Association of Vitamin D Deficiency With Pulmonary Tuberculosis: A Systematic Review and Meta-Analysis

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Abstract
Pulmonary tuberculosis, caused by Mycobacterium tuberculosis, is a significant public health issue, especially in developing countries, affecting millions of people every year. Despite the development of many antitubercular antibiotics and increased awareness of preventive methods, it is still a major cause of mortality worldwide. Vitamin D, a micronutrient known to have a major role in bone and calcium metabolism, has also shown its immunomodulatory effects to suppress mycobacterial growth. We conducted a systematic review and meta-analysis of the available evidence to explore the association between vitamin D levels and tuberculosis. We performed a systematic search for articles from inception to May 2021 in multiple databases. We included 26 studies in our qualitative synthesis and 12 studies in meta-analysis or quantitative synthesis. In our meta-analysis, we used a random-effect model to calculate the odds ratio (OR) of vitamin D deficiency in tuberculosis patients compared to the healthy controls. On pooled analysis, we found that the odds of the participants having vitamin D deficiency was 3.23 times more in tuberculosis patients compared to the healthy group (OR=3.23, CI = 1.91-5.45, p<0.0001). Thus, we concluded that there is an association between low levels of vitamin D and tuberculosis infections. We suggest conducting long-term prospective cohort studies in tuberculosis endemic countries to better understand the causal relationship between vitamin D deficiency and tuberculosis.

Introduction And Background
Tuberculosis (TB), an infectious disease, is one of the top 10 causes of worldwide death, ranking above human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). In 2020, around 10 million people became ill, and 1.4 million died from TB [1-2]. The geographical distribution of TB in 2019 was 44% in the South-East Asia regions, 25% in Africa, 18% in Western Pacific, 8.2% in Eastern Mediterranean, 2.9% in the Americas, and 2.5% in Europe [2]. Immunomodulatory and anti-proliferative responses modulated by active 1,25-dihydroxy vitamin D were seen more than two decades ago. Its high doses were used to treat TB before discovering antitubercular drugs [3-4]. More understanding has been established in recent years regarding the effects of vitamin D in the pathophysiology and possible prevention of human disease, including TB [4].

The biological role of vitamin D in bone metabolism is well-established. However, the active metabolite of vitamin D, 1α,25-dihydroxy vitamin D3 (1,25D) also has pleiotropic effects in the immune system [5]. 1,25D3 upregulates human cathelicidin antimicrobial peptide and protein production from monocytes/macrophages infected with Mycobacterium tuberculosis, resulting in autophagy [6-8]. Vitamin D metabolites also upregulate nitric oxide synthase, which suppresses mycobacterial growth [9-10].

Over the years, more and more studies focusing on exploring the relationship between vitamin D deficiency and TB have been conducted [11-12]. However, existing attempts to relate these two things have been made with conflicting results caused by the different study populations, underlying comorbidities such as HIV and renal disease. Here, we analyzed the studies performed to find the association between vitamin D and TB. The studies we included were conducted in different countries and different age groups. We have tried to exclude any underlying comorbidities that may affect the level of baseline vitamin D.

The previous meta-analysis studies included cross-sectional and case-control studies, which assessed vitamin D status after the active TB disease diagnosis. The studies did not evaluate the efficacy of vitamin D supplementation in preventing TB [11-12]. Tuberculosis is now a global health problem, including in developed countries. The World Health Organization (WHO) End TB Strategy targets to decrease the incidence of tuberculosis by 80% by 2030 [2]. Around 1.7 billion people worldwide have latent tuberculosis infection, of which about 10% develop active tuberculosis in their lifetime [13-14]. To reach the 2030 target,
effective measures to prevent acquiring the latent tuberculosis infection need to be addressed. Vitamin D supplementation is one of the interventions proposed to reduce the risk of latent TB infection in populations with prevalent deficiency\(^{[15-16]}\). To explore more about the vitamin D deficiency and tuberculosis association, we have systematically identified, examined, and pooled the community- and hospital-based studies that performed a comparative study of serum vitamin D in tuberculosis patients and healthy controls. We have also included a recent randomized control trial (RCT) assessing the role of vitamin D supplementation and the impact of pre-existing vitamin D levels on the risk of TB infection\(^{[15]}\). The inclusion of a large number of descriptive studies has made our study more robust. We believe the result will help give a clearer picture regarding the relationship between vitamin D and tuberculosis and help plan and execute future actions to control the tuberculosis infection in the world.

### Review

#### Methods

**Data Source and Search Strategy**

We followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to conduct our study\(^{[17]}\). Two reviewers performed rigorous literature searches on multiple databases, including PubMed, Embase, Scopus, and Cumulative Index of Nursing and Allied Health Literature (CINAHL). We searched for articles using medical subject headings (MeSH) and keywords combined with Boolean connectors, published from inception to May 21, 2021. We used both MeSH headings terms and regular keywords to conduct our literature search. We applied the 'human' filter while searching on PubMed and Embase. Likewise, the filter 'field of medicine' was used while searching on Scopus. The details of our search strategy on multiple databases are shown in Table 1.

| Database | Search Strategy | Records Retrieved |
|----------|-----------------|-------------------|
| PubMed   | (Tuberculosis[MeSH Terms] OR tuberculosis[Title/Abstract]) AND (humans[Filter]) AND ("vitamin d"[MeSH Terms] OR "ergocalciferol"[MeSH Terms] OR "vitamin d"[Title/Abstract] OR "cholecalciferol"[Title/Abstract] OR "ergocalciferol"[Title/Abstract] AND (humans[Filter]) AND (humans[Filter]) OR "ergocalciferol"[Title/Abstract]) AND (humans[Filter]) AND (humans[Filter]) | 800 |
| Scopus   | KEY ( ( vitamin AND d ) AND tuberculosis ) AND ( LIMIT-TO ( SUBJAREA , "MEDI" ) ) | 1295 |
| Embase   | ("vitamin d":ab,ti OR ergocalciferol:ab,ti OR cholecalciferol:ab,ti AND tuberculosis:ab,ti AND "human"/de | 1009 |
| CINAHL   | ((Vitamin D) OR (ergocalciferol) OR (cholecalciferol)) AND (Tuberculosis) | 198 |

**TABLE 1: Search strategy of different databases**

**Study Selection**

We identified 3302 potentially relevant studies, including 800 from PubMed, 1009 from EMBASE, 1295 from SCOPUS, and 198 from CINAHL. The retrieved studies from the databases were imported to the Covidence review manager (CRM). We used CRM to remove the duplicate studies, and a total of 1266 duplicates were removed. Two reviewers independently carried out the whole screening process. We screened the titles and abstracts of 2036 articles and excluded 1739 studies that were not relevant to our research. Again, two reviewers retrieved and read the full text of the remaining 297 articles to check for the eligibility of the articles. The consensus of all six reviewers resolved disagreements during all stages of screening. Additionally, we searched the reference list of the relevant articles to identify any pertinent papers. Finally, we included 26 studies that met the requirement for our systematic review (Figure 1).
Inclusion and Exclusion Criteria

We included articles that have compared the level of serum vitamin D in patients with active tuberculosis and healthy controls of any age group. Given that the studies with small sample sizes may be statistically inconclusive, a study including a minimum number of 100 patients was taken for our review. The studies published in any language were included in our study. Case reports/series, review articles, meta-analysis, editorials, conference presentations, correspondence, commentary, poster presentation, and letters were not included. We excluded studies that had patients with latent tuberculosis, extra-pulmonary TB, and other comorbid conditions as their study participants. Animal studies and cellular models of studies were also excluded. Population Intervention Comparison Outcome (PICO) questions used for checking the eligibility of the studies are shown in Table 2.
| P | Population/Problem/Patient | Patients diagnosed with active tuberculosis |
|---|-----------------------------|---------------------------------------------|
| I | Intervention                | Vitamin D level                             |
| C | Comparison                  | Healthy patients without active tuberculosis |
| O | Outcome of interest          | Mean or median vitamin D level or number of participants with vitamin D deficiency in both tuberculosis and control groups |

**TABLE 2: Population Intervention Comparison Outcome (PICO) questions**

**Data Extraction**

Two reviewers independently completed the data extraction from the finalized 26 studies. We included the following standardized forms: author, publication year, country, sample size, study population, mean age group, male to female ratio, study design, and outcome. All the relevant data from the included studies were extracted to an Excel sheet form (Microsoft Corporation, Redmond, WA). No automated tool was used for the data extraction process.

**Study Risk of Bias Assessment**

We used the Joanna Briggs Institute (JBI) checklist for cross-sectional studies [18] and the JBI checklist for case-control studies [19]. We did a thorough quality assessment using the JBI checklist for 13 cross-sectional studies and 14 case-control studies.

For cross-sectional studies, we assigned score ‘1’ to questions whose answers were ‘yes’ and score ‘0’ to those whose answers were ‘no’ or ‘unclear’ or ‘not applicable (N/A). After calculating the total score of all articles, we classified the studies with 6-8 as low risk, 3-5 as moderate risk, and 0-2 as high risk. Out of 13 cross-sectional studies, 12 cross-sectional studies were low-risk articles, and one was a moderate-risk article. Table 3 shows the quality appraisal for cross-sectional studies using the JBI checklist.
TABLE 3: JBI critical appraisal checklist for cross-sectional studies
JBI: Joanna Briggs Institute

Similarly, for case-control studies, we assigned ‘one’ to questions whose answers were ‘yes’ and ‘zero’ to the questions whose answers were ‘no’ or ‘unclear’ or ‘not applicable (N/A). A score of 7-10 was considered low risk, 4-6 moderate risk, and 0-3 high risk. Out of 13 case-control studies, 11 studies were low-risk and two were moderate-risk articles. Table 4 shows the quality appraisal for case-control studies using the JBI critical appraisal checklist.
TABLE 4: JBI critical appraisal checklist for case-control studies

JBI: Joanna Briggs Institute

Results

Characteristics of the Included Studies

The included studies were published between 2007 and 2021. The included studies were published between 2007 and 2021. Thirteen included studies were case-control, and the other 13 were cross-sectional. Studies are included from various countries from multiple continents. A total of 8101 participants were included in our data synthesis; 4203 were people with TB and 3898 were healthy volunteers. All other studies have participants who are at least 14 years of age. Two of the studies from Pakistan have identical data and outcomes [20-21]. The details about the demographic features of the study participants, study design, and the year of publications are mentioned in Table 5.
|   | Study Title          | Year   | Country | Study Design         | Sample Size | Male | Female | Mean ± SD | Range | Range |
|---|----------------------|--------|---------|----------------------|-------------|------|--------|-----------|-------|-------|
| 4 | Musharaf et al. [21] | 2020   | Pakistan| Cross-sectional study | 140         | 70   | 70     | F=52, M=88 | 20-70 |       |
| 5 | Panda et al. [22]   | 2019   | India   | Cross-sectional study | 150         | 80   | 70     | F=28, M=122 | 18-60 |       |
| 6 | Wang et al. [23]    | 2018   | China   | Case-control study   | 240         | 122  | 118    | M=182, F=58 |      | Cases: 50.83±20.04 Control: 51.97±12.49 |
| 7 | Zhang et al. [4]    | 2018   | China   | Case-control study   | 187         | 128  | 59     | F=46, M=141 |     | NA    |
| 8 | Khan et al. [23]    | 2018   | India   | Cross-sectional study | 216         | 113  | 103    | F=96, M=120 | 22.83-50.45 |     |
| 9 | Balcells et al. [24]| 2017   | Chile   | Cross-sectional study | 262         | 92   | 170    | -          | NA    |       |
| 10| Ralph et al. [25]   | 2017   | Malaysia| Cross-sectional study | 267         | 172  | 95     | F=131, M=136 | 15-70 |       |
| 11| Goyal et al. [26]   | 2017   | India   | Cross-sectional study | 157         | 57   | 100    | -          | 15-70 |       |
| 12| Workineh et al. [27]| 2017   | Ethiopia| Cross-sectional study | 196         | 126  | 70     | F=65, M=131 | 17.9-41.7 |      |
| 13| Oh et al. [23]      | 2017   | Korea   | Case-control study   | 289         | 152  | 137    | F=98, M=191 | 18-80 |       |
| 14| Memon et al. [33]   | 2016   | Pakistan| Case-control study   | 209         | 112  | 97     | F=84, M=125 | NA    |       |
| 15| Junaid et al. [34]  | 2016   | India   | Case-control study   | 372         | 260  | 112    | M=118, F=194 | 14-60 |       |
| 16| Yuvraj et al. [28]  | 2016   | India   | Cross-sectional study | 130         | 65   | 65     | F=74, M=56 | 29.3-52.9 |      |
| 17| Gao et al. [35]     | 2014   | China   | Case-control study   | 227         | 74   | 153    | F=100, M=127 | 31.2 |       |
| 18| Kim et al. [36]     | 2014   | Korea   | Case-control study   | 362         | 165  | 197    | F=195, M=108 | Case=46, Control=50 |     |
| 19| Hong et al. [37]    | 2013   | South Korea | Case-control study | 376         | 94   | 282    | F=184, M=192 |      |       |
| 20| Friis et al. [10]   | 2013   | Tanzania| Cross-sectional study | 1570        | 1223 | 347    | -          | >15   |       |
| 21| Iftekhar et al. [38] | 2013   | Pakistan| Case-control study   | 360         | 105  | 255    | F=155, M=205 | 39.78-57.46 |     |
| 22| Gray et al. [29]    | 2012   | Australia| Cross-sectional study | 247         | 11   | 236    | F=150, M=178 | 0.5-17.5 |      |
| 23| Ho-Pham LT et       | 2013   | Vietnam | Case-control study   | 385         | 166  | 219    | F=159, M=232 | NA    |       |
al.[39] study

| SN | Author          | Mean ± SD of vitamin D level of the TB group | Mean ± SD of vitamin D level of the control group | Median and IQR of TB group | Median and IQR of control group | Number of people with VDD in TB and control group | Criteria for VDD |
|----|-----------------|--------------------------------------------|-------------------------------------------------|----------------------------|--------------------------------|----------------------------------------------|------------------|
| 1  | Wejse et al. [41]| 31.32 ± 9.04 ng/ml                         | 34.12 ± 13.92 ng/ml                              | NA                        | NA                            | 31/362 (TB) 65/494 (control)                | <20ng/ml         |
| 2  | Kim et al. [36]  | 13.5 ± 9.10 ng/mL                          | 18.7 ± 8.33 ng/mL                                | NA                        | NA                            | 73/165 (TB) 21/197 (control)                | <10ng/ml         |
| 3  | Nielsen et al. [40]| NA                                          | NA                                              | NA                        | NA                            | Mild VDD: 9/72 (TB) 1/72 (control). No individuals had severe deficiency | <20ng/ml         |
| 4  | Ho-Pham LT et al. [39]| Log[25(OH)D, ng/mL] Mean 3.40(0.24) | Log[25(OH)D, ng/mL] 3.39(0.18)                      | NA                        | NA                            | 8/166(TB) 4/219 (control)                  | <20ng/ml         |
| 5  | Mastala et al. [30]| 23.88ng/ml                                | 33.68+/−16n g/ml                                  | NA                        | NA                            | 26/157(TB) NA (control)                    | <20ng/ml         |
| 6  | Gray et al. [29]  | 11.84 ng/mL (95% CI: 9.2–15.2)             | 17 ng/mL (95% CI: 15.76–18.36)                   | NA                        | NA                            | 9/11 (TB) 132/236 (control)                | <20ng/ml         |
| 7  | Ifthikar et al. [38]| 23.23 (+6.81) ng/ml | 29.27 (±8.89) ng/ml                               | NA                        | NA                            | 65/105 (TB) 85/255 (control)              |                  |
| 8  | Friis et al. [10]  | 44.36 (14.28) ng/ml                        | 33.76 (10.24) ng/ml                              | NA                        | NA                            | NA                                          |                  |
| 9  | Hong et al. [37]  | 9.86(7.19–14.15) ng/ml                     | 16.03 (12.38–20.30) ng/ml                       | 83/94 (TB) 209/282 (control) |                  | <20ng/ml                                    |
| 10 | Gao et al. [35]   | 365.9 (235.7) microgram/L                   | 464.3(335.6) microgram/L                         | NA                        | NA                            | NA                                          |                  |
| 11 | Yuvaraj et al. [28]| 15.4±6.8 ng/mL                            | 17.5±5.7 ng/mL                                   | NA                        | NA                            | NA                                          |                  |
| 12 | Junaid et al. [34]| 10.92 ng/ml                                | 17.32 ng/ml                                      | NA                        | NA                            | 118/260 (TB) 33/112 (control)              | <20ng/ml         |
| 13 | Memon            | 27.1±9.7 ng/ml                             | 36.8±8.1ng/ml                                    | NA                        | NA                            | 59/112 (TB) 19/97 (control)                | <20ng/ml         |

**Outcomes of the Included Studies**

Twenty-one studies [20-25,27,30-33,35-36,41] showed a significant association between the presence of active TB and vitamin D deficiency (VDD), i.e. VDD was found in active TB patients. Contrarily, in another study, high levels of vitamin D production were found in TB patients [29,39]. The mean of the majority of studies included in our study showed a higher than set criteria of VDD [30,38,41]. Further, few studies showed a lower mean value of vitamin D, which didn’t meet the set criteria of VDD [4,11,20-21,28,31,37]. Some other studies did not mention the reference level. The details of such values are mentioned in Table 6.
| Study | Authors | SD | IQR | TB (N) | Control (N) | VDD Cut-off |
|-------|---------|----|-----|--------|-------------|-------------|
| 14    | Oh et al. [32] | NA | NA | 10.6 (0.49-52.0) ng/mL | 19.3 (6.2-60.5) ng/mL | <20 ng/mL |
| 15    | Workineh et al. [27] | 12.0 ± 7.2 ng/ml | 15.4 ± 8.36 ng/ml | NA | NA | 105/126 (TB) 47/70 (control) | <20 ng/ml |
| 16    | Goyal et al. [26] | 13.9 ± 5.8 ng/ml | 29.5 ± 6.5 ng/ml | NA | NA | NA | NA |
| 17    | Ralph et al. [25] | 229.0 pmol/L, (95% CI 215.4-242.6) | 153.9 pmol/L, (95% CI 138.4-169.4) | NA | NA | NA | NA |
| 18    | Balcells et al. [24] | NA | NA | 11.7 ng/ml | 18.2 ng/ml | 71/92 (TB) 92/170 (control) | <20 ng/ml |
| 19    | Khan et al. [23] | 22.4 ± 8.5 ng/dl | 30.5 ± 8.6 ng/dl | NA | NA | NA | NA |
| 20    | Zhang et al. [4] | 10.42 ± 5.06 ng/ml | 21.97 ± 6.90 ng/ml | NA | NA | 122/128 (TB) 25/59 (control) | <20 ng/ml |
| 21    | Wang et al. [31] | 20.6 ± 10.9 ng/ml | 47 ± 30.2 ng/ml | NA | NA | NA | NA |
| 22    | Panda et al. [22] | -NA | NA | 11.60 ± 5.1 ng/mL | 21.50 ± 7.5 ng/mL | -NA | -NA |
| 23    | Musharaf et al. [21] | 22.79 ± 5.14 ng/ml | 31.76 ± 9.52 ng/ml | NA | NA | 55/70 (TB group) | <25 ng/ml |
| 24    | Arfeen et al. [20] | 22.79 ± 5.14 ng/ml | 31.76 ± 9.52 ng/ml | NA | NA | 55/70 (TB) 18/70 (control) | <25 ng/ml |
| 25    | Elsafi et al. [12] | 10.68 ± 0.64 ng/ml | 46.92 ± 1.28 ng/ml | NA | NA | NA | NA |
| 26    | Jaimni et al. [11] | NA | NA | 19 (7.75, 27.25) ng/dl | 25 (19.75, 32.00) ng/ml | 27/50 (TB group) 13/50 (control) | <20 ng/ml |

**TABLE 6: Outcomes of the included studies**

SD: standard deviation; IQR: interquartile range; TB: tuberculosis; VDD: vitamin D deficiency

**Meta-Analysis**

We conducted a quantitative synthesis of only 12 studies from the total studies included in our systematic review (Figure 2). We used the Revman Manager version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) to conduct our meta-analysis. In our study, we defined VDD as a concentration of vitamin D less than 20 ng/ml. We have included the studies that mentioned the discrete number of participants with vitamin D levels less than 20 ng/ml in both the TB and control groups. Therefore, only 12 studies were included in our meta-analysis. We did not include the studies that used a different cut-off for VDD to maintain the uniformity of the data. These results of the meta-analysis showed that the odds ratio (OR) of VDD in patients with TB to the healthy control is 3.23 with a confidence interval [1.91-5.45] (Figure 2). However, the result of our analysis showed that there is considerable heterogeneity in the included studies (I2 = 84%). The included studies vary in terms of sample size and age group of participants and geographical variation of the study population; therefore, we used the random-effects model to conduct our analysis.
FIGURE 2: Meta-analysis showing the odds ratio of vitamin D deficiency in the tuberculosis group to the healthy control group

| Study or Subgroup | Tuberculosis Events | Healthy Control Events | Odds Ratio | Meta-Analysis, CI, p-Value |
|-------------------|--------------------|------------------------|------------|---------------------------|
| Javed 2021        | 27                 | 50                     | 3.72       | 1.58-8.79, <0.001         |
| Zhang 2018        | 122                | 126                    | 1.00       | 0.57-1.79, 0.98           |
| Babula 2017       | 71                 | 82                     | 2.87       | 1.22-6.73, 0.003          |
| CH 2017           | 102                | 85                     | 1.23       | 0.63-2.42, 0.54           |
| Workshah 2017     | 106                | 126                    | 2.45       | 1.23-4.88, 0.002          |
| Javed 2016        | 116                | 120                    | 1.00       | 0.56-1.79, 0.98           |
| Mehn 2016         | 53                 | 112                    | 4.27       | 2.24-8.15, 0.0001         |
| Hong 2013         | 83                 | 94                     | 2.94       | 1.33-6.42, 0.001          |
| Gray 2012         | 41                 | 112                    | 3.59       | 1.79-7.22, 0.0001         |
| Last Tuber 2010   | 9                  | 100                    | 2.72       | 0.81-8.28, 0.12           |
| Neal 2010         | 9                  | 72                     | 1.24       | 0.46-3.56, 0.63           |
| Nyberg 2007       | 3                  | 60                     | 0.54       | 0.03-0.97, 0.028          |

Total (90% CI) 1125 1986 1030.0% 3.22 [1.57, 6.65]

Discussion

Most studies showed that lower vitamin D levels are more common among patients suffering from tuberculosis than in healthy volunteers. In 25 out of 26 included studies, the mean or median vitamin D concentration was higher in the healthy volunteers than in the TB patients. Also, the number of participants with VDD was found to be lower in the control group than in the TB group. Our review included the data from 8101 participants; 4203 were patients with tuberculosis infection and 3898 were healthy volunteers. Ralph et al. and Friis et al. were the only studies concluding the TB patients were likely to have a higher vitamin D level than healthy participants [10,25]. However, in the study by Ralph et al., the level of 1-25 hydroxyvitamin D was measured while in all other included studies, 25-hydroxy vitamin D was measured [25]. 1-25 hydroxyvitamin D is an active metabolite of vitamin D that is considered to be raised in granulomatous conditions such as sarcoidosis and pulmonary infections. According to Friis et al., the TB patients included in the study were under treatment and might have taken vitamin supplements [10]. These were the likely reasons for the contradictory finding of the higher vitamin D level in TB patients in these studies.

Our meta-analysis showed the TB patients were associated with lower vitamin D levels than the healthy controls. We calculated the odds ratio of VDD among tuberculosis patients to the healthy controls. The analysis’s overall odds ratio (OR) was 5.23 with a confidence interval (CI) of 1.91-5.45 (Figure 2). This showed that the OR calculated was statistically significant, and there was a greater chance of people being vitamin D deficient in the tuberculosis group than in the control group. Our analysis included 1625 patients with tuberculosis and 1998 healthy controls. Out of the 12 studies included in our statistical analysis, the study by Wejse et al. was the only study with OR less than one. The OR of this study was 0.62 with a CI of 0.39-0.97 [41]. However, the mean vitamin D level in the tuberculosis patients was lower than that of the control group in this study [41]. We did not include the studies, which showed higher mean vitamin D levels in TB patients than in healthy volunteers because they had not mentioned the number of people with VDD [10,25]. Although our meta-analysis showed statistically significant increased odds of VDD in patients with TB compared to the healthy group, our analysis showed considerable heterogeneity (I2=84%) in the included studies. This heterogeneity could be due to variable sample size, non-uniformity in the ratio of people among TB and control groups, and larger CI in some studies. Therefore, the findings of this analysis should be applied with careful consideration.

The result of our meta-analysis is consistent with earlier meta-analyses [42-46]. However, in a meta-analysis by Zeng et al., a serum vitamin D level ≤ 25 nmol/L, 26-50 nmol/L, and 51-75 nmol/L was found to have significantly associated with an increased risk of tuberculosis, potential high tuberculosis risk, and no risk, respectively [43]. Moreover, in another meta-analysis done a few years later, Aibana et al. showed a dose-dependent association of Vitamin D and risk of TB where the risk was highest among HIV-positive individuals with severe VDD [44]. Our study did not examine the dose-dependent associations and comorbidities that may interfere with vitamin D levels. Like Huang et al. [42], our analysis found a significant association between TB and VDD, but it did not clarify if VDD was a risk factor for TB or its consequence. But their meta-analysis revealed that VDD was significantly associated with an increased risk of developing active TB in latent TB infected individuals or contacts of TB patients [42]. Since we did not include studies with latent TB infected individuals, our study cannot ascertain such associations. In this regard, vitamin D supplementation remains questionable for TB prevention and treatment [47]. Further studies may shed light on the clinical prospect of Vitamin D supplementation for TB prevention and treatment.

The strength of our study consists of the inclusion of all relevant studies, which justified reasonable quality to present a conclusive picture. Also, in our meta-analysis, we included studies with the same VDD cut-off to provide a decisive result. However, our study has certain limitations. There was a high heterogeneity...
Our study has shown an association between low levels of vitamin D and tuberculosis. However, the studies included in our analysis have high heterogeneity, and they also do not clarify the causal relationship between the low vitamin D level and tuberculosis infection. Therefore, more prospective studies are required comparing the vitamin D-deficient group and healthy population and the development of tuberculosis infection in these groups to determine the causality.

Conclusions

We conducted a meta-analysis to identify the association between vitamin D level and tuberculosis infection. Our study did not analyze the ethnic, environmental, and comorbidities that may have some role in the VDD. Our study supports the opinion of vitamin D supplementation in TB patients. It may also provide substantial evidence for future randomized clinical trials to investigate the role of vitamin D supplementation in TB prevention.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. TB is a pandemic. (2021). Accessed: July 15, 2021: http://www.tballiance.org/why-new-tb-drugs/global-pandemic.
2. Global tuberculosis reports. (2020). Accessed: July 15, 2021: https://www.who.int/reports/global-tuberculosis-programme/tb-reports.
3. Adams JS, Hewison M: Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. Nat Clin Pract Endocrinol Metab. 2008, 4:80-90. 10.1038/ncpendmet0716
4. Zhang Y, Zhu H, Yang X, Guo S, Liang Q, Lu Y, Chen X: Serum vitamin D level and vitamin D receptor genotypes may be associated with tuberculosis clinical characteristics. A case-control study. Medicine (Baltimore). 2018, 97:e11732. 10.1097/MD.0000000000011732
5. Martinez AR, Wilkinson KA, Newton SM, et al.: IFN-gamma- and TNF-independent vitamin D-inducible human suppression of mycobacteria: the role of cathelicidin LL-37. J Immunol. 2007, 178:7190-8. 10.4049/jimmunol.178.11.7190
6. Liu PT, Stenger S, Tang DH, Modlin RL: Cutting edge: vitamin D-mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. J Immunol. 2007, 179:2060-5. 10.4049/jimmunol.179.4.2060
7. Sato E, Imafuji S, Ishii K, et al.: Vitamin D-dependent cathelicidin inhibits Mycobacterium marinum infection in human monocytic cells. J Dermatol Sci. 2013, 70:166-72. 10.1016/j.jdermsci.2013.01.011
8. Yuk JM, Shin DM, Lee HM, et al.: Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. Cell Host Microbe. 2009, 6:251-4. 10.1016/j.chom.2009.08.004
9. Rockett KA, Brooks R, Udalova I, Vidal V, Hill AV, Kwiatkowski D: 1,25-Dihydroxyvitamin D3 induces nitric oxide synthase and suppresses growth of Mycobacterium tuberculosis in a human macrophage-like cell line. Infect Immun. 1998, 66:5314-21. 10.1128/IAI.66.11.5314-5321.1998
10. Friis H, Range N, Changalucha J, et al.: Vitamin D status among pulmonary TB patients and non-TB controls: a cross-sectional study from Mwanza, Tanzania. PLoS One. 2015, 8:e81142. 10.1371/journal.pone.0081142
11. Jaimini V, Shastty BA, Madhyaastha SP, Shetty GV, Acharya RV, Bekur R, Doddamani A: Association of vitamin D deficiency and newly diagnosed pulmonary tuberculosis. Pulm Med. 2021, 2021:5285841. 10.1155/2021/5285841
12. Elassi SS, Nour BM, Akabar AD, Omer IH, Almugadam BS: Vitamin D level and it is association with the severity of pulmonary tuberculosis in patients attended to Kosti Teaching Hospital, Sudan. AIMS Microbiol. 2020, 6:65-74. 10.3934/microbiol.2020004
13. Horsburgh CR Jr: Priorities for the treatment of latent tuberculosis infection in the United States. N Engl J Med. 2004, 350:2060-7. 10.1056/NEJMoa031667
14. Houben RM, Dodd PJ: The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med. 2016, 13:e1002152. 10.1371/journal.pmed.1002152
15. Gamnaa D, Uyangaa B, Zhou X, et al.: Vitamin D supplements for prevention of tuberculosis infection and disease. N Engl J Med. 2020, 383:559-66. 10.1056/NEJMoa1915176
16. Sumartojo E: When tuberculosis treatment fails. A social behavioral account of patient adherence. Am Rev Respir Dis. 1995, 157:1311-20. 10.1164/arrc.1995.157.5.1311
17. Page MJ, McKenzie JI, Bossuyt PM, et al.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021, 372:n71. 10.1136/bmj.n71
18. Checklist for analytical cross sectional studies. (2017). Accessed: July 15, 2021: https://bi.global/sites/default/files/2019-05/BBI_Critical_Apraisal-Checklist_for_Analytical_Cross_Sectional_Study....
19. Checklist for case control studies. (2017). Accessed: July 15, 2021: https://bi.global/sites/default/files/2019-
A meta-analysis

Gou X, Pan L, Tang F, Gao H, Xiao D: Nnoaham KE, Clarke A: Vitamin D and the risk of tuberculosis: a meta-analysis in a West African population. J Infect. 2014, 6:760-4. 10.1093/ije/dym247

Both high and low serum vitamin D concentrations are associated with tuberculosis: a case-control study in Pakistan. Mol Biol. 2019, 193:105419. 10.1093/ijtld.13.0536

Weisse C, Olsen R, Rabna P, et al.: Serum 25-hydroxyvitamin D in a West African population of tuberculosis patients and unmatched healthy controls. Am J Clin Nutr. 2007, 86:1576-83. 10.1093/ajcn/86.5.1576

Huang SI, Wang XH, Liu ZD, Cao WL, Han Y, Ma AG, Xu SF: Vitamin D deficiency and the risk of tuberculosis: a meta-analysis. Drug Des Devel Ther. 2017, 11:91-102. 10.2147/DDDT.S79879

Zeng J, Wu G, Yang W, Gu X, Liang W, Yao Y, Song Y: A serum vitamin D level >25nmol/L pose high tuberculosis risk: a meta-analysis. PLoS One. 2015, 10:e0126014. 10.1371/journal.pone.0126014

Albana O, Huang CC, Aboud S, et al.: Vitamin D status and risk of incident tuberculosis disease: a nested case-control study, systematic review, and individual-participant data meta-analysis. PLoS Med. 2019, 16:e1002907. 10.1371/journal.pmed.1002907

Nooham KE, Clarke A: Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. Int J Epidemiol. 2008, 37:113-9. 10.1093/ije/dym247

Guo X, Pan L, Tang F, Gao H, Xiao D: The association between vitamin D status and tuberculosis in children. A meta-analysis. Medicine (Baltimore). 2018, 97:e12179. 10.1097/MD.00000000000012179

Xia J, Shi L, Zhao L, Xu F: Impact of vitamin D supplementation on the outcome of tuberculosis treatment: a systematic review and meta-analysis of randomized controlled trials. Chin Med J (Engl). 2014, 127:5127-54.