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ORIGINAL RESEARCH

Comparative study on the effect of Vit-D supplementation onthe treatment course of pulmonary tuberculosis

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ABSTRACT

Aim: *Comparative study on the effect of VIT-D supplementation onthe treatment course of pulmonary tuberculosis.*

Material and methods: *Patients presenting with sign and symptoms suggestive of pulmonary TB, diagnosed as TB and who were receiving the treatment from the study institute. TB Score, Smear Conversion, Health Related Quality of Life, Changes in the level of C-Reactive Protein, Erythrocyte Sedimentation Rate (ESR), and Haemoglobin concentration and Serum Vitamin D levels were measured. At the beginning of the treatment patients were divided in the following two groups based on the mutual decision of the treating physician and the participants. 100 patients were include in this study and divided into two equal groups. Supplementation Group: Patients advised category I DOTS therapy and Vitamin D supplementation. Routine Care Group: Patients advised category I DOTS therapy.*

Results: *The mean time to sputum conversion was shorter among patients given Vitamin- D (9.7 weeks) in comparison to control group (11.2 weeks), however, the difference was not statistically significant (p=0.0621). After being on treatment for 8 weeks; the TB score decreased to 4.90 in the Vit-D group and 6.6 in control group, the difference was statistically significant. (p-0.0012). However, there was no statistically significant difference in the TB score at 12 weeks of treatment (p=0.342). After taking the treatment for 8 weeks, the quality-of-life score was 15.1 in Vit D group and in control it was 13.4, the difference is statistically significant (p-0.004). At 12 weeks also the difference in QoL score was significant (p<0.001) among the two groups. Consequently, the overall change in Quality-of-life score was also statistically significant. (p<0.001). The change in Serum Vit-D values was almost similar between both the test and control groups at 0 weeks (42.979 and 40.788 respectively) and the difference is not statistically significant. (p=0.213). At 8 weeks duration the Serum Vit-D level was 62.419 in the test group and in control it was 37.788, the difference is statistically significant. (p<0.0001) and at 12 weeks also the change is significant. (p<0.0001).*

Conclusion: *The rate of seroconversion was faster among Vitamin D group. Vitamin D supplementation can safely and efficiently raise the proportion of sputum smear and culture conversion. However, it may not have enough positive impacts on the time to sputum conversion. The participants who received vitamin D saw a speedier improvement in quality of life and a quicker reduction in the intensity of TB-related symptoms.*

Keywords: *Vit-D, supplementation , pulmonary tuberculosis.*

Introduction

By 2030, the World Health Organization (WHO) aspires to reduce the prevalence of tuberculosis (TB) by 80%(1). India has also made the audacious aim of eliminating TB by 2025. According to the World Health Organization, there were more than 10 million incident cases and over 2 million TB-related deaths globally in 2019(1). India also has the largest burden of TB in terms of latent infection, incident cases, drug-resistant infections, and deaths(2). Reactivation of asymptomatic latent Mycobacterium TB infection is the primary cause of the majority of instances of tuberculosis illness(1). According to estimates, 1.7 billion people worldwide have latent TB infections, and 10% of these people will develop tuberculosis illness over the course of their lives(3). Although tuberculosis disease reactivation typically occurs in adults, primary infection is most frequently acquired in children(3). As a result, if desired reductions in tuberculosis incidence are to be achieved, measures to prevent acquisition of latent tuberculosis infection in children will need to be implemented(1).

The primary strategy for tuberculosis control is treatment of active tuberculosis disease to reduce transmission(1). However, mathematical simulations show that this tactic by itself is unable to meet the challenging goal set by India and the WHO(3). Although TB is a preventable and treatable illness, the increasing incidence of extensively and multidrug-resistant TB, along with the pandemics of diabetes and the human immunodeficiency virus infection, have been it tremendously difficult to achieve the targets set by WHO and India(1,4). Additionally, anti-tuberculosis therapy is lengthy and involves a number of medications, many of which have severe adverse effects. Therefore, it is urgently necessary to create new medications, approaches, regimens, etc., that can accelerate the course of therapy and prevent the spread of both drug sensitive and resistant TB infection(5,6).

The uses of Vitamin D for the treatment of tuberculosis began in 1849, when it was observed that fish liver oil enhanced appetite and vigour(7,8). Prior to the development of efficient antitubercular therapy, people with TB were recommended to rest and get treatment at a sanatorium with abundant sunlight(9). Two recent epidemiological studies found that seasonal fluctuations in blood vitamin D content are closely associated with the incidence of tuberculosis(7,10). There have been studies linking vitamin D deficiency with TB in context of incidence and favourable response to the addition of vitamin D to antitubercular treatment(7,10). Tuberculosis and vitamin D insufficiency are serious public health problems in India (24). There are no comprehensive studies conducted in our country examining the relationship between vitamin D deficiency and tuberculosis (TB) and the potential role of vitamin D-related regulation in cellular immune activity unique to the disease.

Material and methods

A single-centre, hospital based, comparative, prospective, observational study was done in the department of Pulmonary Medicine, Index Medical College, and affiliated hospitals, Indore, Madhya, Pradesh. Patients presenting with sign and symptoms suggestive of pulmonary TB, diagnosed as TB and who were receiving the treatment from the study institute. TB Score, Smear Conversion, Health Related Quality of Life, Changes in the level of C-Reactive Protein, Erythrocyte Sedimentation Rate (ESR), and Haemoglobin concentration and Serum Vitamin D levels were measured. The recruitment of the participants and primary data collection was started once the protocol was approved by the ethical committee. We employed, non-probability, purposive, convivence sampling technique for recruiting participants for the present study.

Inclusion Criteria:

- Patients newly diagnosed with PTB who were on initial anti-tuberculosis treatment, were diagnosed with pulmonary tuberculosis by clinical diagnosis.
- The subjects show tuberculosis toxic symptoms such as cough, hemoptysis and low fever to varying degrees, (no haematological disease).
- The patients did not present with basic diseases before admission, and the body was relatively healthy.
- Patients aged > 16 years.
- Patients consenting to participate in the study.

Exclusion Criteria:

- Patients with severe organ disease or liver dysfunction
- Patient who was allergic to the treatment
- Patient with MDR TB & XDR TB.
- Patient with HIV positive & TB.
- Pregnant Females with TB.

Methodology

At the beginning of the treatment patients were divided in the following two groups based on the mutual decision of the treating physician and the participants. 100 patients were include in this study and divided into two equal groups.

Supplementation Group: Patients advised category I DOTS therapy and Vitamin D supplementation.

Routine Care Group: Patients advised category I DOTS therapy

A detailed history and a thorough clinical examination of every patient were completed by the attending consultants. Appropriate laboratory and radiological investigations were conducted. X-ray chest PA View, CBC with ESR, Sputum AFB, C/S, CBNAAT, RBS, HIV, HBsAg were investigated. Based on the findings of medical history, clinical examination, laboratory findings, and radiological investigations, all presenting patients were diagnosed with TB and were segregated into various categories as per the prescribed National Guidelines.

Statistical Analysis

The data were coded and entered in Microsoft Excel. The coded data were imported into Stata 17.1 version for analysis. For the continuous data, the author calculated the mean, median, mode, and standard deviation. A comparison of continuous variables with baseline values was analysed using a student's t-test in each group. Categorical variables were analysed using chi- square (χ^2) tests. A *P*-value < 0.05 was considered statistically significant. All tests are two-sided; the nominal level of type I error were be 5% and the confidence level for all confidence intervals were be 95%. There was no imputing of missing values. The number of observations used in the analysis was reported.

Results

Table 1: Age group (n=100)

		Group	
Age Group			
	Vit D	Control	Total
	7	7	14
<=30			
	14.00	14.00	14.00
	19	21	40
31-45			
	38.00	42.00	40.00
	12	11	23
46-60			
	24.00	22.00	23.00
	12	11	23
61 -75			
	24.00	22.00	23.00
Total	50	50	100
	P-value = 0.979		
Mean	46.1	44.2	

A total of 100 patients with Tuberculosis were included in the study and half of them received Vit-D (test group) and the other half was control group. There was no significant variation in age between

the groups. The mean age of the participants in the Vitamin D group and Control group was comparable (p=0.979).

Table 2: Gender (n=100)

		Group	
Gender			
	Vit D	Control	Total
	20	29	49
Female			
	40.00	58.00	49.00
	30	21	51
Male			
	60.00	42.00	51.00
Total	50	50	100
	100.00	100.00	100.00
	P-value = 0.0718		

Out of the total 50 patients in the test group, 60% (30) were males and among the 50 patients in the control group 42% were male, there was no significant difference in gender between both the groups. (p-0.0718). Among the 50 patients in the test group, 80% (40) and 78% (39) in the control group were from Hindu/Muslim community. There was no significant difference in both the groups with regard to distribution of religion (p-0.9794)

In both the groups most participants received some level of formal education, test group 74% (37) and control group 72% (36); no significant difference between the groups (p-0.444). Among the 50 patients in the test group, 80% (40) and 78% (39) in the control group were from Lower/Upper Lower/Lower Middle socioeconomic groups. No significant variation in both the groups. (p-0.5517).

Table 3: Symptoms among participants (n=100)

		Group	
Symptoms			
	Vit D	Control	Total
Cough	50 (100.0	50 (100.0)	100(100.0
Fever	21 (42.0)	27 (54.0)	48 (48.0)
Hemoptysis	29 (58.0)	31 (62.0)	60 (60.0)
Weight Loss	31 (62.0)	30 (60.0)	61 (61.0)
Chest Pain	25 (50.0)	32 (64.0)	57(57.0)
Dyspnea	15 (30.0)	19 (38.0)	34 (34.0)
Night Sweat	19 (38.0)	16 (32.0)	35(35.0)

The common symptoms among the groups were cough (100%) and about 60% in both the groups had hemoptysis and weight loss. Chest pain and fever were also common at 42-64% in both the test and control groups. There was no significant difference in the presence of any specific symptoms in between the VitaminD and Control group (p>0.05).

Table 4: Sputum Positivity during follow up (n=100)

Duration of Treatment		Group		
				P-value
	Vit D	Control	Total	
0 week	50 (100.0)	50 (100.0)	100 (100.0)	-
4 weeks	50 (100.0)	50 (100.0)	100 (100.0)	-
8 weeks	21 (42.0)	31(62.0)	52(52.0)	0.0453
12 weeks	11(22.0)	17(34.0)	28(56.0)	0.1814
Mean time	9.7	11.2		0.062

None of the participants in the present study in either group had sputum conversion after 4 weeks of treatment. After 8 weeks of the receiving the treatment, among the group who received Vit-D only 42% were sputum positive and in the control 62% were sputum positive. The difference is statistically significant. (p-0.0453). The mean time to sputum conversion was shorter among patients given Vitamin- D (9.7 weeks) in comparison to control group (11.2 weeks), however, the difference was not statistically significant (p=0.0621).

Table 5: Change in weight during follow up (n=100)

Duration of Treatment	Group		
			P-value
	Vit D	Control	
0 week	53.9	54.4	0.917
4 weeks	55.2	55.4	0.284
8 weeks	55.7	54.8	0.092
12 weeks	56.3	54.5	0.0834
Change in weight	1.93	0.705	<0.0001

Table 5 illustrates the change in the weight among participants of both the groups during the period of follow up. Although, the difference in weight of the participants was statistically insignificant between the two groups at 4-, 8-, and 12 weeks after treatment. However, the gain in weight (1.9 kg) among vitamin D groups was very significantly greater than control group (0.70 kg), (p<0.0001).

Table 6: Change in TB score during follow up (n=100)

Duration of Treatment	Group		
			P-value
	Vit D	Control	
0 week	7.96	8.04	0.785
4 weeks	7.22	6.94	0.089
8 weeks	4.90	6.6	0.0012
12 weeks	4.08	4.94	0.133
Change in TB Score	-3.88	-2.89	0.342

At the start of the treatment, the TB scores in both the groups were almost similar (7.96 in the test group and 8.04 in the control group; pvalue-0.785). After being on treatment for 8 weeks; the TB score decreased to 4.90 in the Vit-D group and 6.6 in control group, the difference was statistically significant. (p-0.0012). However, there was no statistically significant difference in the TB score at 12 weeks of treatment (p=0.342).

Table 7: Change in Quality-of-Life score during follow up (n=100)

Duration of Treatment	Group		
			P-value
	Vit D	Control	
0 week	10.2	10.6	0.823
4 weeks	12.8	12.6	0.193
8 weeks	15.1	13.4	0.004
12 weeks	17.2	14.8	<0.001
Change in QoL Score	7	3.2	<0.001

The change in quality-of-life score was almost similar between both the test and control groups after 4 weeks duration. (12.8 and 12.6 respectively; p-value = 0.193). However, after taking the treatment for 8 weeks, the quality-of-life score was 15.1 in Vit D group and in control it was 13.4, the difference is statistically significant (p-0.004). At 12 weeks also the difference in QoL score was significant

(p<0.001) among the two groups. Consequently, the overall change in Quality-of-life score was also statisticallysignificant. (p<0.001)

Table 8: Change in C-reactive Protein levels (n=100)

Duration of Treatment	Vita- D	Control	P-value
0 week	164.03	169.84	0.253
4 weeks	88.753	93.075	0.074
8 weeks	25.915	49.455	<0.001
12 weeks	5.7	11.59	<0.0001

The C-reactive protein levels was almost similar between both the test and control groups at 0 weeks. After 8 weeks of treatment, the change in C-reactive protein levels was 25.915 in test group and in the control, it was 49.455, the difference is statistically significant. (p< 0.0001) and at 12 weeks also the difference in the CRP levels between the two groups was significant. (p<0.001).

Table 9: Change in Haemoglobin levels (n=100)

Duration of Treatment	Vita- D	Control	P-value
0 week	8.1	8.2	0.82
4 weeks	8.9	8.8	0.74
8 weeks	9.6	9.7	0.63
12 weeks	11.3	11.4	0.53

The change in heamoglobin levels was almost similar between both the test and control groups at 0, 4, 8 and 12 weeks. The difference is statistically not significant.

Table 10: Changes in the ESR values (n=100)

Duration of Treatment	Vit D	Control	P-Value
0 week	39.64	38.34	0.831
4 weeks	27.64	29.34	0.092
8 weeks	18.72	20.74	0.0763
12 weeks	4.3	6.78	0.0782

The change in ESR levels was almost similar between both the test and control groups at 0, 4, 8 and 12 weeks. The difference is statistically not significant.

Table 11 Changes in the Levels of Vitamin D during the treatment (n=100)

Vit D level	Week 0		Week 12	
	Vit D	Control	Vit D	Control
Deficient	9(18.0)	12 (24.0)	0	16 (32.0)
Insufficient	26(52.0)	22 (44.0)	8 (16.0)	25 (50.0)
Sufficient	15 (30.0)	16 (32.0)	42 (84.0)	9 (18.0)
P-value = 0.1872			P-value <0.0001	

At the beginning of the study out of 50 TB patients in the test group 18% (9) had deficient Vit-D levels and 52% (26) had insufficient Vit-D levels; While among the control group (50 TB patients) 24% (12) had deficient and 44% (22) had insufficient Vit-D levels. The difference is not statistically significant. (p-0.1872) At 12 weeks duration of the study among the test group none were deficient and only 16% (8) had insufficient Vit-D levels and among the control group 32% (16) had deficient and 50% (25) had insufficient Vit-D levels. The difference is statistically significant. (p<0.0001).

Table 12: Changes in Serum Vitamin D values during the treatment(n=100)

Duration ofTreatment	Vit D	Control	P-Value
0 week	42.979	40.788	0.213
4 weeks	52.739	44.788	0.058
8 weeks	62.419	37.788	<0.0001
12 weeks	64.758	32.788	<0.0001

The change in Serum Vit-D values was almost similar between both the test and control groups at 0 weeks (42.979 and 40.788 respectively) and the difference is not statistically significant. (p=0.213). At 8 weeks duration the Serum Vit-D level was 62.419 in the test group and in control it was 37.788, the difference is statistically significant. (p<0.0001) and at 12 weeks also the change is significant. (p<0.0001).

Discussion

In the present study, we evaluated the clinical and laboratory outcome/parameters among a group of 100 patients: 50 patients given Vitamin D in addition to TB treatment and 50 patients receiving only standard treatment for TB. The choice of outcome was determined by the prognostic values of various factors.

Sputum Conversion: None of the participants in the present study in either group had sputum conversion after 4 weeks of treatment. After 8 weeks of the receiving the treatment, among the group who received Vit-D only 42% were sputum positive and in the control 62% were sputum positive (p-0.0453). However, there was no difference in the sputum conversion rate among the participants in two groups at 12 weeks. Similar to the findings of the present study, Daley et al., Ganmaa et al., Martinaeu et al., 2011, Salahuddin N et al., and Milly et al., 2015 did not observe any significant difference in the sputum conversion rate between the participants given vitamin D and standard treatment alone(11-14). Wu H et al., 2018 conducted a metanlysis of randomized trial of studies comparing the outcome among patients given vitamin D supplementation in addition to therapy for TB(15). They reported that sputum conversion was statistically significant at multiple time points after starting treatment. They found that the differences in proportion of sputum culture conversion in the overall effects (OR 1.22; $P = 0.02$).

Time to Sputum Conversion: The mean time to sputum conversion was shorter among patients given Vitamin- D (9.7 weeks) in comparison to control group (11.2 weeks), however, the difference was not statistically significant (p=0.0621). Daley et al., Milly et al., Ganmaa et al., and Martineau et al., also reported that the time to sputum smear conversion or the different intervention groups compared to placebo was not significant(12-14,16).

Weight Gain: In the present study, although, the difference in weight of the participants was statistically insignificant between the two groups at 4-, 8-, and 12 weeks after treatment. This can be due to difference and variation in the baseline weight of the participants. However, the absolute gain in weight (1.9 kg) among vitamin D groups was very significantly greater than control group (0.70 kg), (p<0.0001). Salahuddin N et al., (2013) reported that after 12 weeks of antituberculosis therapy, the 25- hydroxyvitamin D supplemented arm had a mean weight gain 3.75 kg v/s 2.61 kg in the placebo arm (p 0.009)(11). Ganmaa et al., (2012) reported there was no significant difference in the weight gain among the participants in the two groups at 4 weeks after initiating the treatment. However, at 8 and 12 weeks after the treatment patients on vitamin D supplementary therapy gained significantly more weight in comparison to the placebo group(13). Similarly, Wejse et al., 2009 showed that a significant difference in weight gain among the participants given vitamin D supplementation along with TBtreatment(17).

TB Score: In the present study, at the start of the treatment, the TB scores in both the groups were almost similar. After being on treatment for 8 weeks; the TB score decreased to 4.90 in the Vit-D group and 6.6 in control group (p-0.0012). However, there was no statistically significant difference in the TB score at 12 weeks of treatment (p=0.342). Thus, although Vit-D group participants had rapid resolution of the TB related symptoms at 8 weeks but at 12 weeks of the treatment the

difference was statistically not significant. Only two other studies have reported the change in TB score among the participants during the course of treatment. Both Milly et al., (2015) and Salahuddin N et al., (2013) did not observed any significant difference in the TB score among the participants in the intervention and the control groups(11,14). Wu H et al., (2018) conducted a metanlysis of studies and reported that there was not difference in the TB score in 8 weeks and 5, 6, and 8 months except 12 weeks(15).

Change in CRP Levels: In the present study, after 8 weeks of treatment, the change in C-reactive protein levels was of greater magnitude in the Vitamin D group than control group ($p< 0.0001$) and at 12 weeks also the difference in the CRP levels between the two groups was significant. ($p<0.0001$). The rate of decline in the CRP among the patients was greater in Vitamin D group. This indicate that there was rapid decline in the cellular inflammation among the participants given Vitamin D. Hu W et al., from their meta-analysis concluded that there was a significant decline in the CRP values after 6 weeks of starting treatment. Milly et al., Ganmaa et al., and Daley et al also reported a significant difference in the CRP Levels after 6 to 8 weeks of starting treatment.(12-15)

Change in Haemoglobin levels: We did not observe any significant difference in the haemoglobin values among the participants of the two group. Similar to the findings of the present study, Milly et al., Daley et al., Salahuddin et al., and Hu et al., did not observe any difference in haemogobin levels(11,12,14,18).

Conclusion: The rate of seroconversion was faster among Vitamin D group. Vitamin D supplementation can safely and efficiently raise the proportion of sputum smear and culture conversion. However, it may not have enough positive impacts on the time to sputum conversion. The participants who received vitamin D saw a speedier improvement in quality of life and a quicker reduction in the intensity of TB-related symptoms.

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