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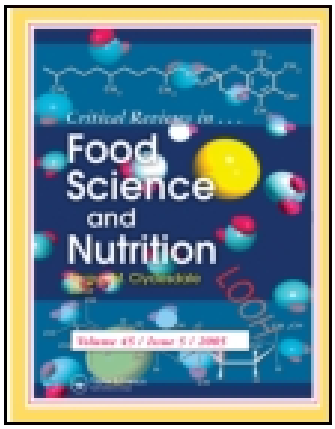

Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

Significance of Nutrition in Pulmonary Tuberculosis

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Accepted author version posted online: 20 Sep 2013.Published online: 28 Jan 2015.

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To cite this article: Surya Kant, Harshita Gupta & Savita Ahluwalia (2015) Significance of Nutrition in Pulmonary Tuberculosis, Critical Reviews in Food Science and Nutrition, 55:7, 955-963, DOI: 10.1080/10408398.2012.679500

To link to this article: http://dx.doi.org/10.1080/10408398.2012.679500

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Critical Reviews in Food Science and Nutrition, 55:955–963 (2015)
Copyright © Taylor and Francis Group, LLC
ISSN: 1040-8398 / 1549-7852 online
DOI: 10.1080/10408398.2012.679500

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Significance of Nutrition in Pulmonary Tuberculosis

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Malnutrition and tuberculosis are both problems mostly of the developing countries. Tuberculosis can lead to malnutrition and malnutrition may predispose to tuberculosis. Poor nutrition leads to protein–energy malnutrition and micronutrients deficiencies which lead to immunodeficiency. This secondary immunodeficiency increases the host's susceptibility to infection and hence increase the risk for developing tuberculosis. Tuberculosis itself leads to reduction in appetite, nutrient malabsorption, micronutrient malabsorption, and altered metabolism leading to wasting and poor nutritional status. Nutritional status and dietary intake and hence nutritional status of patients get improved during antituberculosis treatment.

Keywords Tuberculosis, micronutrients, malnutrition, immunodeficiency

INTRODUCTION

Tuberculosis (TB) is a global public health problem, responsible for more than 2 million deaths each year (WHO, 2003). The association between TB and malnutrition is well recognized; TB can lead to malnutrition and malnutrition may predispose to TB (Macallan, 1999). TB has been found to coexist with malnutrition among patients at the time of starting treatment in both developed and developing countries (Onwubalili, 1988; Zachariah et al., 2002).

Nutritional status is one of the most important determinants of resistance to infection. It is well established that nutritional deficiency is associated with impaired immune functions (Perronne, 1999). While malnutrition limits cell mediated immunity and increases susceptibility to infection, infection can lead to nutritional stress and weight loss, thereby weakening immune function and nutritional status (Chandra, 1990).

Generalized malnutrition evidences itself as low weight-for-height (thinness), and it is sometimes measured as low weight-for-age (underweight) or low height-for- age (stunting) in children. These conditions often co-exist with micronutrient deficiencies. Generalized malnutrition can cause significant impairment of several important mechanisms of immune protection, including phagocytic function, cell-mediated immunity, antibody concentration, and cytokine production and it may lead to TB (Africa's Health, 2008).

During drug treatment of active TB without supplementary nutrition, nutritional status usually improves. This is most likely for a variety of reasons including improved appetite and food intake, reduced energy/nutrient demands, and improved metabolic efficiency (Macallan, 1999). The lean tissue recovery through nutrition support with antituberculosis therapy (ATT) may help restore physical functioning earlier, shortening the convalescent period and allowing earlier return to productive work. Since poor nutrition in TB patients is related with mortality, a more rapid reversal of malnutrition may help to improve TB patient's survival (Paton et al., 2004). This review is the scientific literature on the role of nutrition in tuberculosis treatment outcome, summarize key findings, knowledge gaps, and intended to guide nutritionists with purpose to improve the nutritional management of active TB diseases.

IMPACT OF NUTRITIONAL STATUS ON RISK OF TUBERCULOSIS

It is well established that nutritional deficiency is associated with impaired immune functions (Perronne, 1999). Nutritional status determines normal health and functioning of all systems

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in the body, including the immune system that is responsible for host resistance to various infectious diseases (Cegielski and McMurray, 2004). Because cell-mediated immunity is the key host defence against TB and increase susceptibility to infection, malnutrition is therefore an important risk factor for the development of clinical TB (Cegielski and McMurray, 2004). Malnutrition may be an important factor in the high mortality and morbidity from tuberculosis in population subjected to food shortage (Rao and Gopalan, 1966).

It is important to consider how malnutrition can increase risk of tuberculosis. The host protective immune mechanism of infection with *Mycobacterium tuberculosis* depends critically on the interaction and cooperation between monocyte-macrophages and T-lymphocytes and their cytokines (Rook and Hernamndez-Pando, 1996). Substantial experimental proofs suggests that malnutrition can lead to secondary immunodeficiency that increases the host's susceptibility to disease. Increased risk of tuberculosis can result from alteration in the individual protective function of, or the interaction between T-lymphocytes and macrophages because of nutritional insult (Chan et al., 1997).

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CONSEQUENCES OF TUBERCULOSIS ON NUTRITIONAL STATUS

In active TB, catabolic processes leading to wasting usually begin before the patient is diagnosed; the basal 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 (Macallan et al., 1998). This combination of conditions resulting weight loss with ultimate wasting. Amino acids and protein synthesis utilization may be inhibited due to the presence of pro-inflammatory cytokines. Several nutritional parameters are worse among newly diagnosed TB patients compared to healthy controls:

A study conducted in Indonesia, the mean BMI of active TB patients has recently included for treatment was 20% lower than in controls. And 66% of patients had a BMI $<$18.5 (six times more frequent than in controls). In addition, weight, mid-upper arm circumference (MUAC), skin-fold thicknesses, fat mass, and fat free mass were all significantly lower in those with active TB (Karyadi et al., 2000). Another study in United Kingdom was found in patients with active TB, BMI, muscle mass, and subcutaneous fat stores were 13%, 13%, and 20% lower, respectively, compared with healthy age-, sex-, and ethnic-matched controls (Onwubalili, 1988). Wasting is associated with increased mortality in those with active TB. In a study of 1,181 newly diagnosed TB patients in rural Malawi, 57% were underweight (BMI $<$ 18.5), including 21% with BMI $<$ 16. A BMI $<$ 17.0, indicating moderate to severe malnutrition, was associated with a two-fold increased risk of early death (Zachariah et al., 2002).

EFFECT OF NUTRITIONAL STATUS ON RELAPSE RISK OF TB TREATMENT

Nutritional status may have an effect on relapse of active TB. Weight loss and nutritional depletion are often seen in patients with tuberculosis at the time of tuberculosis diagnosis (Onwubalili, 1988). Navy recruits, the risk of tuberculosis was nearly fourfold higher among men who were at least 10% underweight at baseline than in men who were at least 10% overweight (Edwards et al., 1971). Relapse risk was increased amongst those who were $\leq$90% of ideal body weight or had a BMI $\leq$ 18.5 at the time of diagnosis. In multivariate logistic regression, those patients who were underweight at diagnosis, weight gain of less than 5% between diagnosis and completion of the initiation phase of therapy was significantly associated with relapse. The relationship between changes in weight while receiving ATT and subsequent relapse risk has not been well studied. Additional studies are warranted to identify interventions to decrease risk of relapse in such patients (Khan et al., 2006).

MECHANISM OF ALTERED NUTRITION ON TUBERCULOSIS

For any infection, there is a complex interaction between the host response and the virulence of the organisms, which modulates the overall metabolic response and the degree and the pattern of tissue loss. In patients with tuberculosis, a reduction in appetite, nutrient malabsorption, micronutrient malabsorption, and altered metabolism leads to wasting (Macallan et al., 1998).

In a study, Indian patients with pulmonary tuberculosis were compared with malnourished and normally nourished healthy subjects. Whereas protein synthesis and breakdown in the fasting state were not significantly different between groups, patients with tuberculosis used a larger proportion of proteins from oral feeding for oxidation and hence for energy production than did either control group. Such failure to channel food protein into endogenous protein synthesis has been termed "Anabolic block." This anabolic block represents one of the mechanisms for wasting in tuberculosis and other inflammatory status (Macallan et al., 1998).

Nutrients can have direct actions on specific immune cells and pathways or affect many different types of cells (Cunningham-Rundles et al., 2005). The effect of malnutrition on clinical infection is to increase severity and morbidity (Norton et al., 2004). The mechanism of both cytokine production and activation capacity were impaired in malnourished children. Malnutrition is associated with impaired cytokine response to antigen (Rodríguez et al., 2005) and increase level of circulating proinflammatory cytokines (Dülger et al., 2002). The acute phase response to infection is blunted in malnutrition (Manary et al., 2004). Concurrent infection also complicates the evaluation of malnutrition since transient losses of micronutrients may mimic a true deficiency (Abraham et al., 2003). In infants, appear to have intrinsically weaker ability to produce

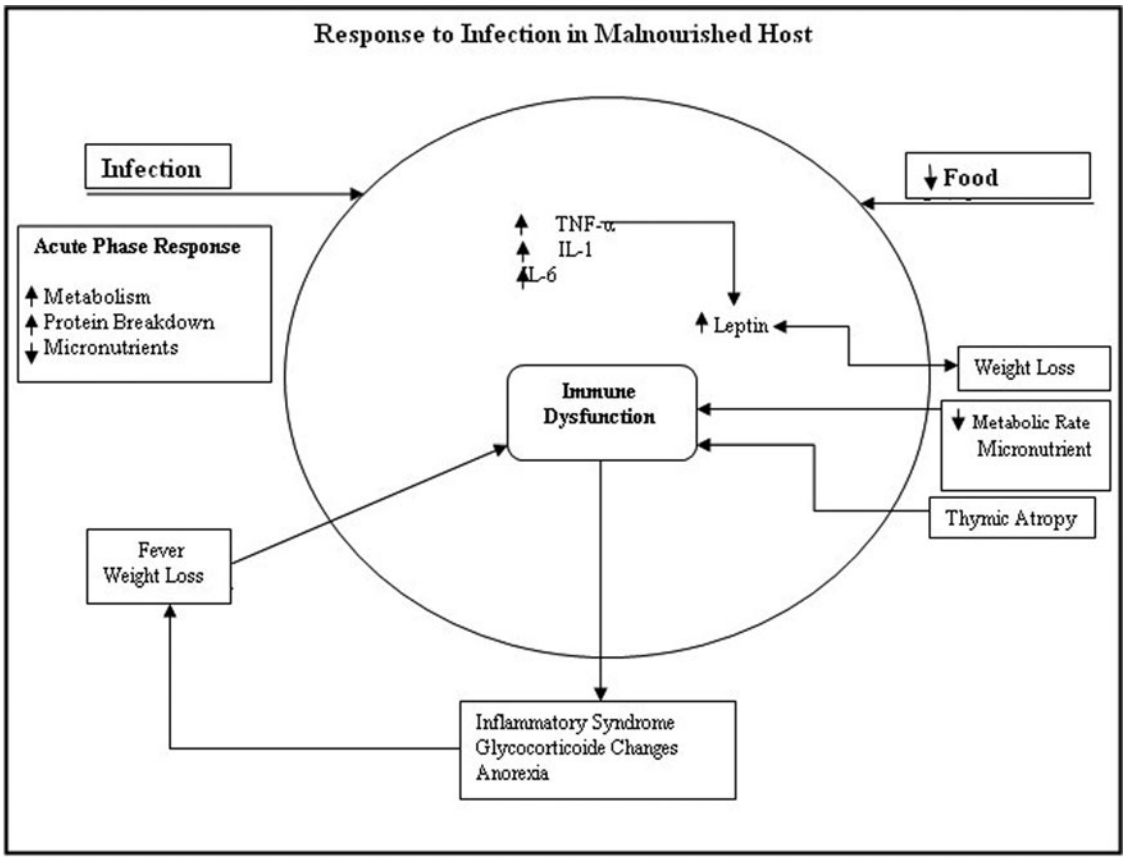

Figure 1 Illustrates some of the key interactions that lead to altered immune response in the malnourished host during infectious exposure.[82] IL = interleukin; TNF = tumor necrosis factor.

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compensatory anti-inflammatory response and therefore may be especially sensitive to the combination of infections and nutrient deficiency (Schultz et al., 2004). Some of the observed effects of malnutrition involve reactivation of opportunistic infection leading to altered activation of the acute phase response[82] as illustrated in Figure 1.

ASSOCIATION OF MICRONUTRIENTS WITH TUBERCULOSIS

Micronutrients have been accepted as essential element for optimum human health because of various metabolic characteristics and functions. Most frequent cause of secondary immunodeficiency is considered to be the micronutrients deficiency and morbidity due to infection including tuberculosis. Vitamins A, C, E, B6, and folic acid and minerals zinc, copper, selenium, and iron all have key roles in metabolic pathways, cellular function, and immune competence (Karyadi et al., 2000). The concentration of these may have a role in host defense against TB (Chandra, 1990). Deficiency of single or multiple nutrients can reduce an individual's resistance to any infection (Crowle and Ross, 1989).

VITAMIN A

Vitamin A has been shown an immunocompetent function in human tuberculosis. It inhibit multiplication of virulent bacilli in cultured human macrophages (Chandra, 1990). Vitamin A, which is usually assessed using serum retinol, also plays important roles in lymphocyte proliferation, generation of antibody responses, and maintenance of mucosal surfaces and epithelial function (Semba, 1998). Vitamin A is essential for normal functioning of T and B lymphocytes, macrophage activity, and generation of antibody response (Mugusi et al., 2003).

As predicted, because of the acute phase response, serum retinol levels are generally lower in patients with active TB, particularly those who are TB/HIV co-infected, and inclined to improve with ATT. A study in Tanzania revealed that after two months of TB treatment, mean vitamin A status improved in the HIV-negative TB patients with fewer classified as vitamin A deficient, but was slightly worse in the co-infected patients with a larger proportion deficient. HIV infection was the strongest predictor of low vitamin A at baseline and at two months (Ramachandran et al., 2004). Study in India observed low serum vitamin A concentration in tuberculosis patients returned to normal after six months of ATT without vitamin A supplementation (Roth et al., 2004).

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VITAMIN D

Susceptibility to TB and severity of active TB may be increased by vitamin D deficiency (Zittermann, 2003; Ustianowski et al., 2005). Vitamin D is required for macrophage activation, which is essential for keeping TB in the latent phase. In addition, vitamin D down-regulates the transcription of a substance that is needed for the intracellular survival of TB bacillus in macrophages, further containing the bacilli (Ustianowski et al., 2005; Wilkinson et al., 2000). Vitamin D deficiency allows the disease to progress to the active form.

Study was conducted among individuals from the Indian subcontinent after moving to the United Kingdom, the role of vitamin D in the TB disease process re-emerged with the increased incidence of active TB in the winter months. A high prevalence of vitamin D3 deficiency, with the lowest concentrations found in those with active TB among Gujarati Indians living in London and England (Grange et al., 1985). Low dietary intake of vitamin D combined with lack of exposure to sunshine are the main factors in vitamin D deficiency that contribute to the acquired susceptibility to active TB in this population (Grange et al., 1985). Adults with untreated tuberculosis in Indonesia were shown to have significantly lower 25-hydroxy-vitamin D compared with controls (Martineau et al., 2007).

Vitamin D supplementation appears to have a beneficial effect on the treatment of tuberculosis and appears to enhance immunity to tuberculosis, and vitamin D deficiency is a risk factor for tuberculosis (Panasiuk et al., 1991).

VITAMIN E

The levels of non-enzymic antioxidants such as vitamin E and reduced glutathione in plasma were significantly depleted in the pulmonary tuberculosis infected subjects. Many studies have been shown that the level of vitamin E in the blood was found considerably significantly lower in case of tuberculosis (Bakaev and Duntau, 2004).

VITAMIN C

Increased TB incidence was associated with low vitamin C intake and lower plasma vitamin C concentrations before drug treatment for active TB (Hemila et al., 1999). Vitamin C, together with vitamin E and glutathione, are important for pulmonary antioxidant defense (Visser and Texeira-Swiegelaar, 2004). Since the lung is exposed to many oxidizing chemicals during normal breathing, an inadequate concentration of vitamin C in the lung and blood can lead to an imbalance between antioxidants and oxidants. The levels of serum ascorbic acid in the TB patients were significantly lower than in the controls (Hemila et al., 1999). The presence of TB lung inflammation leads to decreases in serum ascorbic acid levels and that the reduced metabolites indicate a slowing metabolism of ascorbic acid in this population (Hemila et al., 1999).

Higher intakes of vitamin C were not associated with reduced risk of active TB when consumption of fruits, vegetables, and berries was fixed, suggesting that compounds in these foods other than vitamin C affect susceptibility to active TB. In fact, increased intakes of fruits, vegetables, and berries low in vitamin C content were associated with a reduced risk of TB (Visser and Texeira-Swiegelaar, 2004).

PYRIDOXINE (VITAMIN B_6)

After isoniazid (INH) treatment for active TB noted that patients treated with the drug developed peripheral neuropathy (symptoms include numbness, pain, and burning sensation in the feet), a wide-ranging condition referring to disorders of peripheral nerves that branch out from the spinal cord to all parts of the body. Pyridoxal phosphate (PLP) is a co-enzyme required for the synthesis of neurotransmitters. INH inhibits the phosphorylation of pyridoxine, which results in increased excretion of vitamin B6 (Iqbal and Mohammad, 2000).

Newly diagnosed pulmonary TB patients have suboptimal levels of plasma PLP when they are diagnosed, which worsens with INH treatment, and that routine pyridoxine supplementation is warranted (Iqbal and Mohammad, 2000).

CALCIUM

Calcium abnormalities have been found with pulmonary tuberculosis in various studies. Disturbance in calcium metabolism leading to variations in blood calcium concentration can cause a spectrum of clinical features (Harbener and Potts, 1989). Such patients may be asymptomatic or may have signs and symptoms, which can easily be attributed to primary disease if calcium abnormalities are not suspected.

Calcium abnormalities have been variedly reported in studies carried out on the subject. In a Swedish study hypercalcaemia was found in 25% of 67 patients of Pulm TB (Lind and Ljunghall, 1990). In United States 16–28% patients of Pulm TB have been found to be suffering from hypercalcaemia (Pruitt et al., 1995) though lower incidence of hypercalcaemia has also been reported from United States (Hournay et al., 1997). Hypercalcaemia was detected in 25% Greek patients (Roussos et al., 2001) and in 27.5% of the Malaysian patients (Liam et al., 1998) with pulmonary tuberculosis, with symptoms of hypercalcaemia present in only 5 and 12% of these patients, respectively (Koyanagi et al., 1998).

ZINC

Several studies have demonstrated that the serum levels of zinc decrease significantly during active tuberculosis and increase following recovery after introduction of antitubercular therapy and improvement of nutritional status (Karyadi et al.,

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2002). There was significant rise in zinc level at the end of six months of ATT. Zinc deficiency affects the host defenses in a variety of ways. It results in decreased phagocytosis and leads to a reduced number of circulating T-cells and reduced tuberculin reactivity, at least in animals (Brown and Chan, 1976).

During the intensive phase of ATT, the anti-tuberculosis drugs were used to kill the population of replicating bacilli and zinc may play important role in the macrophage contribution to host defenses at the site of infection (Brown and Chan, 1976). The other possible mechanisms could be the effect of anti-tuberculosis drugs on zinc absorption.

Zinc deficiency impairs the synthesis of retinal binding proteins and reduces plasma retinal concentration in humans and animals (Taylor and Bray, 1991). Therefore, it appears that zinc supplementation be a mandatory constituent for the treatment and has a beneficial effect on vitamin A metabolism that has important role in tuberculosis. An adequate supply of zinc may also limit free radical membrane damage during inflammation (Van Lettow et al., 2005).

IRON AND ANEMIA

Anemia is common in patients with pulmonary TB, and appears to be more common among TB/HIV co-infected patients. Suggested reasons for this include increased blood loss from hemoptysis (presence of blood in sputum for TB patients), bone marrow involvement (decreased red blood cell production), inadequate intake (poor appetite and food intake) resulting in poor micronutrient status, and anemia of chronic inflammation (decreased circulating iron with increased storage iron, making iron less available to microbes) (Lawn et al., 2000; Das et al., 2003).

A study conducted in Ghana, among adults with pulmonary tuberculosis had significantly lower hemoglobin than healthy matched controls. Iron deficiency may also be a contributing factor (Kassu et al., 2006). Study in Malawi reported that decreased concentrations of retinol, carotenoids, and selenium were associated with increasing degree of anemia. Selenium deficiency may contribute to anemia via increased oxidative stress (Das et al., 2003). Devi et al. conducted a study in India on mild to moderately anemic TB patients reported, iron supplementation accelerated the normal hematopoesis only in the initial phases of treatment, possibly because inflammation contributed towards anemia, and further improvement was dependent on the correction of the inflammatory process (Shor-Posner et al., 2002).

SELENIUM

Selenium is an essential part of antioxidative enzymes, such as glutathione peroxidase, which protects cells from oxidative damage (Kassu et al., 2006). It is an essential trace element has an important function in maintaining the immune processes and thus may have a vital role in clearance of mycobacteria. Selenium has been found in HIV positive patients as substantial factor in the relative risk for developing mycobacterial diseases (Reddy et al., 2004). In an recent Indian study evaluated concentrations of circulating antioxidants and markers of oxidative stress in tuberculosis patients. It was found that lower antioxidant potential (lower levels of superoxide dismutase, catalase, glutathione, and ascorbic acid) and enhanced lipid peroxidation products (malonaldehyde) in tuberculosis patients. Antioxidant potential increased with ATT treatment (Keusch, 1990).

COPPER

Serum ferritin and copper are "positive" acute phase reactants that increase when the immune system responds to an infection. Copper, zinc selenium, and iron plays a key role in metabolic pathway, cellular functions, and immune competence (Karyadi et al., 2000). The concentration of these may have a role in host defense against TB (Rao, 2009). A study concluded serum concentration of iron, zinc, copper were altered with infection while that of copper and copper/zinc ratio were significantly higher in tuberculosis patients compared with control group (Rao, 2009).

CHOLESTEROL

Epidemiologic analysis revealed a link between patients cholesterol levels and the outcome of pulmonary tuberculosis. Levels of serum cholesterol, high density lipoprotein (HDL), and low density lipoprotein (LDL) were found to be significantly lower in smear-positive group (Pervez-Guzman et al., 2005). In miliary tuberculosis cases, hypocholesterolemia is associated with mortality and common among tuberculosis patients. Another study concluded that higher serum cholesterol level correlated with reduced radiologic signs of disease and faster sputum sterilization following the initiation of chemotherapy (Pervez-Guzman et al., 2005; Deniz et al., 2007).

POLYUNSATURATED FATTY ACIDS

Omega-3 fatty acids may be associated with tuberculosis. A study was found in guinea pigs fed with omega-6 fatty acids and omega-3 fatty acids. Their eicosanoid synthesis was studied in their macrophages and results showed that supplementation through diet with n-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid can affect the resistance to *M. tuberculosis* but n-6 fatty acids does not (Zent and Smith, 1995).

DRUG NUTRIENT INTERACTION

Administration of antituberculosis drugs and concomitant feeding with food has been shown to result in decreased bioavailability of rifampicin and isoniazid (Rao and Gopalan, 1966). A well-known adverse effect of isoniazid on peripheral neuropathy usually preventable by an adequate intake of pyridoxine (vitamin B6). Though this is reported to be rare in patients receiving dosages of isoniazid of the order of 5 mg/kg, it is frequently found in subjects receiving higher doses (FANTA,

Table 1 TB antibacterial drugs: potential side effects and drug–nutrient interactions

TB Antibacterial Drugs			
Drug	Guidelines	Potential side-effects	Potential drug-nutrient interactions
Isoniazid	Take on empty stomach, 30 minutes before or 2 hours after meal Supplement with 10 mg vitamin B_6 daily	Increased requirements for pyridoxine, folate, niacin (vitamin B_3) and magnesium Hepatitis Constipation Anemia Fatigue	May decrease absorption of pyridoxine, calcium, vitamin D May react with bananas, beer, pickled fish, yeast, and yoghurt.
Rifampin	Take on empty stomach, 30 minutes before or 2 hours after meal Not to be taken with alcohol	GI irritation Anemia Jaundice Pancreatitis Altered taste Anorexia	May interfere with folate and vitamin B_{12}

Source: FANTA (2001).

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2001). Because of malnutrition among poor segments of population; isoniazid-induced peripheral neuropathy is frequently observed. Table 1 showed potential side effects and drug–nutrient interactions.

MICRONUTRIENTS STATUS AND TUBERCULOSIS TREATMENT OUTCOME

As anticipated, at the time of diagnosis active TB patients compared with healthy controls have lower blood concentrations of several micronutrients including retinol, vitamins C and E, hemoglobin, zinc, iron, and selenium. There are so many studies describing the relationship between micronutrients status and tuberculosis treatment outcome are summarized in Annexure 1.

Many studies have reported low concentrations of serum albumin (<35 g/L), an indicator of protein status, at the time of active TB diagnosis (Van Lettow et al., 2003). However, cytokines present during the acute phase response to active infection down-regulate serum albumin levels. A study also found a strong positive association between serum albumin at admission to hospital and in-hospital death due to tuberculosis and a greater risk of death in patients with serum albumin levels $\leq$ 2.7 gm/dL at the time of admission, even when adjusting for potentially confounding variables, such as age, presence of co-morbidities, HIV infection, and a history of default treatment (Matos and Moreira Lemos, 2006; Villamor et al., 2006). Low levels of albumin may reflect the presence of inflammation rather than a protein deficient state (Vijayamalini and Manoharan, 2004).

Study in India on lipid peroxidation and antioxidants found that Thiobarbituric acid reactive substances (TBARS), a marker of lipid peroxidation, was significantly increased in the TB patients compared with controls, while the plasma levels of vitamins C and E were significantly decreased (Madebo et al., 2003). The TB patients had significantly lower serum concentrations of vitamins C and E compared with controls, while malondialdehyde concentration, a measure of lipid peroxidation and oxidative stress, was significantly higher in the TB patients (Vijayamalini and Manoharan, 2004). A higher malondialdehyde concentration was also associated with poor Karnofsky physical performance scores, indicating increased clinical severity (Das et al., 2003).

NUTRITIONAL SUPPLEMENTATION FOR TUBERCULOSIS TREATMENT

Nutritional supplements can reduce the risk of recurrence and improve outcome during tuberculosis (TB) chemotherapy. Inclusion of supplements with nutritional counseling helps to increases energy intake which gives a significant increase in body weight, total lean mass, and physical function after six weeks when started during the initial phase of tuberculosis treatment. And 46% of the early weight gain constituted lean tissue because tuberculosis can mount a protein anabolic response on feeding. Patients from India were followed for six months supplementation of multiple micronutrients (elemental iron as ferrous fumarate, zinc, thiamine, riboflavin, pyridoxine, cyanocobalamine, ascorbic acid, and folic acid), found significant increases in BMI, iron status, and other hematological indices along with radiological and clinical improvement (Paton et al., 2004). Paton et al. conducted a nutritional support study in Singapore concluded that accelerating the recovery of lean tissue through nutrition support may help restore physical functioning earlier, shortening the convalescent period and allowing earlier return to productive work (Safaryan et al., 1990).

Micronutrient supplementation was associated with reduced rates of TB recurrence. Another study were showed improved immune response with vitamins C and E, were added as adjuvant to multi drug tuberculosis therapy (Karyadi et al., 2002). In addition to that, supplementation with vitamin A and zinc also improved the effectiveness of the antituberculosis drugs. The improved outcome was indicated by the higher number of patients with negative sputum for bacilli and significantly lower mean lesion area in the lungs (Villamor et al., 2008). Supplementation with micronutrients (5000 IU of retinol, 20 mg of vitamin B_1, 20 mg of vitamin B_2, 25 mg of vitamin B_6, 100 mg of niacin, 50 μg of vitamin B_{12}, 500 mg of vitamin C, 200 mg of vitamin

E, 0.8 mg of folic acid, and 100 μg of selenium) at multiples of the Recommended Dietary Allowances (RDA) reduced the incidence of TB recurrences among HIV-infected adults with TB who were not receiving antiretroviral treatment (Villamor et al., 2008). Among HIV-negative adults, micronutrients appeared to increase T-cell counts and reduced the incidence of complications. The impact of micronutrient supplementation on TB-related outcomes needs to be insured among HIV-infected patients receiving antiretroviral therapy (Villamor et al., 2008).

Supplementation of food may have a positive impact on quality of life, but there are no published studies that directly examine the impact of food supplementation on quality of life in TB. There is reason to believe that such support will provide direct benefits to adults and children infected with TB both during and following drug therapy (Duggan et al., 2003). The awareness of patients about their entitlement to food supplements could be further improved. Nutritious food is important both in the prevention of adverse reactions to the treatment regimen and in the interaction of TB and the immune system. Hence, food supplements are a valid option for the improvement of treatment outcomes in TB control programmes.

Annexure 1 Summary of studies investigating micronutrient status of patients with Pulmonary Tuberculosis

Nutrients	Subjects/study Design	Findings	Reference
Vitamin A India	47 TB patients 46 healthy household controls 30 health "normal" controls Longitudinal	81% of TB patients with marginal vitamin A status at baseline ↓ Mean vitamin A in TB patients versus household or normal controls ↑ Mean vitamin A in TB patients atsix months Limitation: no acute phase response control	Ramachandran et al., 2004;80
Vitamin A Rwanda	94 TB/HIV+ patients Cross-sectional	29% vitamin A deficient Limitation: no healthy control group, no acute phase response control	Rwangabwoba, 1998;98
Vitamin A, Vitamin C, Vitamin E, hematocrit, albumin Ethiopia	Pulmonary TB patients (100 HIV−, 25 HIV+) 45 Ethiopian healthy controls Cross-sectional	↓ Mean vitamin A, C and E, hematocrit, albumin in TB patients versus controls	Mabedo, 2003;68
Vitamin A, E, ferritin, hemoglobin, zinc, selenium Malawi	370 TB/HIV+ patients 130 TB/HIV− patients	↓ Mean hemoglobin in TB/HIV+ patients, ↑ Prevalence of anemia compared to TB/HIV- patients, ↑ Mean ferritin in TB/HIV+ patients compared to TB/HIV- patients, 59% of all deficient in vitamin A 12% of all deficient in vitamin E 80% of all deficient in zinc 88% of all deficient in selenium	Van Lettow et al., 2005;87
Vitamin A, hemoglobin, zinc, albumin Indonesia	41 TB patients 41 healthy controls Cross-sectional	↓ Mean vitamin A, hemoglobin, zinc, albumin in TB patients versus controls ↑ Prevalence of anemia, vitamin A and zinc deficiency in TB patients	Karyadi et al., 2000;15
Vitamin C, Vitamin E India	30 TB patients 30 healthy controls; Cross-sectional	↓ Mean vitamin C and E in TB patients versus controls	Vijayamalini and Manoharan, 2004;77
Vitamin D England	126 TB patients 116 healthy controls	26% prevalence vitamin D deficiency Vitamin D deficiency associated with active TB (OR 2.9; 95% CI 1.3-6.5)	Wilkinson et al., 2000;14
Iron Zimbabwe	98 TB patients (69 HIV+, 19 HIV−) 98 (15 HIV+, 83 HIV−) controls, matched for age and sex Longitudinal (seven to nine months)	↑ Mean ferritin and transferring saturation in TB patients comparedwith controls ↓ Mean hemoglobin in TB patients, lowest in TB/HIV+ patients ↑ Mean hemoglobin in all patients	Gangaidzo, 2001;89
Copper, zinc, selenium, iron Ethiopia	155 TB patients (74 HIV+, 81 HIV−) 31 healthy controls Longitudinal	↑ Mean copper in all TB patients compared with controls ↓ Mean zinc in TB/HIV+ patients compared to TB/HIV- and controls ↓ Mean selenium in TB/HIV+ patients compared to TB/HIV- and controls ↓ Mean iron in TB/HIV+ patients compared to controls After two mo of therapy, ↓ Mean copper, no change in selenium and iron, ↑ Mean zinc in TB/HIV− but no change in HIV+	Kassu et al., 2005;59

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CONCLUSION

Poor nutrition contributes protein-energy malnutrition and micronutrients deficiencies increase the risk of developing tuberculosis. In patients with tuberculosis, it leads to reduction in appetite, nutrient malabsorption, micronutrient malabsorption, and altered metabolism leading to wasting. Clinically severe patients with tuberculosis showed lower concentration of antioxidant vitamins-C, A, E, and minerals. Vitamin A deficiency increases bacterial adherence to respiratory epithelial cells and vitamin D deficiency appears to impair the body's ability to fight tuberculosis. Iron deficiency may also be a contributing factor. ATT kills the population of replicating bacilli and zinc may play important role in the macrophage contribution to host defenses at the site of infection. Nutritional status of patients improves during tuberculosis chemotherapy. Nutritional supplementation may represent a novel approach for fast recovery in tuberculosis patients. Low-cost interventions such as periodic nutritional assessment and counseling on diet, and nutritional management of symptoms and drug-side effects, may help TB patients to maintain or increase their food intake and adhere to TB medications which improve tuberculosis treatment outcome.

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