Tuberculosis and malnutrition: The European perspective

J. Ockenga [a,*], K. Fuhse [a], S. Chatterjee [b], R. Malykh [b], H. Rippin [b], M. Pirlich [c], A. Yedilbayev [b], K. Wickramasinghe [b], R. Barazzoni [d]

[a] Department of Gastroenterology, Endocrinology and Clinical Nutrition, Klinikum Bremen Mitte, Bremen, Germany
[b] Division of Country Health Programmes, WHO Regional Office for Europe, Copenhagen, Denmark
[c] Imperial Oak Outpatient Clinic, Endocrinology, Gastroenterology and Clinical Nutrition, Berlin, Germany
[d] Department of Medical, Technological and Translational Sciences, University of Trieste, Ospedale di Cattinara, Trieste, Italy

ARTICLE INFO

Article history:
Received 29 October 2022
Accepted 26 January 2023

Keywords:
Tuberculosis
Malnutrition
Chronic disease
Public health
Nutritional status
Treatment outcome

SUMMARY

Tuberculosis (TB) is a leading infectious cause of death worldwide, despite ongoing efforts to limit its incidence and mortality. Although the European Region has made gains in TB incidence and mortality, it now contends with increasing numbers of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). Malnutrition is a major contributor to the burden of TB and may also be directly caused or enhanced by the onset of TB. The presence of malnutrition may worsen TB and MDR/RR-TB related treatment outcomes and contribute to growing TB drug-resistance. Preventing and treating all forms of malnutrition is an important tool to limit the spread of TB worldwide and improve TB outcomes and treatment efficacy. We carried out a scoping review of the existing evidence that addresses malnutrition in the context of TB. Our review found malnutrition increased the risk of developing TB in high-burden settings and increased the likelihood of developing unfavorable treatment outcomes, including treatment failure, loss to follow-up, and death. The potential impact of nutritional care and improved nutritional status on patient prognosis was more difficult to evaluate due to heterogeneity of patient populations, treatment protocols, and treatment durations and goals. High-quality trials that consider malnutrition as a major risk factor and relevant treatment target when designing effective strategies to limit TB spread and mortality are needed to inform evidence-based practice. In TB patients, we suggest that widespread and regular nutritional screening, assessment, and counselling, has the potential to increase effectiveness of TB management strategies and improve patient quality of life, overall outcomes, and survival.

1. Introduction

Tuberculosis (TB) is a leading infectious cause of death worldwide, with an estimated 1.4 million deaths in 2019 [1]. The worldwide incidence of TB in 2019 numbered approximately 10 million [1]. Drug-resistant TB (to at least rifampicin and isoniazid, the two most potent and effective TB drugs) represented almost half a million cases, with the largest burdens affecting India, China, and the Russian Federation. Countries comprising Eastern Europe and Central Asia also made up the highest proportion of previously treated multidrug-resistant TB (MDR-TB) cases globally (>50%). In the *Tuberculosis surveillance and monitoring in Europe, 2019* report the World Health Organization (WHO) European Region made gains in TB incidence and mortality rates, but this was offset by an estimated 70,000 new cases of multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB) in 2019, greatly exceeding the global average [2].

Despite the significant strides made to tackle TB, all WHO regions are falling short to varying degrees of the targets set by the WHO's End TB Strategy to decrease TB incidence by 90% and mortality by 95% between 2015 and 2035 [1,2]. This may be explained by various factors, such as the growing burden of HIV-associated TB, antituberculosis drug-resistance, access to rapid diagnosis of TB leading to greater numbers of diagnosed cases, and socioeconomic conditions that promote and exacerbate TB [3]. Among the

* Corresponding author. Department of Gastroenterology, Endocrinology and Clinical Nutrition, Klinikum Bremen Mitte, Bremen, Germany.
E-mail addresses: johann.ockenga@klinikum-bremen-mitte.de (J. Ockenga), katrin.fuhse@gesundheitnord.de (K. Fuhse), sachatterjee@who.int (S. Chatterjee), malykhr@who.int (R. Malykh), rippinh@who.int (H. Rippin), matthias.pirlich@googlemail.com (M. Pirlich), yedilbayeva@who.int (A. Yedilbayev), wickramasinghek@who.int (K. Wickramasinghe), barazzon@units.it (R. Barazzoni).

latter, hunger-related malnutrition predisposes individuals to TB (increasing the risk by 6–10 times) and is a risk factor for the progression of latent TB infection to active TB, with the reactivation of latent TB often heralded by a low body mass index (BMI) [4]. The risk of TB has been found to increase by 13.8% with each unit decrease of BMI [5]. Malnutrition now represents the leading risk factor for acquiring TB, surpassing that of HIV, and was attributable for 2.3 million cases in 2019 [2]. Poor nutritional status in MDR-TB is associated with a longer time to sputum conversion [16], worse treatment outcomes [6], and higher mortality [4,7]. Multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) patients presenting with malnutrition have a greater risk of experiencing ≥3 side-effects of treatment (OR 1.5, 95% CI 1.1–2.1) and death (OR 1.9, 95% CI 1.1–3.5) compared to nutritionally replete patients [7].

Indeed, the association between TB and malnutrition is bi-directional since malnutrition may also result from TB itself, driven by inflammation-related cachexia, anorexia, and malabsorption [8]. TB-induced malnutrition is characterized by a loss of fat-free mass regardless of BMI, including in individuals living with obesity and overweight [9]. Similarly, non-communicable diseases (NCDs) can cause undernutrition/malnutrition (i.e., disease-related malnutrition) [10], with the highest prevalence of NCDs found within the WHO European Region [11]. TB is commonly accompanied by comorbidities such as diabetes, smoking and alcohol or substance abuse (risk factors for NCDs), which also carry their own nutritional consequences.

Poor nutritional status, a common cause of secondary immunodeficiency, is implicated in impaired innate and adaptive immune responses by attenuating or inhibiting aspects of the mycobactericidal response, cell-based immunity, and cytokine release (such as tumor necrosis factor α (TNF-α), interferon γ (IFN-γ), and interleukin 12 (IL-12)) [12]. Studies show a skewing of the cytokine response away from the T-helper type 1 (Th-1) response and its impaired induction, critical to the adaptive immune defense against intracellular pathogens [4]. It follows that diagnostic testing for TB, including IFN-γ release assays and tuberculin skin testing, may have reduced sensitivity for detection in the presence of malnutrition, although studies have reported mixed findings [4]. In addition, deficiencies in the opsonic capacity of complement factor C3, phagocytic ability and function of macrophages, and antigen presentation, are shown to be associated with malnutrition [13].

Aside from malnutrition characterized by reduced BMI, deficiencies in micronutrients are frequent in patients with TB and may impair immunity through several mechanisms. For example, vitamin D has known immunomodulatory properties and its deficiency has been recognized as a risk factor for airway infections including TB [14]. Zinc and copper deficiency may also limit the mycobactericidal response [15]. Nutritional status can also influence vaccine response; malnutrition has been shown to be associated with a delay in reactivity following BCG vaccination [16]. Moreover, a low BMI, deficiency in micronutrients, malabsorption, and diarrhea, are all associated with reduced vaccination effectiveness [17].

Altered body composition or impaired gastrointestinal function due to undernutrition may alter the pharmacokinetics and pharmacodynamics of TB medications and can result in treatment failure or increased toxicity [18]. This phenomenon is also observed in cancer patients who experience higher toxicity and lower tolerance to chemotherapy in the presence of malnutrition, particularly due to low skeletal muscle mass [19,20]. Malnutrition-associated changes may result in variable drug absorption, volume of distribution, serum concentrations, drug efficacy, and drug toxicity, and can lead to suboptimal dosing, treatment failures, and the development of drug resistance [21,22].

Addressing (mal-)nutrition and its impact on TB has the potential to yield benefits not only for tackling the TB pandemic, but also precipitate a cascade of improvements for public health in general, and advance progress toward Sustainable Development Goals (SDGs) 1, 2, and 3 (no poverty, zero hunger and good health and well-being, respectively). The growth of MDR/RR-TB and its more severe forms have also renewed interest in the role of nutritional interventions as a preventative and therapeutic tool. The following scoping review was planned and performed to provide an updated overview of the current evidence related to the effects of nutrition on TB and MDR/RR-TB. The flow-on public health consequences, recommendations for health systems, and future research needs are discussed.

2. Methods

This scoping review was performed in collaboration with the WHO European Office for the Prevention and Control of Non-communicable Diseases and the European Society for Clinical Nutrition and Metabolism (ESPEN) to collate and review the current literature available related to TB and malnutrition. In preparing the review, we were guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist [23].

We performed a search of PubMed for literature published from January 01, 2000, until December 31, 2021, with a combination of the search terms “tuberculosis” and “malnutrition”, “diet”, or “nutrition”, together with the clinical trials filter. As TB poses a major health problem in Eastern Europe and Central Asia, an additional search for Russian language studies was performed through Google Scholar, Cyberleninka, and PubMed with a Russian language filter. Electronic archives of medical journals specializing in TB were also searched. The 2013 WHO operational guideline *Nutritional care and support for patients with tuberculosis* was used to inform the search terms and search strategy [24].

We included randomized controlled trials (RCTs) or observational trials with adequate control groups which examined the effect of nutritional interventions/dietary counselling in patients with TB. Special interest was given to studies which reported key outcome effects of nutritional interventions on body weight, body composition, handgrip strength, and TB recovery rate, and these results are summarized in Table 1. See Fig. 1 for flowchart of studies screened in the search on these defined outcome measures. Additional relevant controlled trials found using a snowballing approach and which reported a TB-related outcome or proxy outcome are also discussed in the results. Trials without an adequate control group were excluded.

Three authors, a dietitian (KF), a WHO consultant and clinician (RM), and a physician (JO), independently searched and reviewed studies for inclusion and summarized relevant findings.

3. Results

Screened studies examined a range of interventions related to dietetic treatment and calorie/protein intake, micronutrient supplementation, and perioperative nutritional support. Interventions varied in effect on various TB outcome measures. Outcomes related to at least one of weight, body composition, handgrip strength, or TB recovery rate, are summarized in Table 1 and Supplementary Tables 1 and 2 Additional studies with other outcome effects are also included in the results below.

3.1. Dietetic treatments

Most of the reviewed interventional studies based on increasing calorie and protein intake had a positive effect on body weight [25–27], handgrip strength [25,26,28], as well as on TB healing [26]

Table 1
Outcome effects of nutritional interventions on body weight, body composition, handgrip strength, and TB recovery rate. The numerator represents the number of studies that found a positive effect in relation to the total number of relevant clinical studies shown in the denominator (for more details see Supplementary Tables 1 and 2).

Intervention	Body Weight ↑	Body Composition ↑	Handgrip Strength ↑	TB Recovery Rate ↑
Dietary counselling and/or energy-protein-supplements	4/5	1/2	3/3	2/3
Micronutrients	3/5	0/1	1/1	0/1
Zinc	0/2			0/1
Vitamin A				0/1
Vitamin D				1/5
Zinc + Vitamin A	0/1			1/2

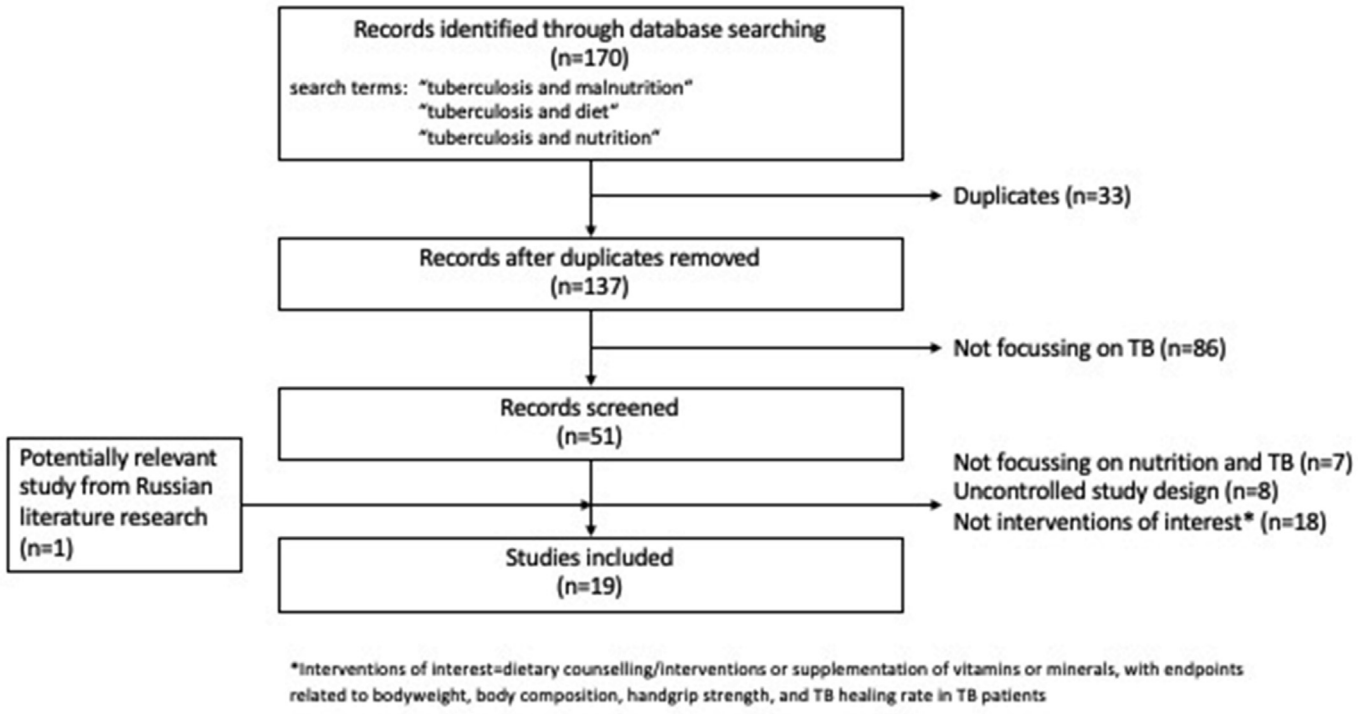

Fig. 1. Flowchart of study selection for defined outcome measures as shown in Table 1 (for further information see Methods).

(see Table 1 and Supplement). A positive change in body composition, by increasing fat-free mass or body cell mass, occurred in 50% of studies [25]. It should be noted that interventions were markedly heterogeneous: all studies used oral nutritional supplements or food supplements (e.g., sweet balls, whole meals, or biscuit bars; for more information see Supplementary Table 2) [26–29], sometimes combined with nutritional counselling [25]. Two studies aimed for an energy intake of 35 kcal/kg bodyweight per day [25,26]. One observational study found that MDR-TB patients exhibited lower body weight and fat-free mass over time despite a similar intake of energy, protein, and fat to drug-sensitive TB patients [30].

3.2. Micronutrient supplementation

The effects of micronutrient supplementation are not conclusive and there is currently no reliable evidence that routine micronutrient supplementation at or above recommended daily amounts is of clinical benefit [28,31–35]. Limitations included heterogenous study design and quality. Further, data collection occurred largely in developing countries, and may not be generalizable to European populations.

Four studies did not find any significant effect of supplementation with zinc [31,32,36,37], neither did three studies for vitamin A/ß-carotene [37–39]. Three studies investigated the effect of combined supplementation of zinc and vitamin A [37,40,41] of which one showed a positive effect on sputum conversion rate [40]. One study found no distinct positive effect of combined zinc, vitamin A and fish oil supplementation [42]. Furthermore, two studies examined the impact of vitamin E with conflicting results. Vitamin E supplementation was associated with an increased risk for TB by 72% in patients who smoked heavily [39]. However, another study found vitamin E improved the immunity against TB by increasing immunoglobulin G (IgG) and M (IgM) levels as well as CD4+ and CD8+ lymphocyte counts [43]. Vitamin D supplementation was examined in six studies [38,44–48], of which one found positive effects on sputum conversion rate [44], whereas the others found no effect. In one study, vitamin C may have lowered the risk for TB [39].

Iron [49] and arginine [50] were not associated with any beneficial effects. Low plasma ferritin, however, was associated with an increased risk of treatment failure and TB recurrence while high plasma ferritin (probably as marker of inflammation) was associated with an increased risk of overall mortality in TB patients [51].

A cholesterol-rich diet appeared to have positive effects on sterilization of sputum culture, bacillary population, and sputum production, but not on respiratory symptoms [52].

3.3. Perioperative nutritional support

One control-arm study found positive outcomes of perioperative nutritional support in TB patients: body weight and albumin levels did not decrease compared to the control group and total wound drainage was lower [53]. A study from the Russian Federation also found positive effects of perioperative enteral nutrition in TB patients [54].

4. Discussion

Our review found an increased risk of developing TB due to malnutrition in high-burden settings, as well as an increased risk of developing unfavorable TB related treatment outcomes, including treatment failure, loss-to-follow up, and death. Evidence for the potential impact of nutritional care and improved nutritional status on patient prognosis was more difficult to evaluate due to heterogeneity of patient populations, treatment protocols, and treatment durations and goals.

Some studies [26,29] indicated promising beneficial effects of optimized nutritional treatment on patient prognosis and response to drug therapy. A Cochrane analysis on nutritional supplements in active TB, which included published data up to February 2016, assessed the effects of oral nutritional supplements (food, protein/energy supplements or micronutrients) on TB treatment outcomes and nutritional recovery in people on anti-tuberculous drug therapy for active TB [55]. It reported a positive signal on body weight, but not on other TB treatment outcomes. Many of the studies included in this Cochrane review had heterogeneous interventions and were underpowered.

The inherent role of nutrition in the TB pandemic highlights the importance of addressing malnutrition to combat its spread. TB-associated malnutrition can worsen prognostic outcomes, increase the severity of disease, render treatments less effective, and increase the risk of relapse [56]. Patients with TB often present in parallel with smoking, alcohol, or other substance abuse, all of which confer additional risk for malnutrition. Malnutrition can also increase the risk of developing frailty, disability, and complications, with worse outcomes in many disease conditions [57]; as such malnutrition is not only a risk factor for TB but also an important treatment target.

Adequate nutritional intake has the potential to support and increase treatment adherence and outcome in patients with TB. Nutritional supplementation support during directly observed treatment strategy (DOTS) is associated with a favorable treatment response [58]. Moreover, the WHO operational guidelines on nutritional care and support for patients with TB recommends personalized nutritional assessment and management, incorporating nutritional counselling and interventions, to counter the potential for treatment failure [24].

Many country experiences have highlighted that food insecurity poses one of the largest barriers to accessing and adhering to TB treatment, as does the increased financial vulnerability brought about by the condition and associated treatment cost. Poverty underlies many of the factors associated with poor nutritional status: sanitation, overcrowding, access, and availability of healthcare, and social stigma associated with TB [3]. Climate change as well as the recent COVID-19 pandemic have laid bare the precarious nature of food security and will undermine attempts to redress malnutrition, particularly among lower socioeconomic groups and low- and middle-income countries [59,60]. Programs that provide a safety net for the provision and acquisition of food have seen an attendant rise in adherence with TB treatment [61]. Nutritional support for patients and their families is an important incentive that increases compliance with treatment regimens and can also help protect patients from the sometimes catastrophic household costs associated with TB [62].

A new more holistic definition of malnutrition has recently been proposed by the Global Leadership Initiative on Malnutrition (GLIM) [57], which recognizes the multifaceted nature of the condition. The top five ranked diagnostic criteria include three phenotypic (weight loss, low BMI, and reduced muscle mass) and two etiologic criteria (reduced food intake or assimilation, and inflammation or disease burden). To diagnose malnutrition, at least one phenotypic criterion and one etiologic criterion should be present, and malnutrition may therefore also be present in patients with normal or even high BMI, particularly in the presence of NCDs and comorbidities [57]. Applying a more comprehensive framework to the diagnosis of malnutrition can ensure more patients, including those with TB, are screened and identified in a timely manner.

4.1. Recommendations

In view of the results of this review and considerations above, the following recommendations are suggested for policymakers and health systems for the systematic inclusion of nutritional status, its assessment, and nutritional care in the prevention and treatment of TB and MDR/RR-TB.

4.1.1. Screening and diagnosis of malnutrition in TB

The prevention of malnutrition among the general population, but particularly so in at-risk groups and in regions where TB is endemic, requires the re-alignment of health systems to encompass nutritional needs with the provision of universal coverage of essential nutritional interventions. Examples of high-risk individuals include people living with chronic diseases such as liver disease, high alcohol intake, the elderly and frail, immunosuppressed individuals and vulnerable social groups (e.g., incarcerated populations, the military, people living in overcrowded settings). Validated and prosaic nutritional screening and diagnostic tools are available and can be implemented by healthcare professionals (e.g., nurses) with minimal training. These include the Malnutrition Universal Screening Tool (MUST) for malnutrition risk screening in the general population [10]. Indication for screening can be based on a simple clinical assessment gauged with questions such as:

- How is your appetite?
- Are you eating normally?
- Has your body weight changed?
- Have you lost weight unintentionally?
  Persons with low BMI below 20 kg/m^2, unintentional weight loss and reduced spontaneous food intake, or intercurrent or chronic disease warrant particular attention. If screening indicates a risk for malnutrition, the GLIM criteria [57] can be used to diagnose malnutrition.

Malnutrition screening and systematic assessment of nutritional status should be performed at diagnosis and regularly (every 4 weeks) throughout the course of TB treatment in all TB patients, with high priority given to patient groups at potentially higher nutritional risk as described above. Systematic nutritional assessment should include a nutrition-oriented history and examination, anthropometric assessment, and dietary and laboratory assessment when appropriate.

4.1.2. Management of malnutrition

Patients with malnutrition or at risk of malnutrition should be assessed by a professional dietitian or other nutrition specialist for counselling and therapeutic and supplementary feeding where required, with the goal of improving nutritional status, including weight gain and/or muscle mass. Given the association between body weight and clinical outcomes, diet optimization should also be performed in normal BMI individuals to mitigate against weight loss during the course of TB. Enhanced food intake and medical nutrition when food intake is not sufficient to cover nutritional goals through oral nutritional supplements and enteral or parenteral nutrition is determined according to the indication (for further information see: https://www.espen.org/guidelines-home/espen-guidelines).

4.1.3. Nutritional goals

Despite a prescribed energy intake of up to 35 kcal/kg bodyweight per day in some studies found in our review, the literature does not identify optimal nutrition targets in terms of calorie and protein intake for TB patients at risk of or with malnutrition. Guidelines, such as those from the ESPEN [63,64], recommend a general energy intake goal of 30 kcal/kg bodyweight per day and at least 1 g protein/kg bodyweight per day, with adjustments based on disease-specific or age-related recommendations, individual assessment, and follow-up. Recommended daily allowances for micronutrients should be ensured, with adequate provision through medical nutrition in patients undergoing nutritional treatment. Sustained micronutrient supplementation should be limited to patients with proven deficiencies. Provision of nutritional support throughout the entire duration of TB treatment should be encouraged to promote treatment adherence and be considered as part of routine programmatic management of TB and MDR-TB. Not only will nutritional recovery reduce the risk of complications from TB, but also assist with earlier return to normal work.

4.2. Future research

Our scoping review highlighted the existing data on malnutrition in TB, with a need for more data from European populations. Heterogeneity existed in study design, patient populations, treatment protocols, quality, and interventions. There remain considerable research gaps on the effects of nutrients on TB, immunity, and malnutrition. Trials designed with sufficient power that capture different populations should also be a priority to determine the caloric demands of patients with TB to provide adequate replacement, the role of nutritional supplementation and physical exercise in the management of TB, and the management of refeeding. Elucidating the precise mechanistic basis of nutrition on host defense against TB and the metabolic and immunological sequelae of malnutrition can also guide future research directions and potential therapies. Examining the impact of off-target effects of nutritional interventions, such as on economic productivity, mitigation of transmission risk, and household financial distress are also important. Further implementation research on integrated care delivery for TB and nutrition with the development of sustainable systems to provide locally acceptable nutritional supplements is also needed.

4.2.1. Optimal nutritional treatment regimens

The authors recommend the commissioning of high-quality, ideally randomized-controlled studies on the impact of nutritional treatment with standardized protocols on TB outcomes, including survival, nutritional status, quality of life, TB activity, and drug resistance. Given the high regional prevalence of TB and MDR/RR-TB among new and previously treated patients in the WHO European Region [2], adequate prioritization is encouraged, including funding and resources allocation from healthcare systems to perform high-quality studies within the European region.

4.2.2. Micronutrients

The important role of micronutrients in the maintenance of immune function, as well as metabolic homeostasis, has been clearly established [65]. Micronutrients including vitamin D, magnesium, and selenium have also been shown to contribute to the regulation of skeletal muscle anabolism and mass, insulin action, and insulin resistance [66,67], also potentially affecting muscle mass maintenance. Controlled, high-quality studies on the potential impact of micronutrient deficiencies and supplementation are needed, with a rigorous design that defines comparable treatment dose, duration, and goals.

4.2.3. Body composition and skeletal muscle mass

Body composition, marked by low skeletal muscle mass, is increasingly recognized as a major feature of malnutrition and this also extends to individuals with high body fat mass and living with obesity [57]. Research related to skeletal muscle mass changes in TB, the potential role as a risk factor for active infection, drug resistance, and poor clinical outcomes is lacking with only one recent study from the United States identified in which composition analysis was performed in patients with newly diagnosed pulmonary TB [30]. Patients exhibited lower body weight and BMI, which appeared to be largely explained by the loss of body fat, with only a minor difference in fat-free mass. The authors call for research on the potential role of body composition and particularly low skeletal muscle mass on TB risk and prognosis. This information would bear important additional clinical value regarding muscle-targeted nutritional and lifestyle approaches, including amino acid and protein provision, the potential use of muscle-anabolic nutraceuticals, and physical activity (e.g., resistance training) recommendations.

5. Conclusion

The association between TB and malnutrition is bi-directional: malnutrition is a risk factor for acquiring TB and TB-associated malnutrition can render treatments less effective and worsen prognostic outcomes. As a result, all patients should be screened for malnutrition routinely using validated tools. Nutritional interventions by dietitians to increase calorie and protein intake are necessary for patients deemed to be malnourished or at risk of malnutrition in order to improve nutritional status and aid disease resolution in TB. Nutrition plays a fundamental role in the public health approach to not only TB care, but NCD care as well, and requires widespread implementation across health systems.

Contributions (from WHO NCD office)

SC, HR, KW conceptualized the manuscript, SC researched, wrote, edited and provided critical revisions of the manuscript, RM performed the literature search, HR, KW reviewed the manuscript.

Funding information

This study has been produced with the financial assistance of the Member States of WHO Europe which supports the work of the WHO European Office for the Prevention and Control of Non-communicable Diseases.

Conflicts of interest

None.

Disclaimer

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

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