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## **Vitamin D deficiency in patients with tuberculosis: prevalence, risk factors and treatment outcomes**

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## **Abstract**

Although vitamin D deficiency is common in tuberculosis (TB) patients, several studies demonstrated that it may not influence treatment response. The aim of this study was to evaluate the prevalence and risk factors of vitamin D deficiency in a group of TB patients and to assess whether vitamin D deficiency influences TB treatment outcomes. All patients  $\geq 18$  years of age undergoing TB treatment at the Alvorada Pulmonology Department were invited to participate in the study. Blood samples were collected to check the level of vitamin D. TB treatment outcomes were collected. In total, 106 patients met the inclusion criteria and were included in the study. The mean vitamin D level was  $35.1 \pm 16.4$  ng/mL. The vitamin D status was classified as normal in 63 (59.4%) patients, insufficiency in 26 (24.5%), deficiency in 12 (11.3%), and severe deficiency in 5 (4.7%). The prevalence of vitamin D deficiency was 16.0%. HIV and diabetes mellitus were more frequent in groups with insufficient and deficient vitamin D compared with the group with normal vitamin D ( $p=0.041$  and  $p=0.011$ , respectively). Cured TB case as the treatment outcome was registered less frequently in the group with deficient vitamin D ( $p=0.016$ ), with confounding factors being HIV and diabetes mellitus. In conclusion, 16.0% of TB patients had vitamin D deficiency in the present study, and HIV and diabetes mellitus were factors associated with vitamin D insufficiency and deficiency. The wide variation in results between studies probably reflects regional variations, which emphasizes the need to understand the local reality. More robust studies are needed to evaluate the effect of vitamin D deficiency on treatment cure rates.

**Key words:** vitamin D, tuberculosis, *Mycobacterium tuberculosis*, treatment outcome, prognosis.

## **Introduction**

Vitamin D, a micronutrient known to play a key role in bone and calcium metabolism, has also demonstrated immunomodulatory effects in suppressing mycobacterial growth. Vitamin D metabolites increase the production of nitric oxide synthase, which suppresses mycobacterial growth [1,2]. Many studies have focused on the relationship between vitamin D deficiency and TB, some with conflicting results [3-5].

Studies have indicated that vitamin D deficiency is a risk factor for active TB [6-9]. In a prospective cohort study conducted in China [3], approximately three-quarters of TB patients were vitamin D deficient. A systematic review of 21 studies concluded that vitamin D deficiency is associated with increased susceptibility to TB infection and progression to active TB [10]. In another meta-analysis including 12 studies [11], the authors concluded that there is an association between low vitamin D levels and TB infection.

Although vitamin D deficiency is common in TB patients, several studies demonstrated that it may not influence treatment response [3,4,12,13]. However, a study conducted in Tanzania reported that low baseline vitamin D concentrations were associated with poor clinical outcomes [5]. Therefore, due to these controversial results, the aim of this study was to evaluate the prevalence and risk factors of vitamin D deficiency in a group of TB patients, and to assess whether vitamin D deficiency influences TB treatment outcomes.

## **Materials and Methods**

### ***Study design and location***

A cross-sectional study with prospective data collection was conducted to assess the prevalence of vitamin D deficiency and the risk factors for vitamin D deficiency in TB patients. Also, a cohort study, with ethics committee permission, was conducted to evaluate the outcomes of TB treatment in patients with and without vitamin D deficiency. The study site was the city of Alvorada, in Southern Brazil.

### ***Patients and data collection***

All patients  $\geq 18$  years of age undergoing TB treatment at the Alvorada Pulmonology Department were invited to participate in the study. Vitamin D supply was considered as exclusion criteria. Blood samples were collected to check the level of vitamin D (Ortho Clinical Diagnostics). The Holick definition was used to assess vitamin D status [14]: concentration

$\geq 30$  ng/ml = normal; 20–29.9 ng/ml = insufficient vitamin D; 10–19.9 ng/ml = vitamin D deficiency; 0 - 9.9 ng/ml = severe vitamin D deficiency. A standardized form was completed for each patient, including the following information: demographic data, smoking habit, alcohol abuse, drug use, prior TB history, comorbidities, TB treatment, and TB treatment outcome.

### ***Statistical analysis***

Data analysis was performed using IBM SPSS Statistics for Windows, version 22.0 (Armonk, NY, IBM Corp). Data were presented as number of cases, mean  $\pm$  standard deviation (SD), or median with interquartile range (IQR). Categorical comparisons were performed by chi-square test using Yates's correction if indicated or by Fisher's exact test. Continuous variables were compared using the *t*-test or Wilcoxon test. A two-sided *p* value  $< 0.05$  was considered significant for all analyses.

### **Results**

In total, 106 patients met the inclusion criteria and were included in the study. The characteristics of the study population are shown in Table 1. The mean age was  $44.4 \pm 19.0$  years and 67.9% were males. Twenty-three patients (21.7%) were HIV positive, and 18 (17.0%) had diabetes mellitus. The mean vitamin D level was  $35.1 \pm 16.4$  ng/mL. The vitamin D status was classified as normal in 63 (59.4%) patients, insufficiency in 26 (24.5%), deficiency in 12 (11.3%), and severe deficiency in 5 (4.7%). The prevalence of vitamin D deficiency was 16.0%.

Table 2 shows the comparison of TB patients with normal, insufficient, and deficient vitamin D status. Male sex was less frequent in the group with normal vitamin D than in other groups ( $p=0.001$ ). HIV and diabetes mellitus were more frequent in groups with insufficient and deficient vitamin D compared with the group of normal vitamin D ( $p=0.041$  and  $p=0.011$ , respectively). Cure was less frequent in the group with deficient vitamin D ( $p=0.016$ ).

Of the cases with vitamin D deficiency, 10 (58.8%) were cured, 7 (41.2%) were lost to follow-up, and no one died. Of the cases with normal vitamin D, 53 (84.1%) were cured, 8 (12.7%) were lost to follow-up, and 2 (3.2%) died.

## **Discussion and Conclusions**

In this cross-sectional study, we found a prevalence of vitamin D deficiency of 16.0% among patients with TB. In addition, HIV and diabetes mellitus were more frequent in groups with insufficient and deficient vitamin D. In the group of patients with TB and deficient vitamin D, the cure rate was lower.

The prevalence of vitamin D deficiency among patients with TB is widely variable, from 8.5% to 80% [3,4,15-17]. In a prospective cohort study [3], conducted in Jilin province, China, 74.2% of TB patients had vitamin D deficiency/severe deficiency. In another prospective longitudinal cohort study [4], 28% of Malawian adults had vitamin D deficiency. In a case-control study [15], the authors found that the prevalence of subnormal vitamin D levels was significantly higher in patients with TB as compared with control subjects. They found that 13.3% of patients were vitamin D deficient, a percentage similar to that found in our study.

In our study, 21.7% of patients were HIV positive. This percentage is similar to the regional average of 20% [18]. HIV was more frequent in groups with insufficient and deficient vitamin D in the present study. People with HIV are at a significantly higher risk for vitamin D deficiency due to a combination of factors, including the effects of the virus itself, certain antiretroviral drugs, and other health issues like chronic inflammation [19]. A cross-sectional study [20] of an HIV-clinical population-based cohort, conducted in Thailand, reported a prevalence of vitamin D deficiency and insufficiency of 58.5% and 35.2%, respectively.

We also found that diabetes mellitus was more common in insufficient and deficient vitamin D groups. In fact, diabetic patients have a higher prevalence of vitamin D deficiency compared to the general population. A meta-analysis of 132 studies found that vitamin D deficiency was the most common deficiency among people with type 2 diabetes, affecting over 60% of participants [21]. In a case-control study [22], the authors demonstrated that vitamin D deficiency among diabetic patients was more prevalent in females, those living in urban areas, and individuals with obesity and dyslipidemia.

Vitamin D deficiency was associated with lower cure rate probably due to existence with comorbidities like HIV and DM that impacted treatment outcome. Vitamin D deficiency was not associated with mortality in our study. Several studies demonstrated that low vitamin D concentrations were not associated with poor clinical outcomes [3,4,12,13]. One cohort study from Tanzania showed that patients with vitamin D insufficiency had an increased risk of experiencing TB relapse, but not greater mortality [5]. The finding of a lower cure rate in patients with vitamin D deficiency that was found in our study should be interpreted with

caution, since many of the “non-cured” patients actually dropped out of treatment wherein compliance/treatment adherence was a major confounder.

Our study has some limitations. First, we recruited patients from a single setting; however, we do not think that this is a limitation for generalizing the results, at least regionally. Second, we did not include a control group, so we cannot assess whether the prevalence of vitamin D deficiency in TB patients is different from that in the general population. Finally, as stated before, treatment adherence, DM and HIV could be significant confounders.

In conclusion, 16.0% of TB patients had vitamin D deficiency in the present study, and HIV and diabetes mellitus were factors associated with vitamin D insufficiency and deficiency. The wide variation in results between studies probably reflects regional variations, which emphasizes the need to understand the local reality. More robust studies are needed to evaluate the effect of vitamin D deficiency on treatment cure rates.

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**Table 1. Characteristics of study population.**

| Characteristics                   | n=106       |
|-----------------------------------|-------------|
| Age, yr, mean ± SD                | 44.4 ± 19.0 |
| Male sex                          | 72 (67.9)   |
| Active smoking                    | 27 (25.5)   |
| Alcohol abuse                     | 7 (6.6)     |
| Drug use                          | 8 (7.5)     |
| HIV positive                      | 23 (21.7)   |
| Diabetes mellitus                 | 18 (17.0)   |
| Previous TB                       | 15 (14.2)   |
| <b>Treatment outcome</b>          |             |
| Cure                              | 87 (82.1)   |
| Death                             | 2 (1.9)     |
| Default                           | 17 (16.0)   |
| Vitamin D level, ng/mL, mean ± SD | 35.1 ± 16.4 |
| <b>Vitamin D status</b>           |             |
| Normal                            | 63 (59.4)   |
| Insufficiency                     | 26 (24.5)   |
| Deficiency                        | 12 (11.3)   |
| Severe deficiency                 | 5 (4.7)     |

SD, standard deviation; TB, tuberculosis.

**Table 2. Comparison of tuberculosis patients with normal, insufficient, and deficient vitamin D status.**

| Characteristics          | Normal vitamin D (n=63)  | Insufficient vitamin D (n=26) | Deficient vitamin D (n=17) | p     |
|--------------------------|--------------------------|-------------------------------|----------------------------|-------|
| Age, yr, mean ± SD       | 45.2 ± 19.8              | 44.0 ± 17.3                   | 41.6 ± 19.4                | 0.780 |
| Male sex                 | 34 (54.0) <sup>a</sup>   | 23 (88.5) <sup>b</sup>        | 15 (88.2) <sup>b</sup>     | 0.001 |
| Active smoking           | 15 (23.8)                | 7 (26.9)                      | 5 (29.4)                   | 0.878 |
| Alcohol abuse            | 6 (9.5)                  | 0                             | 1 (5.9)                    | 0.256 |
| Drug use                 | 6 (9.5)                  | 1 (3.8)                       | 1 (5.9)                    | 0.628 |
| HIV positive             | 9 (14.3) <sup>a</sup>    | 10 (38.5) <sup>b</sup>        | 4 (23.5) <sup>a,b</sup>    | 0.041 |
| Diabetes mellitus        | 5 (7.9) <sup>a</sup>     | 8 (30.8) <sup>b</sup>         | 5 (29.4) <sup>a,b</sup>    | 0.011 |
| Previous TB              | 12 (19.0)                | 1 (3.8)                       | 2 (11.8)                   | 0.166 |
| <b>Treatment outcome</b> |                          |                               |                            |       |
| Cure                     | 53 (84.1) <sup>a,b</sup> | 24 (92.3) <sup>a</sup>        | 10 (58.8) <sup>b</sup>     | 0.016 |
| Death                    | 2 (3.2)                  | 0                             | 0                          | 0.499 |

SD, standard deviation; TB, tuberculosis. \*For all variables with the same letter, the difference between the means is not statistically significant. If two variables have different letters, they are significantly different.