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RESEARCH ARTICLE

VITAMIN D IN PULMONARY TUBERCULOSIS PATIENTS IN RELATION TO DISEASE SEVERITY

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ABSTRACT

Introduction: Among specific nutritional factors that may be in deficit without overt malnutrition, Vitamin D is significant and has been associated with active Pulmonary Tuberculosis (PTB). Previous reports have shown that vitamin D deficient people had higher risk of developing active PTB which in turn also influence disease outcome. **Objective:** To study Vitamin D status in PTB patients and its correlation to disease severity and sputum positivity. **Material and Methods:** 120 adult PTB patients and 60 healthy controls were recruited. Sputum positivity was assessed by counting number of Acid Fast Bacilli in sputum microscopically and disease severity by Bandim TB score. After written consent, serum was used for investigating routine and specific test like Vitamin D and Parathyroid Hormone (PTH). **Result and Discussion:** Serum Proteins, Albumin, Vitamin D and PTH were significantly decreased in PTB patients than controls. Vitamin D correlated moderately to disease severity (r=-0.38) and sputum positivity (r=-0.34) suggesting its role in influencing disease outcome and reactivation of latent infection. CONCLUSION: Vitamin D has specific immunoregulatory function and Its deficiency could enhance disease susceptibility. Supplementation with vitamin D may be beneficial for high risk patients for effective treatment response. Thus, Calcium and its related metabolites including Vitamin D are required to be monitored in PTB due to its influence on disease severity.

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INTRODUCTION

Tuberculosis (TB) is a highly infectious although curable disease that is distributed worldwide. Role of nutrition in prevention of TB has gained momentum in last several years because of growing number of MDR-TB and XDR-TB cases. Here, micronutrients as potential adjuvant in immunotherapy is a field of much interest since role of specific micronutrients in disease pathogenesis has emerged. In this study, specific antibacterial role of Vitamin D will be discussed along with its relation to disease severity. Although the classical effects of vitamin D are Calcium (Ca) absorption and osteoclastic activity but now its role as immunmodulator is increasingly recognized. Calcitriol i.e. the active form of Vitamin D influence Cell mediated immune response by increasing "oxidative burst" potential of macrophages, stimulate release of antibacterial peptides and thereby enhance bacterial killing (Gemma, 2011).

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Linkage between Vitamin D and TB was identified in pre-antibiotic era when cod liver oil, a rich source of Vitamin D and sun exposure were used as modes of TB treatment. Macrophages and other immune cells can express 1 α-hydroxylase, the enzyme that converts circulating 25-hydroxy vitamin D_3 into 1,25 dihydroxy vitamin D_3 i.e. the active form (Patricia Chocano, 2009). The active form improves the ability of macrophages to inhibit mycobacterial growth and influence adaptive immunity by modulating antigen presentation. A particular of vitamin D is that it is barely available in common diet, with only a limited amount coming from sources like oily fish oil. Vitamin D requirement is mainly fulfilled from endogenous synthesis in skin on exposure to ultra-violet (UV) solar radiations. Low UV-B exposure and modern lifestyle are among the factors that contributes to Vitamin D deficiency (VDD) in 30-50% of adults and children worldwide (Balcells *et al*., 2017). Although studies show that Vitamin D deficiency is one of the pre-disposing factor for TB since it compromise Cell mediated immunity, it is also possible that low vitamin D results from TB itself. Apart from infection, factors such as reduce calcium and Vitamin D in diet, pure vegetarianism,

traditional cultural traits, genetic and little exposure to sunlight also affect vitamin D level. Larger and prospectively designed studies are required to determine direction of possible cause effect relationship between vitamin D & TB (Nnoaham, 2008). Association between VDD and Tuberculosis has been reported from many case controlled studies but its relation to disease severity and bacterial load was studied here.

MATERIALS AND METHODS

The study was conducted in the Institute of Respiratory Diseases (IRD) in association with Department of Biochemistry, SMS Medical College, Jaipur. 120 Adult patients (both male and female) from low socio-economic status diagnosed with Pulmonary Tuberculosis (PTB) (both Newly diagnosed and Relapse) were recruited for the study. 60 healthy, age matched individuals tested free of Mycobacteria without any previous or present symptoms of Tuberculosis or any other pulmonary disease and non family member of patients were taken as Controls. Following diagnostic criteria was used for PTB 1.

Positive culture for MTB. 2. Positive (2 consecutive samples) smear for AFB. 3. Typical chest X-ray showing bilateral upper zone involvement with or without cavitations & with/without +ve sputum smear but with typical PTB symptoms. 4. Patients with 2 or 3 criteria had to show clinical and radiological improvements with anti tuberculosis therapy. Patients with multidrug resistant TB (MDR-TB), extra pulmonary Tuberculosis, those with significant renal, cardiac, neoplasm or respiratory disease (other than PTB like lung cancer) etc., diabetes, endocrine or genetic disorder were excluded from the study. HIV positive cases, Pregnant or lactating women and those on oral nutritional supplements were also excluded. All subjects gave their written consent to participate in the study.

Sample collection and bacteriological examination: Two consecutive sputum sample of each patient were collected and subjected to Acid fast Staining. In order to determine sputum positivity, number of Acid Fast Bacilli (AFB) were counted and analysed as follows: 1. No AFB in 100 fields-negative; 1-9 AFB in 100 fields-scanty ; 10-99 AFB in 100 fields- +1 ; 1-10 AFB per field-+2 and more than 10 AFB per field= +3.

Assessment of Disease severity by "Bandim TB Score" system: It classifies PTB into different classes of severity. Severity Class I (for score 0-5) is least severe, Severity Class II (for score 6-7) is moderately severe and Severity Class III (for score 8-13) is most severe. The score was counted on the basis of 5 self reported symptoms i.e. cough, hemoptysis, dyspnoea, chest pain and night sweats as well as 6 signs identified at the time of examination : Anemia, pulse >90 beats/min, positive finding at lung auscultation, temperature > 37º C, BMI <18 Kg/m^2 and Mid Upper Arm Circumference (MUAC) < 220 mm. Each of the above clinical variables contribute to 1 point. BMI <16 Kg/m^2 and Mid Upper Arm Circumference (MUAC) < 200 mm contributed an extra point to the score. Final TB score is the sum of all individual points. Maximum score of any patient could be 13 (Rudolf *et al*., 2013).This method of severity assessment based on clinical features and investigations was validated by number of workers and was sui Table especially in a resource poor setting (Rudolf *et al*., 2013). Measurement of Biochemical parameters: After an overnight fast (12 hrs), venous blood was drawn for all subjects. After routine investigation, Total Ca (Arsenzo method) and Phosphrous (Phosphomolybdate UV method) and Alkaline phosphatase (Kinetic method) were estimated on Randox imola-3 Autoanalyzer. Vitamin D and PTH were estimated by Chemiluminescent method on Advia Centaur (Seimans) immunoassay system.

Statistical analysis: Quantitative data were expressed as Mean ± SD. Comparison was made using student-t test (independent sample t-test). P value less than 0.05 was considered significant. Pearson Correlation was used to assess correlation between various parameters.

RESULTS AND DISCUSSION

Relation between TB and malnutrition is well recognized; in recent years, several lines of evidence suggest link between vitamin D and TB. Vitamin D is a significant micronutrient affecting host susceptibility and immune response to infection due to its immunomodulatory functions. Vitamin D Deficiency is widespread in Indian subcontinent due to inappropriate dietary intake, pure vegetarianism, and cultural as well as genetic factors. In addition, darkly pigmented skin reduces the amount of UV light available in skin for vitamin D production. Prevalance rate of VDD among general healthy Indian population is 74%- 96% (6). Studies have shown that in North India 96% of neonates, 91% of healthy school girls, 78% of healthy hospital staff and 84% of pregnant woman were found to have hypovitaminosis D using criteria of defining 25(OH)vitamin D deficient as serum level below 20 ng/ml (Choudhary *et al*., 2013). Apart from TB, VDD is also associated to enhanced rate of Cancer, Autoimmune diseases and other infectious diseases (Najeeha, 2010). A recent prospective study in Finnish men found that serum 25(OH)D was associated with increased risk of respiratory tract infection and that VDD in TB is a determinant of treatment outcome and co-morbidities (Laaksi *et al*., 2007). Vitamin D and other Calcium profile parameters are studied here in relation to disease severity.

General characterstics of study population is depicted in Table 1. Out of 120 PTB patients, 77.5% were males and 22.5% females. The average age of PTB patients was 51.22±17.2 years. 60 healthy subjects that served as control for comparison includes 83.4% males and 16.6% females and had an average age of 40.9 ± 16.8 years. No significant difference was seen between PTB patients and controls with regard to age and routine biochemical parameters (Sugar, Urea, creatinine) as seen in Table 1. Mean protein and Albumin level in PTB cases was 6.50 ± 0.62 g/dl & 3.22 ± 0.63 g/dl respectively which were significantly lower than controls i.e. 7.65 ± 0.87g/dl & 4.36 ± 0.69g/dl respectively ($p<0.001$). Low Protein and Albumin was related to severe chacexia, weight loss, anorexia and malnutrition in PTB patients. Pre-existing undernutrition and malabsorption due to TB were also responsible for the above. Albumin is a component of plasma antioxidant activity and a negative Acute Phase Protein whose concentration decreases in any inflammatory condition, injury or stress as a result of increased metabolic need for tissue repair and free radical utilization (Akiibinu *et al*., 2007). Difference was significant with regard to serum Ca between PTB patients and controls. No significant difference was seen in serum Phosphrous level ($p=0.765$) (Table 2). Mean serum Calcium in PTB was 8.68±1.18 mg/dl which was slightly higher than than control i.e. 8.26± 0.8 mg/dl ($p=0.013$) (Table 2) (Fig 1). In our study.

Table 1. General characterstics and Biochemical profile of study population

S. No.	General Characterstics	PTB patients	Controls	Significance (p value)
1.	No. of cases (n)	120	60	
2.	No. males	93 (77.5)	50 (83.4)	0.3628
3.	No. females	27 (22.5)	10 (16.6)	
4.	Average Age (in years)	51.22± 17.20	40.9 ± 16.8	0.0018 S
5.	Sputum Status			
	Negative	43 (35.8)	60 (100)	
	+1	52 (43.3)	0 (0)	
	+2	16 (13.33)	0 (0)	
	+3	9 (7.5)	0 (0)	
6.	Average BMI (Kg/m^2)	17.44± 3.80	21.64± 3.16	<0.001 S
7.	MUAC (mm)	188.5 ± 25.2	274.8 ± 42.9	<0.001 S
8.	Blood Sugar (mg/dl)	82.6± 19.0	81.12±17.88	NS
9.	Serum Urea (mg/dl)	31.7 ± 8.77	31.66±8.43	NS
10.	Serum Creatinine (mg/dl)	1.01 ± 0.56	0.92 ± 0.43	NS
11.	Serum Protein (g/dl)	6.50 ± 0.62	7.65 ± 0.87	<0.001 S
12.	Serum Albumin (g/dl)	3.22 ± 0.63	4.36 ± 0.69	<0.05 S

Values are mean ± SD; values in parenthesis are percent. P < 0.05 is significant. NS: Not Significant
PTB: Pulmonary Tuberculosis; BMI: Body Mass Index ; MUAC: Mid upper arm circumference.

Table 2. Calcium and Vitamin D level in PTB patients and Controls

S. No.	Biochemical Parameters	PTB patients (n= 120)	Controls (n= 60)	Significance (p value)
1.	Serum Calcium (mg/dl)	8.68 ± 1.18	8.26 ± 0.8	0.0133
2.	Serum Phosphorus (mg/dl)	4.38 ± 0.89	4.34 ± 0.85	0.765
3.	Serum ALP (IU/L)	232.2 ± 91.0	193.5 ± 77.4	<0.05
4.	Serum Vitamin D (ng/ml)	14.74± 7.71	20.6 ± 10.9	<0.001
5.	Serum PTH (pg/sml)	35.7 ± 21.1	51.0 ± 24.6	<0.001

Values are mean ± SD; P < 0.05 is significant. NS: Not Significant
PTB: Pulmonary Tuberculosis; ALP: Alkaline phosphatase, PTH: Parathyroid Hormone.

Table 3. Calcium and Vitamin D level in PTB patients according to Clinical Severity

S. No.	Biochemical Parameter	Severity Class I N= 19	Severity Class II N= 29	Severity Class III N= 72
1	Serum Calcium (mg/dl)	8.4 ± 1.0	8.2 ± 0.96	8.9 ± 1.2
2.	Serum Phosphorus (mg/dl)	4.5 ± 0.8	4.6 ± 0.79	4.2 ± 0.9
3.	Serum ALP (IU/L)	225.3 ± 73.7	205.3 ± 66.0	245.0 ± 103.3
4.	Serum Vitamin D (ng/ml)	18.9 ± 7.1	16.7 ±7.5	12.8 ± 7.4
5.	Serum PTH (pg/ml)	30.5 ± 19.2	35.6 ± 21.3	37.1 ± 21.7

Values are mean ± SD; PTB: Pulmonary Tuberculosis,
ALP: Alkaline phosphatase, PTH: Parathyroid Hormone.

Table 4. Calcium and Vitamin D level in PTB patients according to Sputum Positivity

S. No.	Biochemical Parameters	Sputum positivity			
		Negative (N= 43)	+ 1 (N= 52)	+2 (N= 16)	+ 3 (N= 9)
1	Serum Calcium (mg/dl)	8.7± 1.2	8.4± 1.0	8.9± 1.1	9.6± 1.5
2.	Serum Phosphorus (mg/dl)	4.3± 0.7	4.4± 0.86	4.3 ± 1.2	4.6 ± 0.9
3.	Serum ALP (IU/L)	232.7 ± 107.7	227.0 ± 66.1	265.0 ±120.7	200.0 ± 60.2
4.	Serum Vitamin D (ng/ml)	16.8 ± 9.38	15.4 ± 5.57	11.4 ± 7.2	6.8 ± 2.67
5.	Serum PTH (pg/ml)	33.4 ± 23.4	38.3 ± 20.3	36.7 ± 23.3	29.5 ± 7.2

Values are mean ± SD; PTB: Pulmonary Tuberculosis; ALP: Alkaline phosphatase, PTH: Parathyroid Hormone.

Serum Calcium correlated weakly though positively to disease severity (r=0.28) as seen in Table 5. No correlation was seen with sputum positivity. The degree of hypercalcemia in Tuberculosis seen in our and other studies shows Ethnic and longitudinal variations, probably because of difference in vitamin D intake, amount of sun exposure, extent of disease severity and laboratory criteria for defining hypercalcemia. For example, the incidence of hypercalcemia in our PTB population was 16.6% and was slightly higher to the incidence rate in Hongkong (15%) and comparable to other studies conducted in India (16%) and lower than that reported in Malaysia (27.5%), USA (28%), much lower from that of Greece (48%)and of Australia (51%) (Roussos *et al*., 2001).

Another study conducted in Ethopia showed hypercalcemia (> 10.5 mg/dl) in 62.6% and 43.2% of TB patients with and without HIV co-infection respectively (Amare *et al*., 2012). Memon ZM *et al*, 2014 acknowledged hypercalcemia in various granulomatous disease with mean Ca level of 16.67± 6.7 mg/dl that was more than normal range (8.4 – 10.4 mg/dl) and controls (8.8 ± 4.3 mg/dl) (Memon, 2014). Although hypercalcemia in TB patients is generally mild and asymptomatic, it may be severe as seen in few of our patients. Therefore, Ca profile is required to be monitored and managed promptly in PTB. Hypercalcemia in granumatous diseases like TB occurs due to excessive extra renal expression of 1α-hydroxylase enzyme in macrophages that hydroxylates

Table 5. Correlation of biochemical parameters and Vitamin D level with Disease severity and Sputum positivity in PTB patients

Biochemical parameters	Disease severity		Sputum Positivity	
	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value
Serum Calcium (mg/dl)	0.287	0.001	0.157	0.09
Serum Phosphorus (mg/dl)	-0.17	0.055	0.07	0.447
Serum ALP (IU/L)	0.201	0.027	-0.007	0.94
Serum Vitamin D (ng/ml)	-0.38	0.000	-0.347	0.0001
Serum PTH (pg/ml)	0.043	0.641	0.002	0.982

P < 0.05 is significant. PTB: Pulmonary Tuberculosis; ALP: Alkaline phosphatase, PTH: Parathyroid Hormone.

Table 6. Vitamin D deficiency (VDD) in Pulmonary Tuberculosis (PTB) cases and controls

Vitamin D Status	PTB patients (N=120)	Controls (N=60)	Total N=180	P value
	N (%)	N (%)	N (%)	
Severe VDD (<10 ng/ml)	32 (26.67)	3 (5.00)	35 (19.4)	<0.001
VDD (10 - 20.0 ng/ml)	59 (49.16)	31 (51.67)	90 (50.0)	
Normal Vitamin D (20-30 ng/ml)	27 (22.5)	19 (31.67)	46 (25.5)	
Vitamin D sufficiency (> 30.0 ng/ml)	2 (1.66)	7 (11.67)	9 (5.0)	

P < 0.05 is significant

25(OH) Vitamin D to 1,25 (diOH)VitD which in turn improves immunological capacity of macrophages and lymphocytes. Phosphorus level did not show significant difference between PTB patients and controls (Table 2) and poor correlation to disease severity. Phosphorus is a widely distributed element with skeleton as the major reservoir providing phosphate for both intracellular and extracellular pools. Since PTB is associated with muscle wasting, there may be slightly high phosphorus level in patients than controls. Further Phosphorus tends to be higher in those with elevated polymorphs suggesting its association with active phase of disease and tissue destruction.

ALP is a plasma membrane derived enzyme and used to assess hepatic functions. There can be direct hepatic invasion by MTB causing granuloma or the use of anti-tubercular drugs (mainly isoniazid and pyrazinamide) may result in hepatotoxicity (Sonika, 2012). Incidence of drug induced hepatotoxicity increases with disease advancement. The risk of recurrence of hepatotoxicity with anti TB drug cannot be excluded during the reintroduction of standard ATT as seen in relapse (Sonika, 2012). 50% of our PTB patients belonged to relapse cases who had taken anti-TB drugs previously. Further, high alcohol intake, pre-exsisting chronic liver disease due to HBV or HCV infection, Asian ethnicity, use of enzyme inducers and poor nutritional status tends to increases risk of hepatotoxicity and may be responsible for the observed significantly high ALP in our patients than controls (Table 2). Majority of our patients were socially and economically weak and showed relative or absolute hepatotoxicity that depends on variable drug combination. The present study revealed high incidence of Vitamin D deficiency (VDD) in PTB cases as compared to normal controls (Table 6). 26.6% of PTB cases had severe VDD which was only 5% in controls. VDD was seen in 49.16% and 51.67% of patients and controls respectively indicating hypovitaminosis D in Indian population. Only 2 out of 120 patients showed sufficient Vitamin D stores. Vitamin D level in PTB was significantly less than controls i.e. 14.74±7.71 ng/ml vs 20.6±10.9 ng/ml respectively (Table 2). Mean Vitamin D level was found to decrease progressively with disease severity (Table 3) and sputum positivity (Table 4) and hence negative and moderate correlation (i.e. r=-0.38 and r=-0.347 respectively) was observed here (Table 5) (Fig 3 and 4).

Studies conducted all over the world have described low Vitamin D level in PTB cases, however variation occurs due to sun exposure, calcium and vitamin D intake in diet, socio-economic factors, prevalence of PTB disease and difference in criteria for defining VDD among countries. For instance, in a study conducted in Greenland, a country with less sunlight, low vitamin D level increases susceptibility to TB.

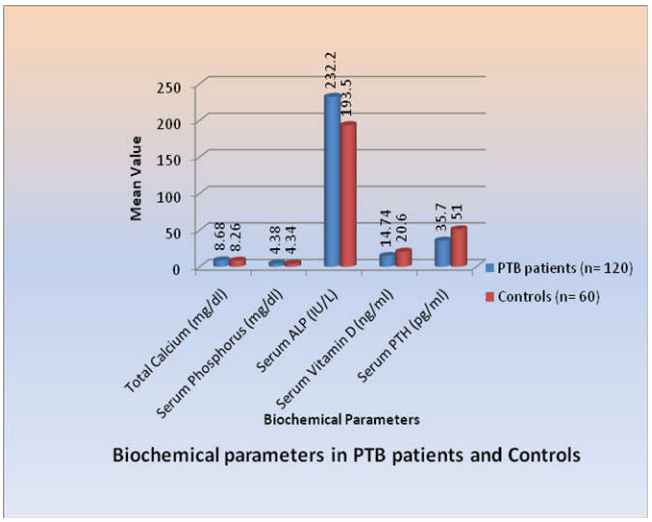

Fig 1. Biochemical parameters in PTB patients and controls

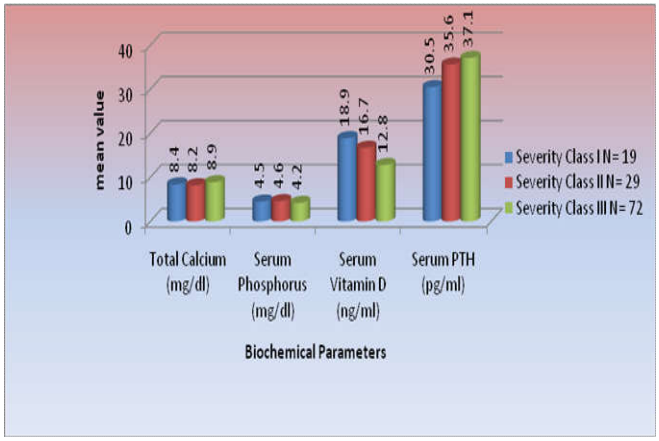

Fig 2. Biochemical parameters in relation to disease severity

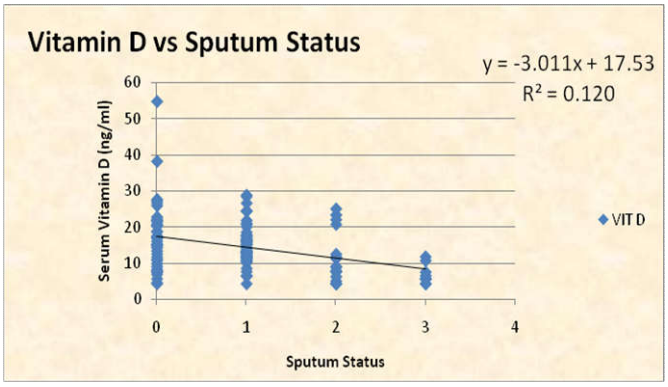

Fig 3. Correlation of serum Vitamin D with sputum positivity

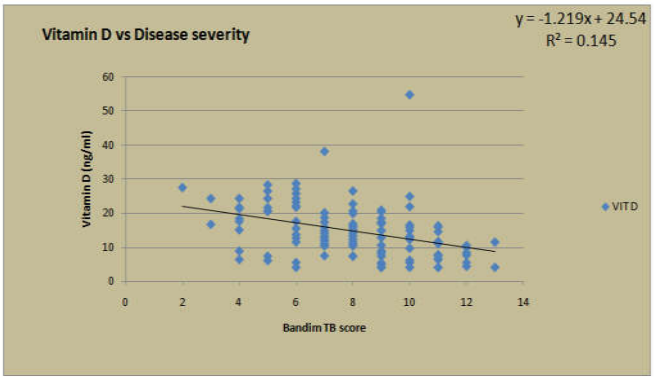

Fig 4. Correlation of serum Vitamin D with Disease severity

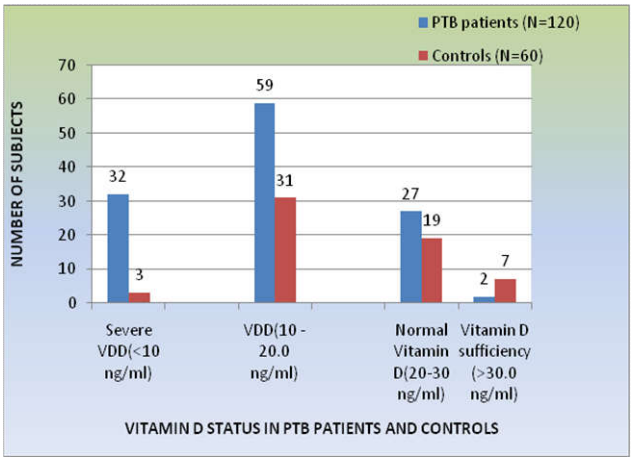

Fig 5. Vitamin D status in PTB patients and controls

Once an individual develops active TB, impaired apettite and confinement to indoor life contribute to low 25(OH) D concentration through reduced Vitamin D synthesis in skin and reduced intake. Further, it was seen that supplementation with vitamin D to normalize serum 25(OH)D causes 29% reduction in number of TB cases (Nielson *et al*., 2010). These and various other studies have shown that vitamin D supplementation during anti-TB treatment in areas endemic for vitamin D deficiency improves response to Treatment (Zhao *et al*., 2017). Evidence of high extra renal production of 1,25(diOH) Vit D has been seen in TB patients with 25(OH)Vit D in deficient range. Ongoing elevation of 1,25(diOH)Vit D, a marker of macrophage activation was associated with worst lung radiological outcome (Ralph *et al*., 2017). The active form of vitamin D (1,25(diOH)VitD) has been shown to inhibit growth of Mycobacterium tuberculosis (MTB) by stimulating cell-mediated immunity and activating Monocytes though ethnic and Geographical factors play important role in such association (Pham Lan *et al*., 2010). All the above discussion suggest that vitamin D deficiency , is a determinant of TB that increases risk of disease reactivation by compromising cell mediated immunity. VDD was associated with 66% higher risk of relapse; the same was 133% in HIV infected patients, since vitamin D insufficiency is associated with decline in CD8 and CD3 T- cells (Mehta *et al*., 2013). Further, infection may affect utilization and catabolism of vitamin D. The active metabolite is carried in serum vitamin D binding protein and serum protein often decline in APR. In addition, infection also influence the time spent exposed to sun (Friies, 2008). Various studies indicate that hypovitaminosis D increases susceptibility of TB infection and is associated to co-morbidities and mortality risk in TB. For instance, mean Vitamin D in PTB patients with AFB+1, AFB+2 and AFB+3 sputum status was 22.2 ng/ml, 16.7 ng/ml and 13.1 ng/ml respectively which strongly support our observation (Yuvraj *et al*., 2016). Similarly in our study, mean vitamin D level in Severity Classes I, II and III was 18.9 ng/ml, 16.7 ng/ml and 12.8 ng/ml respectively ($p<0.001$) (Table 3). Although it showed moderate correlation to disease severity but such difference could be due to less sun exposure and greater consumption of vitamin D by macrophages (for intracellular antimicrobial activity) in more severe PTB disease. Sato *et al* (2012) reported a signisficant negative correlation of serum Vitamin D with duration until sputum conversion.

This relationship suggest that low vitamin D may not only be a risk factor for active TB but it may also be related to poor outcome (Sato *et al*., 2012). Hassanein *et al* also showed shorter conversion time and less severe clinical manifestation of TB when vitamin D was supplemented to TB patients along with first line anti-tubercular drug (Hassanein *et al*., 2016). Our results showed significantly low PTH level in PTB patients (35.7± 21.2 pg/ml) than controls (51.0± 21.6 pg/ml) (Table 2). This difference might be attribu Table to abnormal Ca metabolism, but other mechanisms such as suppression of PTH gland by immune mediators and/or cytokines may play role in reducing PTH level. The later process has some validity as patients with more severe PTB as identified by lung cavitation had significantly low PTH level than those with non- cavitory PTB i.e 15.7 ±8.4 pg/ml vs 21.1±8.8 pg/ml p= 0.040). Further, in their study, mean PTH in PTB patients was lower than controls (18.1±8.9 vs 52.2±19.8 pg/ ml) (Deniz *et al*., 2004). Vitamin D, in addition to numerous effect on Calcium metabolism has direct suppressive effect on PTH synthesis and secretion. Further, inflammatory mediators may also suppress PTH gland and inhibit its release. Receptors of PTH gland are sensitive to variation in ionized calcium and in PTB with altered calcium homeostasis, PTH level was found to be altered.

Conclusion

The present study suggest hypovitaminosis D associated with PTB. Vitamin D correlated moderately to disease severity (r=-0.38) and to sputum positivity (r=-0.347) that suggest its association to clinical severity of disease. Vitamin D estimation is significant not only for nutritional assessment but could help predict disease outcome and mortality in PTB patients as well as identify at risk individuals in vulnerable population like household contacts of patients. Low Vitamin D level causes increase in risk of progression from MTB infection to active disease and also increases probability of

conversion from latent TB to active form by compromising cell mediated immunity. Further, Vitamin D supplementation could be planned for highly deficient ones or critically ill patients so as to improve disease outcome, prevent MTB reactivation and reduce occurrence of relapse. Here, effect of Vitamin D supplementation on sputum bacterial load in tuberculosis patients need to be explored.

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