MMDJ
MEANDROS MEDICAL AND DENTAL JOURNAL

June 2025 26(2):185-192

Meandros Medical and Dental Journal
doi: 10.69601/meandrosmdj. 1612057

Research Article

INVESTIGATION OF THE EFFECT OF 25(OH)D3 LEVELS ON THE DISEASE SEVERITY AND THE COURSE OF THE TREATMENT IN ACTIVE PULMONARY TUBERCULOSIS PATIENTS

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Received: *03 January 2025*
Revised: *21 April 2025*
Accepted: *24 April 2025*
Published: *23 June 2025*

ABSTRACT

Aim: Tuberculosis (TB) remains a significant global health problem, with emerging evidence linking vitamin D deficiency to increased susceptibility and disease progression. Vitamin D regulates calcium, phosphorus, and bone metabolism while playing a crucial role in immune responses, particularly in macrophage activation and antimicrobial defense. This study aimed to assess the relationship between serum 25(OH)D3 levels and clinical, radiological, and treatment outcomes in TB patients.

Materials and Methods: A prospective study involving 70 newly diagnosed TB patients (aged 18-69 years) and 20 healthy controls was conducted over ten months. TB diagnosis was confirmed through clinical, radiological, and microbiological findings, including ARB smear and M. tuberculosis culture positivity. Participants underwent physical examinations, routine blood tests, and serum 25(OH)D3 level measurements. Vitamin D levels were categorized as deficient (<10 ng/mL), insufficient (10-24 ng/mL), or adequate (25-80 ng/mL).

Results: The mean serum 25(OH)D3 level in TB patients (22.01±9.24 ng/mL) was significantly lower than in controls (37.8±18 ng/mL, $p<0.001$). Among TB patients, 61.5% had deficient or insufficient levels, with severe deficiency (<10 ng/mL) observed in 6 individuals. Higher 25(OH)D3 levels correlated positively with hemoglobin, hematocrit, albumin, and calcium, and negatively with WBC count. Patients with higher 25(OH)D3 levels exhibited better radiological improvement after one month of treatment ($p<0.05$, $r= -0.223$).

Conclusion: The study concludes that low 25(OH)D3 levels are associated with greater TB severity and delayed recovery, emphasizing the need for further research on vitamin D supplementation in TB management.

Keywords: tuberculosis; vitamin D; 25(OH)D3; progression; outcomes

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doi: 10.69601/meandrosmdj. 1612057

INTRODUCTION

Tuberculosis (TB) remains an important public health problem as one of the most common infectious diseases worldwide. According to the WHO 2019 Global Tuberculosis Control Report Data, Turkey has a disease incidence of 13 per thousand, and estimated number of multi-drug resistant cases is 330 (1).

TB is a chronic granulomatous infectious disease that involves all organ systems, most often the lungs, and 98% of the cases are infected with *Mycobacterium tuberculosis* strains, although a lesser degree of infection is related to other Mycobacterium species *M. bovis* and *M. africanum.* Approximately 5% of those infected can develop progressive primary disease following the primary infection (2). Individuals with the greatest risk of developing the primary disease are infants and children under five years of age (3). Progressive primary tuberculosis is also frequently seen in immunocompromised adults with advanced HIV infection or AIDS (4).

The relationship between vitamin D deficiency and insufficiency and the development of and susceptibility to TB has been evaluated in various studies (5-7). The most likely explanation is that 1,25-dihydroxycholecalciferol, the active form of vitamin D, binds to its receptor to regulate the expression of genes crucial for immune function and cytokine production. Additionally, the anti-mycobacterial response triggered by specific toll-like receptors (TLRs) in macrophages relies on 25(OH)D levels and genetic variations in the vitamin D binding protein (DBP) and its receptor. Overall, vitamin D plays a key role in the body's immune defense against TB infection by promoting the production of antimicrobial peptides like cathelicidin, and enhancing the phagocytic activity of monocytes and macrophages.

Vitamin D is one of the most important physiological regulators of calcium, phosphorus and bone metabolism. It has a synergistic effect with parathormone (PTH) in the regulation of serum calcium level and contributes to bone mineralization (8). It has also been shown to play a role in the formation of cellular and humoral immune responses, increasing lysosomal enzyme activity in the macrophages, and facilitates the cytotoxic effect via phagocytosis (9).

M. tuberculosis is an intracellular pathogen, located in macrophages in particular and decreased monocyte-macrophage function plays an important role in the pathogenesis of TB infection (10).

In this study, we aimed to evaluate the effect of 25 Hydroxy Vitamin D3 (25(OH)D3) levels on the degree, course, and treatment of microbiological and radiological findings in patients with recently diagnosed TB, who are positive for acid-resistant bacteria (ARB) staining of sputum samples.

MATERIALS AND METHODS

In this prospective study, recently diagnosed 70 TB patients were evaluated in a year between January and October in a tertiary care hospital. The study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all participants.

The study group consisted of 70 patients with active pulmonary tuberculosis diagnosed with clinical, radiological and bacteriological findings of the TB infection [ARB smear (+), culture (+)] with an age interval of 18-69 years. The sputum samples of the patients were analyzed for the presence of ARB, and following the decontamination process, mycobacterium culture was performed using the Löwenstein - Jensen broth and MIGIT tubes. Patients with a positive result for M. tuberculosis complex were included in the study.

All TB patients were given anti-TB therapy of isoniazid, rifampin, pyrazinamide, ethambutol or streptomycin. The patients who were positive for resistance to anti-TB drugs were excluded. Healthy control samples were obtained from 20 volunteers aged between 25-69 years without any comorbidities. 25 (OH)D3 levels were measured in the serum samples of these individuals.

The medical data of the patients diagnosed with active pulmonary tuberculosis were collected and physical examinations were performed. BMI was calculated by measuring the height and weight of the patients. Routine analytical examinations included complete blood count (CBC), and serum levels of fasting blood glucose, blood urea nitrogen, creatinine, AST, ALT, ALP, Total Protein, Albumin, Total cholesterol, Ca, Na, K, Cl, and 25(OH)D3. Blood samples were taken before anti-TB treatment was initiated.

Radiological evaluation of the cases was performed by posterior-anteror chest radiography, and the radiological grading of the disease was evaluated. Microbiological and radiological evaluations were performed at the beginning of the treatment, and the end of the first and second months of treatment, and the response to the treatment was noted.

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doi: 10.69601/meandrosmdj. 1612057

Twenty healthy gender and age-matched volunteers selected from the outpatient patients applied to our center were included as the control group. Patients were classified according to the extent and type of chest radiograph changes, and a total score was calculated individually depending on the number of the lobes involved, presence of visible cavities or pleural involvement, the number and diameter of the visible cavities according to the modified radiological scale by Somoskovi et al (11).

We evaluated initial serum 25(OH)D3 levels and blood chemistry analyses and routine CBC were performed. The relationship between 25(OH)D3 levels and demographic characteristics, biochemical parameters, sputum smear/culture results and radiological grading of the patients were evaluated. The blood samples were centrifuged at 3000 rpm for 15 minutes, the supernatant was taken into opaque tubes in order to protect from light during the collection and storage of the samples, and kept at -40 until the day of analysis. Serum 25 (OH)D3 levels were measured using a high-pressure liquid chromatography [HPLC, Hewlett Packard (Spectrophotometric, fluorometric and electrochemical detector)]. with a commercial HPLC assay (ImmuChrom HPLC, Deutschland). The limit of detection (LOD) and the limit of quantification (LOQ) values were 1.76 ng/mL and 4.28 ng/mL, respectively. Serum 25(OH)D3 levels were categorized into three subgroups according to the reference range determined by the manufacturer as follows: <10 ng/ml as 25(OH)D3 deficiency; 10-24 ng/mL as 25(OH)D3 insufficiency, and 25-80 ng/mL as an adequate level of serum 25(OH)D3.

Statistical Analysis

Statistical analyzes were performed using Minitab 16 (Minitab, State College, Pennsylvania) software. The normality of the data was checked using the Kolmogorov-Smirnov test. The data are shown in the tables as Mean±Standard Deviation (SD). The student's t-test was used for the comparison of the variables, and Person's correlation coefficiency test was used for the evaluation of a correlation between the study variables. The confidence level was determined as 95% CI, and a p-value <0.05 was considered statistically significant.

RESULTS

The mean age of the study group was 39.7 ± 16.8 years. Forty-six of the patients were women and 24 were men. Twenty healthy volunteers were included in the study as a control group with a mean age of 42.3 ± 14.5 years. The mean 25(OH) D3 level was 22.01 ± 9.24 ng/ml in the study group, and 37.8±18 ng /ml in the control group (p < 0.001) (Table 1).

Table 1. Comparison of 25(OH)D3 levels between the study and control groups

Variables	Study group (n=70)	Control group (n=20)	p value
Age	39.7 ± 16.8	42.3 ± 14.5	0.512
25(OH)D3 (ng/ml)	22.01 ± 9.24	37.8 ± 18	0.001

We established a cut-off value of 25 ng/dl for the diagnosis of 25(OH)D3 deficiency and insufficiency, and 27 (38.5%) of the patients were above, whereas 43 (61.5%) of the patients were below the threshold value. Six patients (13.9%) of this group were evaluated as 25 (OH)D3 deficiency with their analyte levels below 10 ng/dl. We did not find a relationship between the study variables among the two groups (Table 2).

While we subgrouped the patients as 25(OH)D3 deficiency, insufficiency, and adequacy, a significant difference was found in the comparison of albumin, Ca, Na, WBC values (p <0.05). There was no significant difference in terms of age, BMI and serum biochemical tests in comparison to the group with severe 25(OH)D3 deficiency with the group with an adequate level of 25(OH)D3 (Table 3). We also found a negative correlation between WBC and 25(OH)D3 levels, and a positive correlation between Hb, Hct, Total protein, Albumin, and Ca values (Table 4).

25 (OH)D3 levels of 33 patients with positive smear findings were found to be 21.88 ± 9.27 ng/ml when compared to the 22.32 ± 9.35 ng/ml of 37 smear-negative individuals (p = 0.84). At the end of the second month of treatment, the mean 25(OH)D3 levels of 6 patients with positive smear result were found to be 20.33±6.74 ng/ml, whereas and the mean 25 (OH)D3 levels of 64 smear-negative cases was 22.27 ± 9.49 ng/ml (p=0.62).

We observed a negative correlation between the radiological grade at the end of the first month of the treatment and 25(OH)D3 level, and the radiological response to treatment was found to be more efficient at the first month in the patients with higher levels of 25 (OH)D3 (p< 0.05, r: - 0.223).

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doi: 10.69601/meandrosmdj. 1612057

Table 2. Comparison of the study variables according to 25(OH)D3 Deficiency & Insufficiency and Adequate Levels of 25(OH)D3 status

Variables	25(OH)D3 Deficiency & Insufficiency (< 25 ng/ml) (n=43)		Adequate Levels of 25(OH)D3 (≥25 ng/ml) (n=27)		
	Mean	±SD	Mean	±SD	p value
Age	41.64	18.01	33.95	13.53	0.139
BMI	20.89	3.48	22.14	2.51	0.281
WBC (10^3)	10.59	3.79	8.25	2.00	0.48
Hb (g/dl)	12.05	1.97	12.91	1.68	0.13
HCT (%)	36.57	5.62	39.11	4.72	0.11
PLT (10^3)	358.1	116.6	314.4	105.3	0.089
Glucose (mg/dl)	125	84.8	97.67	18.65	0.50
Urea (mg/dl)	27.79	14.37	27.05	8.2	0.803
Creatinine (mg/dl)	0.70	0.31	0.71	0.18	0.995
AST (U/L)	30.23	22.73	23.81	13.35	0.92
ALT (U/L)	27.98	32.14	22.52	19.09	0.817
ALP (U/L)	101.35	52.32	87.55	24.17	0.30
Total Protein (g/dl)	7.09	0.66	7.36	0.41	0.78
Albumin (g/dl)	3.48	0.75	4	0.46	0.65
Total cholesterol (mg/dl)	156.26	47.56	158.62	38.08	0.23
HDL-C (mg/dl)	34.95	19.85	45.9	17.7	0.19
LDL-C (mg/dl)	99.62	43.96	93	33	0.30
Triglycerides (mg/dl)	121.6	52.6	122.7	54.1	0.56
Ca (mg/dl)	8.74	0.81	9.27	0.67	0.99
Na (mEq/L)	134.43	4.81	136.71	2.94	0.74
K (mEq/L)	4.41	0.47	4.43	0.36	0.82
Cl (mEq/L)	99.34	4.32	101.43	4.69	0.69
Initial Radiological severity score	7.47	3.37	6.64	0.81	0.54
Radiological severity score on the 1st month of the treatment	6.35	3.48	5.08	0.74	0.33
Radiological severity score on the 2nd month of the treatment	5.46	3.39	4.09	0.68	0.17

DISCUSSION

In our study, we aimed to determine the serum 25(OH)D3 level in recently diagnosed ARB positive TB patients and to investigate its effect on anti-TB treatment response. When the serum 25(OH)D3 levels were compared between 70 sputum smear ARB positive cases and 20 healthy adults, the mean 25(OH)D3 level was found to be significantly lower in TB patients in accordance with previous publications.

TB is a disease known since the ancient years, however, the epidemic has become an important public and medical concern after the industrial revolution when people started to live in cities under intense and harsh conditions (12). The presence of diseases that compromise immunity such as HIV infection, malnutrition, vitamin D deficiency, the long-term intake of immunosuppressive drugs and TNF-alpha inhibitors facilitate the emergence of the disease and worsens the course of the disease.

Vitamin D is key a hormone that regulates calcium and phosphorus metabolism. Recently, effective studies are being conducted on the representation of vitamin D in the development of chronic diseases such as malignancies, diabetes mellitus, and metabolic syndrome (13). Furthermore, in-vitro studies have shown that vitamin D and its metabolites might play an important role in the regulation of granulomatosis reactions and increase the ability to inhibit the growth of mycobacterium species through the activation of alveolar macrophages (14).

There is a variety of meta-analysis and prospective study reports suggesting that TB patients had lower vitamin D levels than the healthy population. In their study, Sato et al. found that 87% of active tuberculosis patients had vitamin D deficiency, whereas another study conducted in India had shown that low vitamin D levels were found to be associated with the development of disease in smear-positive patients (15, 16). 25 (OH) D3 levels were found lower in children with tuberculosis infection, and vitamin D deficiency increased the risk of TB.

In our study, we observed a negative correlation between the WBC count and 25(OH)D3 level, and a positive correlation between Hb, Hct, total protein, albumin and Ca values and 25(OH)D3 levels, suggesting that vitamin D deficiency might be increasing the inflammatory response and delaying the recovery process. Reports show that WBC values were higher and RBC values were lower in TB patients with vitamin D deficiency and that Vitamin D deficient patients had a longer duration of sputum smear ARB positivity (17, 8). Although vitamin D deficiency might not be the sole factor in the pathogenesis and disease severity of TB, the studies reported decreased antimycobacterial activity caused by Vitamin D deficiency is linked to increased inflammatory response and accelerated proliferation of M. tuberculosis (19). On the

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MEANDROS MEDICAL AND DENTAL JOURNAL
June 2025 26(2):185-192
Meandros Medical and Dental Journal
doi: 10.69601/meandrosmdj. 1612057

Table 3. Comparison of the study variables according to 25(OH)D3 Deficiency, Insufficiency and Adequacy status.

Variables	25(OH)D3 Deficiency		25(OH)D3 Insufficiency		Adequate Levels of 25(OH)D3
	<10 ng/ml	p value*	10-24 ng/ml	p value**	25-80 ng/ml
Age	33±14.35	**0.032**	41.78±17.94	0.078	34.08±13.3
BMI	18.44±1.2	0.237	21.123±3.6	0.164	22±2.7
WBC (10^3)	12.89±6.9	0.112	10.68±3.58	**0.004**	8.07±1.82
Hb (g/dl)	10.13±2.27	**0.042**	12.05±1.85	0.199	13.14±1.75
HCT (%)	31.92±6.82	0.073	36.49±5.34	0.153	39.646±4.8
PLT (10^3)	419.5±151.2	0.118	357±119	0.204	310.6±101.5
Glucose (mg/dl)	96.25±15.88	0.279	129.8±94.2	0.085	97.42±18.84
Urea (mg/dl)	19.75±4.92	0.835	28.95±14.92	0.936	26.75±7.71
Creatinine (mg/dl)	0.45±0.1	0.93	0.72±0.32	0.771	0.704±0.18
AST (U/L)	53.25±14.31	0.136	29.3±23.66	0.339	24.54±12.2
ALT (U/L)	20.67±7.23	0.513	26.59±31.19	0.54	24.21±18.23
ALP (U/L)	94.8±25.3	0.879	104.35±57.23	0.135	87.5±23.16
Total Protein (g/dl)	6.575±0.9	0.237	7.1±0.62	0.085	7.42±0.45
Albumin (g/dl)	2.97±0.74	0.057	3.44±0.73	**0.004**	4.05±0.47
Total cholesterol (mg/dl)	117±22.6	0.848	158.54±46.95	0.826	164.33±43.05
HDL-C (mg/dl)	28.3±22.6	0.234	36.5±19.6	0.216	45.9±17.7
LDL-C (mg/dl)	93.3±55.9	0.994	101.1±42.6	0.586	93±33
Triglycerides (mg/dl)	171±89.7	0.388	110.7±36	0.54	122.7±54.1
Ca (mg/dl)	8.45±0.71	0.392	8.67±0.81	**0.009**	9.279±0.655
Na (mEq/L)	131.75±3.86	0.068	134.24±5.08	**0.05**	136.79±2.78
K (mEq/L)	4.65±0.66	0.103	4.37±0.46	0.438	4.37±0.33
Cl (mEq/L)	97.75±4.57	0.143	99±4.39	0.147	101.29±4.37

* p value obtained from the comparison of 25(OH)D3 deficiency and adequacy; ** p value obtained from the comparison of 25(OH)D3 insufficiency and adequacy

other hand, Wejse et al. concluded that additional treatment for the amelioration of Vitamin D status did not yield an efficient treatment response in their randomized double-blind study (20).

The immune system can detect many pathogens and *M. tuberculosis* via the activity of TLRs and with pathogen-related molecular patterns (PAMPs) (21). PAMPs presented by *M. tuberculosis* associate with TLR2 /1 dimers of macrophages, resulting in the up-regulation of both CYP27b1 and vitamin D receptor (VDR). Besides, IL-15 is responsible for CYP27b1 induction, which provides the conversion of 25(OH)D3 to 1, 25 (OH)D2, activation of VDR, and induction of cathelicidin. The cathelicidin gene LL-37 encodes a Vitamin D-dependent anti-microbial peptide, that requires a vitamin D activity in humans. Thus, vitamin D binding provides the LL-37-mediated immune response to *M. tuberculosis*. It has been shown that the cathelicidin gene is expressed in respiratory epithelium cells, vitamin D-dependent cathelicidin is found in many cell lines, such as bronchial epithelium cells (22). While the immunity in the pathogenesis of TB is provided by cytokines secreted by Th 1 cells, macrophage activation, and granuloma formation, the Th2 response causes a delayed-type hypersensitivity reaction that aggravates tissue damage.

The link between low vitamin D levels and delayed TB treatment response may be influenced by several factors. Limited sun exposure during colder seasons — when TB incidence is higher — reduces vitamin D synthesis. Additionally, groups with higher TB rates, such as children, the elderly, and immigrants, often have lower serum vitamin D levels, along with potential nutritional, digestive, and absorption issues. Age-related decline in kidney function also impairs the body's ability to produce vitamin D, leading to lower blood 25-hydroxyvitamin D concentrations. Historically, cod liver oil and sunlight, both rich sources of vitamin D, were used to treat TB, highlighting the long-recognized importance of vitamin D in managing the disease.

While we established a cut-off value of 25 ng/ml for the determination of vitamin D deficiency and insufficiency, the WBC count was significantly higher in the group with vitamin D deficiency and insufficiency, as well as the

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MEANDROS MEDICAL AND DENTAL JOURNAL
June 2025 26(2):185-192
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doi: 10.69601/meandrosmdj. 1612057

significant difference in albumin, Ca, Na, K levels. However, we did not find a relationship between 25(OH)D3 levels of patients and sputum smear negativity. Studies report conflicting data on vitamin D levels and its effect on sputum and culture negativity in TB patients (23, 24). It was also reported that TaqI VDR polymorphism, the dose of the given vitamin D and other clinical differences should be taken into consideration when investigating the efficiency of vitamin D supplementation in active tuberculosis cases (25).

Table 4. The correlation between the study variables and the 25(OH)D3 levels.

Variables	Correlation coefficient	p value
Age	-0.215	0.075
BMI	0.15	0.22
WBC (10^3)	-0.32	**0.007**
Hb (g/dl)	0.258	**0.032**
HCT (%)	0.269	**0.025**
PLT (10^3)	-0.204	0.092
Glucose (mg/dl)	-0.159	0.193
Urea (mg/dl)	-0.065	0.598
AST (U/L)	-0.145	0.236
ALT (U/L)	-0.058	0.635
ALP (U/L)	-0.109	0.375
Total Protein (g/dl)	0.293	**0.014**
Albumin (g/dl)	0.352	**0.003**
Total cholesterol (mg/dl)	0.125	0.304
Ca (mg/dl)	0.255	**0.035**
Na (mEq/L)	0.206	0.09
K (mEq/L)	-0.128	0.295
Cl (mEq/L)	0.199	0.101
Initial Radiological severity score	-0.18	0.144
Radiological severity score on the 1st month of the treatment	-0.239	**0.05**
Radiological severity score on the 2nd month of the treatment	0.283	0.2

One important finding of our study is that the radiological severity of the disease on the different time points as the initiation of the treatment, end of the first month of the treatment and end of the second month of treatment was in concordance with 25(OH)D3 level. We observed a better radiological improvement at the end of the first month of the treatment in patients with higher levels of 25(OH)D3. Similarly, in their randomized controlled study, Nursyam et al. showed that in their 67 TB patients, radiological recovery was better in the group in which they added vitamin D supplementation to the TB treatment.

Although seasonal variations might be expected in 25(OH)D3 levels, we did not detect a season-based difference in our study group. In a similar study conducted by Maceda et al., shared a similar data of TB patients, contrary to the expectations (26).

CONCLUSION

In this study, the relationship between 25 (OH)D3 levels and the clinical course of active tuberculosis patients was investigated. We suggest that 25 (OH)D3 level might be affecting the clinical course and the disease severity of the active pulmonary TB. However, there is a great need for comprehensive studies in TB patients, where vitamin D levels, disease prevalence and response to treatment are evaluated, and the effect of vitamin D supplementation on treatment is examined.

Acknowledgments
None.

Authorship contributions
SAK: Data collection, interpretation, writing; GO: Supervision; critical review

Data availibity statement
Data is available upon request.

Declaration of competing interest
None.

Ethics
Obtained from the institutional review board (24.12.2012 / 6128).

Funding
None.

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