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REVIEW

A narrative review of recent progress in understanding the relationship between tuberculosis and protein energy malnutrition

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Protein energy malnutrition (PEM) and tuberculosis (TB) are the major public health issues, particularly in the developing country setting. Malnutrition is an underlying cause of many deaths and when left untreated devastates normal physical and cognitive development. TB continues to gather momentum as a serious infectious killer. They have both rightly been highlighted as important global health issues by their inclusion in the Millennium Development Goals. But what is known of their relationship with one another? It is historically accepted that PEM and TB have a synergistic relationship adversely having an impact on one another. However, researchers have sought to apply this understanding in an examination of the relationship between TB and PEM with often inconclusive results. This narrative review of recently published research and current knowledge may help delineate the association between PEM and TB mortality. Such results will assist future research in this important area of health—an area lacking evidence-based guidance.

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INTRODUCTION

Despite increased attention in recent years and proven methods of treatment, tuberculosis (TB) and protein energy malnutrition (PEM) continue to be the major public health challenges in the developing country setting.

TB remains second only to human immunodeficiency virus/acquired immunodeficiency syndrome as the leading cause of death by a single infection worldwide.[1] In 2010, TB reportedly killed 1.4 million people and had an estimated incidence of 8.8 million.[2] Some reports approximate that one-third of the world's population has an active or latent TB infection.[2] This represents a huge public health priority, given the magnitude of potential future disease.

Mycobacterium tuberculosis is the name of the bacillus that causes the TB disease.[2] In most circumstances when the TB microbe is inhaled, the body's cell-mediated immunity initiates an important protective response to TB. Among healthy individuals, this acquired immune response is very effective at containing the infection and rendering it latent.[2] The predicament exists when immune-compromised individuals become actively ill with TB from either a recent exposure or the often imperceptible progression from a latent infection status.[2] If left untreated, those with active TB will likely transmit the disease to others and will often die as a result of this disease or a related complication.

PEM profoundly compromises immune function. PEM occurs as a result of insufficient protein, essential for creating and regenerating body tissue and calorie intake. The growth failure classification referring to PEM includes (i) acute malnutrition, the precursor to wasting and (ii) chronic malnutrition, which leads to stunting.[3] Global rates of malnutrition, in its various forms, are difficult to measure. A recent report estimated that 925 million people, more than ever, are malnourished worldwide.[4] Malnutrition is attributable to >2.6 million child deaths every year.[5] It is widely accepted that a child with ongoing malnutrition will most certainly suffer from developmental impairment affecting their cognitive and physical abilities.[6] Subsequently, their capacity as an adult will be suboptimal and will thereby negatively contribute to reduced household and state economies.[6] Those suffering with malnutrition will also generally experience an increased susceptibility to illness and disease.[5] Incidentally, when a fatality transpires, the cause of death is commonly credited to the acquired illness, and thus the role of malnutrition often slides under the radar.[5] Malnutrition is a massive public health problem with far-reaching consequences.

Important contributions to the understanding of TB and PEM within the literature have historically been recognised. Given the growing burden of these two health problems and their augmentation when combined, it is highly germane that further understanding and clarification be established. Despite the assertions of good nutrition being an important factor in the prophylaxis and treatment of TB, there remains no evidence-based guidance regarding nutritional regimes for individuals undergoing TB treatment.[7] Thus, there is a need to identify and collate significant findings relating to this public health dilemma. This narrative review study aims to report on recent research that focuses on the synergistic relationship between TB and PEM, thereby providing a current reference for future clinical trials. The particular objectives of this review are:

1. To identify the trends/prevalence of PEM among those who present with TB;
2. to describe how PEM contributes to TB infection (susceptibility), disease progression and mortality; and
3. to determine whether macronutritional interventions targeted at individuals with PEM and TB are effective/justify further research.

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Therefore, by helping establish research priorities, it is hoped that this study will assist in expediting the formation of best practice nutritional guidelines in the treatment of protein energy-malnourished TB patients.

MATERIALS AND METHODS

Search strategy

This narrative review conducted a systematic literature search of six electronic databases (Ovid MedLine, PubMed, CINAHL, ProQuest Public Health, Global Health Ovid and Science Direct). The goal was to identify documents that have focused on increasing the current understanding of the relationship between PEM and TB in the last decade. The terms 'tuberculosis' and either 'protein energy malnutrition' or 'protein calorie malnutrition' were used to search for pertinent literature published between January 2002 and October 2012. Exclusion terms relating to human immunodeficiency virus and micronutrient deficiency limited certain databases from finding irrelevant papers. This primary search process culminated in a total return of 640 documents. Titles and abstracts were read to discern relevance to the research objectives.

Papers were included in an initial short list ($n = 45$) if they met the following inclusion criteria:

1. A clear observation or examination of the synergistic relationship between PEM and TB;
2. inferred PEM as the form of malnutrition their paper was concerned with; and
3. TB delineated as the focal infection of the study.

After eliminating duplicates, further analysis of items in the initial short list was undertaken by reading the full document in light of the inclusion criteria, and an initial master list was created ($n = 15$). A snowball sampling search of the bibliographies from the master list was subsequently completed. Bibliographic information from all items were cross-searched with word-search-capable software for the identification of multiple citations, indicating their prominence in the literature. Greenhalgh *et al.*[8] asserts the importance of identifying 'landmark papers' by measuring their citation frequency. Items with multiple citations that were deemed pertinent to the research objective and published after 1995 were classified as landmark papers ($n = 6$). Further, during the snowball sampling process of searching bibliographies, four new documents were added to the master list on the basis of their empirical or conceptual contribution to the research aim. Two papers making it to the final selection stage were omitted from being included in this review because of their having an alternative study focus and weak study design, respectively. Unfortunately, two articles that were identified for inclusion at an earlier stage, based on their title and abstract, were not available from either the scholarly databases or their respective publishers.

The preliminary review of the literature revealed a lack of empirically based publications regarding the role of PEM on TB outcomes. Consequently, this study's methodology chose to avoid the traditionally narrow strength of evidence-grading tools normally applied to the systematic review. Such grading tools when applied to the narrative review have been found to exclude important information from experts with remarkable knowledge and pertinent empirical experience from which they have published articles of a more conceptual nature.[9] As a result, this review's triage process consistently placed emphasis on a paper's relevance to the research objectives and avoided triaging based upon strength of evidence criteria. For example, 42% of the items included were classified as expert or narrative reviews. Overall, the search strategy process culminated in 23 documents being included in this review (see Figure A1, Appendix 1).

Synthesis strategy

The method of extracting and synthesising data is an integral component to the success of any review paper. Key details from 25 papers were recorded and collated via a data extraction form adapted for the narrative review design. The data extraction form facilitated a simple summary archive of each paper's bibliographic details; the understanding of key concepts of the topic, that is, the conceptual framework; the findings or results; the arguments put forward; and the author's conclusions.[10] Further, the reviewer's personal impression of the quality and relevance of each document were recorded. Table A1, Appendix 2 outlines the papers included in this review alongside their relevant findings.

Thematic analysis of the data extraction forms, and corresponding papers where necessary, yielded several themes relevant to the study objectives, which are presented in the next section.

RESULTS

Study characteristics

Design and participants. Developing countries would benefit most from relevant research findings regarding the synergistic relationship between TB and PEM. Improvements in knowledge and interventional management would have greatest impact in such populations. Indeed, much of the primary research into the relationship between TB and PEM has been conducted in less developed regions in recent years. Of the 23 papers meeting the inclusion criteria for this review, 10 were recognised as narrative expert reviews—the United States producing six and four from the United Kingdom. Apart from the Republic of Korea (two) and the United States (one), the remaining studies generating primary data emanated from the following middle- to low-income countries: Tanzania (two), Brazil (one), India (one), Malawi (one), Ghana (one), Uganda (one), Peru (one), Pakistan (one) and Latvia (one).

Of the 10 narrative expert review papers, 5 were lead review articles published in academic health journals, 3 were published as authoritative textbook chapters, 1 was a systematic review and 1 was a field expert's opinion in the form of a letter to the editor. Aside from the systematic review, these reviews are regarded as a weak form of evidence for clinical inventions and are often abated by author bias. Nevertheless, it is apparent from our research that such reviews form an important component of the literature regarding the exploration of the relationship between TB and PEM.

The remaining 13 papers were studies published as journal articles. The most common study design was the cohort study (seven), with four of these being prospective and three being retrospective. Three studies were cross-sectional in design and consequently reveal little about the timeline of the relationship between malnutrition and TB. The other observational study included was a case–control study. There were only two experimental studies included in this review; both were murine model studies.

As age and gender are important correlates of both TB and malnutrition, it was decided to examine their distribution in the papers included in the review. From the reviews, there was evidence from adult male and female subjects, children and elderly men. However, one of the narrative reviews did not elicit the age or gender of the participants in the studies it reviewed, merely referring to participants as 'patients' and 'subjects'. Most studies (eight) commonly recruited subjects of both genders in the adult age. Pregnant and breastfeeding mothers were excluded from three of these adult studies. Two studies focused on younger subjects aged <15 years and between 2 months and 12 years respectively. Although none of the studies aimed their sample at the elderly, old-aged subjects were recruited in several of the adult studies.

Evidently, there is a wide variation in the types of papers, study designs and age-related inclusion criteria amid the items confined to this review. As a result, it is difficult to draw simple comparisons between these items.

Approaches to the examination of the TB and PEM relationship

Several different approaches exploring the relationship between TB and PEM emanated from an analysis of the papers included in this review. These thematic approaches were relevant to the study objectives and are presented accordingly.

The trends/prevalence of PEM among those who present with TB. Epidemiological studies using anthropometric indicators provide relevant data pertaining to the presence of PEM among TB patients. Anthropometric indicators are regularly measured and interpreted to assess malnutrition.[11] The body mass index (BMI), deduced from the weight and height measurements, was found to be the most common anthropometric measurement. The six studies below utilising this indicator appeared to follow the World Health Organisation's international classification of undernutrition having a BMI of $<18.5\,kg/m^2$.[12] The following papers provide a current snapshot of the prevalence of PEM among subjects presenting with TB.

Several different African studies reported findings on similar nutritional status from their TB data sets. In their landmark paper, Kennedy *et al.*[13] found that 71.6% of TB subjects from their Tanzanian study presented with a BMI $<18.5\,kg/m^2$, with nearly one-third of these patients' BMI $<16\,kg/m^2$. At the commencement of another TB study, 51% of the subjects were malnourished (BMI $<18.5\,kg/m^2$), with more than half of those malnourished falling into the moderate (BMI $=16.0$–$16.9\,kg/m^2$) and severe (BMI $<16.0\,kg/m^2$) categories.[14] However, researchers concluded that it was particular socio-economic factors that correlated to malnutrition among this sample of TB patients, rather than TB infection *per se*.[14] A similar level of malnutrition (57%) on admission for TB was observed by Zachariah *et al.*[15] in their study in rural Malawi. Another recent study from Africa reported similar findings. In their Ghanaian study, researchers observed 42% of all TB subjects to have 'wasting' (BMI $<18.5\,kg/m^2$), and, of those who underwent biological impedance analysis, 33% had lean tissue mass wasting.[16]

In children, where the BMI is not an appropriate anthropometric measure, Siddiqui *et al.*[17] used the Modified Gomez classification to assess nutritional status. They found 82 (51%) of their paediatric data set to have PEM. Participants under the age of 5 years accounted for 41% of PEM cases. Researchers however highlighted this as being similar to the national childhood PEM prevalence. Nonetheless, they concluded that malnutrition, along with poverty and overcrowding, were the main problems associated with a higher risk of exposure to TB among paediatric subjects. Finally, a recent study investigating the nutritional status of multidrug-resistant TB patients presenting for TB treatment found 20% of subjects to be malnourished (BMI $<18.5\,kg/m^2$).[18] Despite this being a comparatively lower prevalence than previously reviewed studies, researchers discovered that underweight multidrug-resistant TB patients from this data set were more likely to present with advanced disease.

These observations reveal that the prevalence of reduced nutritional status, not always defined as PEM, among TB patients ranged from 20 to 71.6%. Insightfully, some researchers commented on other factors that may have had an impact on nutritional status before presentation. The four studies using African samples returned a comparatively similar prevalence rate of malnutrition, as defined by BMI, on admission. These populations are also likely to come from a similarly low socio-economic background that may have contributed to malnutrition. This was highlighted in a Tanzanian study where poverty and food insecurity were offered as other important grounds for poor nutritional status.[19] Not only will poverty have negative impact on nutritional status, it will also commonly influence health-seeking behaviour. Consequently, some TB subjects may have delayed seeking treatment, thereby allowing their nutritional condition to further deteriorate.

PEM as a contributor to TB infection: susceptibility, disease progression and mortality. A significant portion of the literature contends that PEM exacerbates TB infection. Findings from this narrative review indicate that this exacerbation occurs by the way PEM increases susceptibility, advances disease and contributes to mortality, as explicated in the sections below.

Susceptibility. In their comprehensive review, Schwenk and Macallan[20] pointed out key historical data that described PEM as an important independent influence on TB susceptibility. They referred to two mid-twentieth century studies on prisoners of a German war camp and US navy recruits, respectively. Other authors[21,22] analogously used the same 1946 prisoner of war study from the World War II as strong evidence for PEM's impact on raising the incidence of TB. These reviews also outlined the concept of nutritional immunodeficiency. This was somewhat supported by researchers of a Peruvian data set that found subjects with lower body protein stores were significantly less likely to show a positive reaction to the tuberculin skin test, suggesting an insufficient immune response to TB infection.[23] Despite the acknowledgement of there being limited immunobiological evidence, there is a general agreement that PEM commonly causes immune deficiency, thereby increasing the susceptibility to the onset of active TB disease in humans.[22,24,25] In consideration of several animal studies and the limited human studies, they affirmed that PEM can have a devastating effect on the cell-mediated and vaccine-induced resistance against TB.[20,24,25] Although these findings offer remarkable insight into the immunobiological understanding of the relationship between PEM and TB, the precise mechanisms of how diet influences these effects in humans is still unclear.[24,25] The main reason given for the apparent paucity of human evidence that clearly demonstrates PEM as a contributor to TB disease susceptibility revolves around the difficulty in researching this issue.[24,25,26] PEM is often and logically linked to TB susceptibility, but the process of how remains to be fully understood.

Disease progression. Malnutrition is a common factor in the progression of many diseases. More specifically, the literature that this paper reviewed identified PEM as an important contributor to the disease progression of TB in the domains of severity, immune function and medication efficacy.

Severity. This is often alluded to by reference to disease severity. For example, a recent study showed malnourished TB patients to be at a significantly higher risk of experiencing greater disease severity.[16] The findings from the study by Kim *et al.*[27] concurred with researchers delineating acute respiratory failure as a specific indicator of severity. They reported that the presence of malnutrition, as indicated by BMI and blood analysis before anti-TB therapy was a significant independent risk factor for the development of acute respiratory failure.[27] Other researchers discovered that underweight multidrug-resistant TB patients were more likely to present with advanced TB disease and experience three or more side effects over the course of treatment.[18] Another study assessed disease severity by testing TB subjects' functional status, the ability to carry out activities of daily living (the Karnosky performance score) and density of TB bacilli or bacillary density.[19] They found low BMI, triceps skin-fold and mid-upper arm circumference results to be significantly associated with poor Karnosky performance scores and higher levels of *M. tuberculosis* bacillary density.[19] Subsequently, TB severity was shown to be a correlate of wasting among participants in this study.[19]

Immune function. As already mentioned, PEM in TB patients has been associated with alterations in immune function. This may not only increase susceptibility but may also hasten an active TB infection becoming progressively worse. However, although most analysts on this subject acknowledge that PEM and other nutrient deficiencies weaken immune function, they have highlighted there being limited human evidence that clearly integrates this understanding to TB infection.[28] Indeed, animal studies have

provided important insights into how the immune system responds to TB in subjects with PEM. Identified as a landmark paper by this review, the murine study by Chan *et al.*[29] investigated how PEM curtails the cell-mediated immunity and anti-mycobacterial processes. Researchers discovered a marked reduction of essential molecules involved in the making of mycobactericidal nitrogen oxides, typically responsible for containing the infection, in the lungs of protein-malnourished mice. Researchers found that in the presence of PEM, the cellular immune response to TB is compromised; consequently, susceptibility and disease severity are increased.[29] Another murine study found that the specific antibody that normally responded to the introduced TB vaccine antigen was not present in undernourished mice.[30] Researchers concluded that a restricted diet can compromise both cellular and humoral components of normal immune response to TB infection.[30] These findings correspond to a human study from Peru that showed evidence of PEM being responsible for suppressing the immune system's response to TB antigens.[23] Collectively, these studies point to PEM as a precipitator of reduced immune function and the advancement of TB infection.

Medication efficacy. A further consideration of the disease progression relates to the way PEM affects TB treatment and prophylactic medication. One paper noted that in the individual with PEM, changes in drug disposition often occur as a result of a series of metabolic changes that are activated to preserve limited body tissue.[31] The author reported that Isoniazid, a first-line anti-tubercular drug, has been shown to be more slowly metabolised and more likely to cause hepatotoxicity in children with TB and PEM when compared with normally nourished children with TB.[31] Further, in a small study of malnourished adults with TB who were treated with rifampicin, another first-line anti-tubercular drug, the peak plasma level and protein binding were significantly reduced, and toxicity markers were elevated.[31] This suggests that TB patients with PEM when treated with anti-TB medication may be at an increased risk of toxicity. In terms of reduced prophylactic efficacy, a small study from India suggested that the protective benefit of the Bacillus Calmette–Guérin vaccine against the dissemination of TB in children may be compromised in the presence of PEM and poor socio-economic conditions.[32]

Mortality. A number of papers suggested that the risk of mortality is increased in TB patients as a result of coexisting malnutrition. For instance, a study found that rates of early death were higher among the 35% of patients with moderate (BMI = 16.0–16.9 kg/m^2)-to-severe (BMI < 16.0 kg/m^2) malnutrition than that of the rest of the sample.[15] Researchers concluded that moderate-to-severe malnutrition is an important risk factor for early mortality (death within the first 4 weeks of treatment). However, researchers did concede that the primary cause of such early death may be attributed to severe TB or human immunodeficiency virus-related complications; subsequently, the undernutrition status may merely be a marker of severe disease and not the cause of death.[15] Two review studies noted that malnutrition not only has negative impact on the clinical outcome of TB but, according to the literature, is also responsible for a nearly twofold increase in the risk of death in TB patients.[22,28] Several researchers studying dissimilar study samples independently concurred that the presence of malnutrition was a significant risk factor for mortality among TB subjects.[16,18,27]

TB as a cause of PEM. Because of its prominence in the literature, it is appropriate to mention the reverse phenomena of TB as a cause of PEM. Many articles pertaining to TB often include in their introduction the historical understanding of TB as a 'wasting' or 'consumption' disease.[13,15,19,20,26] Macallan's[26] review paper referred to an earlier study that discovered a metabolic change at the substrate level that impeded the function of nutritional amino acids in building proteins among those with TB.[33] This concept has been articulated in the literature as 'anabolic block'.[33,34] In their letter to the editor, Boelart and Gordeuk[21] support this phenomenon by declaring that TB will impair the nutritional state, which can lead to consumption. This is supported by a further assertion that TB is indeed associated with cachexia or wasting syndrome and low-serum concentrations of leptin, a satiety-regulating hormone, in patients with PEM.[22] Inferring TB to cause PEM, one review compared six studies that investigated serum albumin concentrations, a marker of PEM, in adults with untreated pulmonary TB with that of healthy controls.[34] They found the mean serum albumin to be significantly lower for the TB cases.[34] A more recent study stated that several biological mechanisms, including anorexia because of infections, probably contribute to wasting in TB.[35]

In summary, the literature indicates that PEM exacerbates TB infection by increasing susceptibility, advancing disease and causing mortality. Nutritional immunodeficiency appears to be responsible for an increase in TB susceptibility and severity, and reduced medication efficacy. Conversely, TB has a detrimental impact on nutrition. Despite these assertions, it is difficult to delineate and assign cause and effect in relation to the presence of both TB and PEM. One paper provides an insightful way of understanding this dilemma by describing a vicious cycle in which malnutrition perpetuates infection and infection leads to malnutrition.[22]

The effectiveness of macronutritional interventions targeted at TB patients with PEM. Much of the literature accedes to the importance of targeting nutritional intervention towards malnourished TB patients as an adjunct to conventional treatment.[15,18,26,28,34] However, a corresponding acknowledgement of there being limited evidence from human studies to confirm this is often presented.[7,15,18,20,24,25,26] Emanating from an observational study, one review suggested that normal weight appears to have a preventative benefit against TB.[20] Regarding nutritional recovery, researchers of a murine study established that when malnourished TB-infected mice were given a high-protein (20%) diet, their potentially fatal infection rescinded.[29] In light of the lack of evidence-based nutritional guidance for TB patients, a recent Cochrane review sought to assess the effects of both macro and micronutrient supplementation on TB treatment outcomes and recovery.[7] The six protein-energy interventional trials revealed that nutritional interventions have a statistically significant benefit on treatment completion and recovery; confirm improvements in physical functioning and quality of life associated with intervention; and produce a modest increase in weight gain during TB treatment. The authors concluded that the current research is weak and insufficient to ratify the practice of nutritional interventions aimed at TB patients with PEM.[7] They asserted the need for larger trials in food-insecure regions in order to confirm, or disprove, the clinical benefits of protein-energy intervention.

Nutritional intervention has been recommended and applied as a means to improve TB outcome. However, the rather concerning issue from these reviewed papers is the lack of substantial human evidence to endorse nutritional support as a conjunctive treatment alongside anti-TB therapy.

DISCUSSION

Determining the quality of the papers to be selected is an important component in any review. Randomised control trials and systematic reviews are superlative regarding the confirmation of causality and the guidance of improved evidence-based clinical interventions. This review located only one systematic review and two randomised control trials (albeit both murine studies).

The lack of inclusion of human randomised controlled trials largely reflects the absence of necessary research to guide nutritional interventions regarding this topic. This necessitated a narrative review design to present an updated perspective of the relationship between TB and PEM and not to directly guide clinical practice. Several authors highlighted the mostly impracticable nature of researching human TB subjects because of difficulties in determining nutritional status before TB infection and the inability to passively observe the wasting phase because of the ethical and clinical imperative to intervene with appropriate treatment upon TB diagnosis.[24–26] In terms of establishing the efficacy of nutritional supplementation alongside anti-TB therapy, some randomised controlled trials have attempted to provide greater evidence for or against this. However, more remains to be done.[7] Collectively, the ecological studies included in this review point to the recommendation of nutritional support. However, it must be noted that the ecological design is more helpful in generating hypotheses rather than testing them. If nutritional intervention has not been clearly determined to be effective, then surely it is justified that future efforts are prioritised.

The representativeness of most of the studies was questionable. Of the 12 human studies, only 1 obtained its subjects from a nationally representative sample, with the remaining using regional or district samples. The most popular sampling technique used to target TB subjects was the purposive approach ($n = 11$). One study, using national census data, randomly selected households from a specified geographical area for inclusion in their study. Almost half of the studies ($n = 5$) did not report the response or completion rate. From the remainder that did, response or completion rates varied from a low 38% to a high 98%.

The inclusion criteria for this review stipulated that items should delineate PEM when referring to malnutrition's association to TB. However, often the reference to and definition of PEM was found to be poorly articulated. The terms 'protein energy malnutrition' or 'protein calorie malnutrition' were not mentioned in 11 papers. Authors chose alternatives to refer to this type of malnutrition, including 'protein deficiency' (three); 'protein malnutrition' (three); malnutrition level according to BMI measurements (three); 'nutritional state/status' (two); 'wasting' (two); 'protein undernutrition' (one); and 'macronutrient deficiency' (one). Disappointingly, only one review paper adequately defined this term. This made for a challenging inclusion process. Further, despite the common use of BMI as an indicator for PEM, it is not recognised as the most accurate method for determining the presence of PEM.[36] Several researchers commendably compensated by using additional indicators of protein nutrition status such as biological impedance analysis, blood analysis and mid-upper arm circumference. An economical and more definitive approach to measuring PEM status should be established and utilised to make findings more accurate and comparative.

The 14 studies provided a range of different explanations regarding the types of measurements recorded, the instruments used, their calibration and standardisation. The body weight of subjects was recorded in seven of the studies, with only three of these papers stating they regularly calibrated the weighing scales used in their studies. The BMI was used in seven studies; however, three of these seven did not state the method of acquiring subjects' body weight. Three of the studies that used the questionnaire provided no detail surrounding the facilitation and use of trained personnel, although one did report using a 'pre-tested' questionnaire. Data were collected from a physical assessment on three occasions but was inadequately described in the studies. Collectively, the use and reporting of valid and reliable measurement instruments when researching the relationship between TB and PEM appears to be inadequate.

One limitation of this narrative review relates to there being only one primary researcher involved in the document search and selection process. However, in an attempt to increase the reproducibility and quality of this study, this review has transparently described the systematic search strategy and selection criteria. Another limitation relates to the unavailability of two likely articles for inclusion in this review. Several attempts via phone and email were made to contact the rights-holder of these documents but they did not respond; thus, these papers were omitted.

CONCLUSION

In light of the growing global health burden of TB in the developing setting, the role of PEM as a risk factor and consequent outcome clearly deserves to be a research priority. The outcomes of such research will not only alleviate suffering and death, but in a broader context halt the downward spiral of malnutrition, infection, morbidity, reduced work capacity and subsequent productivity in already economically impoverished populations. Such outcomes, therefore, will favourably impact socio-economical and political aspects of many communities and nations. If good nutritional status, more specifically the absence of PEM, is protective against TB, then this should be confirmed and efforts to increase the fair distribution of food among at-risk populations should be advanced—prevention is better than cure. Likewise, if protein-energy nutritional intervention, in conjunction with anti-TB therapy, improves recovery in TB patients, then this should become the standard practice. Larger interventional trials in the developing setting are necessary to establish or discount associations between TB and PEM. Various anthropometrical measurements have been used as indicators for an often vague definition of PEM. Available technology and methods for measuring indicators that accurately identify PEM should be established and promoted. Although understanding what nutritional interventions will improve TB outcomes is important, perhaps more so is the understanding of how. Further studies elucidating the immune systems's response in the presence of TB and PEM are essential in conjunction with greater biological insight into the relationship between TB and PEM. Ultimately, all research efforts should be working towards the development and establishment of evidence-based guidelines for the nutritional treatment of TB patients with PEM.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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APPENDIX 1

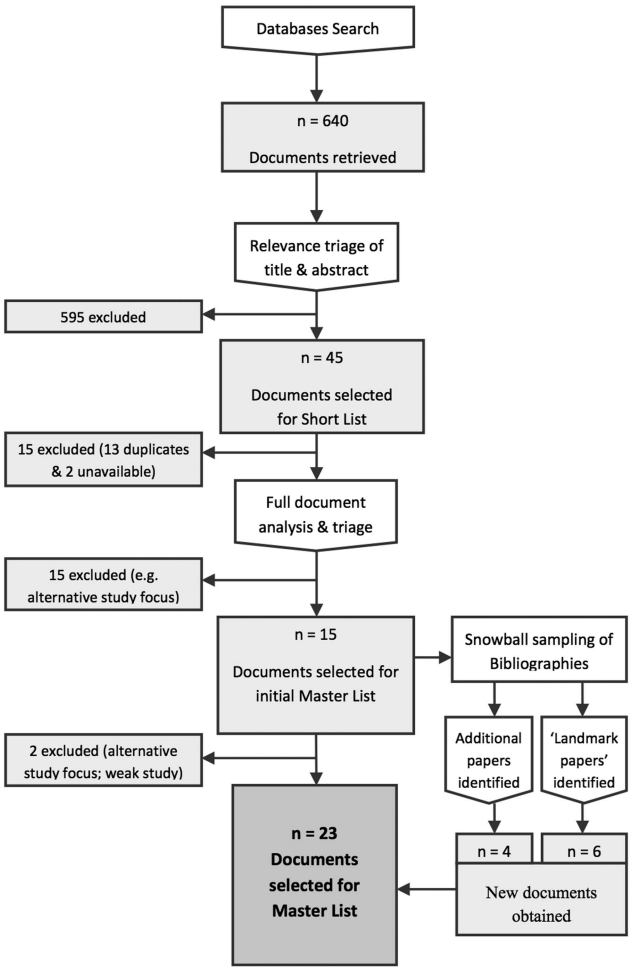

Figure A1. The search strategy process for selecting the documents for this review.

APPENDIX 2

Table A1. Summary table of the items included in this review

Reference	*Paper*	*Methodology*	*Protein status Indicator*
29	Chan *et al.*[29]	Experimental Study Murine intervention model	Referred to PEM. Experimental mice developed PEM on 2% of protein diet.
13	Kennedy *et al.*[13]	Prospective Cohort Study, 148 (TB) adults, Tanzania	BMI
26	Macallan[26]	Expert narrative review	Wasting: reduced BMI, TSF thickness and AMC. Metabolic impairment.
20	Schwenk and Macallan[20]	Expert narrative review	BMI; referred to PEM and wasting.
15	Zachariah *et al.*[15]	Prospective Cohort Study, 1181 (TB) adults, rural Malawi	BMI
21	Boelart and Gordeuk[21]	Expert opinion (Lancet)	Referred to PEM
32	Sushama Bai and Lekshmi Devi[32]	Prospective Cohort Study, 95 (TB) children, India	Indian Academy of Paediatrics (IAP) classification of PEM
34	Van Lettow *et al.*[34]	Expert narrative review	Serum albumin concentrations and total protein
31	Compher[31]	Expert narrative review (textbook chapter)	Referred to PEM
24,25	Cegielski and McMurray[24]	Expert narrative reviews (textbook chapter (2005))	BMI, TSF, MUAC, purified protein derivative (PPD) test; referred to PEM
23	Pelly *et al.*[23]	Cross-sectional Study, 212 adults ($+15$ years), rural and urban Peru	Corrected (bone-free) arm muscle area (CAMA)
28	Cegielski and Demeshlaira[28]	Expert narrative review (textbook chapter)	Referred to PEM
19	Villamor *et al.*[19]	Cross-sectional Study, 2231 (TB) adults, Tanzania	BMI, MUAC, TSF thickness AMC, BIA, total lymphocyte count (TLC) and serum albumin concentration
22	Schaible and Kaufmann[22]	Expert narrative review	Referred to PEM
14	Dodor[14]	Prospective Cohort Study, 570 (TB) adults, Ghana	BMI
27	Kim *et al.*[27]	Retrospective Cohort Study, 56 (TB) adults, South Korea	Nutritional Risk Score: BMI, serum albumin, serum cholesterol, TLC
30	Ishikawa *et al.*[30]	Experimental Study Murine intervention model	Referred to PCM. Experimental mice became undernourished on restricted diet
17	Siddiqui *et al.*[17]	Cross-sectional Study, 160 (TB) children (<15 years), Pakistan	Modified Gomez classification
35	Kim *et al.*[35]	Case–control Study, 23 TB cases and 23 healthy controls, South Korea	%ideal weight, BMI, serum albumin, TLC, cholesterol and haemoglobin
7	Sinclair *et al.*[7]	Systematic review, 6 protein-energy RCTs	Referred to PEM
18	Podewils *et al.*[18]	Retrospective Cohort Study, 995 (MDR-TB) adults, Latvia	BMI
16	Mupere *et al.*[16]	Retrospective Cohort Study, 747 (TB) adults, Uganda	BMI and fat/lean tissue mass (from BIA)

Abbreviations: AMC, arm muscle circumference; BIA, biological impedance analysis; BMI, body mass index; MUAC, mid-upper arm circumference; MDR-TB, multidrug-resistant TB; PCM, protein calorie malnutrition; PEM, Protein energy malnutrition; RCTs, randomised controlled trials; TSF, triceps skin-fold.