Vitamin D and the risk of latent tuberculosis infection: a meta-analysis

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Abstract

Objective

Latent tuberculosis infection (LTBI) may be a risk of developing tuberculosis (TB) and thus a health hazard. The aim of this meta-analysis is to explore the association between vitamin D and LTBI.

Methods

Databases including PubMed, Embase, Scopus, and ProQuest were electronically searched to identify observational or interventional studies that reported the association between vitamin D and LTBI. The retrieval time is limited from inception to September 2021. Two reviewers independently screened literature, extracted data, and assessed risk bias of included studies. Meta-analysis was performed by using STATA 12.0 software.

Results

A total of 5 studies involving 2 case-control studies and 3 cohort studies were included. The meta-analysis result showed that the serum level of vitamin D was associated with the risk of LTBI (OR=0.32, 95%CI: 0.12-0.85, P=0.022). The result from cohort studies suggested that relatively high vitamin D level was a protective factor for LTBI (RR=0.67, 95%CI: 0.48-0.92, P=0.015).

Conclusions

Our meta-analysis suggested that serum vitamin D levels were associated with LTBI, and relatively high serum vitamin D level was a protective factor for LTBI. Further RCTs are needed to verify whether vitamin D supplementation prevents LTBI.

1. Introduction

Tuberculosis (TB) is a major global public health crisis, resulting in 15 million deaths in 2018 [1]. It is estimated that a quarter of the world's population is infected with *Mycobacterium tuberculosis* [2] and thus may be a risk of developing TB, especially soon after infection [2]. Latent TB infection (LTBI) is a state in which *Mycobacterium tuberculosis* survives in a dormant condition in the host, and individuals infected with LTBI have neither symptoms nor infectivity [3]. Approximately 5-15% of LTBI infected will develop active tuberculosis in their lifetime [4, 5]. Multiple studies have reported that a considerable proportion of TB cases were caused by the progression of LTBI [6, 7]. Therefore, tackling LTBI will be a crucial priority as the large number of asymptomatic infected people threaten the elimination of TB [8].

It has been reported that various factors may influence the incidence and progression of TB, one of which was vitamin D deficiency [9–11]. In addition to playing a major role in bone metabolism, vitamin D is also important in preventing infection [12]. Several studies have found that 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}_3$), which is the bioactive form of vitamin D, binds to the vitamin D receptor (VDR), activates the VDR signaling and induces a series of antimicrobial responses, such as inducing autophagy, activation of antimicrobial peptides, and killing intracellular *Mycobacterium tuberculosis* [13–15]. In order to study whether vitamin D was associated with tuberculosis, numerous studies have been conducted. However, only few studies have reported the association between vitamin D and LTBI, and they produced inconsistent and varying results [16, 17].

In view of the previous lack of meta-analysis to explore the relationship between vitamin D status or intake and LTBI, this meta-analysis was conducted for patients with LTBI to explore whether the vitamin D supplementation or high level of serum vitamin D is associated with the decrease of the risk of LTBI, which may provide nutritional support for the prevention of tuberculosis.

2. Materials And Methods

This study does not require ethical approval and informed consent because it is a systematic review and meta-analysis of previously published literature and does not address ethics or patient privacy. Our study was analyzed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18]

Data sources

A systematic search of PubMed, Embase, Scopus, and ProQuest was performed from inception to September 2021 for studies evaluating the efficacy of Vitamin D in TB. The search strategy used subject headings and keywords without language and date restrictions. We searched PROSPERO to confirm that no other similar study was conducted in progress simultaneously. The following terms were used when searching electronically for associations between Vitamin D and the risks of TB: (“Vitamin D” or “25 (OH) vitamin D” or “25(OH) D” or “25-hydroxyvitamin D”) AND (“tuberculosis” or “TB” or “tuberculoses” or “Koch Disease”). Manual reference checks were performed pertinent studies to determine further relevant trials. Any differences in the study selection process were resolved through panel discussions.

Eligibility Criteria

Studies meeting the following criteria were included in the final analysis: All types of prospective studies (including RCTs, cohort study or case-control study, etc) that reported on the association between Vitamin D and LTBI in children or adults. Studies were excluded if: a) did not report the risks of LTBI or Vitamin D; b) were conference reports, case reports, reviews or letters; c) did not report the results of OR, RR or their 95% confidence interval (CI); d) measured vitamin D levels among individuals already diagnosed with TB disease or latent TB infected.

Study selection and data extraction

Two reviewers independently evaluated the titles and abstracts of all articles retrieved in the initial search. A screen form was used to exclude articles that did not meet the eligibility criteria with a hierarchical approach based on study design, population or exposure and outcome. If the article was deemed to be eligible, the full-text was retrieved and its relevance was evaluated by a second reviewer. Any disagreements are discussed and resolved by consensus.

Two independent reviewers extracted data of selected studies separately using a standard data extraction form. Extracted information included: study details (name of the first author, publication year, location, study design, total number of participants and cases), population characteristics (description of the included study population, mean or median age and their SD or IQR, number and percentage of female), exposure (method of measuring Vitamin D, mean/median baseline 25-OH Vitamin D, length of follow-up, and LTBI disease definition), and outcomes (adjusted effect estimate and their 95% CI, such as OR and RR). Any discrepancies in data extraction were discussed and assessed by a third reviewer for resolution.

Quality assessment

Case-control and cohort studies were assessed using the Newcastle-Ottawa scale (NOS) [19] consisting of three domains: (1) selection of subjects, (2) comparability of groups, and (3) assessment of outcome. A score of 0-9 was allocated to each relevant study. While the NOS has no established thresholds, we considered the quality of each study as low (0-3), moderate (4-6), or high (7-9) [20]. When inconsistency exists, a third reviewer will make the final decision after verification and discussion.

Statistical Analysis

In our meta-analysis, OR, RR and their 95%CI were used as the effect measure. Heterogeneity was assessed by I^2 statistics and random effect model was selected when heterogeneity was significant ($I^2 > 50\%$), otherwise, fixed effect model was chosen [21]. Forest plots were used to display the results from individual studies and pooled estimates, and $P < 0.05$ were regarded as statistically significant. Begg's and Egger's test were performed to evaluate potential publication bias [22]. Funnel plots were visually evaluated for asymmetry [23]. Sensitivity analysis was performed to evaluate the robustness of the results. All statistical analyses were performed with Stata 12.0 (StataCorp, College Station, TX, USA).

3. Results

Results of study search

The systematic literature search produced a total of 2761 articles, after excluding the duplicates from the different databases. After initial screening the titles and abstracts, 2739 publications were excluded because they did not meet the study eligibility criteria, leaving 22 articles for full-text assessment. Finally, a total of 5 articles [16, 17, 24–26] meeting the criteria for the quantitative synthesis were included in the systematic review (Figure 1).

Characteristics of the Studies

Of the 5 articles included, 3 were cohort studies, 2 were case-control studies. The total number of the patients included in our study was 1516 patients. 3 articles reported the outcome of RR and 95%CI, 2 articles used OR as outcome. The included studies reported the association between vitamin D and latent tuberculosis infection.

2 case-control and 3 cohort studies were considered as high quality, because the study design had been described in detail (Table 2-3).

Vitamin D level was associated with the risk of LTBI

A total of 2 case-control studies with 41 LTBI cases and 142 control subjects were included in our analysis. Our analysis with a fixed-effect model showed that relatively high serum Vitamin D level was significantly associated with a decreased risk of LTBI (OR=0.32, 95%CI: 0.12-0.85, P=0.022, $I^2=0.0\%$) (Figure 2).

Vitamin D was more likely a risk factor for LTBI than its consequence

3 cohort studies involving 1333 participants were included in our meta-analysis. Our analysis with a fixed-effect model showed relatively high serum vitamin D levels reduced the incidence of LTBI (RR=0.67, 95%CI: 0.48-0.92, P=0.015, $I^2=47.5\%$) (Figure 3).

Between-studies heterogeneity and publication bias

Between-studies heterogeneity varied from none to small for our meta-analyses with I^2 values ranging from 0.0–47.5%. However, sensitivity analysis and publication bias tests were not required because only 2 articles were included in association of vitamin D and the risk of LTBI and 3 in association of vitamin D and the incidence of LTBI.

Discussion

The present meta-analysis of case-control studies showed that the relatively high serum vitamin D level was associated with the decreased risk of LTBI. The result of cohort studies suggested that the decreased incidence of LTBI was associated with the elevated serum vitamin D levels.

After entering into the human body, *Mycobacterium tuberculosis* will be lysed in the phagosomes inside macrophages. If the concentration of Ca^{2+} in cells does not increase, *Mycobacterium tuberculosis* resides in phagosomes are not lysed, thereby resulting in LTBI [27]. LTBI patients may develop TB in the near or distant future [28]. The association between vitamin D deficiency and LTBI remained unclear [29]. However, our meta-analysis showed an association between serum vitamin D levels and LTBI. Before antibiotics, vitamin D was regularly used to treat mycobacterial diseases such as tuberculosis and

leprosy [30]. Vitamin D has been reported to induce interleukin-1- β secretion and further regulate paracrine signaling, which enhances the role of macrophages in innate immune regulation [31]. Tung et al. reported that vitamin D improved the coordinated response of monocytes and T-lymphocytes to *Mycobacterium tuberculosis* in response to frequent MTB exposure [32]. In addition, 1,25-(OH) $_2$ D has long been thought to contribute to the innate and adaptive immune defense of intracellular pathogens, although the effects of 1,25-(OH) $_2$ D on *Mycobacterium tuberculosis* infection are complex and have not been described in detail in previous studies [11, 33]. However, there is ample evidence that serum vitamin D levels are significantly decreased in immunocompromised individuals and tuberculosis patients [34]. These findings may indicate that vitamin D plays a role in the prevention of *Mycobacterium tuberculosis* infection.

However, the hypothesis that vitamin D supplementation can prevent LTBI activation has not been systematically reviewed. This is due to the lack of relevant studies [35]. Our study only demonstrated that higher serum vitamin D levels may be a protective factor for LTBI. Arnedo-pena et al. found that low plasma vitamin D was associated with tuberculin skin test (TST) positive conversion in a small number of contacts at follow-up [25]. Moreover, Gibney et al. observed that higher vitamin D levels were associated with lower LTBI prevalence among sub-Saharan African migrants in Melbourne, Australia [36]. According to previous reports, the vitamin D levels of LTBI patients were significantly lower than that of healthy people [36], the general population receiving vitamin D showed enhanced anti-TB immunity compared with those receiving placebo [37], and the TST conversion rate was lower in school children who received vitamin D, and their height increased [38]. Only a few studies have evaluated the role of vitamin D supplementation in preventing LTBI acquisition in contacts. A randomized controlled trial (RCT) by Martineau et al. found that compared with placebo group, the innate immunity against mycobacteria in vitamin D group was significantly improved, which was shown by recombinant *Mycobacterium* growth restriction (BCG-lux analysis), but the parameters of acquired immune response were not improved [37]. Thus, we can hypothesize that vitamin D may inhibit the progression from LTBI to active TB [39, 40].

One of the limitations of our study is that it is still not resolved whether vitamin D supplementation is conducive to the prevention of LTBI. Previous meta-analysis found that vitamin D deficiency was associated with an increased risk of developing active TB in those subjects with LTBI and with an increased risk of TST conversion/TB infection conversion [41]. However, the meta-analysis did not address the question of whether vitamin D supplementation would be beneficial to LTBI prevention, and our study focused on the effect of higher serum vitamin D levels relative to lower vitamin levels on LTBI, rather than merely vitamin D deficiency, which is different from the previous meta-analysis. In addition, since all the studies included in the meta-analysis were observational studies and RCTs of vitamin D supplementation were few (only two articles were retrieved), we could only acquire the relationship between serum vitamin D level (25(OH)D) and LTBI. We can only assume that vitamin D supplementation prevents the activation of latent TB, and further RCTs are needed to verify this hypothesis.

Conclusion

Our meta-analysis suggested that serum vitamin D levels were associated with LTBI, and relatively high serum vitamin D level was a protective factor for LTBI. Further RCTs are needed to verify whether vitamin D supplementation prevents LTBI.

Declarations

Author Contributions: CY[#], WXJ[#] and LP[#] contributed equally to this work. CY, WXJ and LP performed software and analysed data. SY collected data. YHT and DJL conceived and designed the study. CY wrote the paper. DJL reviewed and edited the paper. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: No conflicts of interest have been declared

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Availability of data and materials

We used the data from published data given its nature of systematic review and meta-analysis.

Declarations

Ethics approval and consent to participate

Not applicable given using data of published data for systematic review and meta-analysis.

Consent for publication

Not applicable given using data of published data for systematic review and meta-analysis.

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Tables

Due to technical limitations, Tables 1, 2 and 3 are only available as a download in the Supplemental Files section.

Figures

Figure 1

PRISMA chart: flow diagram of the process of selection of articles.

Figure 2

Forest plots for the association between Vitamin D levels and the risk of LTBI: overall effect for dichotomous outcome using a fixed-effect model. The diamonds stand for pooled effect.

Figure 3

Forest plots for the association between Vitamin D levels and the incidence of LTBI:overall effect for dichotomous outcome using a fixed-effect model. The diamonds stand for pooled effect.

Supplementary Files

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- [Table2CasecontrolstudiesbiasassessmentusingtheNewcastleOttawaScaleNOS.docx](#)
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- [PRISMA2020checklist.docx](#)