of iron, folate, or vitamin B12. Apart from anemia, serum albumin level may be the most important predictor of nutritional risk for poor outcomes associated with TB. Since albumin is synthesized in the liver with a half-life of 21 days, hypoalbuminemia may reflect inadequate protein intake over a period of weeks or longer, although hypoalbuminemia is also a marker of systemic inflammation which is minimally effected by nutritional support until the inflammatory response remits.

Nutritional support of the TB patients should include a varied diet containing ~50% of calories from carbohydrates, 20–30% from proteins (with an emphasis on high quality proteins), and 20–30% from fats. Energy requirements start at a basal level of approximately 30 kcal kg^{-1} body mass, increasing to 40 kcal kg^{-1} or more for persons with significant deficits or with increased resting energy expenditure (e.g., fever). Respiratory function may be modestly or severely compromised, including both oxygenation and ventilation, in TB. As an energy source, dietary carbohydrates generate 20% more carbon dioxide than proteins and 30% more than fats. Thus, for patients who are short of breath, hypercapnic, or lack adequate ventilation, fats and proteins may be preferred dietary sources of energy. This is generally only a problem when the carbohydrate content of the diet exceeds the energy expenditure where the RQ can exceed 1.0 and substantially increase CO_2 production. Inflammation drives the, utilization of both endogenous and exogenous proteins for energy due to hepatic gluconeogenesis and an anabolic block in protein synthesis created by the immune cell cytokines. Protein requirements may be as high as 1.5 g kg^{-1} body mass/day. TB patients who are acutely ill,

have advanced disease, or substantially compromised nutritional status, and whose dietary intake has been inadequate for an extended period of time may benefit from a gradual increase in dietary macronutrients up to the recommended amounts. Overfeeding is not recommended. Omega-3 polyunsaturated fatty acids in the diet have anti-inflammatory and immunomodulatory effects, including increased susceptibility to TB in guinea pigs and mice, while dietary omega-6 polyunsaturated fatty acids have pro-inflammatory qualities, either of which may prove to be undesirable in the management of TB. The effects of different fatty acids on the nutritional management of TB remain to be established. A multivitamin and mineral supplement is recommended to ensure the availability of micronutrients. Higher doses of individual components to treat specific micronutrient deficiencies should follow guidelines established for the treatment of those conditions. Otherwise, doses of vitamins and minerals above those demonstrated to be safe and beneficial are not recommended.

Iron deficiency and iron replacement also merits special mention. Increased severity of TB has been observed in individuals with hemochromatosis, an iron overload syndrome, and in indigenous societies with high levels of iron intake from drinking a type of traditional beer fermented in iron vessels. Moreover, epidemics of malaria have been reported during refeeding programs in refugee and famine situations, related to the increased availability of iron for the parasite from supplements provided for the treatment of iron deficiency. *M. tuberculosis* acquires iron by means of highly developed scavenging mechanisms that must out-compete the host's iron-binding proteins (e.g. lactoferrin, transferrin). Iron deficiency is not necessarily more deleterious to the host than to the pathogen, and iron replacement therapy may benefit the microbe as well as the patient.

Nutrient-Drug Interactions

The standard treatment for all newly diagnosed patients with active, drug-susceptible TB includes four drugs, isoniazid, rifampin, pyrazinamide, and ethambutol, taken for two to three months followed by two of these drugs, isoniazid and rifampicin, taken for an additional 4 to 6 months. Isoniazid (INH) interferes with the metabolism of vitamin B6 which includes pyridoxine, pyridoxal, and pyridoxamine. Isoniazid combines with pyridoxal or pyridoxal phosphate to form potent inhibitors of pyridoxal kinase, thus, blocking formation of the coenzyme form of the vitamin. In the absence of vitamin B6 supplements, TB patients treated with INH may experience peripheral neuritis, manifested as tingling, numbness, or a painful "prickly" sensation in a stocking and glove distribution. Approximately 20% of patients treated with high doses of INH or patients who are otherwise predisposed to peripheral neuropathy (e.g., alcoholics, diabetes mellitus) will develop peripheral neuritis. Administration of 25 mg daily of vitamin B6 prevents peripheral neuritis in nearly all TB patients treated with INH.

Patients treated with cycloserine, an important second-line drug used in the treatment of MDR TB, should also receive vitamin B6 supplements in doses of 200 mg to 300 mg/day because of central nervous system side-effects (psychosis, depression) also related to pyridoxine metabolism.

Other anti-TB drugs that have adverse consequences on nutrition include para-aminosalicylic acid (PAS) and ethionamide, because these drugs commonly cause nausea, abdominal pain, anorexia, or vomiting. Such side effects will have a significant negative impact on the patient's nutritional status and well being.

Treatment of TB may induce other problems that affect nutritional status and nutrient intake. Three of the first line drugs, isoniazid, rifampicin, and pyrazinamide all carry a small risk of chemical hepatitis characterized by anorexia, nausea, vomiting and decreased nutrient intake. In its more severe forms, drug-induced hepatitis results in disturbances in carbohydrate, protein and lipid homeostasis that clearly impact the patient's metabolic and nutritional status. Although nutritional factors do not contribute to the cause, TB drug-induced hepatitis has many important consequences affecting nutritional status and nutrient intake.

Conclusions

Nutritional support is an important component of comprehensive care for persons with TB which must be adapted to each geographic region and socioeconomic context. Specific nutritional recommendations should be adapted to each patient depending on their clinical condition, nutritional status, and the practical possibilities of supplementation. Simplified, more generic approaches may be most suitable in some circumstances. These considerations notwithstanding, all TB patients should be offered nutritional/dietary advice based upon their nutritional status and accompanying diseases. While a specific, often costly diet that targets the individual nutritional needs of a TB patient may improve treatment outcome, it may be difficult to achieve this level of care in the absence of sufficient economic resources. However, we believe a deeper understanding of the essential role of nutrition in TB pathogenesis and treatment will help improve current TB treatment practices and improve outcomes of TB patients.

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