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Review

The association and interactions of malnutrition, micronutrients, and drug therapy in the management of tuberculosis

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ABSTRACT

Tuberculosis is an infectious lung disease that is the leading cause of death worldwide. Globally, over 3,500 people lose their lives to tuberculosis each day – totalling 1.3 million deaths each year. *Mycobacterium tuberculosis* is the acid-fast bacteria that causes tuberculosis. Fever, coughing, exhaustion, and weight loss are among the symptoms that patients with tuberculosis display. Tuberculosis is transmitted from person to person by inhaling airborne droplets. Immune compromised individuals are at high risk for developing tuberculosis. Direct microscopy of sputum smears and solid media cultures are used as tuberculosis diagnostic techniques. The global effort to combat tuberculosis has so far saved an estimated 75 million lives since 2000. The present review focuses on the association between malnutrition and tuberculosis, micronutrient status, and drugs used in tuberculosis therapy. The greatest risk factor for TB is malnutrition, which weakens immunity by lowering the cells' ability to fight off infections. Many micronutrients are useful in controlling tuberculosis and boosting the host's immunity. These include copper, zinc, selenium, iron, vitamin A, vitamin C, vitamin D, vitamin B6, and vitamin E. Furthermore, the longevity of patients in intensive care units (ICUs) depends on their micronutrient status. Several medications, such as isoniazid, ethambutol, rifabutin, levofloxacin, amikacin, streptomycin, and capreomycin, are used to treat tuberculosis for a certain period of time. Anti-tuberculosis medications can cause vitamin B6 deficiency, arthralgias, gastrointestinal issues, hepatotoxic effects, and allergic reactions as adverse effects. The United Nations Sustainable Development Goals (SDGs) aimed to end the global tuberculosis epidemic by 2023 but more work remains to be done.

INTRODUCTION

Tuberculosis (TB) is the second most common cause of mortality worldwide after HIV and AIDS, according to a WHO report (Natarajan et al., 2020). Respiratory droplets spread the acid-fast bacillus known as *Mycobacterium tuberculosis*, the pathogen that causes tuberculosis (Lu et al., 2020). According to the WHO (2023), 1.3 million individuals died from TB in 2022, a small reduction in the mortality (~1.4 million each) in 2021 and 2020. According to a recent report by the US CDC, one fourth of the world population may be infected with TB, with 10.6 million becoming ill yearly (CDC, 2024). These include 5.8 million men, 3.5 million women and 1.3 million children. In the worst affected country, Pakistan, there are around 510,000 cases of TB recorded each year, of which 15,000 are drug-resistant.

The majority of *Mycobacterium tuberculosis* infections lead to the latent development of tuberculosis. The main risk factor for primary TB is *Mycobacterium tuberculosis* bacteria, although in healthy individuals, the immune system keeps the infection from proliferating and the illness remains latent. These people are still in good health and do not exhibit any symptoms of illness (Palanivel et al., 2023).

The immune system reacts to infection in a complex way (Okoduwa et al. 2023). It starts when bacteria enter the macrophage chamber as a result of the general intrinsic immune system, and as the cellular immune reaction progresses, β-cell and T-cell lymphocytes are infiltrated. Consequently, these cells separate the bacteria from the lung granuloma (Carabal-Isajar et al. 2023).

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In healthy individuals, the lifetime risk of developing active from latent tuberculosis can range from 5% to 10% (Lu et al., 2020), but it can reach 50% in immune-compromised individuals, such as those with HIV infection (Ibrahim et al., 2022; Miiro et al., 2023). According to Lu et al. (2020), symptoms of active pulmonary TB include coughing, chest pain, chills at night, weight loss, and occasionally coughing up blood.

HISTORY OF TUBERCULOSIS

In several cultures throughout history, cases of illnesses with symptoms like those of TB have been documented. In the Vedas, the disease was known by the Sanskrit term Yakshma, which means "Losing Disease." According to Verma et al. (2023), Greek, Chinese, and Arabic literature also mention illnesses like tuberculosis. Pre-Columbian Egyptian and Peruvian mummies have been found to have distinctive tubercular spinal lesions. An ancient Turkish cranium's bone fragment offers the earliest tentative proof of TB in people.

The first known human patient with tuberculosis was a Neolithic newborn, and women from a 9,000-year-old Eastern Mediterranean group were identified by PCR amplification. Girolamo Fracastorius (1483–1553) discovered that certain diseases might be transmitted by particles through direct or indirect human contact. However, Galen demonstrated that TB was transmissible already in the second century. The earliest report on military TB was written by Thomas Willis (1621–1675).

EPIDEMIOLOGY OF TUBERCULOSIS

Nearly one-third of people worldwide have mycobacterium TB, many of whom are carriers of tuberculosis (Ghazy et al. 2023) even with no symptoms. Some cases are becoming more difficult to treat, as mycobacterium TB has mutated so as to be resistant to some treatment options, such as the drug rifampicin. Of the estimated 558,000 new cases of rifampicin-resistant TB, three nations accounted for more than half: India (24%), China (13%), and the Russian Federation (10%) (WHO, 2018).

The lungs are the most often affected organs by TB infection, although it can also affect the joints, lymphatic system, central nervous system, genitourinary system, bones (Pott's disease), and lymphatic system. India accounted for 2.8 million cases of extra-pulmonary tuberculosis (EPTB) reported worldwide in 2023 (WHO, 2023). Data from the Indian Modified National Tuberculosis Control Programme showed that 15% to 20% of incident cases affect people without HIV, while 50% of cases are in HIV-positive individuals. EPTB tends to affect the following: 30% in the pleural cavity, 47% in the pleural nodes, 10% in the abdominal nodes, 8% in the bones and joints, 2% in the central nervous system, and 3% in other areas (Central Tuberculosis Division National Tuberculosis Elimination Programme, 2023).

In Pakistan in 2022-23 for example, the prevalence of EPTB is 15,790, out of which 29% pleural TB, 21% abdominal TB, 9% osteoarticular TB, and 4.6% CNS TB are the affected areas (Jawed *et al*., 2023).

According to WHO (2018), there has been a typical yearly drop of 2% in the rate of tuberculosis infection, and the percentage of fatal cases decreased from 23% in 2000 to 16% in 2017. In thirty high-burden countries, India has performed best, cutting its prevalence by 50%.

Widespread drug-resistant tuberculosis has emerged recently, posing a threat to the worldwide tuberculosis control initiative. Drug-resistant tuberculosis is developed when the mycobacterium tuberculosis becomes resistant to the drugs used for the management of tuberculosis. In Nigeria, the number of TB cases increased from 269,000 in 2000 to 467,000 in 2021 (Oduu 2023). Data show that though there has been a corresponding increase in the incidence and deaths of TB (with a decline in deaths from 2019 to 2021), more victims have survived the disease during the past six years (Oduu 2023).

PATHOPHYSIOLOGY OF TUBERCULOSIS

Mycobacterium tuberculosis enters the alveoli through the lungs, where it causes primary TB and an exudative lesion. It then gets ingested and multiplies inside alveolar macrophages.

Macrophages carry out phagocytosis on the bacteria. A phagosome is a membrane-bound vesicle that macrophages make to stop all bacteria from growing. Following that, phagosomes and lysosomes join to produce phagolysosomes.

Kant et al. (2021) showed that the mycobacterium survives in macrophages by producing a variety of proteins, including tuberculosis necrotizing toxin (TNT), which kills the macrophages, early secreted antigen (ESAT), which decreases the innate immune response, and exported repetitive protein (ERT), which prevents the fusion of phagosomes to lysosomes. This functions mainly where there is minimal cell-mediated immunity due to reduced immune function in the host.

ETIOLOGY OF TUBERCULOSIS

Certain mycobacterium strains i.e. *Mycobacterium bovis, Mycobacterium avium-intracellular* complex, *Mycobacterium kansai, Mycobacterium canetti, Mycobacterium capree*, and *Mpinnipedi* are involved in the pathogenesis of tuberculosis (Mohamed et al., 2023; Roberts, 2020). In people with latent TB, these strains are persisters (viable but non-culturable cells), meaning they can survive both inside and outside the host, which might account for their prolonged persistence within the host through intracellular survival, metabolic adaptation, and immune modulation (Mohamed et al. 2023). *M. tuberculosis* has certain virulence factors such as Phthiocerol dimycocerosate (PDIM) and phenolic glycolipids (PGL) that cause tuberculosis in humans (Pereira et al. 2023).

CLINICAL PRESENTATION

Patients with pulmonary tuberculosis frequently have hemoptysis and cough. Gastrointestinal tract (GIT) tuberculosis is typically detected in patients who have diarrhoea and abdominal pain. The patient may also exhibit erythema nodosum, scrofula, local lymph adenopathy, and painless ulcers. Acid-fast bacteria cultured from a biopsy sample confirm the diagnosis. Testing of adverse medication responses should be included in the prescription lists of patients with Mycobacterium TB. In addition to pathophysiology, it may involve X-rays, CT scans, surgical biopsies, and skin tests for tuberculin. Mycobacterium TB diagnosis requires all patient samples to be presented together with a medical history, physical examination, chest X-ray, and microbiological testing that looks at sputum and

other relevant samples (Kant et al., 2021).

TRANSMISSION OF TUBERCULOSIS

Extra-pulmonary tuberculosis (EPTB) can harm every organ in the body, despite its preference to infect human lung function (pulmonary TB) (Kwaghe et al., 2020). Inhaling the airborne droplets involves the entry of harmful microbes within the body (Mvo et al., 2023). Following infection, the bacilli may be eliminated by the immune system, or they may proliferate and produce primary TB, go latent and remain unnoticed, or reappear after a period of latency (Idoko and Adeyemi, 2022). People with latent infection are estimated to have a lifetime probability of acquiring tuberculosis (TB), but this risk increases with age (childhood and old age) and with immunocompromised diseases (HIV/AIDS, for example) (Pereira et al. 2023). Furthermore, it is thought that each case of TB results in between 10 and 15 more persons getting infected (Pandey et al. 2024).

A number of host and environmental factors work together to predispose people to TB; risk factors found in West Africa include smoking, crowded housing, male sex, and HIV infection (WHO, 2021). These findings show a dose-response relationship with TB and should encourage more research. Prior studies carried out in Gambia also found ethnicity to be a risk factor, but it was clear that the basic environmental and behavioural factors may actually be to blame (Meaza et al., 2023). A recent study from Tanzania found that although those with longer coughs (two weeks or more) were substantially more likely to be diagnosed with TB than those with shorter coughs, this association was not statistically different (Hailemariam et al., 2023). The nation's inadequate healthcare system is said to be the main cause of Nigerians' chronic illness-poverty cycle.

DIAGNOSIS OF TUBERCULOSIS

Approximately 50% of children with TB go undetected, indicating problems in the diagnostic process. To reduce the incidence of TB, a number of novel diagnostic techniques, including point-of-care ultrasound, magnetic resonance imaging, computed tomography-scans, and chest X-rays, have been developed. Methods used for TB identification include stool and nasopharyngeal aspirates, Xpert MTB/RIF Ultra, and C-TB skin tests (Rodrigues and Singhal, 2024). The tuberculous antigen-based skin test (TBST), an alternative to the TST/IGRA test, is used to identify latent tuberculous infection (LTBI) (To et al. 2024). A urine lipoarabinomannan test is used to diagnose TB in children living with HIV. Despite the fact that TB may affect any region of the body, pulmonary TB—particularly reactivated latent infections—is the main method by which the disease spreads throughout populations (WHO, 2024). Specialized diagnostic tests, such as the interferon-gamma release assay, nucleic acid amplification test, and purified protein derivative test, are also available that are practiced in well-developed labs and are expensive. The diagnosis of TB is frequently made on the basis of "possible exposure, a typical medical history, significant clinical signs, typical radiological changes, and positive bacteriological tests" (WHO, 2023). Two of the most widely used laboratory diagnostic methods in the global control of TB are special solid medium culture (Lowenstein-Jensen agar) and direct microscopy of sputum smears. This simplified method is recommended, given the incremental detection yield of three consecutive sputa, in resource-constrained settings. It is anticipated that this new strategy would enhance "quality of assistance, decreased time for evaluation and initiation of treatment, and reduced patients' fallout from the evaluation pathway" to enhance case identification (WHO, 2023).

MALNUTRITION, IMMUNITY AND TUBERCULOSIS

A person's ability to fend off disease is significantly influenced by their nutritional status. It is well recognised that compromised immune systems are associated with poor diets (Zimmer et al. 2022). The capacity of cells to fend off infections is diminished by malnutrition. Disease can also result in weight loss and nutritional anxiety, both of which compromise immunity and nutritional status (Baek et al., 2019). Malnutrition can have a major negative impact on several important immune defence mechanisms, including cell-mediated immunity, phagocytic activity, antibody level, and cytokine generation (Zimmer et al. 2022).

It has long been known that malnutrition and TB are related. Active TB worsens when malnutrition occurs, and vice versa (Abaynew et al., 2023; Nguyen et al., 2023). It has been suggested that by reducing the expression of gamma interferon and tumour necrosis factor-alpha, generalised malnutrition may specifically impair elements of the cell-mediated mechanism essential for limiting and controlling TB (Zimmer et al. 2022).

Studies conducted in Indonesia, England, India, and Japan have shown that people with active pulmonary TB have significantly worse nutritional status than people in healthy conditions (Pant et al., 2023). Total albumin concentrations were observed to be decreased in TB patients compared to healthy individuals (Pant et al., 2023). Research conducted in Uganda indicates that TB is associated with a higher degree of malnutrition than other chronic diseases (Gezae et al., 2023). An Indian study found that TB patients often had BMIs < 18.5 and mid-arm circumferences under 24 cm (Li et al., 2023). Each infection presents a different level and type of tissue death due to the diverse pathogenicity of the bacteria. Wasting in TB patients is caused by the appetite reduction, dietary malnutrition, malabsorption of micronutrients, and poor metabolism (Kusmiati et al., 2022; Wang et al., 2021).

Anorexia is another disorder that causes wasting in TB patients. In a U.S. cohort selected at random, 45% of TB patients experienced weight loss, and 20% experienced anorexia. According to Dasaradhan et al. (2022) there is a rise in the production of cytokines with lipolytic and proteolytic activity in TB. Wasting is most likely the result of several causes in individuals with active TB, including decreased appetite and food intake, increased deterioration, and altered metabolism related to immunological and inflammatory responses (Liu et al., 2023).

THE IMMUNE ESCAPE MECHANISM OF *MYCOBACTERIUM TUBERCULOSIS* DEVELOPMENT

Mycobacterium tuberculosis (MTB) can initiate a series of immunological responses with the help of various receptors (toll-like receptors) and proteins (TLR-8) after it enters the body through its interactions with macrophages (Drain et al., 2018; Davila et al., 2008). The immunological substances such as T lymphocytes in collaboration with premature secretory antigen-6/culture filtrate polypeptide, ATP1/2, and coronin 1 eliminate the intracellular pathogens by inhibiting

the development and acidification of phagolysosomes (Chandra et al., 2022). Coronin-1 is involved in the inhibition of lysosome production that has its effect on the MTB functionality in the microsomes (Zhai *et al.*, 2019). Cytokine interferon (IFN-α) producing IL-10 and PKnG enhance MTB metabolic processes, growth rate, virulence, and drug resistance by down-regulating the levels of Glycerol kinase and Aldehyde dehydrogenase, upregulating the transcription of Ag85A and Ag85C, inhibiting lysosome maturation, and increasing bacterial infectivity, as a result, prevents the union of phagosomes and lysosomes by enhancing signal transmission in host cells (Figure 1) (Maphasa et al., 2021; Bussi and Gutierrez, 2019; Sia and Rengarajan, 2019).

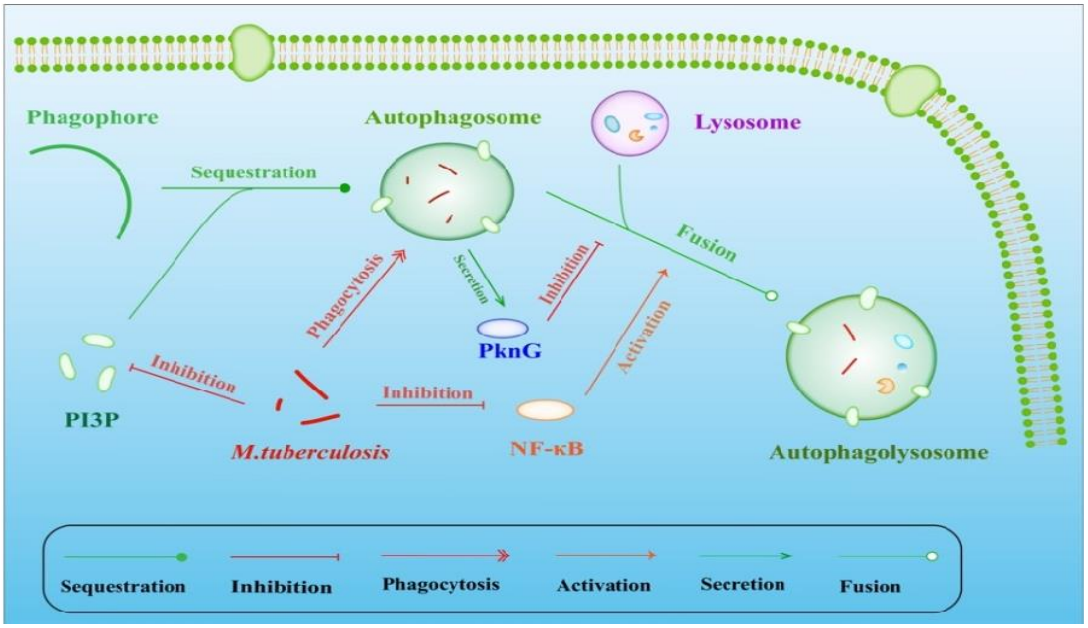

Figure 1. Mode of action of *Mycobacterium tuberculosis* development

MICRONUTRIENTS AND TUBERCULOSIS

Little is known about the association between micronutrient deficiencies and the progression of the disease, despite the fact that the previously mentioned assessment of generalised malnutrition has frequently been observed in patients with active TB (Kalva et al., 2023). According to Jonker and Boele van Hensbroek (2014), immunity, cellular function, and metabolic pathways all depend on the minerals zinc, copper, iron, and selenium, as well as the vitamins A, C, E, B6, and folic acid (Figure 2) (de Araujo Morais et al., 2021). According to Pant et al. (2023), proper micronutrient status may be crucial for the host's defence against TB. One or more nutrient deficits may reduce an individual's ability to fight against viruses (Aranas et al., 2023; de Araujo Morais et al., 2021). A common therapy for strengthening host defence before the use of medications to treat active TB was the administration of cod liver oil, which is rich in vitamins A and D (Anaam and Alrasheedy, 2023). Because of their many metabolic functions and characteristics, micronutrients and phytochemicals such as flavonoids are now understood to be essential for optimal human health (Okoduwa et al., 2024).

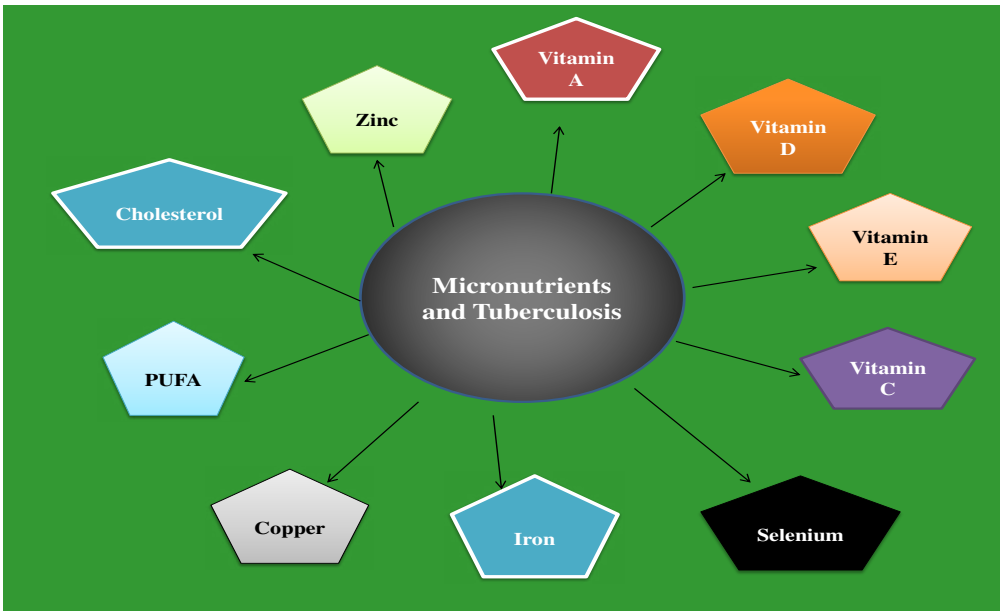

Figure 2. Various micronutrients of significance in tuberculosis

ZINC

Zinc deficiency has several effects on host defences. It leads to decreased phagocytosis, which lowers tuberculin reactivity in the skin (usually tuberculin reactivity is spotted within 5-6 hours) and the quantity of circulating T-lymphocytes, at least in mice (Wagnew et al., 2022).

In many studies, individuals with TB had significantly lower plasma zinc levels than those without the disease, regardless of the foods they consumed. Zinc levels were increased after six months of anti-tuberculosis medication (Brown et al., 2016). Therefore, it is possible that the zinc content of plasma is a marker for determining the severity of the illness and the efficacy of therapy (Wagnew et al., 2022; Gupta et al., 2009).

The reasons for the zinc deficit in TB are probably the movement of zinc from serum to different regions, a decrease in the synthesis of the zinc transporter protein 2-macroglobulin in the liver, and/or an increase in the synthesis of the protein metallothionein, which transports zinc to the liver (Wagnew et al., 2022). After receiving treatment for two months, the plasma zinc concentration of TB patients decreased (Salah, 2022).

The anti-tuberculosis drugs have an inverse association with zinc absorption as ethambutol was shown to increase urinary zinc losses in rats, as well as absorption of zinc, which resulted in a reduction of blood zinc levels (Keflie et al., 2018).

Zinc supplements have been reported to enhance immune function in patients suffering from bacterial pneumonia and pulmonary TB (Wagnew et al., 2022). Appropriate zinc consumption may mitigate free radical-induced inflammatory membrane damage (Pan et al., 2020).

VITAMIN A

It is known that vitamin A helps the immune system fight TB. Vitamin A has been shown to stop pathogenic bacilli from growing in human macrophage cultures (Bahlool et al., 2022). Furthermore, vitamin A is necessary for lymphocyte proliferation and epithelial tissue maintenance (Zhang et al., 2022). In animals, vitamin A is required for the correct function of T and B cells, macrophage activity, and the production of an antibody response (Elefson and Greiner, 2023).

Research from Rwanda revealed that adults with TB were, on average, low in vitamin A. Vitamin A concentrations were shown to be lower in TB patients than in controls in a number of studies (Patti et al., 2021; Belete et al., 2019). In addition to a deficiency in the diet, an insufficient quantity of retinal in plasma may be caused by either poor fat absorption or intake. Numerous other factors, including infections themselves, can impact vitamin A levels. It has been demonstrated that people with fever and those suffering from acute illnesses, including pneumonia, excrete vitamin A in their urine (Bahlool et al., 2022).

According to Hughes et al. (2022), during the acute stage of the reaction, pro-albumin leaks through the endothelium of the arteries, and the liver generates fewer pre-albumin and retinal-binding proteins. The demand for antioxidant vitamin A is further increased during sickness due to the rapid metabolism and removal of the vitamin (Bahlool et al., 2022).

Before chemotherapy was developed, host defence was often increased by using cod liver oil rich in vitamin A and D (Schwalb et al., 2023). Supplemental vitamin A appears to enhance T-lymphocyte and antibody defences against M. tuberculosis, and infected chicks appear to survive longer when given this vitamin (Khan et al., 2023).

VITAMIN D

Vitamin D affects the way macrophages operate, which is an important part of host resistance against TB. Aberrant/deficient vitamin D levels have been connected to TB (Thejaswi et al., 2023). Genetic variations in the vitamin D receptor have a considerable impact on Africans' risk of contracting TB (Pop et al., 2022). Adults in Indonesia with untreated TB had significantly lower 25-hydroxycholecalciferol levels than controls (Cai et al., 2022).

VITAMIN E

According to Patti et al. (2021), vitamin E concentrations in TB patients were significantly lower than in healthy individuals.

VITAMIN C

Research has linked vitamin C deficiency to TB (Patti et al., 2021) in that high concentrations of malonaldehyde, a marker for oxidative stress, were associated with clinical severity. Antioxidants such as vitamin C, vitamin E, and beta-carotene were significantly reduced in Ethiopian TB patients (Abnousian et al., 2023).

SELENIUM

Selenium is an essential trace element that maintains the immune system and is required for the eradication of mycobacterium (Shor-Posner et al., 2002). Estevez et al. (2020) investigated the effect of selenium nanoparticles on the growth of Mycobacterium TB, and it was observed that selenium nanoparticles hinder the growth by disrupting cell wall permeability.

IRON

Anaemia is common in adults with pulmonary TB. According to Ghanaian research, haemoglobin levels were significantly lower in 50% of patients with pulmonary TB than in healthy, matched controls. Iron deficiency may play a role in this anaemia (Teklu et al., 2020). While chronic infections lead to anaemia, low iron levels increase a person's susceptibility to infections like TB (Pant et al., 2023).

COPPER

TB patients' bloodstreams had considerably lower levels of zinc, iron, and selenium when compared to the control group; nevertheless, copper and copper/zinc ratios remained significantly higher (John-Olabode et al., 2023). Serum zinc concentration increased, but systemic copper content and the copper/zinc ratio sharply decreased after anti-tuberculosis medication.

POLYUNSATURATED FATTY ACIDS

The production of eicosanoids by the macrophages of guinea pigs that were fed varying amounts of omega-6 and omega-3 fatty acids (Nienaber et al., 2021). While including (n-6) fatty acids in the diet had no such impact, including (n-3) fatty

acids in the diet can influence a person's susceptibility to M. tuberculosis.

CHOLESTEROL

Hypercholesterolemia, which was associated with mortality in instances of miliary TB, is a common condition in patients with TB (Schutz et al., 2019). In vitro findings showing that a cholesterol-rich diet improved the sterilisation rate of sputum cultures in patients with pulmonary TB, suggesting that cholesterol might be used as an adjunctive therapy in anti-tuberculosis therapy (ATT).

PROTEIN

Karballaei-Mirzahosseini et al. (2022) demonstrated that rats given a high-protein diet recovered from the unfavourable nitrogen imbalance phase of an infection more quickly than rats fed a low-protein diet. Clinical research showed that those with a positive nitrogen balance had a much better prognosis for TB development compared to those with a negative nitrogen balance (Karballaei-Mirzahosseini et al., 2022).

Serum albumin and haemoglobin concentrations in patients with pulmonary TB have been shown to be accurate predictors of survival (Lemos et al., 2022).

TUBERCULOSIS AND CHILDREN'S NUTRITION

The rapid development stages of infancy and childhood can only be sustained if a child eats the appropriate amount of nutrients. TB can cause malnutrition and impaired growth. A child with TB has increased demands because of both growth and TB itself; thus, it's important to provide them with the right nutrition and energy. Children's dietary requirements are already difficult to meet due to their tiny stomachs and poor appetites. TB should be checked for in children who show signs of malnourishment or do not develop as expected.

NUTRITIONAL STATUS AND CLINICAL OUTCOMES

Nutritional status seems to play a significant role in influencing the clinical outcome of TB. In an Indian experiment (Choi and Baek, 2022), patients with TB were treated at a sanatorium with an acceptable diet or at home with an obviously imbalanced diet. While both cohorts had comparable overall responses to treatment, the more nutrient-dense diet group tended to show faster bacterial clearance, radiographic improvements, and greater weight gain (Eworo et al., 2022). Melni (2024) found that in a separate study of TB patients, the death group had lower levels of albumin, cholesterol, cholinesterase, haemoglobin, and weight than the living group.

NUTRITIONAL TREATMENT OF TUBERCULOSIS

A supplemental diet may provide improved outcomes for TB patients. Research has demonstrated that when started at the first stage of TB therapy, nutritional counselling and supplementation to increase energy intake led to a significant improvement in the body's weight, overall lean mass, and endurance after six weeks (Akkerman et al., 2020). The first weight rise was 46% attributable to lean tissue, which lends credence to the idea that TB may initiate a protein anabolic reaction in response to feeding. Vitamins and minerals might also be quite beneficial for the medical treatment of TB. Vitamin B6, vitamin C, intramuscular thiamin, oral multivitamin supplements, or TB treatment alone were administered to study participants in 110 new cases of active TB (Schwalb et al., 2023). The vitamin-supplemented groups all performed significantly better in terms of lymphocyte proliferation responses than the control group.

Studies conducted retrospectively on TB patients hospitalised in the ICU and suffering from respiratory failure suggest that improving the patient's diet early on may be as important to their survival over the long term as providing appropriate ATT and mechanical ventilation (Lemos et al., 2022). For TB patients to recuperate rapidly, supplemental nourishment may be a cutting-edge approach. Enhancing the nutritional status of the populace might also prove to be an effective tactic for lowering TB in developing countries.

NUTRITIONAL SUPPLEMENTS FOR TB

It has been demonstrated that using vitamin supplementation reduces the rate of TB recurrence (Patti et al., 2021). The addition of vitamins C and E enhanced the immune response of a multi-drug regimen for TB therapy (Calder et al., 2020). Supplementing with zinc and vitamin A boosted the effectiveness of anti-TB medicine (Zolfaghari et al., 2021). Better outcomes were indicated by the greater proportion of patients whose sputum tested negative for bacilli and the much lower mean lung lesion size. In adults who were infected with both HIV and TB and were not on drug therapy, starting micronutrient supplements at multiples of the recommended dietary allowance, such as 100 mg of selenium, 20 mg of vitamin B2, 100 mg of vitamin B3, 50 mg of vitamin B12, 500 mg of vitamin C, 200 mg of vitamin E, 20 mg of vitamin B1, 25 mg of vitamin B6, and 5000 IU of retinol, decreased the risk of TB recurrence (Kayode and Anaba, 2020). According to Young et al. (2020), patients who were HIV negative and received vitamin supplementation had a higher T cell count and a lower risk of problems.

A nutritious, nutrient-dense diet is thus essential for both preventing treatment-related adverse effects and facilitating the interaction between TB and the immune system. Dietary supplements can also support current treatment plans in TB control programmes (Kant and Tyagi, 2021). Thus it would be advantageous to also give patients dietary supplement advice.

PHARMACOLOGICAL TREATMENT OF TUBERCULOSIS

For more than 60 years, there have been effective medicines available. Some of these drugs are rifampicin, isoniazid, pyrazinamide, ethambutol, linezolid, fluoroquinolones, delamanid, clofazimine, bedaquiline, cycloserine/terizidone, meropenem/imipenem-cilastatin, amikacin, ethionamide/prothionamide, and P-aminosalicylic (Riccardi et al., 2021). Nevertheless, they usually take at least six months to affect a cure, and the efficacy of the therapies is in jeopardy due to a global rise in drug resistance. A 6-month course of combination treatment was shown to be effective in treating drug-susceptible TB in clinical studies conducted between 1948 and 1986 by the United States Public Health Authorities and the Medical Research Council of the United Kingdom with a 5-8% likelihood of relapse (Feng et al., 2023; Pereira et al., 2023). Relapse often occurs around a year following the end of therapy, indicating that the illness was only partially resolved (Dorman et al., 2021). Based on the

results of these trials, the duration of rifampin and isoniazid combined therapy can be shortened from 18 months to 9 months and can be further reduced to 6 months if pyrazinamide is added for the first 2 months of treatment. Fluoroquinolone was added to the first four months of therapy, but attempts to abbreviate the course of treatment failed in four recent studies, with recurrence rates ranging from 13 to 20% (Paton et al., 2023; WHO, 2022). The standard of treatment is therefore widely acknowledged to be a 2-month induction phase, followed by a 4-month stabilisation period, using the lowest possible doses of isoniazid and rifampin. According to Gopalaswamy et al. (2020), viable microorganisms in individual sputum samples have a distinctive biphasic death curve during the first two months of successful therapy. The suggestion was made that there could exist two separate microbial communities, with one responding to drugs more slowly and the other having a marked intrinsic sensitivity to drugs. The second type of bacilli, which proliferate slowly or not at all, are referred to as persistent bacteria. As per Dartois and Rubin (2022), persistent bacteria are believed to be in a state of altered metabolic function that renders them less vulnerable to drug destruction due to either an immediate modification in an external component (like oxygen levels or the PH level) or the generation of variations in phenotype consequent to host immunological pressure. One theory is that a combination of antimycobacterial drugs is beneficial in modern short-course regimens because of the inconsistent effectiveness of individual therapy against these various bacterial families (Aguilar Diaz et al., 2023). The clearest explication of this paradigm was provided by Mitchison, who distinguished between drugs that have "bactericidal" activity (i.e., the capacity to eliminate rapidly proliferating pathogens) and those that have "sterilising" activity (i.e., the capacity to eradicate non-reproducible or persistent bacteria) (Alffenaar et al., 2022).

CLASSIFICATION OF TUBERCULOSIS DRUGS

Drugs for tuberculosis (TB) are categorised into several groups according to their safety, effectiveness, and mode of action (Table 1) (Kayukova & Berikova, 2020).

Table 1. Classification of tuberculosis medications

Classes of Tuberculosis Drugs	Examples of tuberculosis drugs
First-line anti-TB drugs:	Isoniazid, Rifampicin, Ethambutol, Pyrazinamide, Streptomycin
Second-line anti-TB drugs:	Fluoroquinolones (e.g., Moxifloxacin, Levofloxacin), Macrolides (e.g., Clarithromycin), Carbapenems (e.g., Meropenem), Linezolid, Tedizolid
Third-line anti-TB drugs:	- Bedaquiline, Delamanid
Additive drugs:	Steroids (e.g., Prednisone), Immunomodulators (e.g., Thalidomide)

The following categorization is recognised by the World Health Organisation (WHO). The first-line drugs are the most effective and commonly used drugs for TB treatment. Second-line drugs are used for drug-resistant TB or when first-line drugs are contraindicated. Third-line drugs are reserved for severe cases of drug-resistant TB. Additive drugs are used to manage specific complications or side effects.

DRUG NUTRIENT INTERACTION

Research has shown that when anti-tuberculosis drugs are taken with meals, the absorption of isoniazid and rifampicin is decreased (Karballaei-Mirzahosseini et al., 2022). According to research on rodents, ethambutol decreases blood zinc levels by increasing urinary zinc losses and reducing absorption (Balhara et al., 2022). A well-known adverse effect of isoniazid medication is vitamin B6 deficiency, which can lead to peripheral neuropathy. It is known that this is uncommon in patients receiving dosages of isoniazid at about 5 mg/kg body weight, but that it frequently occurs in those receiving higher doses (Agarwal et al. 2023). In the less affluent areas of the community, isoniazid-induced peripheral nerve injury is frequently observed due to nutrient deficiency particularly vitamin B6 (Kramarz et al., 2024). And lastly, regardless of a person's gender, age, occupation, degree of education, or access to food, unfavourable pharmaceutical reactions are sometimes a result of malnutrition (Hiremath, 2021).

The Heartland National Tuberculosis Centre recommends that isoniazid and rifampin be taken one hour before or two hours after meals. If needed, it can be taken with a small snack. Supplementation with vitamin B6 is required. 25–50 mg is the suggested dosage range. Ethambutol can be taken with food. Para-aminosalicylic acid and pyrazinamide can be taken with meals or shortly thereafter (Heartland National Tuberculosis Centre, 2023).

TOXICITY

When considering the length of therapy for other microbiological infectious illnesses, the conventional 6-month regimen for drug-susceptible TB is quite long (Plata-Menchaca et al. 2022). The two key challenges that must be addressed for the prolonged regimen to be successful are controlling drug sensitivity and making sure that patients finish the whole term of therapy.

It can be challenging to obtain and complete TB therapy, especially when patients are food insecure, impoverished, and have trouble accessing healthcare; adherence failure leads to medicine resistance. Africa is seeing a multidrug-resistant TB epidemic. Effective adherence is enhanced by having a robust social network (Lal, 2019). Adequate instructions for patient surveillance, education, and an incentive to follow the patient are essential components of a TB control programme (Liu et al., 2023).

There is substantial drug toxicity, according to a review of earlier studies that used similar criteria; 3–13% of the subjects are thought to have liver-toxic effects (Shah et al., 2022); 15% of patients with drug-susceptible illnesses receiving traditional TB treatment experienced adverse drug reactions that required stopping or discontinuing one or more drugs (Lei et al., 2023). Hospitalisation, disability, or death resulted from 7.7% of these unfavourable reactions. Although a wide range of events were noted, hepatotoxic effects, gastrointestinal problems, allergic reactions, and arthralgias were the most common ones. According to Mbonde (2022), 16 to 49% of people do not complete the treatment regimen.

Many factors contribute to patients' reluctance to

continue treatment, such as drug side effects, the cost of medical care, stigma, and other concerns, as well as their belief that healing has happened when symptoms have subsided and microbes can no longer be found in the sputum (Navarro et al. 2021). These obstacles still exist, but programmes for direct observation and therapy support improve adherence.

PREVENTION OF DRUG RESISTANCE

Multidrug resistant TB remains a public health crisis and a security threat. Only about 2 in 5 people with drug resistant TB accessed treatment in 2022 (WHO 2023). To eradicate TB, resistant strains must be prevented from spreading. Drug resistance can be prevented by early identification and treatment, patient adherence to therapy, and TB detection in HIV and AIDS patients (Sharma et al., 2021; Chakaya et al., 2022). Global efforts to combat TB has so far saved not less than 75 million lives since the year 2000 (WHO, 2023).

MEASURES FOR TUBERCULOSIS ERADICATION

Treating individuals who have positive sputum smear test findings or who can spread the disease is the first step towards stopping the disease from spreading. Tests and therapy for these individuals can be conducted using directly observed treatment (DOT), a brief course. It's a commonly recommended TB control method that's quite effective and economical. One of the five elements of DOT is the standardised short-course ATT administered under direct and supporting observation. The other four are quality-assured diagnostic processes, controlled reporting and recordkeeping, and a steady supply of excellent anti-TB medications (Mussie et al., 2020).

CONCLUSION

In conclusion, millions of people worldwide are impacted by TB, which is still a common and sometimes fatal infectious illness. There are regional differences in TB prevalence, and high-burden nations have the most difficulty managing the illness. Since the main way that HPV spreads is through the inhalation of contagious respiratory droplets, living in close quarters and having frequent contact are important risk factors. Effective TB care depends on an accurate and timely diagnosis. Drug-resistant strains of TB are a serious hazard because their introduction reduces the effectiveness of pharmacological therapy. While some of these drugs can be toxic in some individuals, medical practitioners need to weigh this risk against the devastation the disease causes when untreated. In addition, treatment regimens can to some extent be varied to individual circumstances.

Sufficient nutrition is essential for boosting immunity and promoting TB patients' healing. Treatment results and the severity of the disease can both be worsened by malnutrition. To sum up, combating TB necessitates a multimodal strategy that addresses nutrition, early diagnosis, drug treatment, prevalence, and transmission while continuously aiming to reduce drug toxicity and battle drug resistance. International collaboration and funding for medical research and infrastructure are crucial to the continuous fight against this age-old yet recurrent illness.

AUTHOR CONTRIBUTIONS

Conceptualization: MTS, MA and MUK. Study design: MTS, SIRO. Literature search and synthesis: AA, MR, MI and MUK. Initial draft of the manuscript: MUK, MM: Critical reviews for important intellectual content: MTS, SIRO. MUK, MTS and SIRO participated in the revisions at various stages. All authors read and approved the final version of the paper and its submission for publication.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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