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Original Article

Internal Medicine Section

Significance of Serum Vitamin D Level in Tuberculosis Patients

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ABSTRACT

Introduction: The role of vitamin D in bone homeostasis is well known but nowadays, its role in various essential body processes including prevention of various infective and chronic illnesses like Tuberculosis (TB), by facilitating adaptive and innate immunity in lungs and peripheral blood, is being a matter of debate. Low levels have been associated with respiratory tract infections like TB. Present study aimed to evaluate the level of vitamin D in tubercular patients.

Aim: To determine serum vitamin D level in patients with TB and compare it with controls. To compare serum vitamin D level among different types of TB, including Pulmonary TB (PTB), tubercular lymphadenitis and tubercular pleural effusion.

Materials and Methods: The present study was a single centre cross-sectional study done during the study period from September 2013 to September 2016 at a tertiary care centre of Uttar Pradesh, India. Total 216 subjects aged between 21 and 60 years were included randomly out of which 113 patients were cases and 103 were controls. Cases of TB were confirmed by sputum Acid Fast Bacilli (AFB) staining, sputum and pleural fluid cytology, Adenosine Deaminase (ADA) of pleural fluid and Fine Needle Aspiration Cytology (FNAC) of lymph nodes. Controls were healthy subjects. Total serum vitamin D levels were measured by Diasorin competitive Radioimmunoassay (RIA) (Autoimmune Diagnostika, GmbH, Strasburg, Germany).

Results: The mean serum vitamin D level for patients with TB was 22.4±8.5 ng/mL. Among controls, it was 30.5±8.6 ng/mL ($p<0.001$). This analysis showed that mean serum vitamin D levels were significantly lower in TB patients as compared with controls and there is no significant difference of serum vitamin D levels in various groups of TB. Also, there was no effect of confounding factors like age, sex and indoor/outdoor activity.

Conclusion: The findings of the present study showed that hypovitaminosis-D was highly prevalent among patients with TB as compared to general population in same geographical area and severity of it is not significantly related to different type of TB.

Keywords: Hypovitaminosis D, Pulmonary tuberculosis, Tubercular lymphadenitis, Tubercular pleural effusion

INTRODUCTION

Vitamin D is important for cell growth, immunity, and metabolism especially musculoskeletal system by intestinal absorption of calcium and phosphate. Deficiency leads to osteoporosis and rickets. Recently, vitamin D is a matter of debate for its role in maintaining health and homeostasis in various essential body processes including prevention of various infective and chronic illness including TB [1]. The role of vitamin D in immune processes is well established through its local production by immune cells such as macrophages, Dendritic Cells (DCs) and lymphocytes, facilitating adaptive and innate immunity in lungs and peripheral blood [2]. In the present study, main concern was to evaluate on association of vitamin D with TB and to establish the hypothesis that hypovitaminosis D is a risk factor for the development of TB.

MATERIALS AND METHODS

This study was a single centre cross-sectional study in which simple randomised selection of TB patients was done to reduce selection bias. A total of 113 TB patients and 103 controls were included in the study. The study was conducted during the period from September 2013 to September 2016 at Jawaharlal Nehru Medical College and Hospital, AMU, Aligarh, Uttar Pradesh, India.

Patients aged 21-60 years with diagnosis of TB confirmed by sputum AFB, cytology, ADA and FNAC of lymph nodes were included for the study. Controls were healthy subjects aged 21-60 years free from any disease and morbidity. They were either patient's relative or healthy volunteers belonging to the same lifestyle and geographical area. All the subjects were divided into males and females, smokers and non smokers (smoker is someone who has smoked greater than 100 cigarettes, including hand rolled cigarettes, cigars, cigarillos etc., in their lifetime), and according to their indoor and outdoor activity (indoor workers were people who work in darker places where there is little exposure to light like mine workers, office workers, factory workers etc., and outdoor workers were defined as people who work in an open place where they were adequately exposed to sun light) to evaluate the effect of these confounding factors on serum vitamin D levels.

All known cases of autoimmune diseases, malignancy, morbid obesity (body mass index >30), known diabetes, primary hyperparathyroidism, chronic kidney disease {decreased Glomerular Filtration Rate (GFR) of less than 60 mL/min/1.73 m^2 for at least three months} and osteomalacia were excluded from the study group.

Chest radiograph, sputum AFB stain, FNAC of lymph nodes, pleural fluid cytology and ADA, were the tests done when required to diagnose TB. Serum vitamin D in form of 25 hydroxyvitamin D {25(OH)D} was measured using RIA in the endocrinology laboratory of the hospital. Blood sugar, complete blood count, renal function test, liver function test and other endocrinological investigations were done as per requirement.

Serum vitamin D analysis: Around 3 mL of blood was collected from each subject following an aseptic protocol by a pathologist and serum separated. We measured total serum vitamin D in the form of 25(OH)D by diasorin competitive RIA (AID Diagnostika, GmbH, Strasburg, Germany). Vitamin D status was defined as: Serum 25(OH)D levels ≤20 ng/mL were used to define vitamin D deficiency, serum 25(OH)D 20-30 ng/mL as insufficiency and >30 ng/mL defined sufficient vitamin D levels [3].

STATISTICAL ANALYSIS

The analyses were done with latest SPSS software for Windows, version 20.0 (SPSS Inc., IBM, Version 20.0, USA). A statistical opinion was taken. Wherever it is applicable for different variables independent sample t-test and ANOVA were used and significant p-value was considered it is $p<0.05$.

RESULTS

In the present study 216 subjects were included with age ranging from 21 to 60 years. The mean age in our study group was 36.64±13.81 years. Out of total 216 subjects 113 were cases and 103 were controls. The mean age of the controls was 35.5±12.7 years and of cases were 30.1±11.6 years [Table/Fig-1].

Baseline characteristics	Cases	Controls
Age (mean±SD)	30.1±11.6 years	35.5±12.7 years
Sex		
Male	59	61
Females	54	42
Smoking status		
Smokers	21	12
Non smokers	92	91
Activity status		
Outdoor	86	70
Indoor	27	33
Total	113	103

[Table/Fig-1]: Baseline characteristics of study groups.

TB patients further categorised into PTB (74), tubercular lymphadenitis (19) and tubercular pleural effusion (20).

The mean serum vitamin D level of TB patients was 22.4±8.5 ng/mL and in controls it was 30.5±8.6 ng/mL with highly significant p-value (<0.001), this analysis significantly shows that mean serum vitamin D levels were low in TB patients as compared with controls [Table/Fig-2].

Study groups	Tuberculosis	Controls	t value	p-value
Vit D (ng/dL) (mean±SD)	22.4±8.5	30.5±8.6	6.762	<0.001*

[Table/Fig-2]: Frequency distribution of serum vitamin D levels among study groups.
Independent sample t-test was used, p-value came out to be significant at <0.05

Observation of Comparison of Vitamin D Levels in Relation to Type of Tuberculosis

There was no significant difference in the vitamin D levels in PTB, tubercular lymphadenitis and tubercular pleural effusion (p-value=0.643). Subjects with PTB had a mean vitamin D level of 22.0±8.5 ng/mL, while subjects with tubercular lymphadenitis had 24.1±8.3 ng/mL and subjects having tubercular pleural effusion had a mean vitamin D level of 22.5±8.8 ng/mL [Table/Fig-3].

Type of tuberculosis	No. of patients (n)	Mean serum 25 hydroxyvitamin D level (ng/mL)	F value	p-value
Pulmonary tuberculosis	74	22.0±8.5	0.359	0.643
Tubercular lymphadenitis	19	24.1±8.3		
Tubercular pleuraleffusion	20	22.5±8.8		

[Table/Fig-3]: Comparison of serum 25(OH) D with respect to type of tuberculosis.
ANOVA was used between the three samples. p-value was not significant (p>0.05).

Observation of Vitamin D Levels with Respect to Sex, Smoking Status and Indoor/Outdoor Activity

There was no significant difference in the vitamin D levels based on sex, smoking status and indoor/outdoor activity [Table/Fig-4].

Study groups with mean age in years	Epidemiological criteria	No. of subjects	Vitamin D (ng/mL±SD)	p-value
Tuberculosis patients with mean age 30.12±11.6 years	Male	59	21.6±7.5	0.26
	Female	54	23.4±9.6	
	Smokers	21	22.2±6.4	0.88
	Non smoker	92	22.5±9.0	
	Outdoor	86	22.7±8.7	0.66
	Indoor	27	21.9±8.0	
Control with mean age 35.0±12.7 years	Male	61	31.3±8.4	0.33
	Female	42	29.6±9.0	
	Smokers	12	27.2±6.5	0.154
	Non smoker	91	31.0±8.0	

[Table/Fig-4]: Observation of vitamin D levels with respect to sex, smoking status and indoor/outdoor activity.
Independent sample t-test was used. A p-value was not significant (p>0.05) for each confounding variable

DISCUSSION

Vitamin D is responsible for intestinal absorption of calcium and phosphate. Most important are vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol), both can be ingested from the diet and supplement and ultraviolet light that helps in the formation of vitamin D in the body [4,5].

Biological Functions

Involvement of vitamin D in immune process is less understood, although the association between vitamin D and bone metabolism has been observed in studies of Vitamin D Receptors (VDR) gene polymorphisms and development of osteoporosis, rickets and occurrence of hip fractures [6-8].

The respiratory system is first line of defence and functions as a physical barrier to prevent the entry of inhaled pathogens. Vitamin D modulates dendritic cell maturation and chemokine profile and macrophage innate immune functions [9]. With the help of this, vitamin-D mediated immune mechanism Alveolar Macrophages (AMs) and DCs recognise, phagocytose and remove inhaled material by producing chemokines. After phagocytosis they migrate to local lymph nodes where they present antigens to major MHC molecules to naïve T cells (CD4 and CD8+ T cells) and induce their activation and differentiation. This immune modulatory effect of vitamin D has been given importance in last few years especially for chronic and autoimmune diseases and susceptibility to infection [10].

Role of Vit D in TB

Following inhalation of *Mycobacterium bacilli*, it is phagocytosed by AMs. Various receptors play a role in endocytosis and triggers complement system proteins and proteases to initiate phagocytosis, and to act as chemoattractants that stimulate inflammation [11]. Once phagocytosed, anti mycobacterial functions of AMs are induced by fusion of phagosome and lysosome. Fusion of lysosome with the phagocytosed *Mycobacterium* results in bacterial degradation [12]. DCs engulf bacteria and migrate to lymph nodes, where they present antigens to T cells and stimulate their proliferation and migration to the site of infection. AMs continue to accumulate and mild inflammation develops, although there is little tissue damage [13]. The production of IL-12 is strongly induced by mycobacterial infection and secreted by macrophages, monocytes, neutrophils and T cells. IL-12 stimulates a strong Th1 response to infection by inducing production of IFN-y [14]. Antigen Presenting Cells (APCs), travel to the lymph nodes and present *M. tuberculosis* antigens to naive T cells. As activation of antigen specific CD4+ cells takes place, large amounts of IFN-y and TNF-a are produced, assisting the infected macrophage in killing intracellular bacilli. The release of chemokines from macrophages and DCs causes more T cells to activate and aggregate to wall off infection, forming a Th1-mediated granuloma [11,12]. In centre of granuloma, are infected

macrophages releasing enzymes that cause cell lysis and necrosis. Necrosis occurs in an effort to reduce or eliminate Mycobacterium TB (MTB) infected macrophages [11]. As described in previous heading Vitamin-D modulates dendritic cell maturation, and chemokine profile, macrophage and innate immune functionand coordination with T cell mediated immunity it maintains integrity of granuloma and augmentation of autophagy which plays an important role in immunity against MTB infection.

The Association of TB and Vitamin D

Now a days, the seasonality of TB diagnosis in some high latitude countries has drawn increased attention to the importance of vitamin D in the immune functioning of individuals infected with *Mycobacterium.* A study in United Kingdom found that diagnosis of active TB was more common during early summer than winter months, a pattern seen commonly among individuals who had recently immigrated to the UK from the Indian subcontinent. This trend may be partially explained by the reduction of 25(OH)D concentration that accompanies immigration to the UK. The loss of endogenous vitamin D production is at its greatest at the end of winter, and reactivation and initiation of symptoms, medical attention and diagnosis may be prolonged until summer. Significant number of immigrant population in United Kingdom develops active TB within five years of immigration [15].

Similarly, recent studies in Spain exploring seasonal trends in TB diagnosis reported a seasonal peak at the end of winter and spring. This type of trend may be explained by several factors such as an increase in indoor exposure to TB during the winter months, long spans of time between the onset of symptoms and diagnosis, and a reduced cutaneous production of vitamin D during winter. However, it seems that reduced production of the vitamin is a common denominator in those cases. Studies have shown that vitamin D deficiency in combination with other factors may increase susceptibility to TB reactivation [16].

Similar studies in the UK reported that serum 25(OH)D concentrations among immigrants from developing countries may decrease by a factor of ten following arrival, recommending supplements to increase 25(OH)D serum concentrations is therefore important. Another study done in Asian immigrants to UK, demonstrated there was no significant improvement in the immunity against TB by doubling the serum vitamin D levels indicating that higher concentrations of vitamin D intake may be required in order to achieve significantly increased levels [17]. In certain populations, genetic differences have been proposed for low vitamin D levels in addition to availability of vitamin D. This genetic variability may partially account for specific immune responses to TB present in specific ethnic groups. In fact, multiple VDR gene polymorphisms could have an effect on host responses to MTB infection. Time to response to anti mycobacterial treatment shows a significant association with certain VDR gene polymorphisms, suggesting that a change in structure or activity of VDRs could change host response to active TB. It is also seen that this VDR gene polymorphism affects the host response and time to respond to antimycobacterial treatment [18]. Vitamin D deficiency was recently shown to be associated with TB reactivation among Gujarati Hindus in the UK. It was seen that in the same population there was increased VDR gene polymorphism which explained vitamin D deficiency better than insufficient dietary intake [19].

The role of vitamin D status in modulating host immune response to respiratory infection and inflammation appears complex. Evidence based information from both clinical and laboratory driven studies are clearly needed to help clarify the complex encircled by vitamin D status, vitamin D metabolism, infection and inflammatory mechanism in human lungs. With all the increasing evidence that vitamin D deficiency is a major a risk factor for TB reactivation, it can be hypothesised that the vitamin somehow plays a vital role in the immune maintenance and integrity of granuloma, thus preventing latent infection from becoming active [20]. Other studies have also shown that ethnic groups considered at high risk for TB have generally lower levels of vitamin D and cathelicidin expression, such as the study by Wang TT et al., who established this difference among African Americans when compared to whites in the United States [21]. The fact that those identified as high risk are dark skinned populations is interesting. Social determinants aside, it may very well be that the interference of dark skin in vitamin D synthesis is playing a significant role among these populations. The WHO data affirms that one third of the world population harbours Latent TB Infection (LTBI) and that the majority of the 8-9 million TB clinical cases per year are due to reactivation of a latent infection [22]. The scientific community is currently engaged in the creation of new vaccines to prevent TB infection and new and better drugs to treat and cure it. At the same time, alternative approaches including immunomodulators are being investigated. Among these, the potential of vitamin D as a low-cost and easily manageable risk factor for developing active TB has been received with much optimism among the scientific and clinical community [23]. This newly established link between the hormonally active metabolite and the innate immune system has greatly contributed to the increasing interest in investigating the beneficial role of vitamin D not only in active TB, but in latent infection as well. If proven beneficial, vitamin D supplementation in individuals with demonstrated LTBI could potentially reduce the global burden of one of the world's most widespread diseases.

The present study has focused on determining the vitamin D status of Indian population, with the particular aim of evaluating the association between vitamin D and TB. There is no available literature from India on vitamin D levels in various types of TB. A South Korean study also showed similar results in which baseline serum vitamin D levels were low in all patients with PTB and extrapulmonary TB [24]. In present study, we did not observe any difference in the serum levels of 25(OH)D in the three types of the TB (PTB, TB LAD and PE). Present study further supported by most of the studies conducted in adult population have suggested that 25(OH)D levels are lower in individuals with TB [25]. A study done by Ho-Pham LT et al., on Vietnamese population showed that prevalence of vitamin D insufficiency was 35.4 and 45.3% in men and women with TB, respectively [26]. Other studies done in West London on Asian and immigrant population from Sub-Saharan Africa in Australia also proved the deficiency of 25(OH)D levels in adult TB patients [27], but none of these studies proved differentiation between PTB and extrapulmonary TB. Present study also showed that most of the patient with TB was either vitamin D deficient or insufficient. In an Indian study it was seen that in patients with PTB, vitamin D deficiency was associated with late sputum conversion at two months [28]. Other studies have also shown association of vitamin D deficiency with increased risk and poor treatment outcome with delayed sputum conversion. For example a Japanese study conducted by Sato S et al., in which they proved that low serum 25(OH)D level may be associated with increase the risk of developing active TB as well as but may also be related to the poor treatment outcomes, which was measured by time taken to obtain three consecutive negative sputum smears or TB bacteria cultures [29]. An older Indonesian study on 40 patients of PTB suggests that the disease was less severe in patients who had sufficient 25(OH)D levels. Sputum conversion rate at two months have been considered as a predictor of relapse of TB in adults with longer time to conversion is predictor higher relapse rates [30]. Martineau AR et al., have demonstrated that a single dose of ergocalciferol "in vivo" has beneficial effects in the overall blood toinhibit the "in vitro" growth of mycobacteria [31]. Morcos MM et al., have demonstrated faster resolution of the TB symptoms and gain of weight in children treated with daily doses of vitamin D as complement to the standard treatment for two months [32]. Many LTBI reactivation studies have been carried out among foreign born populations from TB endemic, tropical or subtropical regions

that have relocated in developed regions at higher latitudes, where sun exposure is reduced, leading to reduced production of vitamin D in the skin [33]. Although, a definitive association has not been established for the relationship between vitamin D deficiency and LTBI reactivation, it remains a potential risk factor for reactivation and progression to active TB. Further study of vitamin D status may contribute to the understanding of LTBI in migrant populations. By concluding above studies, it is strongly evident that vitamin D is a risk factor and not an outcome of TB.

The strengths of present study included a large sample size and the use of a sensitive technique for 25(OH)D level estimation. Present study findings suggest that periodic screening of serum vitamin D and supplementation should be considered in routine care patients with lung diseases, however its safety and cost effectiveness need to be evaluated. Prospective well designed (studies) intervention based trials are needed despite being difficult and costly for further evaluation on the relationship between adequate vitamin D repletion and treatment, prevention of bacterial infections, especially MTB. Emphasis should be put on effectiveness of repletion therapy, large sample size and factors that may confound the results, such as; exogenous intake of vitamin D irrespective of the groups assignment, independent effect of nutritional status improvement with therapy and seasonal variation with vitamin D status.

Given the high frequency of hypovitaminosis D found in present study, there is a need to work more on health promotion activities to this community targeting the importance of physical activities, exposure to sunlight and use of diets rich in vitamin D. Vitamin D has a number of activities in addition to its effect on calcium and bone homeostasis and influences process such as immune regulation, host defence, inflammation, or cell proliferation. Vitamin D deficiency is potentially involved in a number of lung diseases. Several obstacles must be overcome to validate the benefit of vitamin D-based therapies:

1. Basic mechanisms are not clear and the involved molecular pathways are likely difficult to identify because vitamin D impacts on a variety of biological processes in parallel.
2. Conclusive data from interventional studies are not very clear for many disease entities.
3. Since, vitamin D has been used for many years, the pharmaceutical industry might hesitate in starting a development program. Nevertheless, the data available indicate that vitamin D could be extremely beneficial for the prevention or therapy of some very important lung diseases.

LIMITATION

We did not estimate vitamin D intake, duration of sun exposure and degree of skin pigmentation, all of which might have helped in explaining the low serum 25(OH)D levels. More studies are needed to elicit causative relation of serum vitamin D in TB and if proven we will get a strong tool either in form of prophylaxis or adjuvant treatment to fight with this deadly disease and to create a better and healthy world for humanity.

CONCLUSION

Hypovitaminosis D was highly prevalent among patients suffering from TB (p-value<0.001) as compared to general population. However, this decrease in vitamin D level was insignificant when it was compared in different type of TB patients like PTB and extrapulmonary TB. The confounding factors like sex, smoking status and indoor and outdoor activities do not significantly alter serum vitamin D levels. Although, it is not very evident from present study weather vitamin D is a cause or the consequence of TB but in our experience, all the patients with TB should be offered vitamin D supplementation. However, further studies are required to establish the association between vitamin D levels and TB.

Conflict of interest: There is no conflict of interest

This study was passes from institutional Ethical committee and Guidelines according to declaration of Helsinki were followed.

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