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Review

Malnutrition and tuberculosis: the gap between basic research and clinical trials

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Abstract

Mycobacterium tuberculosis (M.tb) is the causative agent of tuberculosis (TB), an infectious disease that leads to numerous deaths worldwide. Malnutrition, smoking, alcohol abuse, Human Immunodeficiency Virus infection, and diabetes are some of the most important risk factors associated with TB development. At present, it is necessary to conduct studies on risk factors to establish new effective strategies and combat this disease. Malnutrition has been established as a risk factor since several years ago; although there is in vitro experimental evidence that reveals the importance of micronutrients in activating the immune response against M.tb, evidence from clinical trials is controversial. Currently, nutritional assessment is recommended in all TB patients upon diagnosis. However, there is insufficient evidence to indicate micronutrient supplementation as adjuvant therapy or prophylactic to prevent micronutrient depletion. Strengthening the interaction between basic and clinical research is necessary to carry out studies that will help establish adjuvant therapies to improve outcomes in TB patients. In this review, we discuss the experimental evidence, provided by basic research, regarding micronutrients in the TB field. However, when these studies are applied to clinical trials, the data are inconsistent, indicating that still missing mechanisms are necessary to propose alternatives to the treatment of TB patients.

Key words: Malnutrition; tuberculosis; latent; diet; micronutrients.

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Introduction

Tuberculosis (TB) is an infectious disease caused mainly by the bacillus *Mycobacterium tuberculosis* (M.tb); although a low frequency of TB case is caused by *Mycobacterium bovis*, usually through a close contact with infected animals [1]. The World Health Organization (WHO) estimated that in 2018, there were 10 million TB patients and 1.2 million TB deaths. Some risk factors associated with the development of TB are human immunodeficiency virus (HIV) co-infection, malnutrition, smoking, diabetes mellitus (DM), and alcoholism. An estimated 2.3 million TB cases were attributed to malnutrition, which is above those attributed to HIV (0.81 million) and DM (0.36 million); thus, national efforts should be prioritized to identify TB patients and reduce TB incidence [2]. TB treatment depends on the susceptibility of M.tb strains to drugs. The first-line anti-TB drugs in susceptible cases are rifampicin, isoniazid, pyrazinamide, and ethambutol for two months, followed by isoniazid and rifampicin for four months, however, when the M.tb strain is resistant to rifampicin and isoniazid (MDR-TB), second-line drugs are required and administered for 18 to 20 months, and these drugs have more toxicity in comparison with drug-susceptible tuberculosis [3]. The predominant form is the susceptible TB (10 million worldwide) but unfortunately, taken the OMS data as reference, in 2018 was estimated there were about half a million persons worldwide developed TB resistant to rifampicin and resistant both rifampicin and isoniazid, thus the resistant TB form is in continually growing [2]. Interestingly, malnutrition in MDR-TB patients is associated with a higher mortality rate [4]. Considering the numbers of TB cases and disease incidence, it is urgent to find new strategies and therapies to shorten and optimize the TB treatment (especially in MDR),

and not least important is to reduce the risk of reactivation in latent TB. After M.tb arrives at the lung, the host activates an immune response to avoid the disease, but it is insufficient to eliminate the bacillus. Mostly, people maintain a latent infection state (latent TB) during their lifetime. WHO data indicate that 1.7 billion people globally have latent TB, and 5–15% of them will experience TB reactivation [5]. The principal factors associated with TB reactivation are HIV infection, anti-tumor necrosis factor (TNF) therapy, silicosis therapy, DM, and malnutrition [6-9]. Macro- and micronutrients are essential to the enhanced immune response against various pathogens, including M.tb. However, the molecular mechanism by which nutritional status triggers the immune response has not been fully elucidated. Malnutrition is a state of nutrition characterised by a deficiency in nutrients. The clinical presentation of malnutrition is diverse, and different diagnosis criteria are reported in the literature [10-12]. In this review, malnutrition refers to a condition that includes wasting (low weight-to-height ratio), body mass index (BMI, kg/m^2) < 18.5 in adults, and micronutrient deficiencies. In 2019, the State of Food Security and Nutrition in the World report showed an estimated 821.6 million hungry people (one in every nine people in the world), that is mainly distributed as 513.9 million in Asia, 256.1 million in Africa, and 42.5 million in Latin America and the Caribbean, thus, the new report in comparison to the previous report, is showing that the prevalence of malnutrition is slowly increasing [13]. Taking data from the previous report, we showed in Table 1 the number of undernourished people in the world during 2017 and 2018. This information provides an overview of the severe problem of malnutrition worldwide. In Mexico, epidemiological reports are alarming because 54% of Mexicans are living in poverty and 9.4 million in extreme poverty; consequently, they are more susceptible to malnutrition. In 2017, the United Nations Children's Fund reported that 51% of children in Mexico are living in poverty, and 2 in every ten children under the age of 5 are malnourished [14,15]. The main aim of this review is to discuss the experimental evidence generated from both *in vitro* and *in vivo* models, where the relevance of micronutrients in the anti-mycobacterial immune response is shown, and how it is in contrast to evidence from clinical trials. This knowledge is essential to achieve the eradication of TB, mainly in developing countries where there is a significant percentage of people who are at risk of developing TB because of malnutrition.

Table 1. Undernourished people in the world during 2017 and 2018.

World	2017	2018
Africa	**248.6**	**256.1**
Northern Africa	16.5	17.0
Sub-Saharan Africa	232.1	239.1
Eastern Africa	129.8	133.1
Middle Africa	43.2	44.6
Southern Africa	5.4	5.3
Western Africa	53.7	56.1
Asia	**512.4**	**513.9**
Central Asia	4.0	4.1
Eastern Asia	138.1	137.0
South-eastern Asia	61.1	60.6
Southern Asia	276.4	278.5
Western Asia	32.7	33.7
Western Asia and Northern Africa	49.2	50.6
Latin America and the Caribbean	**41.7**	**42.5**
Caribbean	7.7	7.8
Latin America	34.0	34.7
Central America	10.7	11.0
South America	23.2	23.7
Oceania	**2.5**	**2.6**

The number indicates millions of hungry people in the word during the years 2017 and 2018, and data is distributed by region and subregion.

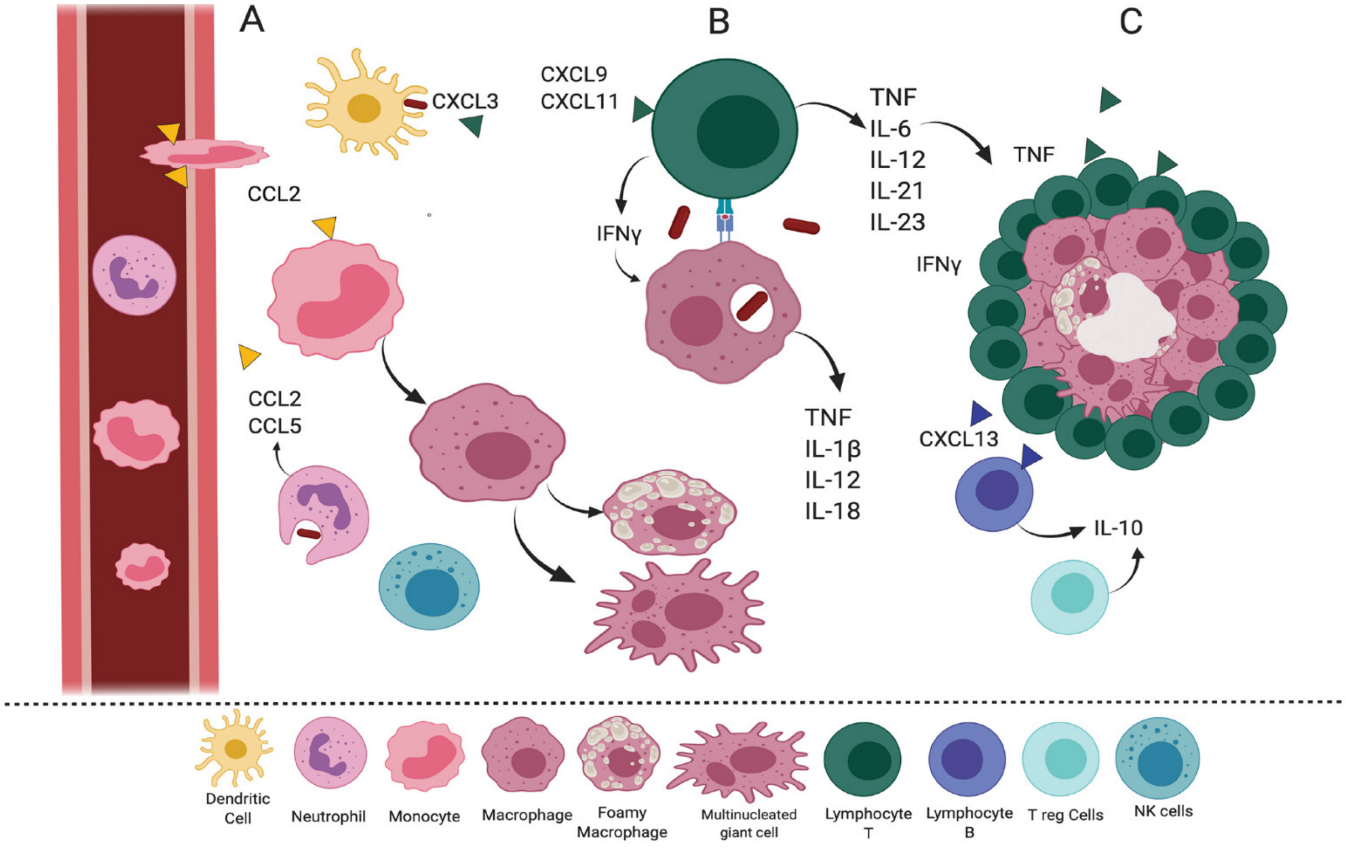
Immune response: from primary infection to latent TB

M.tb enters the host via the respiratory tract. Once in the alveolus, the bacillus is phagocytosed by the alveolar macrophage. This process is mediated by receptors, such as dectin 1 or 2, macrophage-inducible C-type lectin (Mincle), dendritic cell-specific ICAM-3-grabbing nonintegrin (DC-SIGN), and the mannose receptor [16-18]. Once in the cytoplasm, M.tb can activate evasion mechanisms of the immune response; one of the most useful is the inhibition of the fusion of the phagosome with lysosomes to promote its intracellular survival even under hostile conditions [19]. Circulating monocytes have been established as the main precursor of the alveolar macrophage. It was previously found that monocytes from TB patients exhibit mitochondrial damage, and they are more susceptible to cell death, suggesting that these cells may give rise to nonfunctional macrophages [20,21].

At the pulmonary parenchyma, M.tb induces the recruitment of immune cells at the infection site to form a highly organized cell structure called granuloma, where each cell subpopulation has specific functions. For example, dendritic cells and macrophages carry the bacilli to lymph nodes to activate the adaptive immune response [22]. Monocytes migrate from blood vessels to the lung mainly by CCL2-dependent signalling; they are differentiated into macrophages and specialized cells, such as epithelioid cells and multinucleated giant cells (Figure 1A) [23]. However, the bacilli can release

virulence factors in the granuloma to limit cell differentiation. For example, our group has shown that lipoarabinomannan (LAM), a glycolipid inserted in the mycobacterial cell wall, induces the differentiation of monocytes into immature macrophages that are unable to restrict mycobacterial growth [24]. Once the bacillus is phagocytized and degraded, the peptides are presented through specialized molecules to activate T lymphocytes, posteriorly, T cells secrete cytokines and chemokines that are needed to activate and recruit other cell populations (Figure 1B). The granuloma has a caseous center rich in lipids and eicosanoids (e.g., leukotriene B4), antimicrobial peptides (e.g., cathelicidins), reactive oxygen species, and residual amounts of bacilli. Moreover, whereas in the granuloma center is predominate the pro-inflammatory proteins, in the periphery, the anti-inflammatory proteins are predominate, suggesting that immune mechanisms coexist to regulate the granuloma structure [25]. Surrounding the granuloma center, there are layers of myeloid cells and T and B lymphocytes, which are recruited primarily by CXCL9-CXCL11/CXCR3 and CXCL13/CXCR5 chemokine axe (Figure 1C) [26]. CD4+ T cells produce TNF and IFNγ, which are cytokines that promote and maintain the granuloma formation, whereas B lymphocytes and regulatory T (Treg) cells produce IL-10 and TGF-β to induce the negative regulation of the immune response [27,28]. Interestingly, it has been reported that each granuloma, even from the same host, behaves independently with variabilities in the protection and control of mycobacteria [29]. The complexity in the granuloma formation dynamics still has several open questions, and clarifying them would provide invaluable

Figure 1. Immune response and formation of granuloma during M.tb infection.



After the bacillus enters the pulmonary parenchyma: (A) It has contact with innate immune system cells located at the site of infection, which release various chemokines, such as CCL2. The pro-inflammatory monocytes of the bloodstream express CCR2 and perform an extravasation process in response to the CCL2. The monocytes differentiate into macrophages and, subsequently, some of them will give rise to other specialized cells, such as foamy macrophages or multinucleated giant cells. (B) Macrophages degrade the bacillus and present mycobacterial antigens to CD4+ T cells, which are differentiated mainly from a pro-inflammatory profile Th1. The CD4+ T cells mainly produce IFNγ, TNF, and IL1β and help recruit more cell populations. (C) Finally, a highly organised cell structure known as a granuloma is formed, which has a home center rich in reactive oxygen species, lipids, eicosanoids, and a residual amount of bacilli. This is surrounded by uninfected macrophages (which limit mycobacterial growth and contribute to cytokine secretion) and foamy macrophages (which accumulate lipids and lose their phagocytic ability). Finally, there are various layers of lymphoid cells (subpopulations of T, B, and NK lymphocytes) that release pro-inflammatory chemokines and cytokines such as TNF, the main cytokine that maintains the structure of the granuloma. There is also the presence of regulatory cells that produce IL-10 and TGFβ. Figure was done using BioRender software.

information for the development of therapies aimed at maintaining the granuloma structure and avoiding TB reactivation.

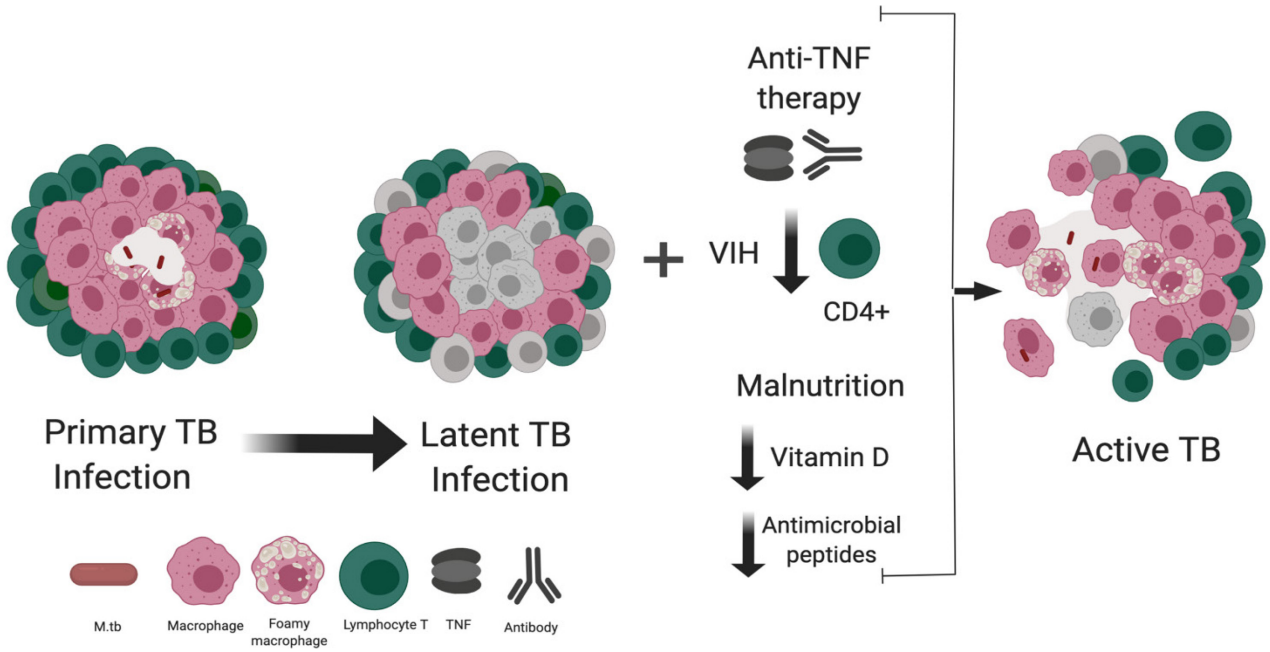
Immune response: from latent TB to active TB

Granuloma integrity could be disrupted in response to a bacillar charge increased inside the caseous center or immunodeficiencies in the host, which promote the spread of the and, consequently, an active TB [30]. M.tb induces the death of infected macrophages mainly by necrosis, favouring the release of the bacilli into the pulmonary parenchyma [31]. TB reactivation is related to immunosuppression factors in the host, such as HIV infection, malnutrition, and the use of anti-TNF therapy (Figure 2 A-C). TNF is one of the central regulators of the immune response in mycobacterial infections, not only from the perspective of its classic pro-inflammatory function but also, the transmembrane form of TNF is indispensable in activating suppressive cells and controlling exacerbated inflammatory processes [32-34]. Lipids were also described as one of the leading players in TB reactivation because M.tb uses the host cholesterol and lipid bodies of the foamy macrophage to maintain chronic infection [35]. Epidemiological studies indicate that malnutrition is one of the most important risk factors for TB reactivation. However, the specific alterations in the granuloma induced by malnutrition have not been completely clarified. Rahman et al. showed that granulomatous lesions from chronic pulmonary TB patients with vitamin D deficiency had reduced levels of antimicrobial peptides, such as cathelicidins (LL-37), in comparison with distal lesions of the lung parenchyma, suggesting that vitamin deficiency compromises an adequate cellular immune response specifically in granulomatous lesions [36].

Malnutrition and tuberculosis

Micronutrients are essential elements in the diet, which are needed for multiple physiological processes, such as energy production, immune responses, and other functions. The most studied micronutrients in the context of TB are vitamin A, vitamin D, and zinc. In this review, we discuss the experimental evidence that has led to clinical trials on these micronutrients. TB patients frequently exhibit weight loss, or they are malnourished owing to suboptimal protein intake, muscle catabolism induced by inflammation during infection, and gastrointestinal symptoms induced by acute-phase proteins, such high TNF levels [37]. Optimal micronutrient concentrations are critical because low vitamin A and D concentrations in HIV+ patients have been associated with an increased risk (2.6–4.3 times) of developing TB [38].

Figure 2. Factors associated with reactivation of *M. tuberculosis* infection.



(A) In primary M.tb infection, efficient immune response is activated, a granuloma is formed for infection control, and a latent TB state is consequently generated. (B) The presence of factors, such as anti-TNF therapy, HIV infection, and malnutrition, affects the immune response that limits bacterial growth. (C) The alteration of the immune response disrupts the granuloma and favours the spread of the M.tb bacilli. Figure was done using BioRender software.

Vitamin A

Vitamin A is obtained from the diet in the form of all-*trans*-retinol (ATR), retinol esters, or β-carotene. Retinol circulates in the blood, forming a complex with retinol-binding protein and transthyretin. ATR is esterified and stored in the liver, and retinol and β-carotene are oxidized to all-*trans*-retinal in tissues by the action of alcohol dehydrogenases. Then, the retinal is oxidized to *all-trans*-retinoic acidic (RA) by retinal dehydrogenases, which is the active metabolite of vitamin A [39]. Vitamin A promotes immune functions, increases IL-2 secretion, and consequently, T-cell proliferation, and depending on microenvironment conditions, and it may enhance or suppress the proliferation of B lymphocytes [40]. Moreover, inflammatory stimuli, such as TNF, have even been shown to encourage RA to enhance dendritic cell maturation and antigen presentation capacity [41]. In the context of TB, evidence from *in vitro* studies showed that RA is needed by infected monocytes or macrophages to mediate antimicrobial mechanisms through an NPC2-dependent pathway, and under this condition, the cellular cholesterol decreases and improves antimicrobial activity [42]. Previously, an animal model showed that hypercholesterolemia increases susceptibility to M.tb infection owing to the induction of a weak proliferative response and delayed activation of adaptative responses [43]. A higher ability to produce nitric oxide to avoid the intracellular survival of M.tb was shown in an *in vitro* study using human macrophages (U937 cell line) stimulated with RA before M.tb infection [44]. In an *in vivo* model, the use of RA as a therapeutic agent was suggested; M.tb-infected rats that received RA showed less severity of TB histopathology and decreased the number of colony-forming units, and their alveolar macrophages secreted high levels of TNF and IL-1β [45].

Vitamin D

Vitamin D is obtained as vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol). D_2 is consumed in the diet, but less than 0.1% is metabolised, whereas D_3 is produced by photolysis and activated in the liver via 25-hydroxylase to 25-hydroxyvitamin D, and as a secondary pathway, 25-hydroxyvitamin D is lysed in the kidney via 1-hydroxylase to the active form 1α25-dihydroxy vitamin D_3 ($1,25(OH)_2D$)-calcitriol. Thus, vitamin D binds to the vitamin D receptor (VDR) and regulates the expression of genes related to the activation of immune responses [46].

There is increasing evidence on the role of vitamin D in TB. Studies have been performed in both animal models and *in vitro*. A murine TB model showed that the VDR/vitamin D interaction induces cathelicidin synthesis (LL-37) and increases the mortality rate [47]. It has also been suggested that D_3 treatment promotes monocyte-to-macrophage differentiation and increases phagocytosis mediated by the mannose receptor [48]. Other studies suggest that treatment with D_3 enhances autophagy dependently with LL-37 and promotes lymphoproliferative processes [49]. In vitro, by adding vitamin D, to cultures of cells from subjects with serum deficiency, the expression levels of antimicrobial peptides were increased, and the fusion of phagosome/lysosome in infected macrophages was improved [50]. Experimental studies suggested that vitamin D also has implications in adaptive immunity regulation; the stimulation of cells with vitamin D and mycobacterial antigens promotes differentiation to Treg cells and decreases chemokine levels, suggesting that it regulates exacerbated inflammatory processes [51]. It can also regulate the inflammatory process by regulating the Cdx2AA gene in T cells and inhibit Th17 cell differentiation through NFκB [52,53].

Zinc

Zinc plays a vital role in the structure and function of proteins; approximately 10% of proteins bind to zinc, including cytokines, transcription factors, and enzymes. In animal models, zinc deficiency has been shown to cause thymus atrophy and lymphopenia with increased risk of infections [54]. Numerous studies suggest that zinc is essential for homeostasis and immune system function; its deficiency decreases the phagocytic activity of macrophages, as well as their ability to recycle nutrients and defend against intracellular pathogens [55]. It is not surprising that zinc deficiency is associated with impaired immune responses against M.tb infection. It has been reported that zinc accumulation in phagosomes is required to shorten the life span of phagocytic pathogens [56]. Zinc transporter proteins (Zrt) are responsible for the biodistribution of zinc. There are several groups of these proteins, and Zrt-/Irt-like proteins (ZIPs) are one of them. During in vitro infections with M.tb, the expression patterns of various ZIPs were observed to change; for example, the expression levels of ZIP10 and ZIP8 decrease and increase, respectively, indicating that M.tb alters zinc homeostasis [57]. Patients with active TB and MDR-TB have low levels of zinc at diagnosis moment, but the zinc level increases after anti-TB treatment [58,59]. This alteration in zinc homeostasis is partly explained as a host strategy against the pathogen; however, the

mechanism by which zinc functions in M.tb control has not been fully elucidated.

Clinical studies using micronutrient supplements in TB

Basic research showed the importance of micronutrients in the immune system and their role in infections, and numerous clinical trials have been performed to evaluate the effect of micronutrient supplementation on subjects at risk and those with active TB. Surprisingly, while data obtained *in vitro* or animal models show the relevance of micronutrients in the anti-mycobacterial immune response, there is no reliable evidence from clinical studies for recommending supplementation strategies as adjuvant therapy for TB and more clinical research is needed to elucidate the molecular mechanisms that remain unclear.

Vitamin A and Zinc as adjuvant therapy in tuberculosis

In a study on TB patients, a daily supplement of multivitamins (A, B, C, E, and selenium) decreases the risk of early relapse (45%), and in HIV+TB patients, increased CD4+ T cell counts improve peripheral neuropathy [60]. In another study on TB patients, vitamin A and zinc supplementation promote sputum conversion only in the first four weeks without differences within two months [61]. Zinc supplements during anti-TB treatment in children did not show improvements on the radiological outcome or weight gain [62]. In TB patients from Mexico, supplementation of vitamin A and zinc in 3 months increased TNF and IFNγ concentrations and decreased IL-10 levels [63].

Vitamin D as adjuvant therapy in tuberculosis

Although studies have been published for more than a decade that associate vitamin D deficiency with an increased risk (up to five times more) of developing TB in subjects with latent TB, some current studies have not supported such finding. No clinical benefit has been demonstrated in systematic reviews in patients with active TB or HIV-infected patients [64,65].

A study that analyzed the effect of vitamin D supplementation on patients with TB and HIV+TB patients showed no difference in mortality [66]. However, in other studies involving TB patients receiving 2.5 mg of vitamin D, the median conversion time of the culture was shorter in the group that received vitamin D than in the group that did not [67]. Moreover, in the SUCCINCT (Study Supplementary Cholecalciferol in recovery from tuberculosis), TB patients received 600,000 UI of vitamin D intramuscularly at 0 and 4 weeks after treatment, and it was found that in subjects with a baseline deficiency of this micronutrient and who received the supplement, clinical and radiological improvements were accelerated significantly. An increase in post-stimulus IFNγ levels was also observed *in vitro* with ESAT-6 and CFP-10 [68]. In another study on patients with the genotype vitamin D receptor TaqI polymorphism tt, who received high doses of vitamin D during the intensive phase of treatment, their conversion of the culture was accelerated, and their lymphocyte and monocyte count increased at eight weeks [69]. Some clinical trials analysed the effect of supplementation at different dosages and times of administration.

New studies have been designed, and recently a report evaluated the supplemental efficacy of vitamin D_3 to reduce the incidence and mortality of pulmonary TB in patients co-infected with HIV, this study was called the Trial of Vitamins-4 (ToV4), patients were recruited between 2014 and 2017, but their results suggested that there was no difference between vitamin D_3 and placebo groups. [70]. A clinical study in phase II is being conducted in South Africa, it has as aim establish a shortening of the time of anti-TB treatment using multiple adjunctive host-directed TB therapies, and one of them is an experimental intervention with vitamin D_3 [71]. There is a recent study named ResolveD-TB, which will determinate if vitamin D_3 has the potential to prevent recurrent TB. A dietary supplement with vitamin D_3 was given to patients who finished anti-TB treatment, and they had chronic inflammation in the lung, which was detectable by positron emission tomography (PET) [72]. Few studies have evaluated vitamin D as prophylaxis for the development of TB, and some studies suggest that in groups at risk, vitamin D levels should be quantified, and underlying diseases that cause its deficiency, such as Crohn's disease, should be considered [73]. In South Africa, the number of cases of vitamin D deficiency in HIV patients was shown to increase in winter. However, when the patients received doses of 50,000 UI of cholecalciferol for six weeks, it was observed that their leukocyte counts increased [74]. These lines of evidence and the close relationship seen among micronutrient deficiency, HIV infection, and TB development should be considered more research about the use of vitamin D as adjuvant therapy for prophylaxis in groups at risk.

Perspectives

There is extensive evidence on the role of malnutrition in M.tb infection and in *in vitro* assays on micronutrient involvement to strengthen the immune

system. However, there is a lack of strong evidence on the use of nutrient supplements from clinical trials. Experimental studies *in vitro* or animal models have not sufficiently clarified the cellular activation pathways involved in response to micronutrients. It is still necessary to search for new knowledge that will reinforce the relevance of the use of micronutrients in clinical trials, in order to develop clinical interventions that will help TB patients improve their quality of life. Even within basic research, few models allow the study of the relationship between micronutrient deficiency and M.tb infection, showing the need to develop more accurate models to find adjuvant therapies that expedite the elimination of the pathogen. Recent research focuses on the study of micronutrients from the perspective of maintaining a healthy gut microbiota, not only to assess the proper absorption of micronutrients but also to propose that the gut microbiota is essential for maintaining homeostasis in the immune system. Malnutrition status also affects the response to anti-TB drugs and is associated with an increased risk of relapse diseases. In developing countries, nutrition status is relevant because significant numbers of TB cases are attributable to undernourishment, leading the countries: India, Pakistan, China, Philippines and Indonesia. Whereas in the region of the Americas, the first countries with TB cases associated with malnutrition are: Haiti, Peru, Brazil, Bolivia and Venezuela [2]. In the Latin American population, few clinical trials assess the impact of malnutrition on tuberculosis. For now, WHO recommends an assessment of nutritional status at baseline in all TB patients and an assessment of post-treatment weight gain, thus TB patients should have an adequate diet with macro- and micronutrients, and if this diet is not guaranteed, supplements can be provided to them. Surprisingly, the doses of supplements together with treatment time have not yet been standardised, reinforcing the urgent need to elucidate the optimal amounts of each micronutrient and when to start supplementation. Nowadays, the treatment of TB should be a comprehensive approach, not only looking for a bacteriologic cure but also focusing on nutritional management, psychological and evaluation of pulmonary sequelae [75]. Therefore, we suggest that National TB Programs must go beyond just providing a pharmaceutical treatment; these programs should evaluate nutritional deficiencies to supply an adequate nutritional supplementation to TB patients, in order to improve quality of life and treatment outcomes.

Authors' contributions

NATN and LCG conceived the original idea. NATN and LARM wrote the manuscript, NATN made the figures, MMT and IAOP provided a critical reading of the manuscript, LCG designed and supervised the manuscript.

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