The relationship between vitamin D levels and clinical symptoms and lesion size in chest radiographs of pulmonary tuberculosis in patients with comorbid diabetes mellitus

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ABSTRACT

Vitamin D acts as an immunomodulator, enhancing the body's immune function. A deficiency of vitamin D in patients suffering from pulmonary tuberculosis (TB) along with diabetes mellitus (DM) can lead to increased morbidity and mortality from the disease. This study aimed to explore the link between vitamin D levels, clinical manifestations, and the extent of chest X-ray lesions in TB patients who also deal with DM. This research is a cross-sectional study that involves pulmonary TB patients with concurrent DM conditions conducted from September to October 2024. The study measured serum vitamin D levels, evaluated clinical symptoms, and assessed the extent of chest X-ray lesions. Data analysis was performed using Fisher's exact test. The study included 40 individuals, with 60% aged between 41 and 59 years, and showed a 65% prevalence of vitamin D deficiency. A significant link was found between vitamin D deficiency and extensive lesions ($p<0.05$). Similarly, vitamin D deficiency was significantly correlated with the severity of symptoms ($p<0.05$). Vitamin D levels are related to the extent of lesions and clinical symptoms of pulmonary TB patients with comorbid DM.

Introduction

Tuberculosis (TB) is a common disease that is spread by infectious diseases such as *Mycobacterium tuberculosis*. People with diabetes mellitus (DM) experience impaired immune response, so that they are easily infected with *M. tuberculosis*, which causes pulmonary TB.[1] Globally, the prevalence of pulmonary TB with comorbid DM is around 13.73%.[2]

Vitamin D plays a crucial role in macrophage activation, inhibiting bacterial growth (an antimicrobial effect) and enhancing skeletal muscle function. Vitamin D deficiency in patients with pulmonary TB with comorbid DM can increase morbidity and mortality of the disease. Vitamin D functions as an immunomodulator, playing a role in macrophage activation. Several previous studies have reported that the active metabolite of vitamin D, specifically 1,25-dihydroxy, can enhance the body's immunity in combating *M. tuberculosis* bacterial infections.[3-7]

In the study, Jaimni *et al.* stated that low vitamin D levels are associated with the extent of chest radiograph lesions in patients with pulmonary TB. Specifically, chest radiograph

findings in patients with pulmonary TB accompanied by vitamin D deficiency tend to have more extensive lesions and are usually bilateral.[8] This is because the active metabolite of vitamin D, 1,25-dihydroxyvitamin D, is known to enhance the immune response to mycobacteria in vitro. Vitamin D binding to toll-like receptors (TLRs) on macrophage membranes induces the expression of the antimicrobial peptide cathelicidin, which inhibits and kills intracellular *M. tuberculosis* bacteria.[9]

The impact of vitamin D levels on the clinical severity and the spread of lesions in pulmonary TB patients who also have diabetes in Indonesia has not been extensively studied. This research seeks to examine the connection between vitamin D levels and the clinical symptoms, as well as the extent of chest X-ray lesions in pulmonary TB patients with coexisting DM.

Materials and Methods

This study is an observational analytical study with a cross-sectional design conducted at Dr. Wahidin Sudirohusodo Hospital, Makassar, in September and October 2024. The study was conducted on pulmonary TB patients with comorbid DM who met the inclusion criteria, namely age ≥18 years, positive molecular rapid test, and without other comorbidities. Patients who refused to participate in the study were excluded from participation. The estimated sample size is calculated using the two-group mean comparison test formula as follows [Eq. 1]:[10]

$$n_1 = n_2 = \frac{2xp(1-p)x(Z_{1-\beta}+Z_{1-\alpha/2})^2}{(p_1-p_2)^2} \quad \text{[Eq. 1]}$$

Where $Z_{1-\alpha/2}$ = α standard deviation at 95%; $Z_{1-\beta}$ = β standard deviation 90% (0.84), p_1 = proportion of vitamin D deficiency in primary TB with DM = 0.25939; p_2 = proportion of vitamin D deficiency in progressive TB with DM = 0.741.[8] Thus, the minimum sample size is 34 people in pulmonary TB patients with DM comorbidity.

This study measured serum vitamin D levels, clinical symptoms of the thoracic lesion area, age, nutritional status, and smoking history. Vitamin D levels were measured using an enzyme-linked immunosorbent assay kit, the results of which were categorized as follows: severe deficiency: <10 ng/mL (25 nmol/L); deficiency: £20 ng/mL (50 nmol/L); insufficiency: 21-29 ng/mL (52.5-72.5 nmol/L); sufficiency: £30 ng/mL (75 nmol/L); and toxic: >150 ng/mL (374 nmol/L).[11] Clinical symptoms were assessed using a 7-symptom scoring system consisting of cough, coughing up blood, shortness of breath, night sweats, chest pain, fever, and weight loss.[12] Score ≤3 = mild-moderate symptoms; and score 4-7 = severe symptoms. The thoracic lesion area was categorized as minimal if the lesion was of low to moderate density without visible cavitation, the total lung volume on one side was above the second chondrosternal junction, and the fourth thoracic vertebra, and there were no visible cavitations, and extensive if the lesion was more extensive than a minimal lesion.[13] Data were analyzed using the SPSS 27 program. Data were analyzed using Fisher's exact test. The research proceeded following ethical approval from the Ethics Commission at the Faculty of Medicine, Hasanuddin University (Approval Number: 733/UN4.6.4.5.31/PP36/2024).

Results

This study consisted of 40 people diagnosed with pulmonary TB with DM comorbidity. This study involved 40 subjects, with the majority aged 41-59 years (60%), ≥60 years (30%), and ≤40 years (10%). Most subjects had a normal nutritional status (85%), while 15% were classified as underweight. In terms of smoking history, 47.5% did not smoke, while 20% were light smokers, 25% were moderate smokers, and 7.5% were classified as heavy smokers (Table 1). Most subjects (80%) exhibited extensive lesions on their chest X-rays, while 20% had minimal lesions. The most common clinical symptoms included cough (75%), weight loss (70%), shortness of breath (60%), night sweats (57.5%), fever (45%), chest pain (42.5%), and coughing up blood (22.5%). Based on severity, 65% of cases were classified as severe, and 35% were classified as mild to moderate. The results of vitamin D level measurements showed that the majority of subjects were deficient (65%), followed by insufficiency (30%). Only 5% (2 people) had vitamin D levels in the sufficient category (Figure 1).

Table 2 shows that lower vitamin D levels were significantly associated with more extensive thoracic lesions in pulmonary TB patients with DM (p=0.029), where 75% of patients with extensive lesions had vitamin D deficiency,

Table 1. Characteristics of research subjects.

Characteristics	n	Percent-
Age		
≤40 years	4	10
41-59 years	24	60
≥60 years	12	30
Nutritional status		
Underweight	6	15
Normal	34	85
Smoking history		
No	19	47.5
Light smoker	8	20
Moderate smoker	10	25
Heavy smoker	3	7.5

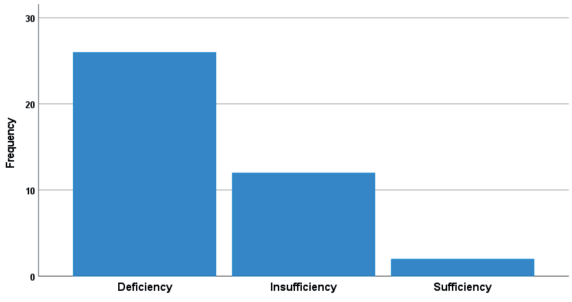

Figure 1. Distribution of vitamin D levels in research subjects.

Table 2. Relationship between vitamin D levels and the area of chest X-ray lesions in patients with pulmonary tuberculosis with diabetes mellitus comorbidity.

Vitamin D	Extent of thoracic X-ray lesion		p
	Minimal, n (%)	Extensive, n (%)	
Deficiency	2 (25.0)	24 (75.0)	
Insufficiency	5 (62.5)	7 (21.9)	0.029*
Sufficiency	1 (12.5)	1 (3.1)	

*Fisher's exact test.

Table 3. Relationship between vitamin D levels and clinical symptoms of pulmonary tuberculosis patients with diabetes mellitus comorbidity.

Vitamin D	Clinical symptoms		p
	Mild-moderate, n (%)	Severe, n (%)	
Deficiency	2 (14.3)	24 (92.4)	
Insufficiency	11 (78.6)	1 (3.8)	<0.001*
Sufficiency	1 (7.1)	1 (3.8)	

*Fisher's exact test.

while 62.5% of patients with minimal lesions were in the insufficiency category. Table 3 shows significant differences in vitamin D levels based on disease severity, with a higher prevalence of deficiency in patients with severe symptoms (92.4%) and insufficiency in those with mild to moderate symptoms (78.6%). This result showed a highly significant association between vitamin D levels and disease severity ($p<0.001$). This result suggests that reduced levels of vitamin D are associated with more severe clinical symptoms, indicating that vitamin D may influence the severity of pulmonary TB in individuals with DM.

Discussion

This study's findings suggest a notable correlation between vitamin D levels and disease severity in patients with pulmonary TB who also have comorbid DM. These results align with the research conducted by Jaimni *et al*., which demonstrates that reduced vitamin D levels are associated with the severity of clinical disease.[8] This study is also in line with the results of a cross-sectional study by Belur *et al*., which found that in TB, low vitamin D levels occurred more frequently in TB cases compared to the control group, particularly regarding the level of positive sputum smears and severe clinical symptoms, as indicated by chest X-ray results.[14]

Research on the relationship between vitamin D status and clinical symptoms of TB patients with comorbid DM is still minimal. Other studies have examined the relationship between vitamin D supplementation and clinical symptoms of TB patients. Cheng *et al*. found that vitamin D-assisted anti-TB drugs can effectively improve immune function and reduce the expression level of inflammatory factors in pulmonary TB patients, thereby reducing adverse reactions. The clinical symptoms of patients improved significantly.[15] Research conducted by Hassanein *et al*. stated that administering vitamin D supplementation together with Anti tuberculosis drugs category I can accelerate sputum conversion and help reduce the degree of clinical severity in patients with pulmonary TB.[16]

The level of clinical symptoms is related to the high inflammation in TB. The relationship between vitamin D and clinical symptoms of TB patients with comorbid DM is associated with the role of vitamin D as an immunosuppressor. Low levels of vitamin D can lead to an inability to suppress excessive inflammatory reactions, potentially increasing inflammation.[5,6,9,17]

Vitamin D deficiency also increases insulin resistance in peripheral tissues and reduces insulin secretion from pancreatic β cells. Vitamin D plays a role in increasing insulin secretion, enhancing insulin sensitivity, and lowering blood glucose levels. Vitamin D helps improve insulin sensitivity by increasing insulin receptor gene expression and reducing inflammatory cytokines.[18]

Different results from this study were reported by Suharti *et al*., who measured the clinical symptoms of TB using the Bandim Tuberculosis Score, finding no significant relationship between vitamin D intake and clinical symptoms in pulmonary TB patients.[19] This difference is possible due to differences in the population in which this study was conducted, specifically regarding TB with comorbid DM. This difference in results can also be attributed to various other factors that influence the clinical symptoms of TB patients, including age, immune status, comorbidities, and Bacillus Calmette-Guerin immunization.[19]

The results of this study indicate that there is a significant relationship between vitamin D levels and the extent of chest X-ray lesions in patients with pulmonary TB with comorbid DM. Vitamin D deficiency is associated with the occurrence of extensive lesions in TB patients with DM. This result aligns with research conducted by Jaimni *et al*., which found that low vitamin D levels are associated with the extent of chest X-ray lesions in patients with pulmonary TB. Specifically, chest X-ray findings in patients with pulmonary TB accompanied by vitamin D deficiency tend to have wider lesions and are generally bilateral.[8] This study is also in line with the results of a cross-sectional study conducted by Belur *et al*., which found that lower vitamin D levels were more common in TB cases compared to the control group and were associated with larger lesions on chest X-ray results.[14]

The relationship between vitamin D and lesion size can also be explained by research on TB patients treated with vitamin D-assisted anti-TB drugs compared to those treated with conventional anti-TB drugs. These results were described in a study by Cheng *et al*., which demonstrated that anti-TB medications, in conjunction with vitamin D, can effectively improve immune function and reduce the expression level of inflammatory factors in patients with pulmonary TB, thereby decreasing adverse reactions and the incidence of closed and invisible lesions.[15] Afzal *et al*. in their research stated that vitamin D supplementation can accelerate the conversion of acid-fast bacilli sputum and reduce clinical severity and improve chest X-ray results in pulmonary TB patients.[20]

The extent of lesions in TB is related to the results of hypersensitive immune reactions to bacteria in various parts of the body. In this study, vitamin D deficiency was associated with extensive lesions in TB patients with DM, which can be explained by its role in suppressing *M. tuberculosis* bacteria. Vitamin D that binds to TLR receptors on macrophage membranes will induce the expression of antimicrobial peptide cathelicidin.[9] Low vitamin D levels reduce the production of cathelicidin in macrophage cells, thereby decreasing their ability to kill *M. tuberculosis* bacteria.[4,17,21,22] This mechanism is supported by the low cathelicidin levels in granulomatous lesions of TB patients with vitamin D deficiency.[9] Low levels of vitamin D also reduce the production of nitric oxide, which plays an essential role in killing M. tuberculosis through the phagolysosome fusion mechanism.[5,6,9,17]

This study measured vitamin D levels only at one time point and did not assess them during treatment at multiple measurement time points. This study also only examined the relationship between vitamin D levels and clinical symptoms, as well as lesion size. Glycemic control, nutritional status, body mass index, sun exposure, and anti-TB treatment status are potential confounding factors that were not examined regarding the extent of lesions and clinical symptoms in this study, which could lead to bias in the results.

Conclusions

This study concluded that most patients with pulmonary TB with comorbid DM experienced vitamin D deficiency. Low vitamin D levels were found to be closely related to the severity of clinical symptoms and the extent of lesions on chest X-ray. Vitamin D deficiency may contribute to the severity of the disease in patients with pulmonary TB who have comorbid DM. The implication is that vitamin D levels can be helpful as a marker of the severity of pulmonary TB patients with comorbid DM. Further longitudinal research can provide more comprehensive results.

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