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Tuberculosis

Manual for Obstetricians & Gynecologists

SN Tripathy
(Mrs) SN Tripathy

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CHAPTER 4

Nutrition, Pregnancy and Tuberculosis

JAYPEE BROTHERS

INTRODUCTION

Nutrition is one of the most important environmental factors which influences health. The interaction between nutritional status on the one hand and infection on the other has been well documented. While malnutrition can predispose to a variety of diseases, repeated infection can cause malnutrition. In addition malnutrition can adversely alter the course and outcome of infectious diseases. The oral traditions of medicine and public health have it that, malnutrition is an important risk factor for the development of tuberculosis (TB). Malnutrition profoundly affects cell-mediated immunity (CMI), and CMI is the principal host defense against TB. It makes biological sense. Although most health professionals readily accept this principle, much of this belief is based on uncontrolled observations such as disaster situations or on backwards logic from the cachexia common among TB patients. In fact, the evidence in humans is surprisingly thin from the perspective of scientific rigor and few data, if any, quantify the extent of the relative or attributable risk of TB due to malnutrition. Moreover, until recently, data from experimental animals were based on animal models that were largely not relevant to human TB infection and disease.[1] Epidemiological, experimental and clinical data suggest that this is true.

About 500 BC, the Indian medical book Sushruta Samhita recommends treating tuberculosis with breast milk, meats, alcohol, and rest The use of nutritional supplements in the treatment as well as prevention of disease is clearly the future of medicine and the hope is, ultimately nutrients will support most drugs used in clinical medicine. But the question arises, whether there is any evidence based work which supports this wistful thinking. Malnutrition is frequently observed in patients with pulmonary TB. Several studies reported that patients with active

pulmonary TB are malnourished, as indicated by reductions in the level of visceral proteins, anthropometric indexes and micronutrient status.[2,3] Nutrition support is necessary for malnourished TB patients.

NUTRITIONAL ASSESSMENT

Nutrition risk assessment is important in providing nutrition support. Six parameters are usually selected as the components of the malnutrition score—predicted ideal body weight (PIBW), body mass index (BMI), serum albumin, total lymphocyte count (TLC), total cholesterol, and hemoglobin . Each factor is assigned a value of 1 if present or 0 if absent and the malnutrition score (0–6) is obtained by summation of the number of abnormal parameters for each patient. Patients with TB are further divided into 2 groups based on the malnutrition score: well-nourished (score< 3) and malnourished (score >3). The Malnutrition Universal Screening Tool (MUST) is a simple, quick, valid and reliable tool to identify patients who are malnourished or at risk of malnutrition. Adoption of a cut-off value of 3.5 improves the predictive ability of MUST score as a prognostic indicator in pulmonary TB patients. MUST appears to be a reliable tool for nutritional risk assessment of patients with pulmonary TB. In addition, MUST may be a useful prognostic indicator of survival in patients with pulmonary TB.[4]

Nutrition and Infection

The term 'malnutrition' is primarily used to refer to macronutrient deficiency (carbohydrate, protein and lipid), manifested as wasting. The most widely used index is BMI (weight in kg/height in m^2);[5,6] this formula normalizes weight for body size, thus distinguishing 'small' from 'wasted.' If height is unavailable, span may be used instead. Malnutrition and infection operate in a vicious mutual synergism. It is a two way interaction (Fig. 4.1). Malnutrition predisposes to infection and increases the severity and mortality of infections. Infection reduces nutrient intake, interferes with substrate utilization and promotes tissue breakdown. Malnutrition and infection tend to occur in the same populations: resource-poor settings, poverty, and extremes of age are major risk factors; hospitalized patients are also at significant risk. A history of weight loss is an important indicator of macronutrient deficiency. Body mass index (BMI) is a useful indicator of wasting and mid-upper arm circumference of protein malnutrition. More complex body composition tools are available but blood tests are difficult to interpret in the presence of an acute-phase response. Infection impairs the ability of the body to utilize energy and protein/amino acids thus nutrition support should be tailored to meet but not exceed requirements in the acute phase. Recovery from infection is often associated with significant anabolism; during this phase nutrient requirements may increase dramatically.

Infection reduces nutrient intake, interferes with substrate utilization and promotes tissue breakdown. In a cyclical manner, each exacerbates the effect of the other. Approaching the two problems together is therefore of paramount importance. Poor outcomes are likely if either side of the equation is ignored.

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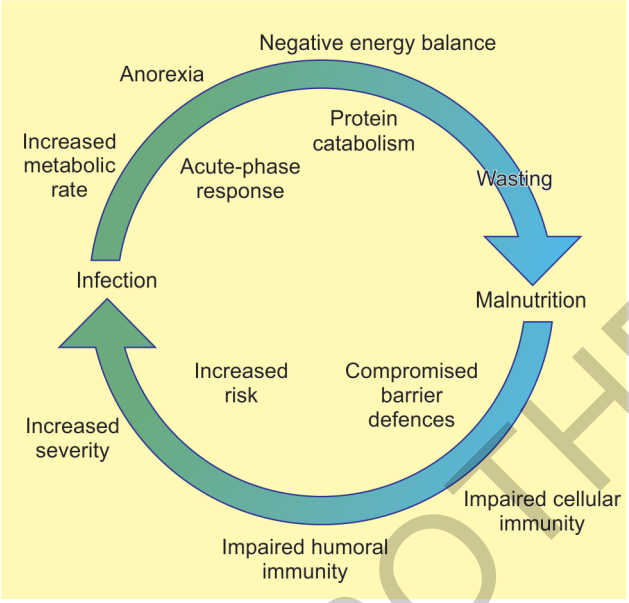

Fig. 4.1: The vicious cycle of infection and malnutrition

Epidemiological Hot-spots

Geographically, resource-constrained countries have the highest incidence of infections and also the highest burden of malnutrition. The extent of malnutrition in hospitalized adult patients in Western countries is striking; in one study, about 40% of a sample of UK hospital patients were undernourished on admission (body mass index, BMI <20 kg/m^2) and most patients lost further weight during their stay (mean change –5.4%); weight loss was greatest in those who were initially most undernourished.[7] It is no surprise therefore that in clinical practice these two problems of malnutrition and infection are intimately linked.

Malnutrition increases susceptibility to and severity of infection In terms of severity, nutritional deficiency may turn relatively mild illnesses into life-threatening conditions.

Infection as a Cause of Malnutrition

For centuries chronic infections have been recognized as causes of wasting. Tuberculosis was known as phthisis (wasting) by the Greeks and more recently as "consumption". HIV/AIDS was initially recognized by its propensity to cause a wasting syndrome (an AIDS-defining diagnosis).

The effect of infection on nutritional state can be considered under four broad headings—anorexia, increased metabolic rate, catabolism of protein and specific nutrient requirements. Anorexia is common to many infective processes and is the most important contributor to wasting in chronic infections such as HIV and tuberculosis. Pro-inflammatory cytokines activates neuropeptides such as neuropeptide (NPY) to suppress appetite centers in the hypothalamus.

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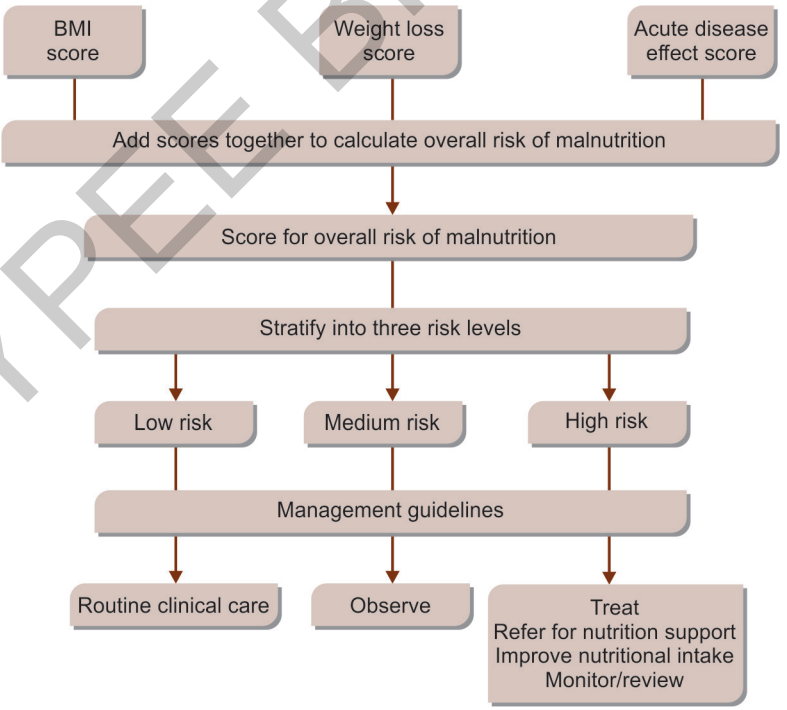
Resting (basal) energy expenditure is usually increased by acute infection, partly as a consequence of fever. However, this increase in energy expenditure is often more than offset by reduced energy requirements resulting from reduced activity. Thus, total energy expenditure may not be elevated in sick, inactive patients; energy requirements are easily overestimated in such situations. Although negative energy balance is common, the usual cause is reduced intake, not increased expenditure. Nutritional intervention in at-risk populations provides a cost-effective means of reducing the risk and mortality of infections.[8-10] In an infected patient, the key principle in approaching nutritional support is to provide adequate but not excessive nutrients. Adequate nutrients are required to prevent further wasting. Inadequate nutrition leads to wasting, and such wasting increases morbidity, delays recovery, and predisposes patients to further infective episodes. However, excess energy intake should be avoided as it tends to accumulate as fat rather than 'useful' lean tissue. Similarly, excess amino acids may not reverse catabolism and require metabolism themselves, consuming essential co-factors. This may explain why high levels of nutrition support, hyperalimentation tend to increase morbidity and mortality in critically ill patients. Potent anabolic agents, such as growth hormone, should be avoided; they have deleterious effects in severely ill ICU patients which may be mediated by a similar mechanism, redirection of substrate metabolism toward tissue anabolism and away from the acute-phase response (Flow chart 4.1).

Flow chart 4.1: An approach to screening for malnutrition



Note: Summarized from the Malnutrition Universal Screening Tool; see BAPEN website *(www.bapen.org.uk/must_tool.html)* for more details

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Dietary advice may be helpful and has been the subject of a recent Cochrane review.[11] When oral intake is possible but inadequate, supplements may be helpful in achieving weight gain or limiting weight loss. Enteral nutrition is the route of choice whenever possible but, where it is not possible to achieve desired intakes by this route, parenteral nutrition should be considered.[12] In severely ill patients, energy is usually provided at a rate of 25–30 kcal/kg/day. Optimal protein intakes are about 1–1.5 g/kg/day.

Micronutrients should be given to all acutely unwell patients unable to maintain adequate intake or losing weight, either as part of 'complete' nutritional formulas or as supplements. Use of specific nutrient formulations has been proposed for infective illnesses, but there is currently no evidence for this approach, although some nutrients (e.g. glutamine) may become 'conditionally essential' in the acutely infected patient.[13-15]

Pivotal to the management of such patients however is the identification and treatment of the underlying infective precipitant. Once infection is treated, the Asia-Pacific Region (APR) usually resolves very rapidly and anabolic pathways become operative again. Indeed in the recovery phase energy and protein intake may increase dramatically to fuel such recovery. Derek Macallan[16] in his article, "Infection and Malnutrition" described extensively about the relationship between the two and how to combat it.

Tuberculosis and Nutrition

Malnutrition and tuberculosis are both problems of considerable magnitude in most of the underdeveloped regions of the world. It is important to consider, how these two problems tend to interact with each other. The term consumption has been virtually synonymous with tuberculosis throughout the history. Before the advent of antituberculosis chemotherapy, a diet rich in calories, proteins, fats, minerals, and vitamins was generally considered to be an important, if not essential factor in treatment of tuberculosis. The introduction of specific antituberculosis drugs, however, has so radically altered the management of the disease that the role of diet should be considered in the light of the advances in treatment.

In the 21st century, tuberculosis is still the most frequent underlying cause of wasting worldwide. However, pathophysiology of wasting in tuberculosis remains poorly understood. The prevalence of widespread malnutrition in the population may be expected to pose some special problems with regard to the control of the tuberculosis in the developing countries from the larger point of view of prevention and therapeutic management of individual cases, from the narrower clinical point of view.[17,18]

The direct evidence of effect of nutrition on tuberculosis is difficult because of whole complex of coincident environmental factors. Despite these limitations, the weight of evidence still favors the view that malnutrition may be an important factor in the high mortality and morbidity from tuberculosis in population subjected to food shortage.[19] In any consideration of the role of nutrition in tuberculosis, three important questions arise. Does malnutrition predispose to tuberculosis infection? Does malnutrition influence or modify the course of established tuberculosis infection? Do nutritional factors influence the response to chemotherapy ?

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High prevalence of human immunodeficiency (HIV) infection in the underdeveloped countries further aggravates the problem of malnutrition and tuberculosis. HIV infection is an important risk factor for development of tuberculosis and adversely affects the nutritional status of patient. Nutritional supplementation may represent a novel approach for fast recovery in tuberculosis patients. In addition, raising nutritional status of population may prove to be an effective measure to control tuberculosis in underdeveloped areas of world.

Role of Diet in the Treatment of Tuberculosis

Before the advent of specific chemotherapy for tuberculosis, bed rest was the sheet anchor of treatment along with good diets and drugs to provide symptomatic relief. Diets which contained high quality of protein, a considerable proportion of which came of animal sources were recommended. These diets had also high calorie content. The recommendation was not purely empirical, but had indeed a scientific basis.

Diseases both chronic and acute adversely affects the metabolism of a number of nutrients including that of protein and tuberculosis is no exception. Tuberculosis decreases nitrogen retention.

In experimental studies and the diseased persons, there is a negative nitrogen balance. Increase in requirements of nutrition in this stage coupled with an increased rate of tissue catabolism can precipitate malnutrition unless the diets are supplemented by additional nutrition.

This holds good particularly of individuals whose nutritional status was already marginal, before the disease process sets in. The men having positive nitrogen balance has got a quicker recovery rate in comparison to those patients who started the disease with a negative nitrogen balance. The calorie content of the diet is also of importance. As a result of infection and fever, even the basal energy expenditure increases and unless compensated for by increased intake through diet, wasting would occur. It is now well recognized that due to calorie inadequacy, part of the dietary protein would be oxidized for purposes of energy and conditioned proteins inadequacy can ensue leading to loss in body weight. This can be prevented by diets which provide adequate amounts of both protein and calories. The advent of chemotherapy has revolutionized the treatment and management both dietary and otherwise. Ramkrisna[19] demonstrated that the single most important factor to cure tuberculosis is chemotherapy. Though the weight gain is better in the sanatorium regimen, than the domiciliary patients, there is no stastifically significant results over the cure rate of tuberculosis. This does not mean that tuberculosis and nutrition are not related. While the response to drug therapy may be relatively independent of the dietary intake, the risk of contracting the disease does appear to be related to the adequacy of the habitual diet and a satisfactory diet and good nutritional status are important factors in the control and prevention of the disease.[17,18]

EFFECTS OF MALNUTRITION ON TUBERCULOSIS

There are several experimental, clinical, and epidemiological studies demonstrating the effects of malnutrition on tuberculosis.[20]

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Epidemiological Studies

It has been pointed out that tuberculosis mortality rates in different economic groups in a community tend to vary inversely with their economic levels. There are also numerous observations pointing to increase in tuberculosis mortality in various countries during times of war and famine.[21]

There are numerous studies dealing with the effects of different diets on tuberculosis patients, and widely divergent and contradictory claims have been made. Difficulty in interpretation of these studies is, influence of other factors on infection. Among tuberculin skin test positive US navy recruits, the risk of tuberculosis was nearly four-fold higher among men who were at least 10% underweight at baseline than in men who were at least 10% overweight.[22] In a study among 1,717,655 Norwegians, >15-years old who were followed for 8–19 years after intake into a radiographic screening program, the relative risk of tuberculosis among persons in the lowest body mass index (BMI) category was more than five-fold higher than the group in the highest BMI category, and it was independent of sex, age, and radiographic findings.[23]

In a study conducted in London, it was found that Hindu Asians had an increased risk of tuberculosis compared with Muslims. Religion had no independent influence after adjustment for vegetarianism (common among Hindu Asians).[24] There was a trend of increasing risk of tuberculosis with decreasing frequency of meat or fish consumption. Lacto-vegetarians had an 8.5-fold risk compared with daily meat/fish eaters. Decreased immunocompetence associated with a vegetarian diet may result in increased mycobacterial reactivation.

Poor nutrition among patients who have undergone gastrectomy may be a risk factor for the reactivation of tuberculosis. There are other studies indicating that incidence of tuberculosis is unusually high among malnourished people.[25]

Now 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.[26] Substantial experimental evidence suggests that malnutrition can lead to secondary immunodeficiency that increases the host's susceptibility to infection. 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.[27] The reactivation of latent or previously subclinical tuberculosis infection may be related, in part, to deteriorating nutritional status.[28] Protein malnutrition has been identified as an important risk factor for the predisposition to intracellular infection leading to death.[29]

Animal Studies

Though there are several studies on experimental animals that have concluded contributory role of malnutrition on tuberculosis, an important snag in the interpretation of experimental data is the question as to how far these data obtained in the experimental animals are really applicable to human subjects. The natural history and evolution of tuberculosis in the animals and human beings need not necessarily be the same, and of course, the nutritional requirements of the animals and human subjects are also different.[20] It was reported that protein

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calorie malnutrition markedly enhanced bacterial growth and dissemination in mice resulting in rapidly fatal tuberculosis infection and a markedly elevated bacillary load in the lungs of protein deficient mice.

Study on guinea pigs demonstrated that protein malnutrition impairs the protective interaction between macrophages and T-lymphocytes and/or the acquisition of mycobactericidal and mycobacteriostatic activity by macrophages in the presence of adequate activation signals.[30] Protein deficiency prevented guinea pigs from generating a population of antigen-specific-immune lymphocytes and/or impaired the proliferation capacity of these cells.[31]

There are some studies which do not prove the role of malnutrition in tuberculosis. A 4-year follow-up of treated cases of pulmonary tuberculosis in a study at the Madras Tuberculosis Chemotherapy Center showed that about 90% of patients maintained quiescence throughout the 4-years period follow-up in spite of the fact that they were living under great stress of socioeconomic conditions including poor diet. Furthermore, the few patients who had a bacteriological relapse were at no special dietary disadvantage in comparison with those who had quiescent disease throughout.[19]

EFFECTS OF TUBERCULOSIS ON NUTRITIONAL STATUS

Nutritional status is significantly lower in patients with active pulmonary tuberculosis compared with healthy controls in different studies in Indonesia, England, India, and Japan.[32] Tuberculosis patients have been found to have lower serum albumin concentration than controls.[32] Tuberculosis is probably associated with more severe malnutrition than other chronic illnesses; in an Indian study, the nutritional status of patients with tuberculosis was worse than that of those with leprosy. An Indian study demonstrated that, tuberculosis patients were respectively 11 and 7 times more likely to have a BMI <18.5 and mid-arm circumference <24 cm.[33]

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.[34,35]

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.[35,36]

Anorexia is also a contributing factor for wasting in tuberculosis. In an unselected US cohort of patients diagnosed with tuberculosis, 45% lost weight and 20% had anorexia. Increased production of cytokines with lipolytic and proteolytic activity cause increased energy expenditure in tuberculosis.[37] Leptin may also play an important role in wasting. In a study, malnutrition has been associated with atypical presentations of tuberculosis.[38]

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Role of Micronutrients

Because of diverse metabolic characteristics and functions, micronutrients have presently been accepted as essential for optimum human health. Micronutrients deficiency is considered to be the most frequent cause of secondary immunodeficiency and infection related morbidity including tuberculosis.

Zinc

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. In vitro cellular killing by macrophages was found to be reduced during zinc deficiency and rapidly restored after zinc supplementation.

Various studies on patients with tuberculosis had shown significantly lower plasma zinc level than those without tuberculosis, irrespective of their nutritional status. There was significant rise in zinc level at the end of 6 months of antituberculosis therapy (ATT). Thus, it may be suggested that plasma zinc status is likely a marker for monitoring the severity of disease and response to therapy.[39,40] Zinc deficiency in tuberculosis is likely due to redistribution of zinc from plasma to other tissues or reduction of the hepatic production of the zinc carrier protein α2-macroglobulin and to a rise in the production of metallothionein, a protein that transports zinc to the liver.

Reduction in plasma zinc concentration was shown in tuberculosis patients after 2 months of treatment. This phenomenon may be because during the intensive phase of ATT, the antituberculosis 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.[38] The other possible mechanisms could be the effect of antituberculosis drugs on zinc absorption. Ethambutol was shown in rats to increase not only zinc absorption but also urinary zinc losses, resulting in reduced circulating zinc concentration.[39]

Zinc supplementation of patients with pulmonary tuberculosis and bacterial pneumonia was shown to increase immune function. Purified protein derivative (PPD) indurations were larger in children receiving zinc and zinc increases the PPD induration size in children irrespective of nutritional status.[40]

Zinc has essential role in vitamin A metabolism. Studies in humans and animals have shown that zinc deficiency impairs the synthesis of retinal binding proteins and reduces plasma retinal concentration.[41] Therefore, it appears that zinc supplementation has a beneficial effect on vitamin A metabolism which has important role in tuberculosis.[42-44] An adequate supply of zinc may also limit free radical membrane damage during inflammation.[45]

Vitamin A

It has been shown that vitamin A has immunocompetent role in human tuberculosis. Vitamin A was reported to inhibit multiplication of virulent bacilli in cultured human macrophages. In addition, vitamin A has a vital role in lymphocyte proliferation and in maintaining the function of epithelial tissues.

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Vitamin A is essential for normal functioning of T and B lymphocytes, macrophage activity, and generation of antibody response.[46]

Concentration of vitamin A was found to be lower in tuberculosis patients than that in controls in many studies.[47,48] Additionally, infection itself can compromise vitamin A status in number of ways.[49] Vitamin A is excreted in the urine in patients with fever and this has been confirmed in subjects with acute infection including pneumonia.[50] During the acute phase response, leakage of proalbumin through the vascular endothelium occurs; and production of retinal binding proteins and prealbumin by liver is reduced. In addition, requirement of vitamin A during infection is raised by its increased rate of excretion and metabolism.[49,50]

The low vitamin A levels observed in tuberculosis patients returned to normal at the end of ATT without vitamin A supplementation.[51] Vitamin A deficiency increases bacterial adherence to respiratory epithelial cells.[52] In the pre-chemotherapeutic era, cod liver oil rich in vitamin A and D was used regularly to strengthen host defence.[53] Supplementation of vitamin A appears to increase survival among chicks infected with *M. tuberculosis* and enhances both T-lymphocyte and antibody responses to *M. tuberculosis*.

In a double-blind, placebo-controlled trial Sita-Lumsden et al. had concluded that vitamin A and zinc supplementation improves the effect of tuberculosis medication after 2 months of antituberculosis treatment and results in earlier sputum smear conversion.[54]

Vitamin D

There are several studies regarding the role of vitamin D in tuberculosis like vitamin D deficiency increases the risk of tuberculosis after exposure. Vitamin D deficiency contributes to progression from latent to active tuberculosis. Vitamin D plays a role in the function of macrophages, key factor in host resistance in tuberculosis. Abnormalities in vitamin D status have been reported in tuberculosis. Genetic variations in the vitamin D receptor were identified as a major determinant of the risk for tuberculosis in Africans.[55] Vitamin D deficiency itself was shown to be a risk factor for tuberculosis.[56] Adults with untreated tuberculosis in Indonesia were shown to have significantly lower 25-hydroxy-vitamin D compared with controls.[57] Deficient serum vitamin D levels have been associated with incidence of tuberculosis (TB), and latent tuberculosis infection LTBI: Arnedo et al.[58] suggest that sufficient serum 25 (OH) D levels protect against tuberculin skin test (TST) conversion.

Ralph et al.[59] in their extensive review taking into account the literature of one hundred years duration came to the conclusion that improved understanding of the association between tuberculosis and vitamin D is needed. Vitamin D has both immunostimulatory and immunosuppressive effects relevant to human antimycobacterial responses. Ultraviolet radiation, the main source of vitamin D, also induces immunomodulation and could affect the relation between vitamin D and tuberculosis. Clinical trials of vitamin D supplementation in patients with tuberculosis have produced largely negative results. Well controlled studies with proper dosage in both active and latent tuberculosis is needed to come to a conclusion.

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Calcium

Inconsistent findings regarding serum or plasma calcium concentration during tuberculosis has been reported. Hypocalcemia was noticed in moderate to extensive radiographic disease.[60]

Vitamin E

In many studies, concentration of vitamin E was found to be significantly lower in tuberculosis patients than healthy controls.[61]

Vitamin C

Studies have linked vitamin C deficiency with tuberculosis.[61] In Ethiopians, concentrations of antioxidant vitamin C, vitamin E, and vitamin A were significantly lower in tuberculosis patients and high malonaldehyde concentration was associated with clinical severity.[62]

Selenium

The essential trace element selenium has an important function in maintaining the immune processes and thus may have a critical role in clearance of mycobacteria. Selenium has been found as significant factor in the relative risk for developing mycobacterial diseases in HIV positive patients.[63]

A recent Indian study measured concentrations of circulating antioxidants and markers of oxidative stress in tuberculosis patients. Results showed 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 treatment.[64]

Iron

Anemia is a common complication of pulmonary tuberculosis, the reported prevalence ranging from 16 to 76% in different studies. 50% adults with pulmonary tuberculosis had significantly lower hemoglobin than healthy matched controls. Iron deficiency may also be a contributing factor.[65]

Elevated concentration of zink prote-porphyrin (ZPP), a measure of free erythrocyte porphyrin, is indicative of iron deficient erythropoiesis.[66] High ferritin levels have been found to be associated with non-infectious as well as infectious causes including tuberculosis. In one case report of 41-year-old male with multidrug resistant tuberculosis (MDRTB) and type 2 diabetes mellitus the laboratory findings showed iron 280 g/dL, total iron binding capacity (TIBC) 61 g/dL, and ferritin 92,945 ng/mL which indicates that iron is an essential nutrient for the survival of the pathogen *Mycobacterium tuberculosis*.[67]

The precise mechanism of anemia in pulmonary tuberculosis is not known. Several hypotheses, including blood loss because of hemoptysis, bone marrow involvement with tubercular granuloma in disseminated tuberculosis (nutritional deficiency caused by fever and loss of appetite, etc. have been proposed. It may also occur as a consequence of chronic inflammation, and

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without apparent loss of blood or bone marrow suppression. Blunted response of erythropoietin due to release of tumor necrosis factor or other cytokines have been observed. Tuberculosis is a chronic infectious disease, so anemia of inflammation may contribute significantly. Hypoferremia induced by the shift of Fe from a transferrin-bound available state to a ferritin-incorporated storage state is considered to be a major factor in the pathogenesis of anemia of chronic inflammation. The condition may have evolved as a cytokine-mediated defense against microbial pathogens, effectively withholding Fe from microbes, which incidentally also deprives erythroid precursors of their Fe supply. Therefore, Fe-deficiency status may be a protective response against invading microbes: Mild anemia may be a small price to pay for the attenuation of infection. The only effective treatment for anemia of chronic inflammation is correction of the underlying disorder. The widespread presence of Fe-deficiency anemia has been reported from many developing countries. In fact, anemia has become synonymous with Fe-deficiency and Fe supplementation is the usual practice in therapy for all anemic patients in most developing countries irrespective of the etiology. However, anemia of inflammation is considered a major contributor to anemia observed in developing countries and anemia of inflammation may even be associated with asymptomatic and sub-clinical infections. Pulmonary tuberculosis is a chronic infective disease occurring predominantly in socio-economically deprived populations. Therefore, both anemia of inflammation as well as Fe-deficiency may coexist in pulmonary tubecculosis. While Fe supplementation is the only therapy for Fe-deficiency anemia, its efficacy in anemia of inflammation is questionable. Several studies have indicated deleterious effects associated with Fe supplementation in tubercular infection.[68]

Copper

In a recent study, compared with the control group, the concentrations of iron, zinc, and selenium were significantly lower while that of copper and copper/zinc ratio were significantly higher in the serum of tuberculosis patients.[69] The serum concentration of zinc increased and serum copper concentration and copper/zinc ratio decreased significantly after antituberculosis chemotherapy.

Polyunsaturated Fatty Acids

In a study, eicosanoid synthesis was studied in macrophages of guinea pigs fed with different amounts of omega-6 fatty acids and omega-3 fatty acids. It was concluded that supplementing the diet with (n-3-) fatty acids can affect resistance to *M. tuberculosis*, whereas supplementing with (n-6-) fatty acids does not.[70]

Cholesterol

Hypocholesterolemia is common among tuberculosis patients and is associated with mortality in miliary tuberculosis cases. In vitro studies concluded that cholesterol-rich diet accelerated the sterilization rate of sputum culture in pulmonary tuberculosis patients suggesting that cholesterol should be used as a complementary measure in ATT.[71]

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Ghrelin and Leptin

The appetite-related hormones, leptin, has emerged as a new causative candidate of TB-associated malnutrition.[72-76] Leptin, secreted by adipocytes, is increased in high fat mass conditions, and is implicated as an anorexigenic factor that reduces appetite.[77] Conversely, ghrelin, a novel 28-amino-acid peptide, is produced by the stomach and has recently attracted interest as a novel anticatabolic and orexigenic factor that is increased in anorexic conditions and stimulates appetite and a positive energy balance.[78] Many studies have also revealed that both leptin and ghrelin are immune system regulators in addition to their effect on food intake.[79] Plasma levels of leptin and ghrelin can be altered in disease states associated with anorexia.[80-84]

Little is known about the role of the appetite-related hormones, ghrelin and leptin, in malnutrition in tuberculosis. Several conflicting results have been reported for leptin levels in patients with TB: increased, decreased, or not changed. However, many investigators did not find a correlation between the leptin levels and anorexia in TB, although changes in leptin levels during TB were observed. Some study also indicates that leptin cannot account for the malnutrition associated with TB. Concerning the relationship between the leptin and body composition, leptin levels had positive correlation with BMI. Since BMI was significantly lower in TB patients than in the controls, the difference in leptin levels between the TB patients and controls could be affected by BMI. Normal leptin levels in the malnourished TB patients may therefore indicate the relatively increased and not suppressed leptin levels in the patients. Interestingly, ghrelin has anti-inflammatory activity, while leptin has pro-inflammatory effects. Indeed, in a recent animal study, ghrelin indirectly down-regulated tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in sepsis through activation of the vagus nerve.[85] A few recent studies suggested a "cytokine–leptin hypothesis" that higher multiple cytokine levels are correlated with increased leptin levels.[86] Previous studies on TB showed a positive correlation between the levels of leptin and inflammatory cytokines, while others showed negative or no correlation. Ghrelin levels tended to be negatively correlated, and leptin levels positively correlated with inflammatory cytokines.

Ghrelin but not leptin levels were significantly lower in the malnourished tuberculosis group than in the well-nourished tuberculosis group. Malnutrition score was negatively correlated to ghrelin, but not to leptin levels. TNF-α and IL-6 levels were significantly higher in the malnourished tuberculosis group than in the well nourished tuberculosis group and controls. Plasma levels of ghrelin tended to decrease as inflammatory cytokines increased before treatment. Decreased plasma ghrelin levels, in addition to increased plasma inflammatory cytokine levels, may be associated with malnutrition in active pulmonary tuberculosis. Kim et al.[87] had shown that ghrelin but not leptin levels were significantly lower in the malnourished tuberculosis group than in the well-nourished tuberculosis group [44.0 (43.0–54.0) vs. 122 (108–158) pg/mL; $p < 0.05$]. Malnutrition score was negatively correlated to ghrelin (r¼_0.76, $p < 0.01$) but not to leptin levels. TNF-α and IL-6 levels were significantly higher in the malnourished tuberculosis group than in the well nourished tuberculosis group and controls. Plasma levels of ghrelin tended to decrease as inflammatory cytokines increased before treatment.

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SN Tripathy MD TDD FNCCP FICA is Ex-Professor and Head, Department of Pulmonary Medicine, Shri Ramachandra Bhanj (SCB) Medical College, Cuttack, Odisha, India. He is a well-known pulmonologist of India, and a man of unusual conviction and a master of intuitive clinical skills. His incisiveness, inventiveness and originality coupled with his broad knowledge of pulmonary medicine and tuberculosis. Also, his unwavering dedication to the application of techniques of contemporary science on the advancement of respiratory medicine played a vital role in bringing the Department of Pulmonary Medicine of Odisha to the forefront. A distinguished investigator, recipient of many prestigious academic and social awards, Teacher par Excellence and academician. His method of diagnosis and treatment, and the empathetic attitude towards patients is legendary.



(Mrs) SN Tripathy MD FICOG is Ex-Professor and Head, Department of Obstetrics and Gynecology, Shri Ramachandra Bhanj (SCB) Medical College, Cuttack, Odisha, India. She is a well-known figure across the world for her basic research in genital tuberculosis for which she has been honored by the Tuberculosis Association of India (1995), and a proud recipient of many prestigious academic, social and literary awards. She is an innovative researcher. She has edited various books, contributed chapters to many books. She was the Member, Editorial Board of many journals, in the Indian Editorial Advisory Board, and Journal of Federation of Obstetrics/Gynaecology (2010–2014). She is a peer reviewer of many international and national journals. She is an academician through and through, a Teacher par Excellence, a lucid speaker and prolific writer both in scientific and literary fields.

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