Influence of Micronutrient Consumption by Tuberculosis Patients on the Sputum Conversion Rate: A Systematic Review and Meta-analysis Study

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ABSTRAK

Latar belakang: *penyakit menular merupakan salah satu tantangan kesehatan global di dunia, termasuk penyakit tuberkulosis (TBC). Beberapa faktor secara signifikan terkait dengan peningkatan keberhasilan pengobatan, termasuk lamanya pengobatan atau kepatuhan pengobatan, menggunakan lebih dari tiga obat sensitif, rejimen individual, dan berat badan yang terkait dengan mikronutrien.* ***Metode:*** *tinjauan sistematis dan studi meta-analisis dari uji coba kontrol secara acak yang dilaporkan oleh item pelaporan pilihan untuk tinjauan sistematis dan meta-analisis. Sumber data primer adalah publikasi online, terdiri dari tiga basis data, yang berlangganan oleh Universitas Indonesia, yaitu Proquest, EBSCO CINAHL, EBSCO Dentistry. Risiko bias dinilai menggunakan alat risiko bias Cochrane, dan data dianalisis menggunakan Review Manager 2015.* ***Hasil:*** *terdapat delapan studi yang relevan. Ada perbedaan efek yang signifikan antara kelompok intervensi dibandingkan kelompok kontrol (atau kelompok plasebo). RR dari estimasi yang dikumpulkan adalah 1,12 (95% CI: 1,06 - 1,18) dengan studi heterogenitas 36%. Sementara itu, kutub yang dihitung berdasarkan jenis mikronutrien dari tujuh penelitian menunjukkan tidak ada perbedaan konversi dahak antara Vitamin D dan kelompok plasebo (RR-1,05, 95% CI 0,99-1,12) dengan studi heterogenitas 0% dan hasil yang signifikan tampak di antara intervensi zinc dan retinol (RR = 1.21, 95% CI 1,09 - 1,35) dengan studi heterogenitas 40%.* ***Kesimpulan:*** *intervensi mikronutrien selama pengobatan TB memiliki efek positif terhadap konversi sputum di antara pasien. Zinc dan retinol mempengaruhi konversi dahak sedangkan vitamin D tidak.*

Kata kunci: *tuberkulosis, penyakit menular, konsumsi mikronutrien, konversi dahak.*

ABSTRACT

Background: *infectious disease is one of the global health challenge in the world, including tuberculosis. Some factors significantly associated with increased treatment success, including the duration of treatment or treatment compliance, use more than three sensitive drugs, individualized regimen, and weight-related to micronutrient.* ***Methods:*** *a systematic review and meta-analysis study of randomized control trial studies conducted and reported by preferred reporting items for systematic reviews and meta-analyses. The primary data source was online publications, consist of three bases data, which subscribed by Universitas Indonesia, they are Proquest, EBSCO CINAHL, EBSCO Dentistry. Risk of bias was assessed using the Cochrane risk-of-bias tool, and data were analyzed using Review Manager 2015.* ***Results:*** *there were eight full paper rates as relevant studies. There was a significant difference of effect among the intervention group compared the control group (or placebo group). RR of the pooled*

estimate was 1.12 (95% CI: 1.06 - 1.18) with heterogeneity study 36%. While, the poled calculated based on type of micronutrient from seven studies showed there was no difference of sputum conversion between Vitamin D and placebo group (RR=1.05, 95% CI 0.99 – 1.12) with heterogeneity study 0% and a significant result seems among Zinc and Retinol intervention (RR=1.21, 95% CI 1.09 – 1.35) with heterogeneity study 40%. ***Conclusion:*** *micronutrient intervention during tuberculosis treatment has a positive effect toward to sputum conversion among patient. Zinc and retinol influence sputum conversion while vitamin D did not.*

Keywords: *tuberculosis, infectious disease, micronutrient consumption, sputum conversion.*

INTRODUCTION

Infectious diseases, including tuberculosis, are a global health challenge. According to the World Health Organization (WHO), there were an estimated 1.3 million tuberculosis deaths in 2017.[1] This was a marked increase in the number of reported cases in 2014 and 2015 (300,000 and 430.000 cases, respectively).[2,3] Globally, the total incidence of new TB cases was 133 per 100,000 population in 2017.[4]

According to targets set by the WHO, using the 2015 figure as a baseline, there needs to be a 90% reduction in the absolute number of TB deaths and an 80% reduction in the TB incidence rate.[1] The first step in ending the global TB epidemic is the treatment of all people with TB, including drug-resistant TB, and patient support.[1]

Although TB treatment is lengthy and expensive, previous studies reported highly successful outcomes in several countries where comprehensive treatment programs were initiated.[1-3] Several studies showed that treatment regimens were successful in more than 60% of TB cases.[1-3] Factors significantly associated with successful treatment outcomes included the treatment duration and treatment compliance, use of more than three sensitive drugs, use of fluoroquinolones, individualized treatment regimens, micronutrients, and patient weight.[4-7] A previous study reported that plasma retinol concentrations of patients were significantly associated with their body mass indexes[8-10] Several studies suggested that TB programs should consider the use of various interventions, including supplementation with micronutrients, in conjunction with anti-TB treatment.[11-13] Micronutrients, such as vitamin D, modulate inflammatory and immune responses to TB and mediate the induction of the antimicrobial peptide cathelicidin.[14] Previous research suggested that deficiency of 25-hydroxyvitamin D and single nucleotide polymorphisms in the vitamin D receptor gene may increase the risk of TB and decrease culture conversion rates in drug-susceptible TB.[14]

This systematic review and meta-analysis aimed to investigate the influence of micronutrient consumption on sputum conversion rate among TB patients and to identify optimum micronutrient levels during TB treatment.

METHODS

This review study was performed according to the preferred reporting items for systematic review and meta-analysis (8).[15,16] The study was registered in the PROSPERO database. A meta-analysis study conducted by using preferred reporting items for systematic reviews and meta-analyses.

Participants

The study population consisted of 1,311 TB patients who received anti-TB treatment as part of a government program based on WHO guidelines. Patients receiving treatment as part of non-government programs or from private health facilities were also included. The population comprised adult male or female patients newly diagnosed with TB and patients with a history of treatment failure or default. Patients with/without comorbidities (e.g., HIV infection and diabetes) were also included.

Intervention and Comparator

The study intervention was micronutrient supplementation with any or a combination of the following micronutrients during anti-TB treatment: selenium, potassium, albumin, vitamin A, vitamin D, vitamin E, zinc, and iron. The comparator was TB patients or non-TB patients who did not consume any additional

Table 1. Inclusion criteria.

Population, intervention, comparator, outcome; timeframe (PICOT)	Inclusion criteria
Participants	Adult patients newly diagnosed with multi-drug resistant TB and patients with a history of treatment failure, default, or drop-out receiving TB treatment in public or private hospitals/clinics
Intervention	Micronutrient supplementation, including selenium, potassium, albumin, vitamin A, vitamin D, Vitamin E, zinc, and iron in partial doses, single, or combination doses
Comparator	No micronutrient supplementation or supplementation with lower doses than those in an intervention group
Outcome	Sputum conversion and time to sputum conversion
Timeframe	Studies published in the last ten years (2008–2018)
Setting	All countries and facility-based or community-based interventions

micronutrients or consumed lower doses than those in the intervention group.

Outcome

The primary outcome was treatment success, as determined by the sputum conversion rate.

Inclusion Criteria

This systematic review included primary studies published worldwide in the last ten years. TB treatment programs were in place decades ago in several countries and also for the first study related to outcome among patients.

Information Sources

This systematic review included only primary studies published in English or Bahasa. The primary data source was online publications deposited in three databases that was subscribed by Universitas Indonesia : ProQuest, MEDLINE, EBSCO CINAHL and EBSCO Dentistry. The review included only full-text papers with free access and analytical (randomized controlled trials [RCTs] and non-RCTs) studies.

Search Methods/Strategy

In the search strategy, we used synonyms of PICOT-related terms. We also conducted a search using the following MeSH terms and keywords: micronutrient, selenium, potassium, albumin, vitamin A, vitamin D, vitamin E, zinc, iron, tuberculosis, RCT, patient(s), and adult. PB and a librarian at the University of Indonesia with experience of performing literature searches conducted the searches.

Study Selection

At the start of the review, PB screened duplicate titles using Endnote software. Next, all six authors (PB, RD, WK, NK, DG, and SR) assessed the relevance of the titles and abstracts. We excluded all primary studies that did not include details on methodology contained fewer than five patients and had a patient response rate of less than 50%. We also excluded other systematic review studies and meta-analysis studies.

Data Collection Process

PB extracted the selected studies, together with their titles and abstracts, in tabular format and then entered the data into Microsoft Excel spreadsheets. Three authors (RD, DG, and SR) then checked the accuracy of the selected data. The data extraction consisted of the origin of the study (i.e. country where the research was conducted), authors and publication year of the study, journal name, study population, study design, sample size, comorbidities (e.g. HIV infection and diabetes), history of TB, intervention (type and strategy), and outcome.

Risk of Bias in Individual Studies

All the authors assessed the quality of the studies, including the risk of bias in each research. To evaluate the risk of bias, they used the rating and scoring Cochrane Risk of Bias Tool for RCTs. Using this tool, they rated the quality of the studies as good, fair, or poor. The disagreement was resolved by discussion and consultation with an expert in the field.

Summary Measures

There were eight similar exposure and outcome categorizations. Thus, a meta-analysis was conducted. The analyzed to obtain a pooled estimate of risk ratio (RR) and its 95%

confidence interval (CI). Data processing was performed used RevMan software of a fixed-effect model to obtain the pooled estimate of RR, with its 95% CI and heterogeneity.

RESULTS

Of 704 studies identified through the search of the literature, 657 relevant studies were from ProQuest, and the others were from EBSCO CINAHL and EBSCO Dentistry. We excluded one study due to duplication and excluded 618 studies after screening the titles. We excluded 41 studies because the abstracts were not relevant to the present study, and we excluded two studies because the full paper was not open access. Thus, 42 studies were subjected to a full review. Of these, we excluded observational research studies (n=14), review articles (n=4), in vitro studies (n=4), studies with different primary outcomes (n=11), and ongoing studies (n=1). **Figure 1** presents information on the study selection process.

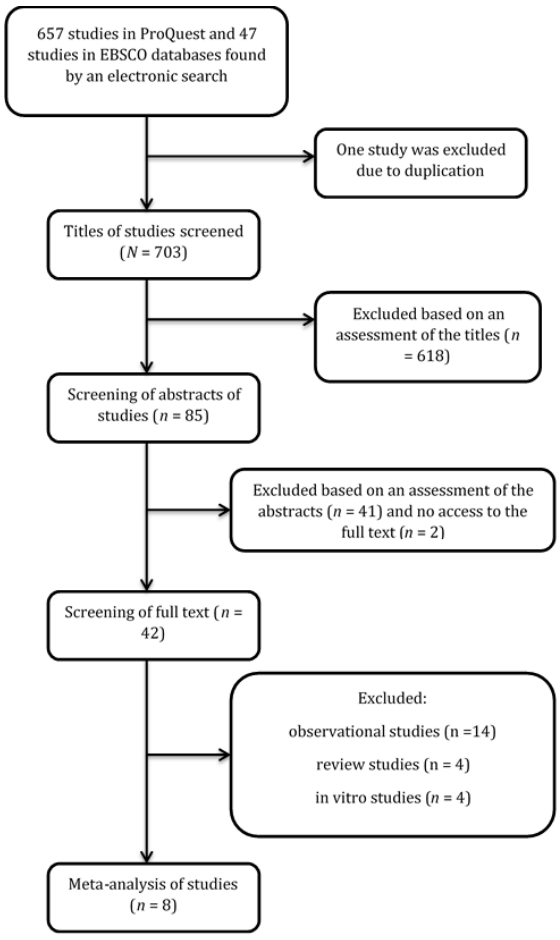

Figure 1. PRISMA chart.

Study Characteristics

Of the eight full-text papers included in the present study, the publication years were as follows: 2003 (n=1), 2004 (n=1), 2005 (n=2), 2009 (n=2), 2013 (n=1), and 2015 (n=1). Regarding location, two of the studies were conducted in Pakistan, and the others were performed in Mexico, India, Nigeria, the UK, Indonesia, and Tbilisi. All the studies used an RCT design, and four of the studies were double-blinded RCTs. Based on the type of micronutrient, the interventions in the eight studies consisted of vitamin D (n=4), zinc and retinol (n=3), and a local food supplement (n=1).

Risk of Bias Within the Studies

Table 2 presents the results for the risk of bias in the eight selected studies, with the risk assessed using the Cochrane Risk of Bias Tool studies. Using this tool, we rated five of the eight studies as good quality, two of the studies as fair quality, and one study as poor quality.

Results of Individual Studies

As shown in **Figure 2**, there was a significant difference in the sputum conversion rate in the intervention group as compared with that in the control group, depending on micronutrient supplementation. The RR of the pooled estimate was 1.12 (95% CI: 1.06, 1.18), with a heterogeneity of 36%. **Figure 3** shows the combined estimates based on the type of micronutrient. In seven of the eight studies, we separated micronutrient supplementation into two categories: 1) vitamin D; 2) zinc and retinol. The results revealed no difference in the sputum conversion rate between the intervention group and control group (RR = 1.05, 95% CI: 0.99, 1.12), with a heterogeneity of 0%. In contrast, there was a significant difference in the sputum conversion rate between the intervention group that received supplementation with zinc and retinol versus that in the control group (RR = 1.21, 95% CI: 1.09, 1.35), with the heterogeneity of 40%.

Table 2. A descriptive summary of the eight studies.

Source	Study year	Country	Sample size	Study design	Micronutrient
Afzal et al. (11) 2018[17]	2015	Pakistan	120	120	Vitamin D
Armijos et al. (12)[18]	2005	Mexico	39	39	Zinc and retinol
Jahnavi, 2010[19]	2005	India	100	100	Food supplement
Lawson, 2010[21]	2003	Nigeria	350	350	Zinc and retinol
Martineau, 2013[22]	2013	UK	126	126	Vitamin D
Pakasi, 2010[23]	2004	Indonesia	300	300	Zinc and retinol
Salahuddin, 2013[24]	2009	Pakistan	259	259	Vitamin D
Tukvadze, 2015[25]	2009	Tbilisi	199	199	Vitamin D

Table 3. Risk of bias in randomized and stepped wedge studies.

No	Component	Afzal, 2018	Armijos, 2010	Lawson, 2010	Jahnavi, 2010	Martineau, 2013	Pakasi, 2010	Salahuddin, 2010	Tukvadze, 2015
1	Random sequence generation (selection bias)	+	+	+	+	+	+	+	+
2	Allocation concealment (selection bias)	?	+	+	+	+	+	+	+
3	Blinding of participants and high-risk open-label research (performance bias)	-	+	+	+	+	+	+	+
4	Blinding of outcome assessment (detection bias)	?	+	+	-	+	?	+	+
5	Incomplete outcome data (attrition bias)	?	+	+	+	+	+	+	+
6	Selective reporting (reporting bias)	+	+	+	+	+	+	+	+
7	Other bias	-	?	?	?	-	?	?	-

Note: High risk of bias: -; Low risk of bias: +; Unclear:?

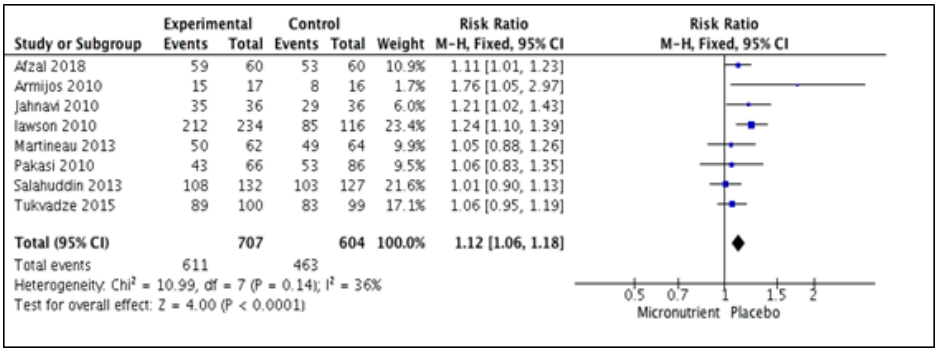

Figure 2. Pooled micronutrient consumption and sputum conversion.

DISCUSSION

This study investigated the influence of micronutrient supplementation on sputum conversion among TB patients. In the eight included studies, there was a significant difference in a treatment outcome, as reflected by sputum conversion of the intervention group (micronutrient supplementation group) as compared with that of the group that received no intervention.

Regarding the type of micronutrient, zinc, and retinol, supplementation had a statistically significant effect on sputum conversion. This was likely due to the role of retinol as a metabolite of vitamin A, the concentration of which is affected by the inflammatory status of the patient.[26] The

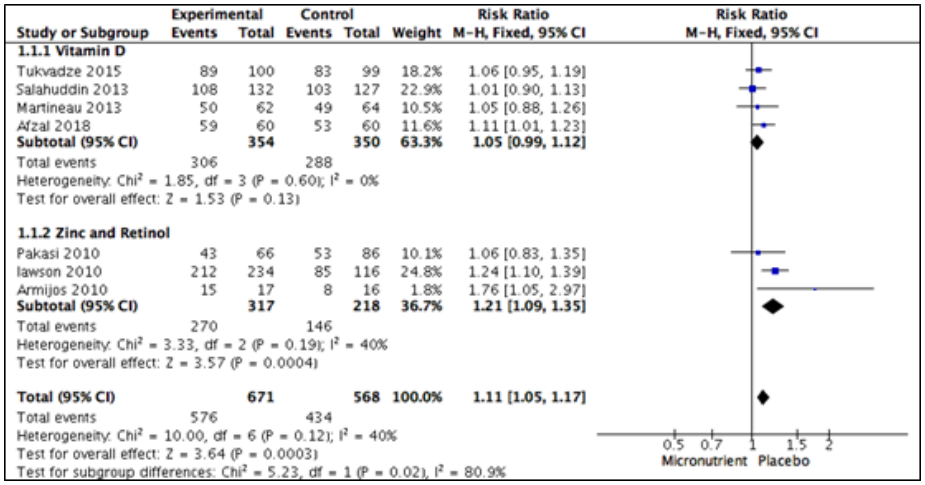

Figure 3. Effect of pooled micronutrient consumption on sputum conversion based on the type of micronutrient.

findings of the present study are in contrast to those of a previous study, which found no difference in the rates of sputum conversion or radiographic improvements among TB patients receiving zinc or zinc plus retinol supplements as compared with those of patients receiving placebos.[21]

In the present study, vitamin D did not influence the treatment outcome. This finding is in accordance with that of previous research on vitamin D3.[27] However, there is a wealth of observational epidemiological evidence linking vitamin D deficiency to an increased risk of reactivation disease, and many studies have suggested that vitamin D supplementation can be considered as combination therapy in patients with pulmonary TB.[28-29] Data are lacking in regards to daily dietary consumption of vitamin D, zinc, and retinol.

There were several limitations to this study. First, it included a search of studies in only three databases (ProQuest, EBSCO CINAHL, and EBSCO Dentistry). Second, the study included only open-access papers, with the result that two articles were excluded. Third, the search was limited to only English and Bahasa language studies, therefore excluding potentially relevant items in other languages. In terms of strengths, the selected databases are representative of studies in health science. Also, this review included only original research and excluded grey literature or previous meta-analysis studies.

CONCLUSION

Micronutrient supplementation during TB treatment had a positive effect on sputum conversion of TB patients. Zinc and retinol influenced sputum conversion, whereas vitamin D did not.

CONFLICT OF INTEREST

The authors declare that they have no competing interest.

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