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**Original Research Article**

# Serum vitamin D level in newly detected tuberculosis-a case control study

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## ABSTRACT

**Background:** Vitamin D has a significant role in host immune defence against *Mycobacterium tuberculosis*. It has been suggested that pulmonary tuberculosis may be associated with lower levels of vitamin D. Present study was undertaken to identify the association between vitamin D deficiency and tuberculosis.
**Methods:** A case-control study was conducted in a tertiary care hospital, including 25 adult newly diagnosed tuberculosis patients as cases and 25 age and sex-matched healthy participants as control groups. All participants in the study group had undergone detailed clinical examination and routine laboratory investigations, including vitamin D level estimation. The clinical characteristics, investigations including vitamin D levels were analysed and compared with data obtained from healthy controls.
**Results:** Majority of the study population were in the age group of 40-50, with a mean age of 46.6±14.2. There were 20 pairs of males and 5 pairs of females. Out of the cases, 18 patients had pulmonary tuberculosis while 7 had extra pulmonary tuberculosis. Nine of the cases (36% of study population), 4 (16%) of the controls were underweight. The 15 (60%) of the cases and 20 (80%) of the controls were in the normal range and 1 case and 1 control were in the pre obese range. A total of 17 cases (68%), 8 controls (32%), had some degree of vitamin D deficiency (p=0.011) which is significant and suggests an association between the two.
**Conclusions:** The prevalence of vitamin D deficiency in pulmonary tuberculosis cases is very high.

**Keywords:** Pulmonary Tuberculosis, Mycobacterium Tuberculosis, Serum Vitamin-D Level

## INTRODUCTION

Tuberculosis (TB) is a major public health problem and cause of mortality globally.[1]

TB caused mainly by *M. tuberculosis* that most often affects lungs leading to pulmonary TB. The host susceptibility to TB infection depends on a complex interaction between host, bacteria and several factors such as poverty, malnutrition, overcrowding, and exposure to other pathogens. Previously, it has been estimated that about one-third of the world's population is infected with latent *M. tuberculosis*, and only 10% of which will develop active disease.[2,3] Vitamin D plays an important role in host immune defence against TB infection by improving phagocytic capacity of monocytes and macrophages.[4,5] Increasing production of anti-microbial peptides as cathelicidin, immune modulation.[5,6] Vit D acts by binding to nuclear receptors on target cells. Therefore, both low levels of vit and abnormalities in receptor structure and function may result in impairments in host immunity to the tubercle bacilli.[7]

Previously, many studies presented that the polymorphisms in the vitamin D receptor influence host susceptibility to TB.[8] Likewise, studies have shown conflicting results on the level of vitamin D in TB patients and community controls.[9,10] Notably, serum vitamin D level varies considerably between populations and is influenced by many geographical and cultural factors.[11,12]

Aim of our study was to determine serum vitamin D level in newly detected tuberculosis patients compared to healthy control.

## METHODS

The present study was a case control study carried out in academy of medical science, Pariyaram, Kannur (presently known as govt. medical college, Kannur) for a period of one year from march 2015 to February 2016.

Institutional research committee and ethical committee approval was taken before conducting study. Informed written consent was taken from all the participants.

Study population were split in the cases and controls. Cases comprised 25 patients attending the outpatient department in various departments of ACME, Pariyaram proven to have active tuberculosis and control group formed 25 age and gender-matched healthy controls enrolled from the general population that included relatives of admitted patients and health care workers with the similar ethnic and socio-economic background as that of cases.

### *Inclusion criteria*

All newly diagnosed cases of tuberculosis (pulmonary and extra pulmonary) registered under RNTCP during the study period.

### *Exclusion criteria*

Patients who have already commenced anti tuberculous treatment, Participants with diseases like human immune deficiency (HIV) virus infection, diabetes mellitus, cancer; patients who were on corticosteroids and chemotherapeutic drugs; sarcoidosis, and parathyroid disorders were excluded. Participants who were on vitamin D, calcium supplements, anti-convulsant, diuretics, or any other drug which inter acts with vitamin D and patients with chronic liver or renal disease, malabsorption conditions, gastric, or bowel resection were excluded. Pregnant ladies and lactating mothers were also excluded.

All participants underwent a detailed medical history and clinical examinations. Routine lab investigations like complete blood count, liver and kidney function tests, blood glucose levels, HIV ELISA, HBsAg and anti-HCV serology, serum calcium, and albumin levels were done in all participants. Chest radiograph and at least two baseline sputum samples were obtained from each participant for acid-fast staining. Serum 25(OH)D level was measured before initiating antitubercular therapy (ATT). Five mL of venous blood will be collected in a serum tube and sent to lab. Serum separated by centrifugation and 25(OH)D3 levels measured by ID-LC-MS/MS. As per the endocrine society clinical practice guidelines, 25(OH)D levels were divided into three categories.[13] 25(OH)D level ≤20 ng/ml was considered as deficient, 25(OH)D level 21-29 ng/ml as insufficient, and 25(OH)D level more than 30 ng/ml was considered as optimal.

### *Statistical analysis*

All the data collected was entered and analysed using epi SPSS. Descriptive statistical methods like mean deviation, frequency and proportions were used. Inferential statistical methods like chi square test and students t test were used. P value of less than 0.05 is taken as significant.

## RESULTS

A total of 25 cases and 25 age and sex matched controls were studied.

### *Age*

Majority of the study population were in the age group of 40-50. With a mean age of 46.6±14.2. There were 8 pairs in age group of 40-50, 6 pairs in 50-60, 4 pairs in 30-40 and>60 age groups.

### *Sex*

There were 20 pairs of males and 5 pairs of females, with a M:F ratio of 4:1.

### *Type of tuberculosis*

Out of the cases 18 (72%) patients had pulmonary tuberculosis while 7 (28%) had extra pulmonary tuberculosis.

### *Smoking*

There were 12 pairs of smokers in the study group amounting to 48% of study population.

### *BMI*

Nine of the cases (36% of study population) 4 (16%) of the controls were under weight. The 15 (60%) of the cases and 20 (80%) of the controls were in the normal range and 1 case and 1 control were in the pre obese range. The case in the pre obese category was an extra pulmonary TB.

Mean BMI of the control group was 22.32 (SD=2.717), cases were 19.09 (SD=2.301), (p≤0.001).

***Vitamin D level***

Sufficient levels of vitamin D was found in 2 of cases and 11 controls, who accounted for 8% of the study and 44% of control groups. 6 cases and 6 controls had insufficient vitamin D levels, 15 cases and 5 controls were deficient in vitamin D and 2 of the cases and 3 of the controls had severe deficiency of vitamin D (Figure 1).

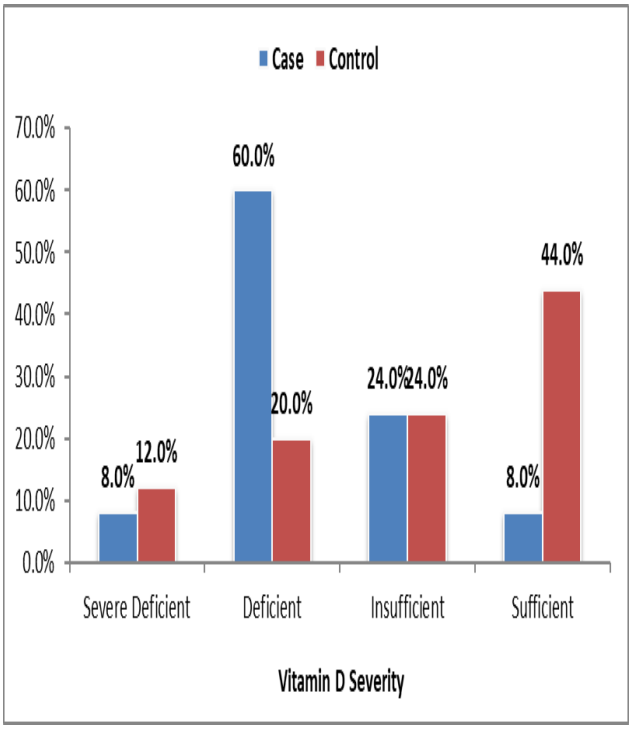


**Figure 1: Comparison of vitamin D levels in cases of tuberculosis and controls.**

A total of 17 cases (68%), 8 controls (32%), had some degree of vitamin D deficiency (p=0.011). Which is significant and suggests an association between the two.

***Association of vitamin D with other measured parameters***

Mean age of vitamin D deficient individuals was 44.16, 38.46% of those above 50 were deficient in vitamin D.

Average vitamin D level in males was found to be 23.21 and that of females 19.49 (p=0.092). The difference is not statistically significant.

Relationship between smoking and vitamin D status 11 (45.8%) smokers and 14 (53.2%) non-smokers were deficient in vitamin D (p=0.571) (54.2%) smokers and 12 (46.2%) non-smokers had sufficient vitamin D level.

***Relation of BMI to severity***

Severe deficiency was more common in under-weight and sufficient vitamin D level in normal BMI group (Figure 2).

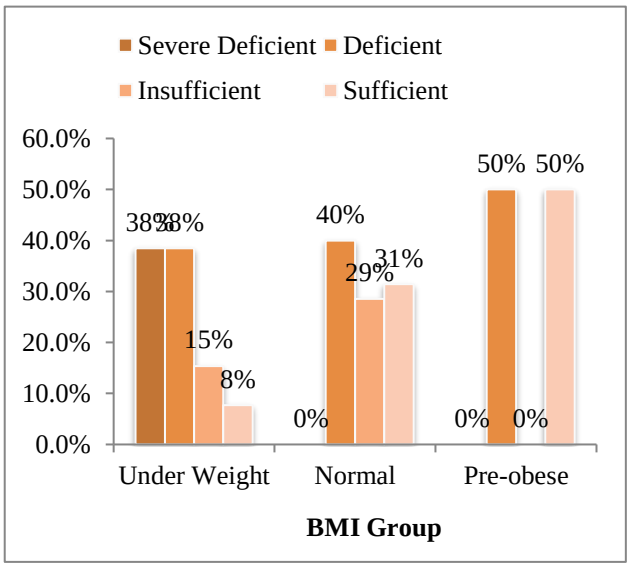


**Figure 2: Relation between BMI and vitamin D deficiency severity.**

**Table 1: Relationship between age group and vitamin D severity.**

| Group | Severe deficient (%) | Deficient (%) | Insufficient (%) | Sufficient (%) | P value |
|---|---|---|---|---|---|
| **Up to 20** | 0 (0.0) | 1 (33.3) | 0 (0.0) | 2 (66.7) | 0.860 |
| **21-30** | 0 (0.0) | 2 (66.7) | 0 (0.0) | 1 (33.3) | |
| **31-40** | 1 (12.5) | 5 (62.5) | 2 (25) | 0 (0) | |
| **41-50** | 1 (6.7) | 6 (40) | 4 (26.7) | 4 (26.7) | |
| **51-60** | 2 (16.7) | 3 (25) | 3 (25) | 4 (33.3) | |
| **Above 60** | 1 (11.1) | 3 (33.3) | 3 (33.3) | 2 (22.2) | |

**Table 2: BMI group wise division and vitamin D deficiency status.**

| BMI group | Deficient, (n=25) (%) | Sufficient, (n=25) (%) | P value |
|---|---|---|---|
| **Under Weight** | 10 (76.9) | 3 (23.1) | 0.051 |
| **Normal** | 14 (40) | 21 (60) | |
| **Pre-obese** | 1 (50) | 1 (50) | |

## DISCUSSION

A total of 50 subjects were included in the study with 25 cases and 25 age, sex matched controls. Previous studies by Sasidharan et al had 35 cases and 16 age and sex matched controls, Chan et al used 22 cases and 23 controls in their study.[14,15] A pioneering study in this field was conducted in Calicut Sasidharan et al where they concluded that there is an association between Vitamin D and tuberculosis and it is possibly a cause rather than effect. The mean age of cases was 46.6±14.2, that of controls were 46.2±14.2. This was similar to previous studies like Davies et al, where cases had a mean age of 43.1±18.8, controls were 42.2±17.9.[16] Tuberculosis affects people of all ages, and it was thought to be a disease of young adults. A recent change in the age of incidence have been noticed in many countries, with a shift towards older age group. This could be due to better health care and socio-economic conditions, that the disease is commoner now among the elderly who are relatively less immunocompetent.[17] The incidence of atypical presentations and extra pulmonary TB is also higher among older population. these were more difficult to diagnose in the past, with better health care and case finding, diagnosing techniques, there is an increased probability of being diagnosed.[18,19]

There were 20 pairs of males as against 5 pairs of females, with a male female ratio of 4:1. This was different from studies by Sloan et al where they noted a M:F ratio of 2.2:1 Davies et al had a M:F ratio of 2.8:1.[16,20] The reason for this could be because of the male preponderance in the incidence of tuberculosis in the post adolescent age group. Gender disparity in the notification rates and treatment adherence of tuberculosis has also been noted by Mukherjee et al and Holmes et al they attribute it to the socioeconomic factors of women being financially and logistically dependent on men for health care.[21,22] A recent South Indian study by Balasubramanian et al challenges this.[23] The question of under reporting among female tuberculosis patients, even in a state like Kerala with an HDI and health indicators comparable to that of developed countries, needs further research.

Out of the cases 18 patients had pulmonary tuberculosis while 7 had extra pulmonary tuberculosis. which shows a ratio of 2.57:1, this incidence is close to that reported in the global tuberculosis report.[24] Some of the similar studies Chan et al and Davies et al sampled only pulmonary tuberculosis.[15,16]

There were 12 pairs of smokers in the study group amounting to 48% of study population (p=1.00). No significant association could be suggested between smoking and tuberculosis in current study.

Smoking as a risk factor for tuberculosis has garnered much attention and quite a few studies have been undertaken to validate it, a meta-analysis by Maurya et al consolidating 12 studies identified that a relationship might exist.[25] Den Boon et al suggested a positive relationship between pack years and risk.[26] Bothamley explained that this could be due to a reduced specific and enhanced non-specific inflammatory response, seen in smokers.[27] Although current study could not establish a significant relationship, advice to quit smoking may decrease risk for progression to active TB, according to current literature.

Nine of the cases (36% of study population), 4 (16%) of the controls were underweight. The 15 (56%) of the cases and 20 (76%) of the controls were in the normal range and 1 case and 1 control were in the pre obese range. The case in the pre obese category was a Female patient with extra pulmonary TB. Mean BMI of cases was 19.01 (SD 2.30), that of controls was 22.32 (SD 2.717), p<0.001. This difference is statistically significant and is similar to the finding of Wejse et al.[28] This could be explained by the fact that vitamin D is related to malnutrition both as a cause and as an effect. Malnutrition leads to decreased immunity and predisposition to TB and the inflammatory mediators produced by TB such as TNF leads to cachexia.

A total of 17 cases (68%), 8 controls (32%) (p=0.011), had vitamin D deficiency. This was a statistically significant finding and corroborates with the findings of Ifthikar et al, Davies et al and Wejse et al.[16,28,29] Mean Vitamin D level in cases were 17.65 (SD=7.611) and that in controls were 27.28 (SD=11.22), (p=0.001) which is also a statistically significant difference. Significant difference in the mean vitamin D level was noted by Davies et al (p=0.005), Wejse et al (p<0.001) and Ifthikar et al (p<0.001).[16,28,29]

Mean age of the subjects with vitamin D deficiency was 44.16, 38.41% were older than 50 years, 23.07% in 31-40 age group and 26.92% in 41-50 range. Severe deficiency of vitamin D was also more common in the >50 age group.

The 70% of the total female study population was deficient in vitamin D, whereas only 45% males were deficient (p=0.289). All of the female patients with TB and 60% of men with TB were deficient in vitamin D (p=0.08).

This was not consistent with other studies where the deficiency among TB patients were nearly same in both sexes Davies et al M=20.84, F=25.03).[16] This could be explained by the fact that 60% of the women were also deficient in sunlight exposure, and due to the socio-cultural factors prevalent in the study location including clothing and sun protection that leads to less sunlight exposure among women.

The mean BMI of the vitamin D deficient subjects were 19.24 and that of subjects with a normal vitamin D level was 22.16 (p<0.001). Recent literature has conflicting

opinions on relationship between BMI and vitamin D. While there is a general consensus that Obese males, are more susceptible to vitamin D deficiency, obese females may not be predisposed at all or may be to a lesser extend to vitamin D deficiency.[30,31] Obesity being defined as BMI>30. Only one of our matched female pairs were in the pre obese category (BMI≥25), the case was deficient while the control was not deficient in vitamin D. Moreover, tuberculosis can also cause loss of body weight and directly influence BMI, so an independent relationship may not be established in current study.

**Table 3: Comparison of results with published studies.**

| Parameters | | Present study | | Davies et al[16] | P | Ifthikar et al[29] | P | Mashhadi et al[32] | P | Wejse et al[28] | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Vit D | Level in case | 17.65 (SD 7.61) | <0.001 | 6.4 nmol/L | <0.005 | | | 20.688± 14.065 nmol/l | <0.001 | 78.3± 22.6 | <0.001 |
| | Level in control | 27.28 (SD 11.22) | | 10.9 nmol/L | | | | 57.197± 18.197 | | 85.3± 34.8 | |
| | Cut off value | 20 | | | | | | 50 nmol/L | | | |
| | Deficiency case (%) | 68% | 0.011 | | | 57 | <0.001 | | | 46 | |
| | Deficiency control (%) | 32% | | | | 33 | | | | 39 | |
| | Male | 23.21 | | | | 20.84 | | | | | |
| | Female | 19.49 | | | | 25.03 | | | | | |
| | Male (%) | 45 | | | | | | 93.52% | | | |
| | Female (%) | 70 | | | | | | 95% | | | |
| RR | | 4.516 | | | | | | | 3.8 | 1.18 | |
| OR | | 2.125 | | | | | | | | | |
| Conclusion | | S* | | S* | | S* | | S* | | Role present | |

*S-significant.

***Limitations***

Small sample size and single centred study were the limits of the study. Differences in sunlight exposure among study participants were not studied and hence its possible role in serum vitamin D deficiency.

## CONCLUSION

In our study vitamin D deficiency is prevalent among tuberculosis patients compared to age and sex matched healthy controls.

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