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Research Article

THE ROLE OF VITAMIN D SUPPLEMENTATION TO FIRST-LINE ANTI-TUBERCULOSIS TREATMENT IN TREATMENT COURSE OF PULMONARY TUBERCULOSIS

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ABSTRACT

Objectives: The objective of the study was to study the role of Vitamin D supplementation to first-line anti-tuberculosis treatment (ATT) in the treatment course of pulmonary tuberculosis (TB).

Methods: This study was conducted on sputum acid-fast bacilli (AFB) positive outpatient department and inpatient department patients who had presented to Batra Hospital and Medical Research Centre, New Delhi. We had included 66 patients who were newly diagnosed sputum smear AFB positive. The patients were divided into two groups. Each subject signed a special consent form that was written in simple phrase. The procedure and the aim of the work were explained to all the subjects in simple language and due consent was taken.

Results: Majority of the patients in Group 1 (cases) were in age group of 51–60 years (30%) and in Group 2 (controls) were in age group of < 30 years (27%). Mean age was found to be comparable in both groups, which was 46.3±17.91 years in Group 1 (cases) and 47.46±17.27 years in Group 2 (cases). Gender ratio was also comparable in both groups with 60.61% males and 39.9% females in Group 1 (cases), and 72.73% males and 27.7 % females in Group 2 (controls). In Group 1 (cases) mean TB score was 5.82±1.01 and in Group 2 (controls) mean TB score was 5.94±1.09 (p=0.683). After 2 months mean TB score in Group 1 was 1.7±1.38 and in Group 2 was 2.94±1.82. There was a statistically significant difference in TB score between the two groups (p=0.0002).

Conclusion: In the present study, we found that the majority of the patients enrolled were males, this could have been due to less accessibility of females to medical healthcare facility due to social factors. Patients who received Vitamin D along with first-line ATT had early sputum smear conversion as compared to those who were on ATT only. Furthermore, patients who received Vitamin D with ATT had better TB score after 2 months of therapy as compared to patients on first-line ATT only. Thus, Vitamin D supplementation to first-line ATT can reduce time to sputum conversion and accelerate clinical improvement.

Keywords: Tuberculosis, Vitamin D supplementation, Anti-tuberculosis treatment, Treatment course.

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INTRODUCTION

Pulmonary tuberculosis (TB) is a highly communicable disease associated with high morbidity and mortality. According to the World Health Organization (WHO) report, in 2015 there were 10.4 million new TB cases (including 1.2 million among PLHIV), of which 5.9 million were men, 3.5 million were women and 1.0 million were children. Overall, 90% of cases were adults and 10% children, and the male-to-female ratio was 1.6:1.9 [1]. As per the India TB 2018 annual status report, India accounts for about one-fourth of the global TB burden. In 2016, an estimated 27,90,000 cases occurred and 4,23,000 people died due to TB. The incidence of TB was 211/lakhs/year and the mortality was 32 per lakhs in 2016 [2]. TB is caused by organisms of the *Mycobacterium tuberculosis* complex, which includes *M. tuberculosis*, the most common and important agent of human mycobacterial disease, and *Mycobacterium bovis*, which (like other mycobacterial species) is acquired through ingestion of unpasteurized milk. *M. tuberculosis* is a thin aerobic bacillus which is neutral on Gram's staining but if once stained with acid-fast; that is, it cannot be decolorized by acid alcohol due to the cell wall has a high content of mycolic acids and other lipids. Acid-fast bacilli (AFB) that reach alveoli are ingested by macrophages. The bacilli impair phagosome maturation, multiply, lyse the macrophages, and spread to regional lymph nodes from which they may disseminate throughout the body. A granuloma formation occurs at the site of the primary lesion and at sites of dissemination. The lesions then get healed either by fibrosis or undergo further evolution. Despite "healing," viable bacilli can remain dormant within macrophages or in necrotic material for years. Adult-type disease presents initially with non-specific and insidious signs and symptoms, such as diurnal fever, night sweats, weight loss, anorexia, malaise, and weakness. As the disease progresses, patients develop cough and purulent sputum production often with blood streaking. Extensive cavitation may develop, with occasional massive hemoptysis following erosion of a vessel located in the wall of a cavity. Disease is usually localized to the apical and posterior segments of the upper lobes and the superior segments of the lower lobes [3]. The hydroxylated metabolites of Vitamin D, 1,25 dihydroxy Vitamin D3 being the most potent, can cause inhibition of growth of *M. tuberculosis* in normal human monocytes [4]. Vitamin D acts as both vitamin and hormone and has various actions. 1,25 dihydroxy Vitamin D is the major biologically active metabolite, it plays a major role in maintaining calcium and phosphate homeostasis. It also has anti-proliferative, pro-differentiation, and immunosuppressive effects [5]. Humans receive Vitamin D from exposure to sunlight, from diet, and dietary supplements. Vitamin D is synthesized in the skin by conversion of 7-dehydrocholesterol to pre-vitamin D3 on exposure to UV B radiation (wavelength 219–315 nm). Vitamin D formed is metabolized in the liver to form 25-hydroxy Vitamin D3, which is used to determine patient's Vitamin D status. 25-hydroxy Vitamin D3 is converted to its active form 1,25 dihydroxy Vitamin D3 in kidneys

by enzyme 25-hydroxy Vitamin D-1-alpha hydroxylase [6]. This active metabolite of Vitamin D can increase the ability of monocytes to control proliferation of *M. tuberculosis in vitro* [4]. This action is mediated by induction of reactive nitrogen and oxygen intermediates [7,8], attenuation of *M. tuberculosis*-induced increase in expression of MMP-7 and MMP-10, and suppresses secretion of MMP-7 by *M. tuberculosis*-infected peripheral blood mononuclear cells (matrix metalloproteinases are implicated in the pathogenesis of pulmonary cavitation) [9] and induction of cathelicidin mediated autophagy [10-12]. Vitamin D receptors in humans are polymorphic. Carriers of FokI FF genotype had faster sputum mycobacterial culture and auramine stain conversions and carriers of TaqI Tt genotype had faster sputum culture conversion demonstrating the potential clinical relevance of immunomodulatory functions of Vitamin D metabolites acting via the VDR in the host response against pulmonary TB [13]. Lower level of Vitamin D was reported to have been associated with a higher risk of developing active pulmonary TB [14]. The role of Vitamin D in modifying the treatment course of pulmonary TB is still a matter of debate [15,16]. The aim of this study was to evaluate the role of Vitamin D supplementation to the first-line anti-tubercular drugs in the treatment course of patients with active pulmonary TB based on sputum AFB smear conversion and TB score. TB score is a simple and low-cost tool for clinical monitoring of TB patients in low-resource settings and may be used to predict mortality risk. WHO clinical manual is used to choose signs and symptoms including cough, hemoptysis, dyspnea, chest pain, night sweating, anemia, tachycardia, lung auscultation findings, fever, low body-mass index, low mid-upper arm circumference giving patients a TB score from 0 to 13. TB score is grouped in severity classes I (0–5 points), II (6 or 7 points), or III (8 points or more). The risk of dying during treatment increased with a higher TB score at inclusion. Low TB score or fall in TB score at treatment completion may be used as a measure of improvement [17].

Objectives

The objective of the study was to study the role of Vitamin D supplementation to first-line anti-TB treatment (ATT) in the treatment course of pulmonary TB.

METHODS

After getting approval from the Institutional Ethical Committee, this study was conducted in the Department of General Medicine, Batra Hospital and Medical Research Center, New Delhi from December 2017 to December 2018. A total of 66 patients who met the inclusion criteria were enrolled in the study and were divided into two groups.

- Group 1 (case) – Patients who received oral 60 k Vitamin D once every week for the period of 8 weeks along with first-line ATT drugs.
- Group 2 (control) – Patients who received first-line ATT only.

Study design

It was a hospital-based prospective interventional study.

Sample size

Two groups consisting of 33 patients each with a total sample size of 66.

In a study done by Hassanein *et al*., the mean conversion time in cases and controls were 3.57±0.73 and 7.00±1.08 weeks respectively [22]. The sample size was calculated using the following formula (Charan J and Biswas T) [18].

$n=2X(Z\alpha/2+Z\beta)2\ SD2/d2$

where n: Sample size per group

SD: Assumed standard deviation.

d: Difference in the means (effect size)

$Z\alpha/2$: Level of significance, $Z\beta$: Power

Assuming 80% power, 5% significance level with 95% confidence interval as well as assuming standard 5, the required sample size per group is 33.

Inclusion criteria

- Adults who were 14 years or more than 14 years of age and also who had active pulmonary TB were diagnosed by sputum examination (smear microscopy).

Exclusion criteria

- Corticosteroid or immunosuppressive treatment, HIV positive, multidrug-resistant-TB, liver cirrhosis, renal failure, Vitamin D supplementation, malignancies, hypercalcemia.

Methodology

This study was conducted on outpatient department and inpatient department patients with sputum AFB positive who were presented in Batra Hospital and Medical Research Centre, New Delhi. Each subject signed a special consent form that was written in simple phrase. The procedure and the aim of the work were explained to all the subjects in simple language and due consent was taken. A total of 66 newly diagnosed sputum smear AFB-positive patients were enrolled in the study based on inclusion and exclusion criteria. The patients were randomly divided into two groups with 33 patients in each group. In Group 1 (cases), patients received oral ATT as per RNTCP guidelines 28 along with oral 60,000 IU of Vitamin D once a week for the period of 8 weeks. In Group 2 (controls), patients received oral first-line ATT only. On the basis of clinical signs and symptoms, including cough, hemoptysis, dyspnea, chest pain, night sweating, anemic conjunctiva, tachycardia, lung-auscultation finding, fever, body-mass index, mid-upper arm circumference TB score was given from 0 to 13. TB score was grouped in severity classes 1 (0–5 points), 2 (6 or 7 points), or 3 (8 points or more). Vitamin D and calcium as well as albumin levels were recorded in Group 1 before supplementation of oral Vitamin D. Patients having Vitamin D levels <30 ng/mL were considered low Vitamin D levels. Serum albumin was measured to correct serum calcium for low albumin levels. Patients in both groups were followed up on weekly basis and sputum was sent for AFB smear examination every week for 8 weeks. Time to sputum smear conversion was recorded. TB score and severity class were again recorded after 2 months starting of therapy in both groups. All of the patients completed the study. All data were recorded in study pro forma, tabulated, and analyzed by Statistical Package for the Social Sciences (SPSS) version 21.0.

Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD and median. Normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected then non-parametric test was used.

Statistical tests were applied as follows:

1. Quantitative variables were compared using Independent T-test/ Mann–Whitney Test (when the data sets were not normally distributed) between the two groups and Wilcoxon signed-rank test was used for comparison between pre and post within the group.
2. Qualitative variables were correlated using the Chi-square test/ Fisher's exact test. A $p<0.05$ was considered statistically significant.

The data were entered in MS Excel spreadsheet and analysis was done using SPSS version 21.0.

RESULTS

Above Table 1 shows that baseline characteristics were comparable in Group 1 (cases) and Group 2 (controls) at the beginning of the study. Majority of the patients in Group 1 (cases) were in the age group of 51–60 years (30%) and in controls were in the age group of <30 years (27%). Mean age was found to be comparable in both groups, which was 46.3±17.91 years in Group 1 (cases) and 47.46±17.27 years in Group 2 (cases), there was no significant statistical difference in the age distribution (p=0.734).

Above Table 2 shows that the gender ratio was also comparable in both groups with 60.61% males and 39.9% females in Group 1 (cases), and 72.73% males and 27.7 % females in Group 2 (controls) (p=0.296), that is, there were more sputum smear positive males than females.

Table 3 shows that Group 1 (cases) included 9 patients (27.27%) who were sputum smear negative by 3rd week, 16 patients (48.48%) who were sputum smear negative by 4th week, 7 patients (21.21%) who were sputum smear negative by 5th week and 1 patient (3.03%) who was sputum smear-negative by 6th week. While Group 2 (controls) included 3 patients (9.09%) who were sputum smear negative by 3rd week, 2 patients (6.06%) who were sputum smear negative by 4th week, 7 patients (21.21%) who were sputum smear negative by 5th week, 10 patients who were sputum smear negative by 6th week, 9 patients (27.27%) who were sputum smear negative by 7th week and 2 patients (6.06%) who were sputum smear negative by 8 weeks.

Table 4 shows that TB score at the beginning of the study regarding sample size, mean ±SD, median, Min-Max, and interquartile range in Group 1 were 33, 5.82±1.01, 5, 5–8, 5–6.25 respectively. In Group 2 TB scores regarding sample size, mean ±SD, median, Min-Max, and interquartile range in Group 1 were 33, 5.94±1.09, 6, 5–8, and 5–7, respectively. There was no significant statistical difference in severity class in the two groups.

Table 5 shows that in Group one severity class regarding I, II, and III were 17 (51.52%), 13 (39.39%), and 3 (9.09%), respectively. In Group 2 severity class regarding I, II, and III were 16 (48.48%), 13 (39.39%) and 4 (12.12%), respectively. There was no significant statistical difference in severity class in the two groups, 2 months after treatment.

Table 6 shows that TB score after 2 months of treatment regarding sample size, mean±SD, median, Min-Max, and inter quartile range in Group 1 were 33, 1.7±1.38, 1, 0–6, and 1–2, respectively. In Group 2 TB score regarding sample size, mean±SD, median, Min-Max, and Inter quartile range in Group 1 were 33, 2.94±1.82, 2, 0–7, and 2-3, respectively. There was having significant statistical difference in TB score after 2 months in the two groups.

Table 7 shows that 2 months after therapy, in Group 1 (cases) 31 patients (93.94%) were in severity Class I, and 2 patients (6.06%) were in severity Class II. In Group 2 (controls) 27 (81.82%) patients were in severity class I and 6 (18.18%) were in severity class II. There was no significant statistical difference in severity class in the two groups, 2 months after treatment.

DISCUSSION

In the present study, there were more male patients than females. Group 1 included 20 males and 13 females. Group 2 included 24 males and 9 females. In total, there were 44 male patients and 22 female patients. This was similar to the finding in study done by Nursyam *et al.* [15] where there were more male patients than females (39:28). Vitamin D levels were checked in Group 1. All the patients were

Table 1: Age-wise distribution of patients in both Group 1 (cases) and Group 2 (controls)

Age distribution	Sputum smear AFB-positive patients		Total (%)
	Case (%)	Control (%)	
Age (in years)			
≤30	27	24	25.76
31–40	9	12	10.61
41–50	9	18	13.64
51–60	30	15	22.73
61–70	18	24	21.21
>70	6	6	6.06
Total	100.00	100.00	100.00

AFB: Acid-fast bacilli

Table 2: Gender-wise distribution of patients in both Group 1 (cases) and Group 2 (controls)

Gender wise distribution	Case (%)	Control (%)	Total (%)
Sex			
Female	39.39	27.27	33.33
Male	60.61	72.73	66.67
Total	100.00	100.00	100.00

Table 3: Time to sputum smear conversion (in weeks) in Group 1 (cases) and Group 2 (controls)

Sputum conversion (week)	Group		Total (%)	p-value
	Case (%)	Control (%)		
3	9 (27.27)	3 (9.09)	12 (18.18)	<.0001
4	16 (48.48)	2 (6.06)	18 (27.27)	
5	7 (21.21)	7 (21.21)	14 (21.21)	
6	1 (3.03)	10 (30.30)	11 (16.67)	
7	0 (0.00)	9 (27.27)	9 (13.64)	
8	0 (0.00)	2 (6.06)	2 (3.03)	
Total	33 (100.00)	33 (100.00)	66 (100.00)	

Table 4: Mean TB score in Group 1 (cases) and Group 2 (controls) at the beginning of the study

TB score	Group 1 (cases)	Group 2 (controls)	p value
Sample size	33	33	0.683
Mean±SD	5.82±1.01	5.94±1.09	
Median	5	6	
Min-Max	5–8	5–8	
Inter quartile range	5–6.250	5–7	

SD: Standard deviation

Table 5: Severity class distribution of patients in Group 1 (cases) and Group 2 (controls) at the beginning of study

Severity class	Group		Total, n (%)	p value
	Group 1 (cases), n (%)	Group 2 (controls), n (%)		
Severity class				
I	17 (51.52)	16 (48.48)	33 (50.00)	0.917
II	13 (39.39)	13 (39.39)	26 (39.39)	
III	3 (9.09)	4 (12.12)	7 (10.61)	
Total	33 (100.00)	33 (100.00)	66 (100.00)	

Table 6: TB score in Group 1 (cases) and Group 2 (controls), after 2 months of therapy

TB score (after 2 months)	Group 1 (cases)	Group 2 (controls)	p value
Sample size	33	33	0.0002
Mean±SD	1.7±1.38	2.94±1.82	
Median	1	2	
Min-Max	0–6	0–7	
Inter quartile range	1–2	2–3	

Table 7: Severity Class distribution of patients in Group 1 (cases) and group 2 (controls), 2 months after therapy

Severity class (after 2 months)	Group		Total (%)	p-value
	Group 1 (cases), *n* (%)	Group 2 (controls), *n* (%)		
I	31 (93.94)	27 (81.82)	58 (87.88)	0.258
II	2 (6.06)	6 (18.18)	8 (12.12)	
Total	33 (100.00)	33 (100.00)	66 (100.00)	

found to have low vitamin D levels (< 30ng/mL). Mean Vitamin D level was 11.99±5.98 ng/mL (mean value of Vitamin D was 29.93 nmol/L when converted from ng/mL to nmol/L).

Mean 25-hydroxycholecalciferol concentrations were significantly lower in the patients with TB than in healthy contacts (20.1 (0.95) nmol/l vs 30.8 (1.7) nmol/l, 95% CI 7.1 to 14.3; p<0.001). A similar outcome was observed in a study done by Deshpande *et al.* [19] at a tertiary care hospital in which the mean Vitamin D levels were significantly low in cases (12.23±5.99 ng/mL) as compared to controls (18.7±10.19 ng/mL) (p<0.001). Mean Vitamin D levels were significantly lower in sputum-positive cases (10.90±6.82 ng/mL) as compared to sputum-negative cases (13.74±6.08 ng/mL) (p<0.05).

In the present study, mean time to sputum smear conversion was 4±0.79 weeks in Group 1(cases) in which Vitamin D supplementation was given along with first-line ATT whereas it was 5.79±1.34 weeks in Group 2 (controls) in which only first-line ATT was given. There was a statistical difference in mean time to sputum smear conversion in Group 1 (cases) and Group 2 (controls) (p<0.0001). Thus, the patients in which Vitamin D supplementation was done along with first-line ATT had earlier sputum smear conversion as compared to patients who were on ATT only. Similar significant findings were also observed in a study done by Nursyam *et al.* [15] where sputum conversion in 34 subjects of the Vitamin D group (100%) and in 25 subjects of the placebo group (76.7%) was observed at 6th week, which was statistically significant (p=0.002).15 Furthermore, Martineau *et al.* [20] did a randomized control trial in which it was observed that patients who received 4 oral doses of 2.5mg vitamin D along with first-line intensive phase ATT, the median time to sputum culture conversion was 36 days as compared to 43.5 days in patients receiving placebo along with first-line intensive phase ATT. Similar findings were observed in study done by Kota *et al.* [21] in which, patients receiving ATT along with oral 60.000 IU Vitamin D, sputum smear conversion was at 6 weeks as compared to 8 weeks in patients receiving ATT only. Similar statistically significant findings were also reported by Hassanein *et al.* [22] in a study in which 60 patients with pulmonary TB were included. In the group receiving Vitamin D with ATT, mean sputum conversion time was 3.57±0.73 weeks whereas in the group receiving ATT only, the mean sputum conversion time was 7.0±1.08 weeks (p<0.001). On the contrary, in a four-arm randomized, double-blind, placebo-controlled factorial trial in adults with smear-positive pulmonary TB study done by Ralph *et al.* [23], at 4th week of therapy 62% of the patients were sputum AFB culture negative. This proportion did not significantly differ between patients who received active intervention as compared to those who received placebo. It was concluded that 50,000 IU of Vitamin D supplemented at baseline and day 28 did not had any significant effect on microbiological or clinical outcome of pulmonary TB. Similarly, a study was done by Tukvadze *et al.* [24] in which patients with pulmonary TB were divided into two groups. One of the groups received Vitamin D along with standard ATT and other group received placebo along with standard ATT. There was no significant difference in the median time to culture conversion between subjects who received standard ATT plus high-dose Vitamin D3 (29 days; 95% CI: 24, 36 days) and those who received standard ATT plus the placebo (27 days; 95% CI: 23, 36 days) (p=0.99; log-rank test). These contrasting findings could have been due to the difference in dosage of Vitamin D given and the statistical method used.

In the present study after 2 months of therapy, mean TB score in Group 1 was 1.7±1.38 and in Group 2 was 2.94±1.82. There was a statistically significant difference in TB score between the two groups. (p=0.0002). These observations were similar to those found by Hassanein *et al.* [22] in their study in which, in the group receiving Vitamin D with ATT mean TB score at the time of sputum smear conversion or 2 months was 1.13±0.35, whereas in the group receiving ATT only mean TB score at the time of sputum smear conversion or 2 months was 1.40±0.50. There was a significant difference between the two groups regarding TB score at the time of conversion of sputum smear or at the end of 2nd month (p=0.020).42 On the contrary, Wejse *et al.* [17] did a study in which intervention was 100000 IU of cholecalciferol or placebo at inclusion and again at 5 and 8 months after start of treatment. It was concluded that Vitamin D does not improve clinical outcome among patients with TB [16]. Furthermore, in a study done by Salahuddin *et al.* [25] no significant difference was observed in TB score at weeks 4, 8, and 12 between the patients receiving 6,00,000 IU of Vitamin D IM along with 4 drug ATT, and patients receiving IM normal saline and ATT. These differences in observation could have been probably due to different doses of Vitamin D and time intervals at which these doses where administered along with ATT.

CONCLUSION

In the present study, we found that the majority of the patients enrolled were males, this could have been due to less accessibility of females to medical healthcare facility due to social factors. Patients who received Vitamin D along with first-line ATT had early sputum smear conversion as compared to those who were on ATT only. Furthermore, patients who received Vitamin D with ATT had better TB score after 2 months of therapy as compared to patients on first-line ATT only. Thus, Vitamin D supplementation to first-line ATT can reduce time to sputum conversion and accelerate clinical improvement. We recommend Vitamin D checking in patients with sputum smear-positive pulmonary TB and supplementing Vitamin D along with first-line ATT.

CONFLICTS OF INTEREST

None declared.

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Nil.

AUTHOR CONTRIBUTION

Shivalik Gupta: Own thesis work, study design, review of literature, data analysis, revision of draft; U Maheswarchandrakantham: Concept, study design, revision of draft; DD- Concept, daily guidance, data analysis, revision of draft; DN Jha: Guide and mentor of our study, concept, daily guidance, data analysis, revision of draft.

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