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Review

Serum selenium levels in tuberculosis patients: A systematic review and meta-analysis

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ABSTRACT

Introduction: Tuberculosis (TB) is associated with increased mortality. The high risk of micronutrients deficiency, including selenium, in TB patients is of great concern because it increases the risk of death. However, it is not clear whether selenium supplementation could improve the treatment outcomes in TB patients. We conducted a systematic review and meta-analysis to provide an update on the existing evidence about low selenium levels in TB patients.

Methods: In this systematic review and meta-analysis, EMBASE, Medline and the International Journal of Tuberculosis and Lung Disease were searched to identify observational studies on selenium and TB published up until April 2018. Studies comparing blood selenium levels in TB patients to controls were included. Data extraction was performed by two investigators. The quality of the studies was assessed using the Newcastle-Ottawa Quality Assessment Scale. Random effects analysis was performed to calculate the pooled effect size and 95% confidence interval (CI).

Results: Of the 605 studies initially identified, only six were eligible. Of them, four were carried out in Asia, and one each in Africa and South America. The random pooled effect size was 1.6 (CI: 0.9, 2.4). This means that the probability is 160% for an individual with TB to have low levels of selenium as compared to an individual without TB. Heterogeneity across the studies was substantial (I^2 = 95.1%). Potential sources of heterogeneity included study design and selenium measurement methods.

Conclusion: Our review provides compelling evidence that serum selenium is lower in TB patients as compared with controls. Therefore, it is advisable to individually assess selenium status in TB patients and decide whether selenium supplement is needed or not.

1. Introduction

Many aspects of selenium and tuberculosis (TB) relationship are not yet explored. Research has demonstrated that micronutrients play a crucial role in the pathophysiology of tuberculosis [1]. Oxidative stress and regulatory T cells (Tregs) are also known to be involved in the pathogenesis of TB [2]. Selenium can modulate TB because it possesses antioxidant and anti-inflammatory properties and plays a crucial role in immune responses. Notably, an adequate selenium status can boost the cellular immune response through calcium mobilization, oxidative burst, and translocation of the nuclear factor of T cells [3]. Selenium supplementation may help natural killer (NK) cells to proliferate through up-regulation of interleukin-2 [4,5], whereas selenium deficiency has been associated with reduced T cells proliferation and reduced NK cell activity, all of which are crucial for antibacterial immunity [6].

Moreover, animal studies have shown that selenium supplementation could reduce [7] or increase [8] Tregs which helps *Mycobacterium tuberculosis* to escape from the host immune system [2]. Individual assessment of selenium levels in TB patients is of critical importance because TB patients could benefit from selenium supplementation which in theory has the potential to enhance the effect of TB treatment. However, a previous review looking at the importance of nutritional supplements in TB patients was inconclusive; i.e. it failed to discover a beneficial association between micronutrients supplementation including selenium and treatment outcome [9], although the authors

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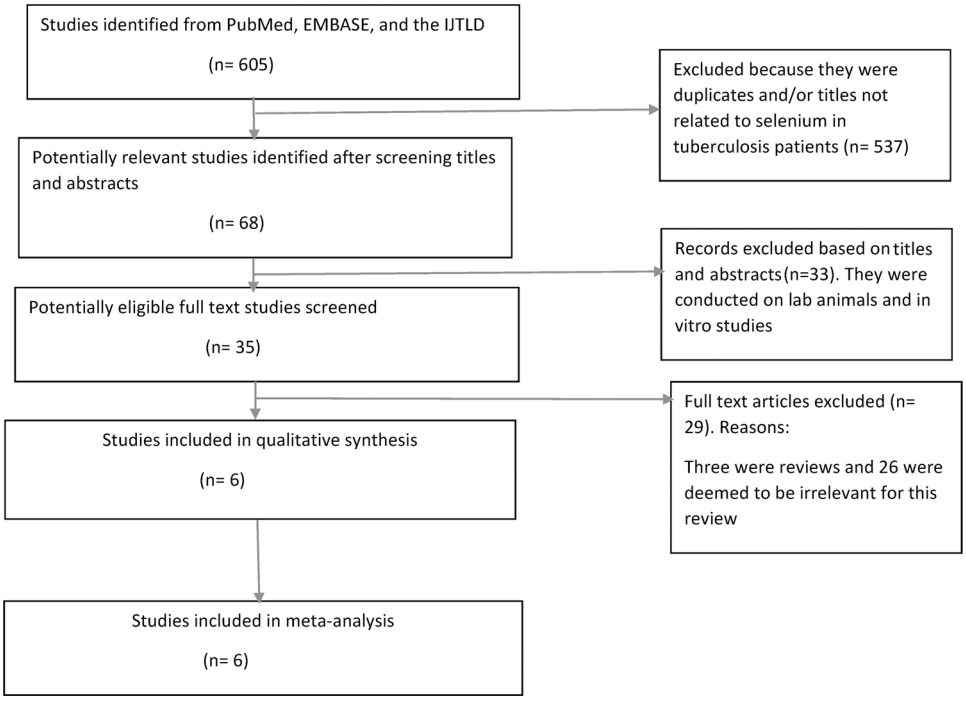

Fig. 1. Flowchart of study selection. IJTLD, International Journal of Tuberculosis and Lung Disease.

recognized that micronutrients such as selenium status can be improved by supplementation during TB treatment. However, there are studies that have demonstrated an increase of antioxidant status upon selenium supplementation [10,11] which in theory would improve TB outcome. This study aims at providing an update on the existing evidence about low selenium levels in TB patients.

2. Methods

2.1. Search strategy and selection criteria

We performed systematic searches in EMBASE, Medline databases and the International Journal of Tuberculosis and Lung Disease for articles published up until April 2018. The search terms used included: ('serum selenium' OR 'plasma selenium' OR 'selenium") AND ('tuberculosis' OR 'patients with tuberculosis'). Additionally, manual searching for the reference lists of the identified papers was done. There was no language restriction in the search process. To be included in this review, a study had to be carried out in untreated adults with TB, to be published as an original paper comparing blood selenium in TB patients and controls, and to be related to *Mycobacterium tuberculosis*. Studies clearly outside of our scope and those that did not report the aforementioned data were excluded (for example animals and in vitro studies). Two authors (BAM and NCM) independently reviewed the titles/abstracts of eligible studies along with data extraction.

2.2. Data analysis

Duplicate studies were removed using Endnotes X7. Extracted information included first author, publication year, study setting, selenium assay methods and selenium levels in patients and controls along with their body mass index (BMI) values. Information required to assess the quality of individual studies was also recorded. Assessment of study quality was performed using the Newcastle-Ottawa Quality Assessment scale [12]. Data synthesis was performed using the Comprehensive Meta-Analysis Software version 3 (Biostat Inc., Englewood, NJ, USA). Standardized difference in mean was considered as the effect size. Random effects model was applied to generate effect sizes from means and standard deviations. The degree of heterogeneity across the included studies was investigated using I^2 statistics [13]. Data on TB patients affected with human immunodeficiency virus (HIV) were not included in the meta-analysis because adding those data were deemed to be inappropriate.

3. Results

Of the 605 titles and abstracts that were identified from the literature search (Fig. 1), six case-control studies met the inclusion criteria [14–18]. As shown in Table 1, the included studies were published in English from 2006 to 2017. Sample size ranged from 44 to 320 participants. Of the six studies, involving 985 participants (589 cases and 396 controls), two included TB patients co-infected with HIV [18,19] and they all compared serum selenium levels in TB patients versus controls. All the studies used controls from the same living area. Most studies were carried out in Asia [14,15,17,18], and one each in Africa [19] and South America [16]. The overall reporting quality of the primary studies was generally acceptable. However, only one study stated that selenium levels were adjusted for potential confounders [15]. The reporting score was evaluated as ranging from 5 to 7 (Table A1 in Appendix A). Most TB patients were reported to have a lower BMI compared to the controls, however in one study means BMI were similar in TB patients and controls [14] and in another study BMI results were not reported [17]. Atomic absorption spectrometry (AAS) [14,16,18] and inductively coupled plasma-mass spectrometry (ICP-MS) [15,17,19] were used to measure serum selenium levels and results were presented as mean and standard deviation in all studies. Assays conducted using ICP-MS were likely to report high values of selenium compared to those performed with AAS (Table 1).

The mean serum selenium in primary studies were lower in cases as compared with controls. The lowest value was observed in TB patients co-infected with HIV. The effect sizes (95% CI) from all the studies were positive, ranging from 0.4 (0.1, 0.9) to 12.3 (10.0, 14.5) (Table 2). The highest effect size was reported in a study conducted in India including TB patients co-infected with HIV [18]), whereas the lowest was in a study conducted in Ethiopian TB patients [19]. The random pooled effect size suggested that patients with TB have lower serum selenium