# "ASSESSMENT OF SERUM VITAMIN D LEVELS IN PATIENTS WITH PULMONARY TUBERCULOSIS – A COMPARATIVE CROSS-SECTIONAL STUDY IN A TERTIARY CARE CENTRE IN KOLAR"


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# ABSTRACT

**Background & objective:** Tuberculosis remains as one of the deadliest disease affecting humankind and vitamin D deficiency is a global health problem. The evidence is increasingly pointing towards increased susceptibility to TB among individuals with vitamin D deficiency and worse disease progression if infected with TB. Hence the current study was undertaken to assess the prevalence of vitamin D deficiency in patients with pulmonary tuberculosis and to compare it with non-tuberculosis cases.

**Materials & methods:** This study was a comparative cross-sectional study conducted in R.L. Jalappa hospital among 100 individuals divided into two groups. Group 1 consisted of 70 sputum positive pulmonary TB case and group 2 consisted of 30 community healthy controls matched for age and gender. The subjects were investigated for biochemical parameters and serum vitamin D level using Electro-chemiluminescence immunoassay (*ECLIA*).

**Results:** The mean age of TB and non-TB cases were 52.53 ± 15.68 years and 56.07 ± 10.06 years respectively. Mean vitamin D level in the study population was 29.51± 28.19 ng/ml. Vitamin D deficiency was found in 54(77.14%) cases with TB and in 10(33.33%) non-TB cases. The mean difference in serum albumin (3.89 ± 0.89 g/dl vs 3.42 ± 0.76 g/dl); calcium levels (7.3 ± 1.59 mg/dl vs 8.5 ± 1.37 mg/dl) and vitamin D level (22.02 ± 23.8 ng/ml vs 47 ± 30.22 ng/ml) were statistically significant (p value<0.01) across the group.

**Conclusions:** This study concludes that vitamin D deficiency is associated with an increased prevalence of tuberculosis. This recommends the screening for vitamin D deficiency and encourages vitamin D supplementation for all tuberculosis patients.



Keywords: vitamin D deficiency, Tuberculosis, Immunity

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# LIST OF ABBREVIATIONS

| Abbreviations | Glossary |
|---|---|
| AFB | Acid Fast Bacilli |
| DBP | Vitamin D Binding Protein |
| eCLIA | Electro-chemiluminescence immunoassay |
| 25(OH)D3 | 25-hydroxyvitamin D3 |
| LTBI | Latent TB Infection |
| TB | Tuberculosis |
| VDD | Vitamin D deficiency |
| VDI | Vitamin D insufficiency |
| VDR | Vitamin D receptor |
| WHO | World Health Organisation |

# INTRODUCTION

## INTRODUCTION

Tuberculosis (TB) remains as a major global health problem. Despite extensive tuberculosis-control efforts on the part of the World Health Organization (WHO) and local health departments, the tuberculosis epidemic continues to ravage the developing world, affecting all susceptible individuals. According to 2017 WHO estimates, globally around 10 million people had developed TB in the year. This includes 5.8 million men,3.2 million women and 1 million children's. All countries and age groups have reported TB and are the leading cause of death due to a single causative agent (above HIV/ADIS)[1]

It is a cause for concern as India stands first regarding an absolute number of cases. India has scaled up basic TB services in the public health system, treating more than 19 million TB patients under RNTCP. The rate of TB decline is too slow to meet the 2030 Sustainable Development Goals (SDG) and End TB targets 2035.[2] According to the worldwide TB report 2017 the estimated incidence of TB in India was approximately 28, 00,000 accounting for about a quarter of the world's TB cases.[2] The host susceptibility to TB infection depends on a complex interaction between host, microbial and other factors, such as poverty, malnutrition, overcrowding, and exposure to other pathogens.[3] Vitamin D deficiency (VDD) is one among the various factors that affect TB progression and incidence.[4]

Vitamin D plays a significant role in both development and maintenance of skeleton along with extraskeletal functions like wound healing and regulation of immune response.[5] Exposure to sunlight is the main source of vitamin D for human and induces the conversion of 7-dehydrocholesterol to vitamin D3 via pre-vitamin D3 in the skin.[6] Vitamin D has found to play an important role in the host immune defence against TB by improving the phagocytic capacity of monocytes and macrophages[7, 8], increasing the production of antimicrobial peptides such as

cathelicidin[1], and by immunomodulatory effects.[3] Clinical and epidemiological evidence supports a decreased risk of all-cause mortality (29 %), infectious disease frequency and severity (50–95 %), colorectal cancer (34 %), and cardiovascular disease-related mortality (30 %) with sufficient circulating 25-hydroxyvitamin D (25(OH)D).[9]

Deficiency of vitamin D is common worldwide. India, being a tropical country and majority of the people being exposed to sunlight throughout the year, there was a wrong notion that VDD is uncommon in India.[10] However, extensive data from the literature show that VDD is very common in India.[11] The prevalence of vitamin D deficiency varies between 74% to around 96% among the general healthy Indian population.[12, 13]

Vitamin D deficient individuals have a greater susceptibility to developing TB[14] and worse disease progression if infected with TB.[15, 16] Literature reports that the possible mechanism by which vitamin D prevent the infection of TB bacteria is by binding the 1,25-dihydroxycholecalciferol to the vitamin D receptor (VDR). It is a polymorphic nuclear receptor. It governs the gene expression needed for immune function and in cytokine production.[17-19 20].

Vitamin D supplements promoted anti-mycobacterial activity[21], improved clinical outcomes (improved weight gain and decreased tissue involvement on imaging studies), increased sputum smear and culture conversion [22], reduced inflammation[23], and increased mediators of anti-microbial activity (cathelicidin LL-37[24]and IFN-γ). However, these findings were not essentially primary endpoints in their respective studies or applicable outside of specific subgroups.[20]

Studies have found that 1,25(OH)2D3 binds to vitamin D receptor (VDR), activates VDR signalling and induces a series of antimicrobial responses such as induction of autophagy, phagolysosomal fusion, antimicrobial peptide cathelicidin discharge and activation, and killing

of intracellular Mycobacterium tuberculosis.[6, 25] Various other studies have shown that polymorphisms in the vitamin D receptor influence host susceptibility to TB[26].

Various studies have been undertaken to study the association of vitamin D deficiency with TB; however, they produced inconsistent and varying results.[27-33]. Several meta-analyses on the association between VDD and TB were conducted and concluded that a lower level of vitamin D in serum was related with increased risk of active TB. [4, 34-36]. Variants of the VDR have also been found to affect vitamin D status[37], in addition to susceptibility to TB[20, 38]. The ethnicity- and geography-dependent susceptibility and resistance patterns to TB appear to be linked to the varying prevalence of these polymorphisms in different populations.[20, 39] However there are only very limited studies conducted among Indian population assessing the association of Vitamin D and TB. Hence the present study was undertaken to assess the prevalence of vitamin D deficiency in patients with pulmonary tuberculosis and to compare it with non-tuberculosis cases.

# AIMS & OBJECTIVES

**AIMS AND OBJECTIVES:**

- To estimate the prevalence of vitamin D deficiency in patients with pulmonary tuberculosis and to compare it with non-tuberculosis patients.

# REVIEW OF LITERATURE:

## I. GLOBAL BURDEN OF TUBERCULOSIS:

Tuberculosis is the major cause of death from a single infectious agent[40] According to the global estimates it is reported that around 10 million people were diagnosed with TB in 2017. Of the 5.8 million were men, 3.8 million were women, and 1 million constituted children. This suggests that TB has been recorded across all countries and age group. Whereas, of these, 90% were adults aged greater than or equal to 15 years and 9% were HIV infected people mainly from Africa (72%). Two third of them were reported from 8 countries: - including India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%). According to 2017 estimates, TB alone caused 1.3 million deaths (range, 1.2–1.4 million) and HIV/AIDS and TB together caused 300 000 deaths (range, 266 000–335 000).

EURO and AMRO constituted 3% each. The severity of national epidemics varies widely among countries. In 2017, there were fewer than 10 new TB case per 1 lakh people in most high-income countries, 150–400 in most of the 30 high TB burden countries, and above 500 in a few countries including Mozambique, the Philippines and South Africa.[40] Worldwide, 3.5% of new TB cases and 18% of previously treated cases had MDR/RR-TB. The highest proportions (>50% in previously treated cases) are in countries of the former Soviet Union. Among cases of MDR-TB in 2017, 8.5% (95% confidence interval, 6.2–11%) were estimated to have extensively drug-resistant TB (XDR-TB).[6] About 1.7 billion people, i.e. 23% of the world's population, are estimated to have a latent TB infection and are thus at risk of developing active TB disease during their lifetime.

The disease burden caused by TB is falling globally, in all WHO regions, and most countries, but not fast enough to reach the first (2020) milestones of the End TB Strategy. By 2020, the TB incidence rate should fall by 4–5% per year; case fatality ratio needs to fall to 10%.

Worldwide TB incidence is falling by about 2%. The major contribution was from EURO (5% yearly) and AFRO (4% yearly) between 2013and 2017. Worldwide the TB mortality rate reduced by 29% between 2000 to 2017, i.e., from 1.8 million to 1.3 million. Similarly, among population co-infected with HIV a reduction of 20% was seen since 2000. Among the WHO regions, the fastest reduction was reported from SEARO (11% yearly) and EURO (4% yearly).[40]

**BURDEN OF TUBERCULOSIS IN INDIA:**

The burden of TB in India was re-estimated in 2017. The below mentioned table shows the current statistics of TB and MDR/RR TB incidence, HIV TB Co-morbidity and TB related mortality.

**Table 1: Estimates of TB burden in India and Global.2016**

| Indicator | No. | No/ Lakhs | Global statistics |
|---|---|---|---|
| Incidence of TB (including HIV) | 27,90,000 | 211 | 1,04,00,000 |
| Mortality due to TB (Excluding HIV) | 4,23,000 | 32 | 13,00,000 |
| Incidence of MDRTB/RR | 1,47,000 | 11 | 6,01,000 |
| Incidence of HIV-TB | 87,000 | 6.6 | 10,30,000 |
| Mortality due to HIV-TB co-morbidity | 12,000 | 0.92 | 3,74,000 |

Source: Global Tuberculosis Report 2017

The National Strategic Plan is aiming to achieve the elimination of TB, by 2025. During the plan period, targets for TB are 1. 80% reduction in TB incidence (i.e. reduction from 211 per lakh to 43 per lakh) 2. 90% reduction in TB mortality (i.e. reduction from 32 per lakh to 3 per lakh) 3. 0% patient having catastrophic expenditure due to TB Below table highlights the targets of the

NSP that highlights the four priority areas that include private sector engagement, ensuring a seamless, efficient TB care cascade, active TB case-finding among key population (socially vulnerable and clinically high risk) and preventing progression from latent TB infection (LTBI) to active TB in high risk groups. [2]

**Table 2: NSP 2017-25 Results framework**

| | Baseline | Target | | |
|---|---|---|---|---|
| **IMPACT INDICATORS** | **2015** | **2020** | **2023** | **2025** |
| To reduce estimated TB Incidence rate (per 100,000 population) | 217 (112-355) | 142 (76-255) | 77 (49-185) | 44 (36-158) |
| To reduce estimated TB prevalence (per 100,000 population) | 320 (280-380) | 170 (159-217) | 90 (81-125) | 65 (56-93) |
| To reduce estimated mortality due to TB (per 100,000 population) | 32 (29-35) | 15 (13-16) | 6 (5-7) | 3 (3-4) |
| To ensure no family should suffer catastrophic cost due to TB | 35% | 0% | 0% | 0% |

| | Baseline | Target | | |
|---|---|---|---|---|
| **OUTCOME INDICATORS** | **2015** | **2020** | **2023** | **2025** |
| Total TB patient notification(in millions) | 1.74 | 3.6 | 2.7 | 2 |
| Total patient Private providers notification (in millions) | 0.19 | 2 | 1.5 | 1.2 |
| MDR/RR TB patients notified | 28,096 | 92,000 | 69,000 | 55,000 |
| Proportion of notified TB patients offered DST | 25% | 80% | 98% | 100% |
| Proportion of notified patients initiated on treatment | 90% | 95% | 95% | 95% |
| Treatment success rate among notified DSTB | 75% | 90% | 92% | 92% |
| Treatment success rate among notified DRTB | 46% | 65% | 73% | 75% |
| Proportion of identified targeted key affected population undergoing active case finding | 0% | 100% | 100% | 100% |
| Proportion of notified TB patients receiving financial support through Direct Benefit Transfers (DBT) | 0% | 80% | 90% | 90% |
| Proportion of identified/eligible individuals for preventive therapy / LTBI s - initiated on treatment | 10% | 60% | 90% | 95% |

## PHYSIOLOGICAL ROLE OF VITAMIN D

Vitamin D is a prohormone that has a key role in Ca and $Po_4^{3-}$ haemostasis and bone structure.[9] The term 'Vitamin D' collectively refers to vitamin D3 and D2.[41]

Vitamin D2 and D3 are inactive products and differ only by D2's C22–C23 double bond and C24 methyl. The major source of vitamin D for most humans is exposure to sunlight. Vitamin D3 is produced in animals by UVB photolysis of the C9–C10 bond of provitamin 7-dehydrocholesterol to pre-vitamin D3 (cholecalciferol) followed by double bond rearrangement to vitamin D3.[41]

The biologically active 1,25(OH)2D is obtained through two cycles of hydroxylation; in the liver to 25(OH)D and in the kidney or target tissue to the biologically active 1,25(OH)2D. Different forms of vitamin D circulating free or bound to vitamin D binding protein (DBP) or albumin and cross membranes in the free form, through diffusion, or bound to DBP, mediated by the megalin receptor and cubilin co-receptor. Intracellularly, vitamin D receptor (VDR) transcription factor, orchestrating the expression of hundreds of genes is the receptor for 1,25(OH)2D.[41]

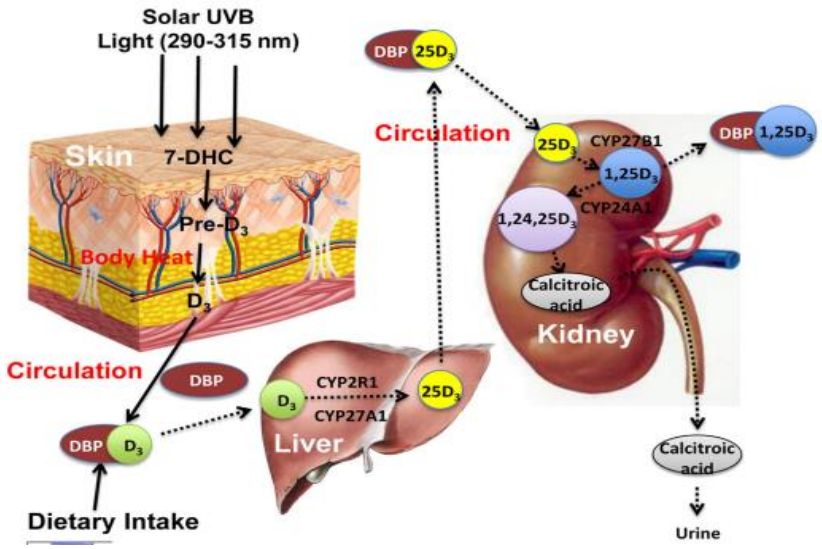

**Figure 1: Photosynthesis and cytochrome P-450 enzyme-dependent metabolism of vitamin D3**[39]

**Mechanism of action**

The mechanism of action of the calcitriol is mediated by the VDR, which belongs to a subfamily of nuclear receptors that act as transcription factors into the target cells after forming a heterodimer with retinoid X receptor (RXR).

Calcitriol upregulates the plasma ionised calcium and phosphate levels by acting on their intestinal absorption, renal excretion, and calcium bone mobilisation as described below (Figure:2)[42]

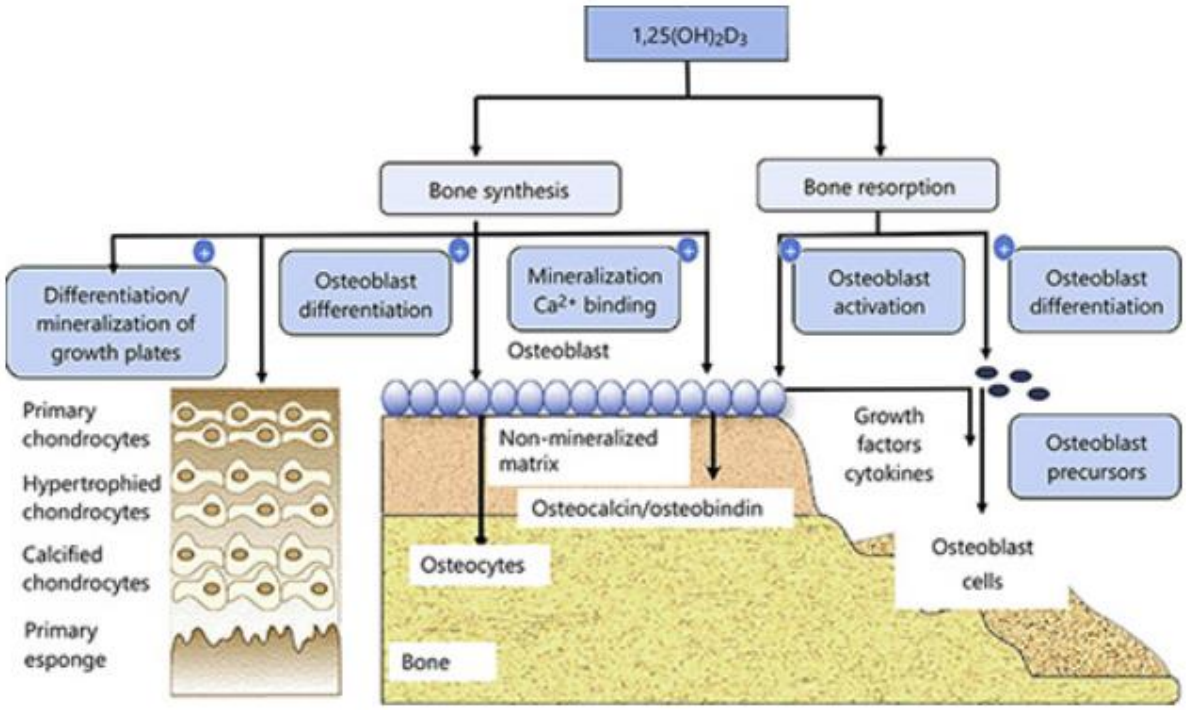


**Figure 2: Vitamin D action on bone metabolism**

$1,25(OH)_2D_3$ has important immunomodulatory actions, namely, the enhancement of the innate immune system and inhibition of the adaptive immune responses. Also, the increased synthesis

of interleukin (IL)-4 by T helper (Th)-2 lymphocytes and the upregulation of regulatory T lymphocytes (T-reg). Vitamin D has also several other actions including xenobiotic detoxification, oxidative stress reduction, neuroprotective functions, antimicrobial defence, immunoregulation, anti-inflammatory/anticancer actions, and cardiovascular benefits. (Figure:3)[42, 43]

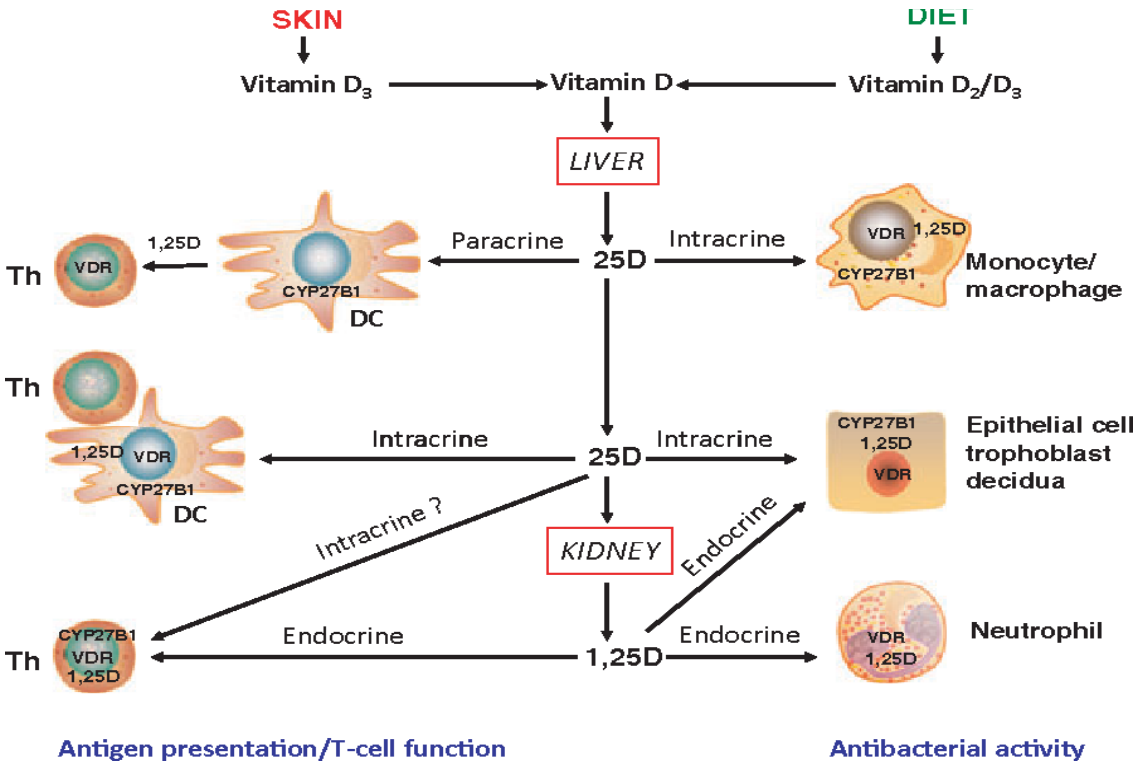


**Figure 3: Vitamin D action on innate and adaptive immunity**

**Assessing vitamin D status**

Vitamin D status is evaluated by determining the prohormone 25(OH) D, which is an indicator of supply rather than function. 25(OH)D is the most stable metabolite of vitamin D and has a half-life of about three weeks, making it the most suitable indicator of vitamin D status. The Institute of Medicine has recently recommended that serum 25(OH)D is adequate when it is higher than 50 nmol/l similar to the recommendation of the Standing Committee of Europe Doctors[44]

**Table 3: Classification of Vitamin D status by 25(OH) D concentration**

| 25(OH)D concentration | Classification |
|---|---|
| ≤10 ng/mL | Deficient |
| 11-20 ng/mL | Insufficient |
| >20 ng/mL | Optimal |

[a] 25(OH)D = 25-hydroxyvitamin D.
[b] To convert from ng/mL to nmol/L, multiply by 2.496.

**Vitamin D deficiency:**

The most under-diagnosed and undertreated nutritional deficiency in the world is vitamin D deficiency, even though it is pandemic.[11, 44] Vitamin D deficiency is widespread in individuals irrespective of their age, gender, race and geography. Avoiding sun exposure, including heavy sunscreen use (sun protection factor [SPF] 8 reduces vitamin D production by 92.5%, and SPF 30 reduces vitamin D production by about 95%), season, latitude, and time of day strongly influence cutaneous vitamin D production. However, vitamin D deficiency is widely prevalent despite plentiful sunshine even in tropical countries like India.[11] Also, increased skin pigmentation reduces the Vit D production due to sun screening action of melanin. Aging is also considered a risk factor because the ability of the skin to produce vitamin D decreases with age (70% reduction of vitamin D in a 70-year-old). Inadequate dietary and supplemental vitamin D intake is another important cause.[11, 45]

**ASSOCIATION BETWEEN VITAMIN D AND TUBERCULOSIS:**

The risk of TB infection is associated with vitamin D.[20] Vitamin D deficiency (serum 25(OH)D level <20 ng/mL or <50 nmol/L) and insufficiency (serum 25(OH)D level <30 ng/mL or <75 nmol/L) results in increased susceptibility to vitamin D.[39] Higher doses of vitamin D were commonly given to patients with tuberculosis before the invention of antibiotics.[9]

The hypothesis that VDR variants might associate with susceptibility to active TB was first investigated by Bellamy et al[46]; Human VDR is encoded by the VDR gene located on chromosome 12q. This gene is polymorphic[47]. Wilkinson et al[30] subsequently reported that associations between susceptibility to TB and VDR polymorphism were restricted to vitamin D-deficient individuals

**PATHOPHYSIOLOGICAL BASIS:**

Vitamin D deficient individuals have a greater susceptibility to developing TB[14] and worse disease progression if infected with tuberculosis. 1,25-dihydroxycholecalciferol binds to the VDR receptor. This VDR receptor residing in immune cells, bronchial and pulmonary epithelial cells function by controlling the expression of gene-regulating immune function and cytokine production. 1,25-dihydroxycholecalciferol modulates immune responses by ligating membrane VDR to induce rapid effects (within minutes) or nuclear VDR to induce genomic effects (within hours). Experiments using selective agonists and antagonists of these two receptors indicate that ligation of nuclear VDR is both necessary and sufficient for induction of antimycobacterial responses by 1,25(OH)2D in vitro. 1,25(OH)2D modulates the host response to mycobacterial infection by pleiotropic mechanisms including the induction of reactive nitrogen and oxygen intermediates, down-regulation of the gene encoding tryptophan-aspartate containing coat protein, promotion of phagolysosome fusion, suppression of matrix metalloproteinase enzymes implicated in the pathogenesis of pulmonary cavitation and induction of antimicrobial peptides including cathelicidin LL-37 and human b-defensin. Cathelicidin LL-37 possesses antimycobacterial activity and also induces autophagy(20,21); 1,25(OH)2D3-induced antimycobacterial activity has been reported to be dependent on expression of the gene encoding cathelicidin LL-37.][47]They suppresses matrix metalloproteinase enzymes that degrade the

pulmonary extracellular matrix. Orally ingested vitamin D is freely converted to 25(OH)D, and this provides the rationale for administering 'parent' vitamin D to induce antimycobacterial responses at the site of disease

vitamin D stimulates macrophage-mediated killing of M tuberculosis through the innate immune system. Vitamin D itself induces mechanisms for inactivation of vitamin D and vitamin D-mediated innate immune responses and inflammation. Regarding the adaptive immune response, vitamin D suppresses T helper type 1 cellular responses crucial in host defence against tuberculosis, promoting a T helper type 2 predominance associated with immunological tolerance, humoral immunity, and defence against viral infections.][48]

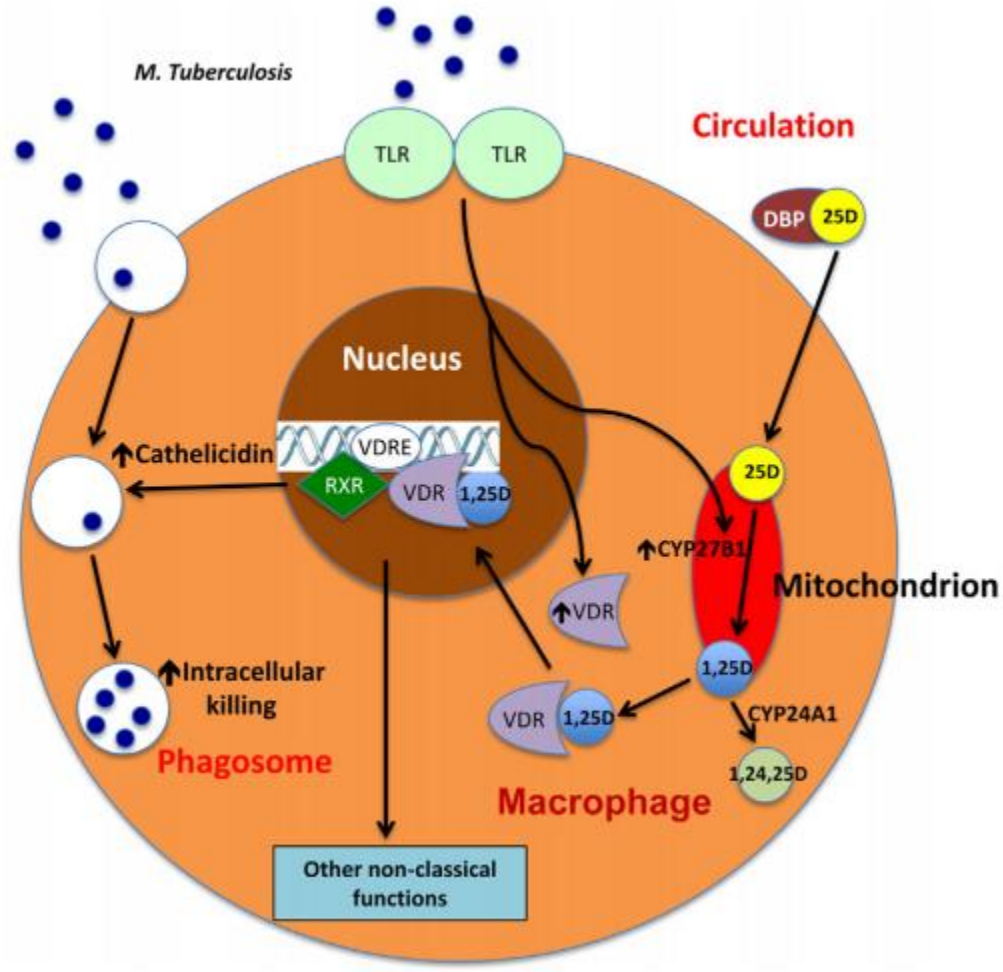

**Figure 4: Vitamin d mediated activation of innate immune system in the macrophages.** [39]

A study by Kim JH et al. [27] in 2014 evaluated the association between VDDand TB, regardless of other nutritional factors. Baseline serum 25-hydroxyvitamin D (25(OH)D3) levels in TB patients were measured before treatment and one year after treatment onset using liquid chromatography-tandem mass spectrometry. In total, 165 active pulmonary TB patients and 197 age-matched controls constituted study population. Significantly higher prevalence of 25(OH)D3 insufficiency (<20 ng/mL) and deficiency (<10 ng/mL) in TB patients was showed compared to controls. Serum 25(OH)D3 levels and nutritional parameters were significantly lower in untreated TB patients than in controls. One year after TB treatment onset, nutritional parameters significantly increased; however, serum 25(OH)D3 levels in TB patients did not improve significantly compared to baseline. The study finding was that low serum 25(OH)D3 level might be a risk factor for TB, independent of nutritional status.

A study by Workineh M et al[3] in 2017 to determine the prevalence and associated factors of vitamin D deficiency in newly diagnosed tuberculosis patients, household contacts and community controls in Gondar, Ethiopia. The study design was a comparative cross-sectional. Serum 25(OH)-vitamin $D_3$ was determined by an ELISA. A serum level of 25(OH)-vitamin $D_3$ below < 50 nmol/L was defined as vitamin D deficiency and <25 nmol/L as severe VDD. One twenty six newly diagnosed smear-positive TB patients, 57 household contacts and 70 apparently community controls were included in the study. The mean ± SD age (years) of TB patients, household contacts and community controls were $29.8 \pm 11.9$, $24.3 \pm 14.7$ and $27.3 \pm 7.6$ respectively. The mean 25(OH)-vitamin $D_3$level of TB patients ($30.1 \pm 19.3$ nmol/L) was significantly lower than community controls ($38.5 \pm 20.9$ nmol/L, $P = 0.005$ and household contacts ($37.7 \pm 12.8$ nmol/L, $P$ =0.031).). The prevalence of vitamin D deficiency was higher in

TB patients (83.3%) than in community controls (67.1%) and household contacts (80.7%). Severe vitamin D deficiency reported in 30% (21/70), 19.3%(11/57) of TB patients, community controls and household contacts respectively. Low BMI (AOR = 2.13; 95%CI: 1.02, 3.28) and being positive for tuberculosis (AOR = 1.93; 95%CI: 1.06, 2.86) were significant predictors of severe vitamin D deficiency. The study confirms the finding of VDD in newly diagnosed TB patients.

Arnedo-Pena, A et al[49] conducted a study from 2009 to 2012 to evaluate serum baseline 25-hydroxyvitamin D (vitamin D) status and the incidence of tuberculosis (TB) among 572 contacts of 89 pulmonary TB patients in Castellon, Spain. Three new cases of pulmonary TB occurred, with an incidence density of 3.6 per 1000 person-years. Mean vitamin D status was 13.7 ng/ml for cases and 25.7 ng/ml for non-cases. Vitamin D status showed a significant inverse association with TB incidence (adjusted HR 0.88, 95%CI 0.80-0.97).

Arnedo-Pena, A et al[50] in 2015 estimated the relationship between serum vitamin D (VitD) status and tuberculosis (TB) infection conversion (TBIC), measured by the tuberculin skin test (TST) and an interferon-gamma release assay, the QuantiFERON-TB Gold In-Tube (QFT-GIT) test, in the contacts of pulmonary TB patients in Castellon (Spain) in a prospective cohort study from 2010 to 2012. Initially, the participants were negative to latent TB infection after a screening that included TST and QFT-GIT tests, and other examinations. A baseline determination of 25-hydroxyvitamin D [25(OH)D] was obtained by chemiluminescence immunoassay. After 8-10 weeks, participants were screened for a second time to determine TB infection conversion. Of the 247 participants in the cohort, 198 (80·2%) were screened twice, and 18 (9·1%) were TBIC cases. The means of Vitamin D concentration in the TBIC cases and the non-cases were 20·7±11·9 and 27·2±11·4 ng/ml (P = 0·028), respectively. Adjusted for high exposure and TB

sputum acid-fast bacilli (AFB)-positive index case, higher serum Vitamin D concentration was associated with low incidence of TBIC (P trend = 0·005), and an increase of 1 ng/ml Vitamin D concentration decreased the incidence of TBIC by 6% (relative risk 0·94, 95% confidence interval 0·90-0·99, P = 0·015). The results suggest that sufficient Vitamin D level could be a protective factor of TBIC.

Neilson O N et al[51] assessed the association between vitamin D status and TB to assess the feasibility of vitamin D supplementation in Greenland. This was examined in a case-control study involving seventy-two matched pairs of TB patients (cases) and controls aged 8–74 years. Cases were diagnosed with TB during 2004–6 based on clinical findings in combination with either (1) positive *Mycobacterium tuberculosis* culture, (2) characteristic X-ray abnormalities together with a positive tuberculin skin test or a positive interferon-γ release assay or (3) characteristic histology. Controls were individually matched on age ( ± 5 years), sex and district. Serum 25-hydroxyvitamin D (25(OH)D) concentrations were measured, and OR of TB was the outcome. Compared with individuals with 25(OH)D concentrations between 75 and 140 nmol/l, individuals with concentrations < 75 nmol/l (OR 6·5; 95 % CI 1·8, 23·5) or>140 nmol/l (OR 6·5; 95 % CI 1·9, 22·2) had higher risks of active TB (*P* = 0·003; adjustment for alcohol and ethnicity). Supplementing individuals with low vitamin D to normalise serum 25(OH)D concentrations was estimated to result in a 29 % reduction. The study indicated that vitamin D supplementation may be beneficial to individuals with insufficient vitamin D concentrations but may increase the risk of TB among individuals with normal or high

Hong JY et al[52] compared vitamin D deficiency between patients with tuberculosis (TB) and healthy control subjects and identified risk factors for vitamin D deficiency. This was age- and sex-matched case-control analysis of 94 TB cohort and 282 Korean national survey participants.

The median baseline 25-hydroxyvitamin D (25[OH]D) level in the TB group (9.86 ng/ml, IQR 7.19-14.15) was lower than in controls (16.03 ng/ml, IQR 12.38-20.30, P < 0.001). 51.1% of the TB patients were found to be with vitamin D deficiency compared to controls (8.2%, P = 0.001). The median 25(OH)D level increased from 11.40 ng/ml (IQR 7.85-15.73) to 13.18 ng/ml (IQR 10.60-19.71) after treatment completion (P = 0.037). On multivariate analysis, the presence of TB and severe vitamin D deficiency are independently associated. The median 25(OH)D level increased after TB treatment. Increased prevalence of tuberculosis was found among patients with VDD.

To determine the frequency and association of Vitamin D deficiency in patients with tuberculosis a case control study was conducted by Ifthikar R et al[53] in 2013 at Medical Department, Combined Military Hospital, Kharian, from July 2010 to June 2012. One hundred and five outdoor patients of tuberculosis were selected with 255 gender-matched controls. Acid-fast bacilli in sputum smears, positive culture for Mycobacterium tuberculosis or demonstration of chronic caseating granulomatous inflammation in tissue specimens were assessed for TB diagnosis. Controls were drawn randomly from the general population. Serum 25 hydroxyvitamin D [25 (OH) D3] levels < 25 ng/ml was considered Vitamin D deficiency. The results were analysed on SPSS version 17. Mean Vitamin D levels were 23.23 ± 6.81 ng/ml in cases, 29.27 ± 8.89 ng/ml in controls (p < 0.0001). VDD in 57% of cases and 33% controls (p < 0.0001). Mean BMI in patients of tuberculosis with Vitamin D deficiency were 19.51 ± 1.77 kg/m2 and in patients with normal Vitamin D were 21.65 ± 1.79 kg/m2 (p < 0.0001). Mean Vitamin D levels in patients with multi-drug resistant tuberculosis was lower to a mean of 15.41 ± 4.67 ng/ml (p < 0.0001). A significant deficiency of Vitamin D was observed

in patients with tuberculosis as compared to controls. This deficiency is more pronounced in females, individuals with low BMI, extrapulmonary and MDR tuberculosis.

Wejse C et al[31] in 2013 compared the degree of vitamin D insufficiency (VDI) and VDD in TB patients and healthy adult controls in a West African population at a Demographic Surveillance Site in Guinea-Bissau. Serum 25-hydroxyvitamin D(3) [25(OH)D(3)] concentrations were measured in 362 TB patients and 494 controls. Hypovitaminosis D [25(OH)D(3) </= 75 nmol/L] was more common in TB patients, but VDD [25(OH)D(3) </= 50 nmol/L] was more common and more severe in controls. They observed hypovitaminosis D in 46% (167/362) of the TB patients and 39% (193/494) of the controls; the relative risk (RR) of hypovitaminosis D was 1.18 (95% CI: 1.01, 1.38). Vitamin D deficiency reported in 31/362 of the TB patients and 13.2% (65/494) of the controls. They found that even after adjusting confounding factors vitamin D deficiency was more prevalent in patients with TB.

Ralph AP et al[54] in 2017 investigated determinants of 25D and its immunologically active form, 1,25-dihydroxy vitamin D (1,25D), their inter-relationship in tuberculosis, longitudinal changes and association with outcome in a prospective observational study of adults with smear-positive pulmonary tuberculosis in Sabah, Malaysia, they measured serial 25D, 1,25D, vitamin D-binding protein (VDBP), albumin, calcium, parathyroid hormone, chest x-ray, week 8 sputum smear/culture and end-of-treatment outcome. 1,25D was elevated in 172 adults with tuberculosis (mean 229.0 pmol/L, 95% confidence interval: 215.4 - 242.6) compared with 95 controls (153.9, 138.4-169.4, $p < 0.001$), directly proportional to radiological severity ($p < 0.001$), and fell rapidly within one week of treatment commencement. Tuberculosis patients with higher baseline 1,25D achieved significantly higher percentage weight gain over time, including when controlling for baseline weight, however persistently elevated 1,25D was associated with worse residual x-ray

changes and lower end-of-treatment BMI. 1,25D was inversely associated with PTH ($p < 0.001$), consistent with the extra-renal origin of the 1,25D. 25D did not differ between tuberculosis patients (mean 63.9 nmol/L, 95% CI: 60.6 - 67.3) and controls (61.3, 57.2- 65.3, $p = 0.24$), and was unassociated with outcomes. Among tuberculosis patients in multivariable analyses, sex, age and VDBP were associated with 25D, and age and albumin with 1,25D. 1,25-dihydroxyvitamin was not significantly associated with 25D. Vitamin D deficiency <25 nmol/L was uncommon, occurring in only five TB patients; 1,25D was elevated in three of them. In an equatorial setting, high extra-renal production of 1,25D was seen in tuberculosis, including in individuals with 25D in the deficient range; however, the severe 25D deficiency was uncommon. Baseline elevation of 1,25D, a marker of macrophage activation, was associated with better weight gain but the persistent elevation of 1,25D was associated with worse radiological and BMI outcomes.

A study was conducted by Talat N et al[14] in 2010 to assess the association between vitamin D deficiency and tuberculosis disease progression. They studied vitamin D levels in a cohort of tuberculosis patients and their contacts (N = 129) in Pakistan. Household contacts (n = 109) of 20 patients with recently diagnosed sputum-positive pulmonary TB (index case-patients) were enrolled. Visiting health workers reviewed clinical charts and at a final home study visit. Most (79%) persons showed a deficiency. Median level of vitamin D was 9.1 ng/mL (interquartile range [IQR] 5.3–14.7); levels were 9.6 ng/mL (IQR 5.8–19.1) for 100 disease-free contacts, 7.9 ng/mL (IQR 4.7–10.3) for 20 TB index case-patients, 4.6 ng/mL (IQR 4.0–5.2) for 2 co-prevalent TB case-patients who were receiving antituberculous treatment at recruitment, and 5.1 ng/mL (IQR 3.4–14.3) in 6 household contacts with a history of TB treatment (2–10 years). In the 100 disease-free household contacts, Vit D was higher than in the 28 participants with a history of TB diagnosis at baseline (p = 0.02; Mann-Whitney U test). And it was significantly

lower in the 74 female patients than in the 54 male patients (7.8 vs 11.9, Mann-Whitney U test, p = 0.0004). When they stratified the cohort by vitamin D level, 79% had deficient (<20 ng/mL), 14% had insufficient (20–30 ng/mL), and 7% had sufficient (>30 ng/mL) levels of vitamin D. (75%) of 8 patients whose TB progressed were females.

Pham HO et al[55] designed aa matched case-control study, which involved 166 TB patients (113 men and 53 women), who were age-and-sex matched with 219 controls (113 men and 106 women). 25-hydroxyvitamin D [25(OH)D] and PTH were measured before treatment by an electrochemiluminescence immunoassay (ECLIA) on a Roche Elecsys. A serum level of 25(OH)D below 30 ng/mL was deemed to be vitamin D insufficient. The prevalence of vitamin D insufficiency was 35.4% in men with TB and 19.5% in controls ($P$ = 0.01). In women no differences in serum 25(OH)D and serum PTH levels between TB patients and controls. The prevalence of vitamin D insufficiency in women with TB (45.3%) was not significantly different from those without TB (47.6%; $P$ = 0.91). However, in both genders, serum calcium levels in TB patients were significantly lower than in non-TB individuals. Smoking (odds ratio [OR] 1.25; 95% confidence interval [CI] 1.10 - 14.7), reduced 25(OH)D (OR per standard deviation [SD]: 1.14; 95% CI 1.07 - 10.7) and increased PTH (OR per SD 1.13; 95% CI 1.05 - 10.4) was also associated.

Ustianowski A et al[32] determined the incidence and associations of vitamin D deficiency in TB patients diagnosed at an infectious diseases unit in London, UK. Case-note analysis of 210 unselected patients diagnosed with TB who had plasma vitamin D (25(OH)D3) levels routinely measured. Prevalence of 25(OH)D3 deficiency and its relationship to ethnic origin, religion, site of TB, sex, age, duration in the UK, month of 25(OH)D3 estimation and TB diagnosis were determined. Of 210 patients 76% were 25(OH)D3 deficient, and 56% had undetectable levels.

70/82 Indian, 24/28 East African Asian, 29/34 Somali, 14/19 Pakistani and Afghani, 16/22 Sri Lankan and 2/6 other African patients were deficient (with 58, 17, 23, 9, 6 and 1 having undetectable levels, respectively). Only 0/6 white Europeans and 1/8 Chinese/South East Asians had low plasma 25(OH)D3 levels. Association between 25(OH)D3 level and site of TB or duration of residence in the UK was not associated. There was no apparent seasonal variation in either TB diagnosis or 25(OH)D3 level. The authors concluded that 25(OH)D3 deficiency commonly associates with TB among all ethnic groups apart from white Europeans, and Chinese/South East Asians.

A cross-sectional study was conducted by Friis H et al[33] in 2008 among pulmonary tuberculosis (PTB) patients in Mwanza, Tanzania to identify the predictors of their vitamin D status. Data on socio-demography, season, and intake of food, alcohol, tobacco, and soil were collected, anthropometric measurements are taken, and serum alpha(1)-antichymotrypsin (ACT), ferritin and soluble transferrin receptor (sTfR), and serum 25-hydroxy-(ergocalciferol+cholecalciferol) [25(OH)D] determined. Of the 655 patients studied, 79.7% (508/637) were culture-positive (PTB+) and 47.2% HIV infected. Mean serum ACT, an acute phase reactant, was 0.73 +/- 0.25 g/L with 69.2% >0.6 g/L. Mean serum 25(OH)D was 86.6 +/- 32.9 nmol/L, with 41.2% <75 nmol/L. Serum 25(OH)D was highest during the harvest season, May to July, compared with the remaining year. Single subjects had lower [10.4 (95% CI 4.0; 16.9) nmol/L] serum 25(OH)D concentrations than married subjects and PTB+ patients had concentrations lower [8.2 (95% CI 1.5; 14.9) nmol/L] than PTB- patients. Serum 25(OH)D increased with consumption of a large freshwater fish but not of small dried fish or other foods. BMI and serum TfR were positive predictors of serum 25(OH)D, whereas neither elevated serum ACT nor HIV were predictors. In conclusion, serum 25(OH)D is a valid measure of vitamin D status during the acute phase

response. The lower concentrations in PTB+ patients may reflect lower sun exposure or increased utilisation.

Memon A et al[56] evaluated Vitamin D in Pulmonary tuberculosis and normal healthy adults. A sample of 209 diagnosed pulmonary tuberculosis patients were selected through non-probability purposive sampling according to inclusion and exclusion criteria. After taking informed written consent from the participants, Vitamin D was measured by I 1000 system for estimation of 25-OH- D3. The significant p-value was taken at $\leq 0.05$. The mean ±S.D serum level of 25-hydroxyvitamin D3 in cases and controls were 27.1±9.7 and 36.8±8.1 (ngdl-1 ) respectively (p=0.0001). The 25-hydroxyvitamin D3 levels as low as 6 ng/dl were observed in pulmonary tuberculosis subjects. The normal, insufficiency and deficiency of 25-hydroxyvitamin D3 were observed in 37(33%), 16 (14.2%) and 59 (52.6%) in cases respectively compared to controls as 57 (58.7%), 21(21.6%) and 19 (19.5%) respectively. Patients with pulmonary tuberculosis are significantly Vitamin D deficient. Vitamin D supplements may be prescribed, however further studies are warranted.

**Indian Studies**

A study by Agarwal A et al[57] in 2017 investigated serial serum 25 hydroxyvitamin D concentrations in children suffering from osteoarticular tuberculosis treated with multidrug antitubercular drugs to assess whether altered vitamin D levels observed with osteoarticular tuberculosis change during treatment in a child or modify the disease course. The prospective study enrolled 19 untreated immunocompetent children with an established diagnosis of osteoarticular tuberculosis. None of the patients was offered any therapeutic vitamin D supplementation at initiation or during the treatment. The patients were followed for response to

multidrug antitubercular therapy (DOTS) at 2 months interval. Mean values of vitamin D were calculated at 0, 2, and 6 months and statistically compared. The following laboratory references for defining the vitamin D status were used: 75 nmol/L = sufficiency. All the patients responded to antitubercular therapy. Out of the enrolled children, 73.67% had low vitamin D levels at initial presentation. There was no statistically significant difference in vitamin D levels in affected children at either 0–2 ( p = 0.452), 2–6 ( p = 0.240), or 0–6 months ( p = 0.854) following antitubercular treatment. Although the mean vitamin D levels were higher in male patients when compared to female patients at all times, there was no statistically significant difference in vitamin D levels during treatment stages in either sex. The author concluded that vitamin D levels were low at the initiation of treatment and could not improve during multidrug antitubercular treatment.

Panwar A et al[58] evaluated serum vitamin D, and VDR and TLR-2 gene polymorphisms in patients with spinal tuberculosis. The study comprised of 3 groups: spinal tuberculosis, pulmonary tuberculosis, and controls (each with 106 subjects). Patients with spinal tuberculosis (P < 0.001) showed a higher prevalence of vitamin Dand pulmonary tuberculosis (P ¼ 0.011), versus controls. The heterozygous and mutant genotypes of VDR TaqI gene with spinal tuberculosis was associated (P < 0.001; odds ratio [OR] 4.74 [2.45–9.18]) and pulmonary tuberculosis (P < 0.001; OR 3.52 [1.80–6.88]) when compared with controls. The heterozygous and mutant variants of VDR ApaI gene were significantly more common in patients with spinal tuberculosis in comparison with patients with pulmonary tuberculosis (P < 0.001; OR 2.90 [1.65–5.10]) and controls (P < 0.001; OR 6.56 [3.41–12.61]). VDD and VDR gene polymorphisms are significantly more prevalent in people with pulmonary and spinal

tuberculosis. They may, in isolation or collectively, confer susceptibility to pulmonary and spinal tuberculosis.

Afzal A et al[59] conducted a study to determine the efficacy of Vitamin D supplementation in achieving an early sputum conversion in vitamin D deficient smear-positive pulmonary tuberculosis patients. This randomised clinical trial was done at Mayo hospital Lahore from November 2015 to August 2016. 120 patients with sputum smear-positive pulmonary tuberculosis were selected and randomised to Group-A (taking anti-tuberculous therapy (ATT) only) and Group-B (taking ATT with Vitamin D supplementation). Four doses of 100,000 IU of Vitamin D injection intramuscularly were given after every 14 days during intensive-phase. Sputum examination was repeated at $2^{nd}$, $4^{th}$, $6^{th}$, $8^{th}$, $10^{th}$ and $12^{th}$ weeks. There were 63 (52.50%) males and 57 (47.50%) females. The mean serum Vitamin D was 17.07±1.44 in Group-A and 17.23±2.37 in Group-B at baseline, and 12th week, the levels were 21.77±2.23 in Group-A and 29.24±0.72 in Group-B. In Group-A, 7 (11.7%) patients showed positive sputum examination, and in Group-B, only one (1.7%) patient had positive sputum examination at $12^{th}$ week. The difference was statistically significant (p-value= 0.028). They concluded that four doses of intramuscular vitamin D given after every 14 days corrected vitamin D deficiency and improved the rate of sputum smear conversion in patients of pulmonary tuberculosis.

Kandelwal D et al[60] in 2014 determined the baseline 25-hydroxy vitamin D levels in children suffering from intrathoracic tuberculosis and its association with type and outcome of tuberculosis. Two hundred sixty-six children (mean age of 106.9 ± 43.7 months; 57.1% girls) were enrolled. Chest X-ray was suggestive of primary pulmonary complex, progressive disease and pleural effusion in 81 (30.5%), 149 (56%) and 36 (13.5%) subjects, respectively. Median

serum 25-hydroxyvitamin D level was eight ng/ml (IQR 5, 12). One hundred and eighty six (69.9%) children were vitamin D deficient (serum 25-hydroxyvitamin D <12 ng/ml), 55 (20.7%) were insufficient (12 to <20 ng/ml) and 25 (9.4%) were vitamin D sufficient (≥ 20 ng/ml). Levels of 25-hydroxyvitamin D were similar in all three types of intrathoracic tuberculosis and microbiologically confirmed and probable cases. Levels of 25-hydroxyvitamin D did not significantly affect the outcome of the disease. Children who were deficient or insufficient were less likely to convert (become smear/culture negative) at two months as compared to those who were 25-hydroxyvitamin D sufficient ($P$<0.05). The authours concluded that the majority of Indian children with newly diagnosed intrathoracic tuberculosis were deficient in vitamin D. Type of disease or outcome was not affected by 25-hydroxy vitamin D levels in these children. However, children without sputum conversion after antitubercular therapy had lower baseline 25-hydroxy vitamin D levels as compared to those who did.

Joshi L et al[61] examined the serum 25(OH) vitamin D levels and its receptor (VDR) polymorphisms with susceptibility to tuberculosis in patients, household contacts and healthy controls. Serum 25(OH) vitamin D levels were measured in 75 cases (25 patients, 25 household contacts and 25 healthy controls), and polymorphisms (BsmI and FokI) were carried out in 335 cases (110 patients, 110 household contacts and 115 healthy controls). The proportion of serum 25(OH) vitamin D deficiency and insufficiency were high in patients (44, 58%) and household contacts (40, 48%) compared to controls (48%). The BB and Bb genotypes of BsmI were significantly associated in patients (P < 0.014; OR: 0.509; CI: 0.265-0.876) (P < 0.001; OR: 2.351; CI: 1.368-4.041) and household contacts (P < 0.04; OR: 0.575; CI: 0.336-0.985); (P < 0.002; OR: -2.267; CI: 1.32-3.895) when compared to healthy controls. diplotype and MDR

analysis showed the high-risk genotypes of BsmI and FokI polymorphisms. VDR gene polymorphisms may be useful to identify the high-risk group individuals.

A case-control study was conducted by Tessema B et al[62] in 2017 among TB patients and healthy controls. VDD reported among one thirty-four individuals. Results showed a significantly higher vitamin D deficiency among tuberculosis cases ($p < 0.001$), females ($p = 0.002$), and urban residents ($p < 0.001$) than their respective comparison groups. Moreover, age groups of 35–44 ($p = 0.001$), 45–54 ($p = 0.003$) and ≥55 ($p = 0.001$) years had significantly higher vitamin D deficiency compared with age group <15 years. The authors concluded that study participants with tuberculosis have a significantly higher prevalence of vitamin D deficiency.

Yuvaraj et al[13] conducted a study to assess the alterations in serum 25-hydroxyvitamin D levels in newly diagnosed sputum acid-fast bacilli (AFB) positive pulmonary tuberculosis patients and to study the association, if any, between serum vitamin D levels and different levels of sputum smear positivity. Serum 25-hydroxyvitamin D levels were estimated in 65 TB cases and 65 age and gender-matched healthy controls. The levels of serum 25 hydroxy-vitamin D in tuberculosis patients were not statistically different from the levels of serum 25 hydroxy-vitamin D in healthy controls. However, among patients with pulmonary tuberculosis, there was a significant negative correlation between the levels of serum 25 hydroxy-vitamin D and levels of sputum positivity. Serum vitamin D levels negatively correlate with bacterial load in patients with active pulmonary tuberculosis.

Sashidharan PK et al[63] conducted a study to find out the normal level of 25 hydroxyvitamin D in healthy individuals b) To look for evidence of vitamin D deficiency in patients with active

tuberculosis. There were 35 cases of pulmonary and extra-pulmonary tuberculosis and 16 controls, whose clinical characteristics, dietary intake of vitamin D and biochemical characteristics including serum vitamin D levels were assessed. A significant difference ($p < 0.005$) in mean vitamin D levels between controls (19.5 ng/ml) and study subjects (10.7 ng/ml). Sixteen patients out of 35 had values well below the lower limit of normal (9 ng/ml). Sunlight exposure was adequate in those with deficiency, but there was reduced dietary intake of vitamin D. Vitamin D deficiency exists in patients with tuberculosis, and it is possibly a cause rather than the effect of the disease; deficiency is due to decreased dietary intake. Vitamin D deficiency can occur without any symptoms. If symptoms are present, it indicates severe deficiency.

Rajkumar V et al[64] assessed the serum vitamin D levels among patients with pulmonary tuberculosis and its association with the severity of the disease. A total of 300 patients with pulmonary tuberculosis confirmed by sputum AFB were included in the study. Vitamin D levels were found to be normal in 34% of the subjects, and it was insufficient in 11% and found to be a deficit in fifty-five per cent. Multi-logistic regression analysis was applied to identify the factors influencing deficiency of vitamin D among patients with tuberculosis among males and females. It was proved that age more than 30 years, female gender, sputum results showing 1+ or more, BMI found to have a statistically significant association with a reduction in the vitamin D levels among patients with tuberculosis.

**MOST RELEVANT SYSTEMATIC REVIEWS/META-ANALYSIS:**

A systemic review and meta-analysis were reported by Junli Zeng et al[36] in 2015 to identify the association between tuberculosis and serum Vitamin D levels via synthesis of available evidence. A search of EMBASE, Medline, ISI Web of knowledge, and Pubmed was conducted. The

number of subjects of tuberculosis and no-tuberculosis groups in four Vitamin D range. Meta-analyses were performed and presented by odds ratios (ORs) and corresponding 95% confidence intervals (CIs). A total of 15 studies involving 1440 cases and 2558 controls were included. No statistically significant risk of tuberculosis was found in the range of 26–50 nmol/L (pooled OR = 1.561, 95% CI =0.997-2.442). In range 51–75 nmol/L, no positive association was found (pooled OR =1.160, 95% CI = 0.708-1.900). This study concluded that serum Vitamin D level ≤ 25 nmol/L was related with an increased risk of tuberculosis while the range of 51–75 nmol/L. The range 26-50nmol/L posed potential high tuberculosis risk. The study has recommended for future large-scale, well-designed studies to verify these results.

Wang J et al. in 2018[35] conducted a systematic review and meta-analysis to evaluate the efficacy and safety of vitamin D in patients with pulmonary TB. Medline, SCOPUS, Google Scholar, EMBASE, Springer, and Science Direct were searched electronically from inception to Oct 2016. Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) assessing the effect of vitamin D plus anti-tuberculosis treatment (ATT) versus placebo plus ATT on the treatment of pulmonary TB were included. Two investigators independently searched articles, extracted data, and assessed the quality of included studies. Data were analysed using RevMan 5.3 software. Overall, compared with placebo intervention, vitamin D supplementation was found to have no significant effect on sputum smear-negative conversion rates (RR=0.99; 95% CI=0.91 to 1.07; P=0.77), BMI (MD=0.11; 95% CI=-0.85 to 1.07; P=0.82) and ESR (MD=-2.29; 95% CI=-8.87 to 4.30; P=0.50). This meta-analysis concluded that vitamin D supplementation showed no influence on the improvement of sputum smear-negative conversion rates and BMI, as well as the decrease in ESR.

Facchini et al[65] conducted a systematic review in 2015 to critically summarise the available data on the correlation between vitamin D level and tuberculosis (TB) infection. A literature search covering English language articles published up to 20 October 2014 was conducted in MEDLINE database. Three hundred ninety-seven articles were initially identified, of which 147 studies were initially selected, and other 13 pertinent studies were included. The systematic review concluded that a significant association between low vitamin D levels and susceptibility to TB infection exists.

A systematic review and meta-analysis conducted by Gao L et al[34] in 2010 assessed whether Host genetic susceptibility plays any role for inter-individual differences in tuberculosis (TB) risk. The vitamin D receptor (VDR) gene has been studied as a candidate locus due to genetic polymorphisms that affect the activity of the receptor and subsequent downstream vitamin D-mediated effects. They reviewed published studies on VDR polymorphisms and TB susceptibility up to 15 April 2009 and quantitatively summarised associations of the most widely studied polymorphisms (FokI, TaqI, ApaI and BsmI) using meta-analysis. This meta-analysis assessing the association of VDR polymorphisms with risk of TB observed in our analyses supports the hypothesis that vitamin D deficiency might play a role as a risk factor for TB.

A systematic review and meta-analysis were conducted by Nnoaham KE et al[16] in 2008 to explore the association between low serum vitamin D and the risk of active tuberculosis in humans. Observational studies published between 1980 and July 2006 (identified through Medline) that examined the association between low serum vitamin D and risk of active tuberculosis. For the review, seven papers were eligible from 151 identified in the search. The pooled effect size in random effects meta-analysis was 0.68 with 95% CI 0.43-0.93. This 'medium to large' effect represents a probability of 70% that a healthy individual would have

higher serum vitamin D level than an individual with tuberculosis if both were chosen at random from a population. There was little heterogeneity between the studies. The authors concluded that although more prospectively designed studies are needed to firmly establish the direction of this association, it is more likely that VDD increase the risk of active tuberculosis.

Gou X et al[66] conducted a meta-analysis to explore the association between vitamin D status and TB in children. Web of Science, Ovid Medline, and EMBASE were searched for studies in English that discussed vitamin D status and TB in children before January 22, 2018. From the 585 initially identified studies, we selected those that addressed an association between vitamin D status and TB according to our preselected inclusion criteria. Our meta-analysis included 10. TB was significantly associated with VDD (ORs, 1.70; 95% CI, 1.20-2.42; P<.05) in children. VDD was more prevalent in TB patients, d=-5.49nmol/L (95% CI, -10.42 to -0.55; P<.05), indicating that VDD was significantly associated with TB (OR, 1.78; 95% CI, 1.30-2.44; P<.05) in children. TB may contribute to VDD in children. Therefore, VDD may be associated with TB in children.

Huang S et al[4] in 2017 undertook a systematic review to find the association between vitamin D and tuberculosis (TB). PubMed and Web of Knowledge were searched for all properly controlled studies on vitamin D and TB. Pooled odds ratio, mean difference or standardised mean difference, and its corresponding 95% confidence interval was calculated with the Cochrane Review Manager 5.3. A significantly lower vitamin D level was found in TB patient's vs controls; vitamin D deficiency (VDD) results in high TB incidence, although such an association was lacking in the African population and the human immunodeficiency virus-infected African population. A significantly lower vitamin D level was found in human immunodeficiency virus-TB-coinfected African patients receiving antiretroviral treatment who developed TB-associated

immune reconstitution inflammatory syndrome vs those who did not develop TB-associated immune reconstitution inflammatory. The trend toward a lower vitamin D level in active TB patients vs latent TB infection subjects did not reach statistical significance, indicating that VDD was more likely a risk factor than a consequence of TB. These findings were confirmed with our study results that anti-TB treatment did not affect vitamin D level in TB patients receiving the treatment. VDD is more likely a risk factor for TB than its consequence.

**LACUNAE IN LITERATURE:**

Several studies have shown conflicting results on the level of vitamin D in TB patients. The most recent systematic review by Huang S et al. [4] reported that VDD is more likely a risk factor for TB than its consequence. Serum vitamin D level varies considerably between populations and is influenced by many geographical and cultural factors.[3] Moreover, the association between 25-hydroxyvitamin D [25(OH)D] and tuberculosis has been studied in many Western countries, whereas in India only limited and conflicting data were available regarding the same. [13]

# MATERIALS & METHODS

**Study site:** This study was conducted in the Department of General Medicine, R.L.Jalappa hospital and research centre.

**Study population:** This study was conducted in R.L.Jalappa hospital in patients of 2 groups. Group 1 consists of sputum positive pulmonary TB and group 2 consists of non-tuberculosis patients belonging to the same age, community and the ethnic group without tuberculosis who fulfilled inclusion and exclusion criteria.

**Study design:** The current study was a comparative cross-sectional study

**Sample size:** Was estimated by using the Mean Vitamin D levels in TB subjects as 11.2 +/- 6.5 ng/ml and in control as 30.6 +/- 10.8 ng/ml from the study Ritu Karoli et al. using this values at 99% Confidence limit and 90% power sample size of 7 was obtained in each group. With 10% nonresponse sample size of 7 + 1 ≈ 8 subjects will be included in each group.

However, 70 TB cases were included in the study (based on the approximated TB caseload in our centre) and 30 controls of age and gender-matched were included in the study.

Hence a sample of 70 cases and 30 controls were included in the study.

**Sample Size Estimation Formula:**

$$\text{Sample size} = \frac{2SD^2(Z_{\alpha/2}+Z_{\beta})^2}{d^2}$$

SD – Standard deviation = From previous studies or pilot study

$Z_{\alpha/2} = Z_{0.05/2} = Z_{0.025} = 1.96$ (From $Z$ table) at type 1 error of 5%

$Z_{\beta} = Z_{0.20} = 0.842$ (From $Z$ table) at 80% power

d = effect size = difference between mean values

So now formula will be

$$\text{Sample size} = \frac{2SD^2(1.96+0.84)^2}{d^2}$$

**Sampling method:** All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size is reached.

**Study duration:** The data collection for the study was done between October 2016 to October 2018 for a period of 2 years.

**Inclusion Criteria:**

- Patients of either sex aged more than 18 years
- Newly diagnosed sputum positive patients
- patients who are under ATT treatment
- Patients who do not have any condition known to affect calcium or vitamin d deficiency

**Exclusion criteria:**

- Patients who had risk factors for hypovitaminosis D (such as malnutrition, liver disease, renal disease, gastric or bowel resection, malabsorption states).
- Patients are taking drugs antagonist to vitamin D such as phenytoin, phenobarbital etc.
- current or recent (<1 year) use of vitamin D and/or calcium supplements

**Ethical considerations:** Study was approved by the institutional human ethics committee. Informed written consent was obtained from all the study participants, and only those participants willing to give informed consent were included in the study. The risks and benefits involved in the study and the voluntary nature of participation were explained to the participants before obtaining consent. Confidentiality of the study participants was maintained.

**Data collection tools:** All the relevant parameters were documented in a structured study proforma.

**Methodology:** The serum 25(OH) D concentrations were determined by Electro-chemiluminescence immunoassay (eCLIA). serum 25(OH)D concentrations levels were defined as :

| Condition | | serum 25(OH)D concentrations |
|---|---|---|
| Deficient | - | 0-20 ng/ml |
| Insufficient | - | 21-29 ng/ml |
| Sufficient | - | 30-100 ng/ml |
| Toxic | - | >100 ng/ml |

**The study requires investigations such as:**

- Complete hemogram
- Sputum AFB
- Chest X-ray
- Serum Vitamin D levels
- A standard 12 lead ECG
- Blood urea
- Serum creatinine
- FBS, PPBS, RBS
- Urine routine
- Liver function tests
- Serum calcium

**Statistical Methods:**

Vitamin D levels were the primary outcome variable.

Study group (tuberculosis Vs non-tuberculosis) was considered as a primary explanatory variable. Age, gender, religion, sunlight exposure, haemoglobin, albumin etc., were secondary explanatory variables.

All Quantitative variables were checked for a normal distribution within each category of an explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro-wilk test was also conducted to assess normal distribution. Shapiro wilk test p value of >0.05 was considered as a normal distribution.

For normally distributed Quantitative parameters the mean values were compared between study groups using Independent sample t-test.

Categorical outcomes were compared between study groups using Chi square test.

P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.[67]

# RESULTS

## RESULTS

A total of 100 people were included in the final analysis.

**Table 4: Distribution of study participants based on diagnosis of tuberculosis (N=100)**

| Group | Frequency | Percentage |
|---|---|---|
| Tuberculosis | 70 | 70% |
| Non-tuberculosis | 30 | 30% |

Among the study population 70 (70%) participants were tuberculosis patients and 30(30%) were non-tuberculosis cases. (Table 4& Figure 5)

**Figure 5: Bar chart of Group distribution in study population (N=100)**

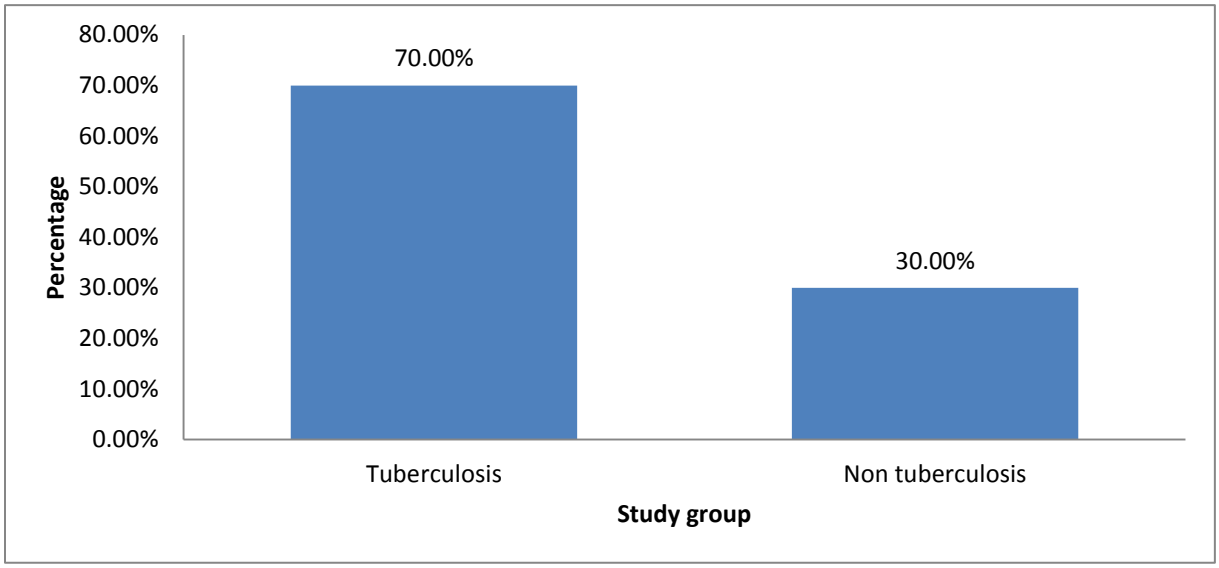


**Table 5: Grade of Sputum-AFB positivity among TB patients study population (N=70)**

| A grade of Sputum-AFB positivity | Frequency | Percentage |
|---|---|---|
| 1+ | 20 | 40.00% |
| 2+ | 31 | 62.00% |
| 3+ | 19 | 38.00% |

Among the study population 20(40%) were with 1+ sputum -AFB, 31(62%) were with 2+ Sputum-AFB and 19(38%) were with 3+ Sputum-AFB. (Table5 & Figure 6)

**Figure 6: Bar chart of Grade of Sputum-AFB positivity among TB patients study population (N=100)**

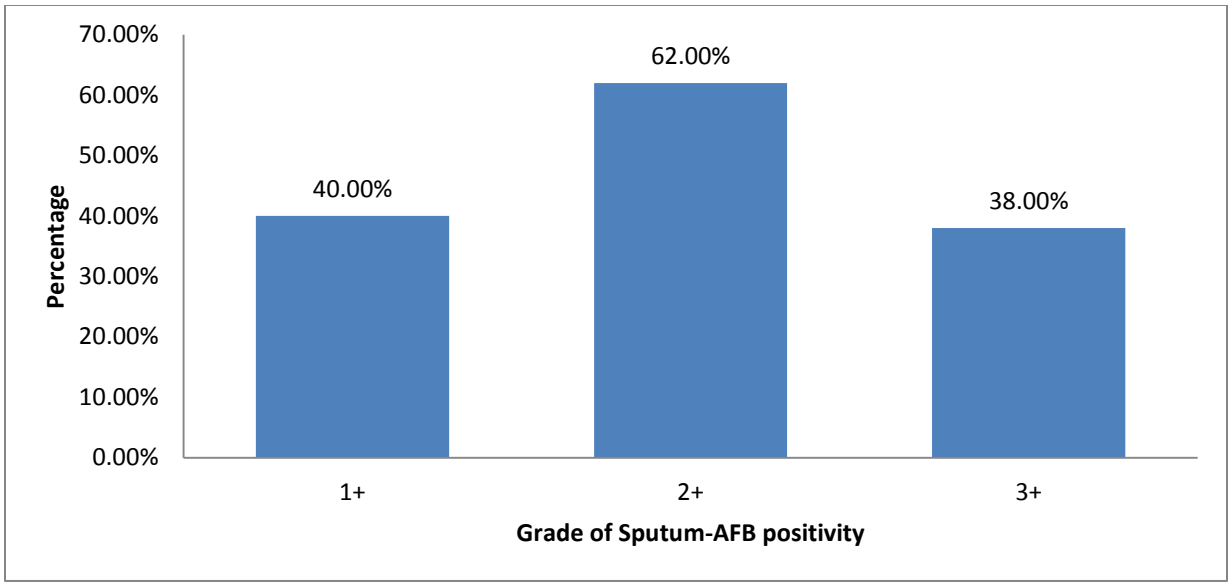


**Table 6: Comparison of mean age between study groups (N=100)**

| Parameter | Mean ±SD | | P value |
|---|---|---|---|
| | Tuberculosis (N=70) | Non tuberculosis (N=30) | |
| **Age** | 52.53 ± 15.68 | 56.07 ± 10.06 | *.258* |

Mean age of TB and non-TB cases were 52.53 ± 15.68 years and 56.07 ± 10.06 years. There was no significant difference in the mean age group between the study participants. (P value>0.05). (Table 6)

**Table 7: Comparison of Gender Between study groups (N= 100)**

| Gender | Group | | Chi square | P-value |
|---|---|---|---|---|
| | Tuberculosis(N=70) | Non-tuberculosis(N=30) | | |
| **Female** | 16 (22.85%) | 10 (33.33%) | 1.19 | 0.27 |
| **Male** | 54 (77.14%) | 20 (66.66%) | | |

Among the tuberculosis patients, 16 (22.85%) were female, 54(77.14%) were males. Among non-tuberculosis cases 10(33.33%) were female, and 20(66.66%) were males. The difference in the proportion of male and female between tuberculosis and non-tuberculosis cases was statistically not significant (P value >0.05). (Table 7)

**Table 8: Comparison of the mean of lab parameters between study groups (N=100)**

| Parameter | Mean ±SD | | P value |
|---|---|---|---|
| | Tuberculosis (N=70) | Non-tuberculosis (N=30) | |
| **I. HB (g/dl)** | 11.16 ± 2.84 | 10.69 ± 2.69 | *.441* |
| **II. Albumin (g/dl)** | 3.89 ± 0.89 | 3.42 ± 0.76 | *.012* |
| **III. Calcium levels (mg/dl)** | 7.3 ± 1.59 | 8.5 ± 1.37 | *.000* |

Mean haemoglobin in tuberculosis patients was 11.16 ± 2.84 g/dl and 10.69 ± 2.69 g/dl in non-tuberculosis cases. Mean difference was statistically not significant (P value>0.05). Mean Albumin in tuberculosis patients was 3.89 ± 0.89 g/dl and 3.42 ± 0.76 g/dl in non-tuberculosis cases. This was statistically significant (P value<0.05). Mean Calcium level (mg/dl) in tuberculosis patients was 7.3 ± 1.59 mg/dl and 8.5 ± 1.37 mg/dl in non-tuberculosis cases. This difference was statistically significant (P value<0.001). (Table 8)

**Table 9: Comparison of sunlight exposure (>30minutes/day) between study Groups (N=100)**

| Sunlight exposure (>30minutes) | Group | |
|---|---|---|
| | Tuberculosis(N=70) | Non-tuberculosis(N=30) |
| **Yes** | 65 (92.85%) | 30 (100%) |
| **No** | 5 (7.142%) | 0 (0%) |

- *Since the data did not satisfy the assumptions of chi square test/ Fisher's exact test, P value could not be calculated*

Among the tuberculosis patients, 65 (92.85%) were exposed to sunlight >30 minutes, 5(7.14%) were not exposed to sunlight >30 minutes. Among non-tuberculosis cases, all 30 (100%) were exposed to sunlight >30 minutes. (Table 9)

**Table 10: Vitamin-D levels of the study population (N= 100)**

| Parameter | Mean ±STD | Median | Min | Max | 95% C.I. for EXP(B) | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| **Vitamin-D LEVELS (ng/ml)** | 29.51± 28.19 | 19.80 | 6 | 150.00 | 23.92 | 35.11 |

Mean vitamin D level in the study population was 29.51± 28.19 ng/ml with minimum 6 and maximum 150. (Table 10)

**Table 11: Comparison of the mean of Vitamin-D levels between study groups (N=100)**

| Parameter | Mean ±SD | | P value |
|---|---|---|---|
| | Tuberculosis (N=70) | Non-tuberculosis (N=30) | |
| **Vitamin-D levels (ng/ml)** | 22.02 ± 23.8 | 47 ± 30.22 | *<0.001* |

The mean of Vitamin D levels in tuberculosis patients was 22.02 ± 23.8 ng/ml, and it was 47 ± 30.22 ng/ml in non-TB cases. This difference in the vitamin D level was statistically significant (P value<0.001). (Table 11)

**Table 12: Comparison of vitamin D levels (sufficient vs insufficient vs deficient) between study Groups (N=100)**

| Vitamin D levels (ng/ml) | Group | | Chi square | P-value |
|---|---|---|---|---|
| | Tuberculosis(N=70) | Non-tuberculosis(N=30) | | |
| **Sufficient** | 16 (22.85%) | 20 (66.66%) | 22.27 | ***<0.001*** |
| **Insufficient** | 18 (25.71%) | 8 (26.66%) | | |
| **Deficient** | 36 (51.42%) | 2 (6.666%) | | |

Among the tuberculosis patients, 16 (22.85%) had sufficient Vitamin D levels, 18(25.71%) had insufficient Vitamin D levels whereas 36(51.42%) had deficient Vitamin D levels. Among non-tuberculosis cases 20 (66.66%) had sufficient Vitamin D levels, 8(26.66%) had insufficient Vitamin D levels and only 2 (6.67%) had deficient vitamin D. This difference in the vitamin D level status between tuberculosis and non-tuberculosis cases were statistically significant (P value<0.001) (Table 12)

**Table 13: Comparison of vitamin D levels (sufficient vs low) between study Groups (N=100)**

| Vitamin D levels | Group | | Chi square | P-value |
|---|---|---|---|---|
| | Tuberculosis (N=70) | Non-tuberculosis (N=30) | | |
| **Sufficient** | 16 (22.85%) | 20 (66.66%) | 17.49 | ***<0.001*** |
| **Low** | 54 (77.14%) | 10 (33.33%) | | |

Among the tuberculosis patients, 16 (22.85%) had sufficient vitamin D levels, 54(77.14%) had Low Vitamin D levels. Among non-tuberculosis cases 20 (66.66%) had sufficient vitamin D levels, 10(33.33%) had low vitamin D levels. The difference in the proportion of vitamin D levels between tuberculosis and non-tuberculosis cases was statistically significant (P value<0.001) (Table 13)

# DISCUSSION

## Discussion

Tuberculosis (TB) remains a major public health problem globally. Various factors that could affect the incidence and progression of TB have been reported, one of them is vitamin D deficiency. Vitamin D modulates monocyte-macrophage activity in the body and plays a role in human innate immunity to certain infectious agents. This role may be important in the body's defence against tuberculosis, in which attack of macrophages is a key step in pathogenesis.[16] Numerous studies have been conducted to study whether VDD was associated with TB; however, they produced inconsistent and varying results. Therefore, the present study was undertaken with the aim of estimating the vitamin D deficiency prevalence among patients with pulmonary tuberculosis and to compare it with non-tuberculosis cases.

The study population comprised of 100 individuals. Of these 70 (70%) were diagnosed with TB and 30(30%) were non-tuberculosis patients.

### Age

Mean age of TB cases and non TB cases were 52.53 ± 15.68 years and 56.07 ± 10.06 years respectively. The mean difference in age between the two groups was not statistically significant (P value>0.05). These results were consistent with other studies.

**Table 14: Comparison of mean age of the study population with other studies**

| Studies | TB cases | Non-TB cases | P value |
|---|---|---|---|
| **Current study** | 52.53 ± 15.68 | 56.07 ± 10.06 | NS |
| **Yuvaraj B et al[13]** | 42.2 ± 10.7 | 41.1 ± 11.8 | NS |
| **Wejse C et al[31]** | 37.4±13.7 | 37.3±12.9 | NS |
| **Sashidhran PK et al[63]** | 17-65 | 14-65 | - |
| **Memom A et al[56]** | 39±6.7 | 40±9.1 | NS |
| **Hong JY et al[52]** | 35.4±15.5 | 35.4±15.2 | NS |
| **Workineh et al[3]** | 29.8±11.9 | 21.4±2.84 | NS |

**Gender**

Among the tuberculosis patients, 16 (22.85%) were female, and 54(77.14%) were males. Among non-tuberculosis cases 10(33.33%) were female, and 20(66.66%) were males. The difference in the proportion of male and female between tuberculosis and non-tuberculosis patients was statistically not significant. This was consistent with other study findings. Similarly, Joshi L et al[61] reported that there was no significant difference between age along the group.

**Table 15: Comparison of gender difference among study groups with other studies.**

| Studies (Male vs females) | TB cases | Non TB cases | P value |
|---|---|---|---|
| **Current study** | 16% vs 77.14% | 33.3%% vs 66.6% | NS |
| **Yuvaraj B et al[13]** | 47 % vs 52% | 38.4% vs 61.6 | - |
| **Tessema B et al[62]** | 40.4% vs 26.2% | 59.6% vs 73.8% | P value< 0.05 |
| **Joshi L et al[61]** | 38% vs 62% | 77% vs 23 % | <0.001 |
| **Memom A et al[56]** | 59.8% vs 40.1% | 59.7% vs 40.2% | NS |
| **Workineh et al[3]** | 62% vs 38% | 76% vs 24% | 0.049 |

**AFB positivity grades**

Among the study population 20(40%) were with 1+ sputum -AFB, 31(62%) were with 2+ Sputum-AFB and 19(38%) were with 3+ Sputum-AFB.

**Table 16: Comparison of grades of sputum AFB positivity with other studies**

| Grade of Sputum-AFB positivity | Current study | Kim JH et al[27] |
|---|---|---|
| 1+ | 40% | 6.06% |
| 2+ | 62% | 6.67% |
| 3+ | 38% | 7.88% |

**Serum Calcium level**

The mean calcium level (mg/dl) of TB and non TB cases were 7.3 ± 1.59 and 8.5 ± 1.37 respectively. The difference in serum calcium level statistically significant (P value<0.001). This finding was similar to that reported by Yuvaraj B et al[13], Pham HO et al[55] and Memom A et al[56]. Literature has reported both hypercalcemia and hypocalcaemia associated with the TB.[68] Low level of serum calcium among the TB patients in the current study is consistent with the physiologic understanding that the vitamin D hormone system and parathyroid hormone are the principal regulators of serum concentrations of calcium.[55]

**Table 17: Comparison of serum calcium level with other studies**

| Studies | Serum calcium level (mg/dl) | | P value |
|---|---|---|---|
| | TB cases | Non-TB cases | |
| Current study | 7.3 ± 1.59 | 8.5 ± 1.37 | 0.000 |
| Yuvaraj B et al[13] | 2.18±0.19 | 2.3±0.18 | <0.01 |
| Memom A et al[56] (mg/dl) | 8±1.9 | 9.2±1.7 | <0.01 |
| Pham HO et al[55] | 2.35±0.26 | 2.11±0.38 | <0.01 |

**Serum albumin level**

The mean albumin level in tuberculosis patients was 3.89 g/dl and 3.42 g/dl in non-tuberculosis cases. This difference in mean albumin level was statistically significant (P value<0.05). This was similar to the findings by Wejse C et al[31] and Kim JH et al[27]. The possible causes for the low serum albumin in PTB patients were considered to be nutritional factors, enteropathy and acute phase reactant proteins. The hepatic synthesis of acute phase reactant proteins is induced by cytokines such as interleukin-6 and tumor necrosis factor, which inhibit the production of serum albumin and cause dramatic shifts in the plasma concentration of certain essential micronutrients and albumin.[69]

**Table 18: Comparison of serum albumin level with other studies.**

| Studies | Serum albumin level (g/dl) | | P value |
|---|---|---|---|
| | Tuberculosis | Non-tuberculosis | |
| Current study | 3.89 ± 0.89 | 3.42 ± 0.76 | 0.012 |
| Yuvaraj B et al[13] | 37.9±6.2 | 39.5±4.7 | NS |
| Wejse C et al[31] µMol/l | 471±98 | 642±78 | <0.001 |
| Kim JH et al[27] | 4.01±0.628 | 4.56±0.256 | <0.01 |

**Haemoglobin**

In the current study, mean haemoglobin in tuberculosis patients were 11.16 ± 2.84g/dl and 10.69 ± 2.69g/dl in non-tuberculosis patients. This difference in haemoglobin level was statistically not significant (P value>0.05). This confirms the findings by Memom A et al[56] whereas it was contrary to that by Kim JH et al[27]. Literature had documented several chronic infections can cause anaemia. Tuberculosis is one among them. TB- associated anaemia has been explained by various pathogenesis. Whereas maximum studies have reported suppression of erythropoiesis by inflammatory mediators (as a cause of anaemia). The severity of anaemia is further worsened by nutritional deficiency and malabsorption syndrome.[70]

**Table 19: Comparison of serum haemoglobin level with other studies**

| Studies | Serum haemoglobin level | | P value |
|---|---|---|---|
| | TB cases | Non-TB cases | |
| Current study | 11.16 ± 2.84 | 10.69 ± 2.69 | 0.441 |
| Memom A et al[56] | 11±3.9 | 12±2.9 | 0.031 |
| Kim JH et al[27] | 13.1±1.86 | 14.7±1.53 | <0.01 |

**Vitamin D level and tuberculosis**

The mean vitamin D level for the whole study population was 29.51± 28.19 ng/ml. The best determinant of vitamin D status is the serum concentration of 25-hydroxyvitamin D (25(OH)D). There is no universal agreement on the required serum 25(OH)D for an adequate vitamin D status. Most investigators agree that serum 25(OH)D should be higher than 50 nmol/l.[44] or >20ng/ml.[5] Our study results suggest that the mean vitamin D level for the whole population was optimal. But, when the mean serum vitamin D levels in tuberculosis patients (22.02 ± 23.8 ng/ml) was compared with non-TB cases (47 ± 30.22), a statistically significant difference was found (P value<0.001). This was consistent with the studies done by Panwar et al[58], Wejse C et al[31], Sashidharan PK et al[63], Memom A et al[56], Kim DY et al[27], Workineh et al[3]. A meta-analysis by Huang SJ et al[4] on the association between vitamin D and TB showed a significantly lower level of vitamin D in TB patients vs controls. Further, the meta-analysis reported that vitamin D deficiency increases the TB risk. This finding parallels with the meta-analysis findings by Nnoaham et al[16]. Joshi L et al[61] reported that the total mean 25[OH] vitamin D levels were found to be significant in APTB ($P < 0.002$) compared to controls. Rajkumar V et al[64], after using multivariate analysis found that low BMI levels and being positive for TB were significant predictors for severe vitamin deficiency. The active form of vitamin D enhances the ability of macrophages to suppress the intracellular growth of Mycobacterium tuberculosis. On triggering of Toll-like receptors by molecules of the tubercle bacillus, the production of microbe-killing cathelicidin is impaired in the absence of adequate serum vitamin D[16]

**Table 20: Comparison of mean vitamin D level between the study groups**

| Studies | Serum mean vitamin D(ng/ml) | | P value |
|---|---|---|---|
| | TB cases | non-TB cases | |
| Current study | 22.02 ± 23.8 | 47 ± 30.22 | <0.001 |
| Yuvaraj B et al[13] | 15.4±6.8 | 17.5 ± 5.7 | NS |
| Panwar et al[58] | 12.964 ± 8.380 | 16.359 ± 7.991 | <0.001 |
| Joshi L et al[61] | Not mentioned | Not mentioned | <0.01 |
| Wejse C et al[31] (nmol/l) | 78.3±22.6 | 85.3±34.8 | <0.001 |
| Sashidharan PK et al[63] | 10.7 (1-30) | 19.4(9-58) | <0.005 |
| Memom A et al[56] | 27.1±9.7 | 36.8±8.1 | <0.001 |
| Kim DY et al[27] | 13.2±1.86 | 18.7±8.33 | <0.001 |
| Workineh et al[3] | 30.1±19.3 | 38.5±20.9 | <0.005 |

Subsequently, we categorised the participants based on their vitamin D level to 2 groups: with sufficient and with a low level of vitamin D. Among the tuberculosis patients 16 (22.85%) had sufficient Vitamin D levels, 54(77.14%) had Low Vitamin D levels. Among non-tuberculosis patients, 20 (66.66%) had sufficient Vitamin D levels, 10(33.33%) had Low Vitamin D levels.This difference was also found to be statistically significant. (P value<0.001). This is consistent with the studies reported by Tessema B et al[62], Wejse C et al[31]. Wejse C et al[31] reported that the relative risk (RR) of hypovitaminosis D was 1.18 (95% CI: 1.01, 1.38) in TB patients compared with controls. Hong JY et al[52] also documented a significant difference(<0.01) in serum Vit D level among TB cases and non TB cases at both 20ng/ml (88.3% vs 74.1%) and 10ng/ml (51.1% vs 8.2%) cut-off point.

**Table 21: Comparison of serum vitamin D level (sufficient vs low) among the groups with other studies**

| Studies | Serum vitamin D level (sufficient vs low) | | P value |
|---|---|---|---|
| | **Tuberculosis** | **Non-TB cases** | |
| Current study | 22.85% vs77.14% | 66.66% vs 33.3% | ***<0.001*** |
| Tessema B et al[62] | 61.5% vs 38.7% | 38.5% vs 61.3% | <0.01 |
| Wejse C et al[31] | 54%Vs 46% | 61%vs 39% | <0.001 |

Among the tuberculosis patients, 16 (22.85%) had sufficient Vitamin D levels, 18(25.71%) had insufficient Vitamin D levels whereas 36(51.42%) had deficient Vitamin D levels. Among non-tuberculosis cases, 20 (66.66%) had sufficient Vitamin D levels, 8(26..66%) had insufficient Vitamin D levels, and only 2 (6.67%) had deficient vitamin D levels. We found that this difference in the vitamin D status between tuberculosis and non-tuberculosis cases was statistically significant (P value<0.001). These findings were similar to other studies.

**Table 22: Comparison of serum vitamin D level (Deficient vs insufficient vs sufficient) with other studies**

| **Studies** | **Deficient vs insufficient vs sufficient** | | **P value** |
|---|---|---|---|
| | **TB cases** | **Non-TB cases** | |
| Current study | 51.42% vs 25.71% vs 22.85% | 6.66% vs 26.6% vs 66.6% | <0.001 |
| Tessema B et al[62] | 61.5% vs 20.8% vs 17.7% | 38.7% vs 41.2% vs 20.1% | <0.001 |
| Panwar et al[58] | 48.1% vs 47.2% vs 4.7% | 28.3% vs 64.2% vs 7.5% | 0<0.05 |
| Joshi L et al[61] | 44% vs 48% vs 8% | - 48% vs 52% | NS |
| Memom A et al[56] | 52.6% vs 14.2% vs 33% | 19.5% vs 21.6% vs 58.7% | <0.05 |
| Nielson et al[51] | 35% vs 26% vs 21% | 17% vs 72% vs 11% | <0.001 |

Wejse D et al[31] divide the group based on Vit D level of insufficient (51–75 nmol/L); moderately deficient (26–50); severely deficient (≤25 nmol/L). Median 25(OH)D was substantially lower in patients with tuberculosis than in controls (77·5 vs 83·0 nmol/L); moderate to severe deficiency (≤50 nmol/L) more common in healthy controls than in patients with tuberculosis (65/494=13·2% vs 31/362=8·6%). Nielson et al[51] documented that after adjusting for ethnicity and alcohol, the association between 25(OH)D and risk of TB was U-shaped, with an OR of 6·5 (95 % CI 1·8, 23·5) among individuals with a 25(OH)D concentration, 75 nmol/l, and an OR of 6·5 (95 % CI 1·9, 22·2) among those with a concentration. 140 nmol/l, when compared with individuals presenting concentrations between 76 and 140 nmol/l. Workineh et al[3] also reported a significant difference ( p vlue<0.01) in serum vitamin D level between TB cases and non-TB cases in all Vit D level including deficient (83.3% vs 67.1%) and severe vitamin D deficiency (53.2% vs 30%).

The significance of an association between vitamin D deficiency and tuberculosis is 2-fold. First, already low vitamin D levels in tuberculosis patients may fall further on commencement of treatment.[16] Further drops can predispose to other vitamin D deficient states. Secondly, the incidence of tuberculosis is high in CKD partly as a result of impaired cell-mediated immunity. But if low serum vitamin D levels also predisposed to tuberculosis, the growing population of people with CKD from underlying causes like DM may need early attention to their body vitamin D levels to mitigate the risk of active tuberculosis.[16] It is well known from the causal factors of vitamin D deficiency that sunlight exposure and adequate dietary intakes are key ways to ensuring enough levels of vitamin D in the body.[16] But, we could not assess the association of vitamin D level and sunlight exposure with TB in the current study due to low sample size.

Overall the present study suggests that the serum vitamin D level among tuberculosis patients is considerably low compared to healthy controls. Even though there is sufficient evidence to suggest that a fall in serum vitamin D levels compromises cell-mediated immunity and leads to the activation of latent tuberculosis, it is also possible that low serum vitamin D levels result from tuberculosis itself.[16] Hence further studies of longitudinal nature are recommended to explore this dilemma of association.

# CONCLUSION

# CONCLUSION

The present study was undertaken with the aim of estimating the vitamin D deficiency prevalence among patients with pulmonary tuberculosis and to compare it with non-tuberculosis cases. The following conclusions were obtained from the study. The study population comprised of 100 individuals. Of these 70 (70%) were diagnosed with TB and 30(30%) were non-tuberculosis patients.

Mean age of TB cases and non TB cases were 52.53 ± 15.68 years and 56.07 ± 10.06 years respectively.

Mean haemoglobin in tuberculosis patients was 11.16 ± 2.84 g/dl and 10.69 ± 2.69 g/dl in non-tuberculosis cases. This difference was not statistically significant.

Mean Albumin among tuberculosis and non- TB cases were 3.89 ± 0.89 g/dl and 3.42 ± 0.76 g/dl respectively. Mean Calcium level (mg/dl) in tuberculosis patients was 7.3 ± 1.59 mg/dl and 8.5 ± 1.37 mg/dl in non-tuberculosis cases. The difference in mean of serum albumin and calcium levels were statistically significant between the TB and non-TB cases (P value<0.001).

Among the study population 20(40%) were with 1+ sputum -AFB, 31(62%) were with 2+ Sputum-AFB and 19(38%) were with 3+ Sputum-AFB.

The mean of Vitamin D levels in tuberculosis patients was 22.02 ± 23.8 ng/ml, and it was 47 ± 30.22 ng/ml in non-tuberculosis cases.

Sufficient level of serum vitamin D was present in 16 (22.85%) TB cases and 20(66.6%) non-TB cases. Prevalence of vitamin deficiency was 77.14%(54 cases) among TB cases and 33.33%(10 cases) among non-TB cases. This difference in vitamin D status between tuberculosis and non-tuberculosis cases was statistically significant (P value<0.001).

**LIMITATIONS:**

1. The key limitation of the study was the cross-sectional nature of the study. Hence the temporal relationship between the tuberculosis and the vitamin D level could not be established by the current study.
2. Another key limitation of the study was limited sample size, which was not sufficient to conduct appropriate regression analysis to establish the independent association between tuberculosis and the vitamin D levels.

**RECOMMENDATIONS:**

1. There is strong need to prospective observational study to assess the association between tuberculosis and vitamin level, after accounting for the effect of various potential confounders. The prospective studies also will aid in establishing the temporal association between the tuberculosis and vitamin D level.
2. The impact of vitamin D deficiency on the treatment outcomes of tuberculosis patients and the effect of treating vitamin D deficiency also needs to be evaluated, to guide the clinical practice.

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# PROFORMA

**ASSESSMENT OF SERUM VITAMIN D LEVELS IN PATIENTS WITH PULMONARY TUBERCULOSIS –A COMPARATIVE CROSS SECTIONAL STUDY IN A TERTIARY CARE CENTRE IN KOLAR**

Name: DOA:

Age/sex: IP NO:

Occupation:

Address:

Date:

| **Presenting complaints**: | Yes | No |
|---|---|---|
| Fever | | |
| Cough that last for 3 or more weeks | | |
| Coughing up blood | | |
| Chest pain | | |
| Night sweats and chills | | |
| Others | | |

Past history:

Personal history:

Weight loss

Loss of appetite

Smoking

Alcohol

General physical examination

Pulse: RR:

BP: Temp:

Pallor: Icterus: Cyanosis:

Clubbing: Lymphadenopathy: Pedal edema:

Systemic examination

RS:

Abnormal breath sounds

Lymphadenopathy

Per abdomen:

CVS:

CNS:

## Investigations

- Complete hemogram
- Sputum AFB
- Chest X ray
- Serum Vitamin D levels
- A standard 12 lead Ecg
- Blood urea
- Serum creatinine
- FBS,PPBS,RBS
- Urine routine
- Liver function tests
- Serum calcium

# ಮಾಹಿತಿಯುಕ್ತ ಸಮ್ಮತಿಯ ನಮೂನೆ

**ಕ್ಷಯರೋಗ ಇರುವ ರೋಗಿ ಗಳಲ್ಲಿ ವಿಟಮಿನ್ ಡಿ ಮಟ್ಟದ ನೋಡುವ ಅಧ್ಯಯನ**

ಅಧ್ಯಯನದ ಉದ್ದೇಶ: ಕ್ಷಯರೋಗ ಇರುವ ರೋಗಿ ಗಳಲ್ಲಿ ವಿಟಮಿನ್ ಡಿ ಕೊರತೆ ಕಂಡುಹಿಡಿದು ಕ್ಷಯರೋಗ ಇಲ್ಲದಿರುವ ರೋಗಿ ಗಳಲ್ಲಿ ವಿಟಮಿನ್ ಡಿ ಮಟ್ಟ ಸಂಬಂಧ ನೋಡುವ ಅಧ್ಯಯನ

ಇದು ಸೂಕ್ತ ಪೂರ್ವಸೂಚಕ ಅಂಶಗಳಲ್ಲಿ ಜ್ಞಾನ ತೀವ್ರ ನಿಗಾ ಚಿಕಿತ್ಸೆಯ ಅಗತ್ಯ ಹೆಚ್ಚಿನ ಅಪಾಯ ರೋಗಿಗಳ ಆರಂಭಿಕ ಗುರುತಿನ ಉಪಯುಕ್ತ ಇರಬಹುದು ಭರವಸೆಯಿದೆ . ನೀವು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪುತ್ತೀರಿ ವೇಳೆ ನೀವು ಅಥವಾ ನೀವು ಅಥವಾ ಎರಡೂ ಜವಾಬ್ದಾರಿ ವ್ಯಕ್ತಿಯಿಂದ ಮಾಹಿತಿ ( ಪ್ರತಿ proforma ಮಾಹಿತಿ ) ಸಂಗ್ರಹಿಸುತ್ತದೆ . ನಿಮ್ಮ ಆಸ್ಪತ್ರೆ ದಾಖಲೆಯಿಂದ ಚಿಕಿತ್ಸೆ ಮತ್ತು ಸೂಕ್ತ ವಿವರಗಳನ್ನು ಸಂಗ್ರಹಿಸುತ್ತದೆ . ಸಂಗ್ರಹಿಸಿದ ಈ ಮಾಹಿತಿ ಮಾತ್ರ ಪ್ರೌಢಪ್ರಬಂಧದಲ್ಲಿ ಮತ್ತು ಪ್ರಕಟಣೆ ಬಳಸಲಾಗುತ್ತದೆ . ಈ ಅಧ್ಯಯನವು ಸಾಂಸ್ಥಿಕ ನೈತಿಕ ಸಮಿತಿಯು ವಿಮರ್ಶಿಸುತ್ತದೆ ಮಾಡಲಾಗಿದೆ . ನೀವು ಭಾಗವಹಿಸಲು ಇಚ್ಛಿಸದಿದ್ದರೆ ನೀವು ಪಡೆಯುತ್ತಾನೆ ಆರೈಕೆ ಬದಲಾಗುವುದಿಲ್ಲ . ನೀವು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿಕೊಂಡಲ್ಲಿ ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು ಸೈನ್ / ಒದಗಿಸುವ ಅಗತ್ಯವಿದೆ .

ನಾನು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನದಿಂದ ಹಿಂತೆಗೆದುಕೊಳ್ಳುವಂತೆ ಮತ್ತು ಈ ನನ್ನ ಮುಂದಿನ ಆರೈಕೆ ಬದಲಾಗುವುದಿಲ್ಲ ಉಚಿತ ಉಳಿಯಲು ಎಂದು ಅರ್ಥ . ನಾನು ಓದಲು ಅಥವಾ ನನಗೆ ಓದಲು ಮಾಡಲಾಗಿದೆ ಮತ್ತು ಅಧ್ಯಯನದ ಉದ್ದೇಶ , ಬಳಸಲಾಗುವ ವಿಧಾನ , ಅಧ್ಯಯನ ಮತ್ತು ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಸಂಗ್ರಹಿಸಿದ ಮತ್ತು ಬಹಿರಂಗ ನಡೆಯಲಿದೆ ಮಾಹಿತಿಯನ್ನು ಪ್ರಕೃತಿಯಲ್ಲಿ ನನ್ನ ಒಳಗೊಳ್ಳುವಿಕೆ ಸಂಬಂಧಿಸಿದ ಅಪಾಯ ಮತ್ತು ಲಾಭಗಳನ್ನು ಅರ್ಥ . ನಾನು ಅಧ್ಯಯನ ಮತ್ತು ನನ್ನ ಪ್ರಶ್ನೆಗಳಿಗೆ ವಿವಿಧ ಅಂಶಗಳನ್ನು ನನ್ನ ತೃಪ್ತಿ ಉತ್ತರಿಸುವ ಬಗ್ಗೆ ನನ್ನ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ಅವಕಾಶ ಹೊಂದಿದ್ದರು . ನಾನು , ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಮತ್ತು ಪ್ರೌಢಪ್ರಬಂಧದಲ್ಲಿ ನನ್ನ ವೈಯಕ್ತಿಕ ಮಾಹಿತಿಯ ಸಂಗ್ರಹಣೆ ಮತ್ತು ಡಿಸ್ಕ್ಲೋಸರ್ ಅಧಿಕೃತಗೊಳಿಸಲು ಒಪ್ಪುತ್ತೀರಿ ರುಜುಮಾಡಿರುವ .

ವಿಷಯದ ಹೆಸರು

( ಪಾಲಕರು / ಗಾರ್ಡಿಯನ್ಸ್ ಹೆಸರು )

DATE : ಸಹಿ / ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು

ಒಪ್ಪಿಗೆ ತೆಗೆದುಕೊಳ್ಳುವ ವ್ಯಕ್ತಿಯ ಹೆಸರು ಮತ್ತು ಸಹಿ

# INFORMED CONSENT FORM

**STUDY TITLE: ASSESSMENT OF SERUM VITAMIN D LEVELS IN PATIENTS WITH PULMONARY TUBERCULOSIS – A COMPARATIVE CROSS-SECTIONAL STUDY IN A TERTIARY CARE CENTRE IN KOLAR**

**SUBJECT'S NAME:** **HOSPITAL NUMBER:**

**AGE:**

**Objective**: To estimate the prevalence of vitamin D deficiency in patients with pulmonary tuberculosis and compare with non-tuberculosis patients.

If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. We will collect the treatment and relevant details from your hospital record. This information collected will be used for only dissertation and publication. This study has been reviewed by the institutional ethical committee. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

I understand that I remain free to withdraw from the study at any time and this will not change my future care. I have read or have been read to me and understood the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study. I have had the opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction. I, the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for dissertation.

Subject name
(Parents / Guardians name)

DATE: SIGNATURE /THUMB IMPRESSION

# ರೋಗಿಯ ಮಾಹಿತಿ ಹಾಳೆ

ಸ್ಟಡಿ ಶೀರ್ಷಿಕೆ : **ಕ್ಷಯರೋಗ ಇರುವ ರೋಗಿ ಗಳಲ್ಲಿ ವಿಟಮಿನ್ ಡಿ ಮಟ್ಟದ ಅಧ್ಯಯನ**

ಸ್ಟಡಿ ಸೈಟ್: ಆರ್. ಎಲ್. ಜಾಲಪ್ಪ ಆಸ್ಪತ್ರೆ, ತಮಕ, ಕೋಲಾರ

**ಅಧ್ಯಯನ**ದ ಉದ್ದೇಶ: ಕ್ಷಯರೋಗ ಇರುವ ರೋಗಿ ಗಳಲ್ಲಿ ವಿಟಮಿನ್ ಡಿ ಕೊರತೆ ಕಂಡುಹಿಡಿದು ಕ್ಷಯರೋಗ ಇಲ್ಲದಿರುವ ರೋಗಿ ಗಳಲ್ಲಿ ವಿಟಮಿನ್ ಡಿ ಮಟ್ಟ ಸಂಬಂಧ ನೋಡುವ ಅದ್ಯಯನ

ಕೆಳಗಿನ ಮಾಹಿತಿಯನ್ನು ಓದಲು ಮತ್ತು ನಿಮ್ಮ ಕುಟುಂಬ ಸದಸ್ಯರು ಚರ್ಚಿಸಬೇಕು ದಯವಿಟ್ಟು. ನೀವು ಅಧ್ಯಯನ ಬಗ್ಗೆ ಯಾವುದೇ ಪ್ರಶ್ನೆ ಕೇಳಬಹುದು. ನೀವು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪುತ್ತೀರಿ ವೇಳೆ ನಿಮ್ಮಿಂದ (ಪ್ರೋಫಾರ್ಮ ಪ್ರಕಾರ) ಮಾಹಿತಿ ಸಂಗ್ರಹಿಸುತ್ತದೆ. . ಸಂಗ್ರಹಿಸಿದ ಈ ಮಾಹಿತಿಯನ್ನು ಪ್ರೌಢಪ್ರಬಂಧದಲ್ಲಿ ಮತ್ತು ಪ್ರಕಟಣೆಗೆ ಬಳಸಲಾಗುತ್ತದೆ.

ನೀವು ಸಂಗ್ರಹಿಸಿದ ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಗೌಪ್ಯವಾಗಿ ಇಡಲಾಗುತ್ತದೆ ಮತ್ತು ಯಾವುದೇ ಹೊರಗಿನವರ ಬಹಿರಂಗ ಮಾಡಲಾಗುವುದಿಲ್ಲ. ನಿಮ್ಮ ಗುರುತನ್ನು ತೋರಿಸಲಾಗುವುದಿಲ್ಲ. ಮೇಲೆ ತನಿಖೆ ಅಗತ್ಯವಿದೆ ವೆಚ್ಚಗಳು ಅಧ್ಯಯನ ಸಂಶೋಧಕ ಹಣಕಾಸು ಒದಗಿಸುವುದಾಗಿತ್ತು. ಈ ಅಧ್ಯಯನವು ನೈತಿಕ ಸಮಿತಿಯ ವಿಮರ್ಶೆ ಮತ್ತು ನೀವು ನೈತಿಕ ಸಮಿತಿಯ ಸದಸ್ಯ ಸಂಪರ್ಕಿಸಲು ಉಚಿತ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಒಪ್ಪಿಕೊಳ್ಳಲು ಯಾವುದೇ ಕಡ್ಡಾಯ ಇಲ್ಲ. ನೀವು ಭಾಗವಹಿಸಲು ಇಚ್ಛಿಸದಿದ್ದರೆ ನೀವು ಪಡೆಯುತ್ತಾನೆ ರಕ್ಷಣೆ ಬದಲಾಗುವುದಿಲ್ಲ. ನೀವು / ಸೈನ್ ನೀವು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪುತ್ತೀರಿ ಮಾತ್ರ ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು ಒದಗಿಸುವ ಅಗತ್ಯವಿದೆ.

ಯಾವುದೇ ಸ್ಪಷ್ಟೀಕರಣ ನೀವು ಅಧ್ಯಯನ ಸಂಶೋಧಕ ಸಂಪರ್ಕಿಸಬಹುದು:

ಡಾ. ಮಹಾರಾಜ್ ಮೊಬೈಲ್ ಸಂಕೆ: 9553601601 ಮೇಲ್ ಐಡಿ: lalammaha@gmail.com

## PATIENT INFORMATION SHEET

**Study Title**: **ASSESSMENT OF SERUM VITAMIN D LEVELS IN PATIENTS WITH PULMONARY TUBERCULOSIS – A COMPARATIVE CROSS-SECTIONAL STUDY IN A TERTIARY CARE CENTRE IN KOLAR**

**Study site**: R.L Jalappa hospital, Tamaka, Kolar.

**Objective**: To estimate the prevalence of vitamin D deficiency in patients with pulmonary tuberculosis and compare with non-tuberculosis patients.

This information is intended to give you the general background of the study. Please read the following information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. This study has been reviewed by the Institutional Ethics Committee and you are free to contact the member of the Institutional Ethics Committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

**For any further clarification you can contact the study investigator:**

Dr. MAHARAJ L S Y M J

Mobile no: 9483413092

E-mail id: lalammaha@gmail.com

# MASTERSHEET

| S.No | Ip.No | Group | Age | Gender | SputumAFB | VitaminDLEVELS | vitaminDnewvariable | Grade | Gradestwocategories | HB | VitaminDstatus | Albumin | Calciumlevelsmgdl | Sunlightexposuregt30 min | Religion |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 613752 | Tuberculosis | 65 | Male | 2+ | 8.00 | 8.00 | Deficient | Low | 10.30 | Deficient | 3.70 | 6.00 | Yes | Hindu |
| 2 | 616411 | Tuberculosis | 40 | Male | 3+ | 8.00 | 8.00 | Deficient | Low | 9.70 | Deficient | 2.90 | 5.00 | Yes | Hindu |
| 3 | 618001 | Tuberculosis | 65 | Male | 1+ | 28.20 | 15.00 | Insufficient | Low | 9.70 | Sufficient | 4.20 | 8.00 | Yes | Hindu |
| 4 | 613275 | Tuberculosis | 50 | Male | 3+ | 18.00 | 8.00 | Deficient | Low | 11.10 | Insufficient | 3.90 | 7.00 | Yes | Hindu |
| 5 | 624426 | Tuberculosis | 62 | Male | 2+ | 12.30 | 9.00 | Deficient | Low | 10.30 | Insufficient | 4.00 | 6.60 | Yes | Hindu |
| 6 | 627578 | Tuberculosis | 39 | Male | 2+ | 10.80 | 10.00 | Deficient | Low | 12.50 | Insufficient | 3.20 | 5.40 | Yes | Hindu |
| 7 | 627946 | Tuberculosis | 44 | Male | 3+ | 8.00 | 8.00 | Deficient | Low | 13.90 | Deficient | 2.80 | 7.10 | Yes | Hindu |
| 8 | 628615 | Tuberculosis | 53 | Male | 3+ | 8.60 | 8.60 | Deficient | Low | 12.10 | Deficient | 4.10 | 8.00 | Yes | Hindu |
| 9 | 630103 | Tuberculosis | 70 | Male | 1+ | 14.50 | 9.80 | Deficient | Low | 8.80 | Insufficient | 4.80 | 8.60 | No | Hindu |
| 10 | 558466 | Tuberculosis | 56 | Male | 2+ | 9.03 | 9.03 | Deficient | Low | 2.80 | Deficient | 4.70 | 4.00 | Yes | Hindu |
| 11 | 561500 | Tuberculosis | 23 | Male | 1+ | 150.00 | 150.00 | Sufficient | Sufficient | 14.00 | Sufficient | 3.65 | 13.00 | Yes | Hindu |
| 12 | 570190 | Tuberculosis | 57 | Male | 2+ | 28.10 | 18.00 | Insufficient | Low | 11.80 | Sufficient | 3.90 | 6.40 | Yes | Hindu |
| 13 | 612704 | Tuberculosis | 60 | Male | 1+ | 12.50 | 10.00 | Deficient | Low | 12.70 | Insufficient | 1.90 | 5.30 | Yes | Hindu |
| 14 | 556682 | Tuberculosis | 28 | Male | 2+ | 16.90 | 9.00 | Deficient | Low | 12.20 | Insufficient | 1.67 | 7.60 | Yes | Hindu |
| 15 | 558466 | Tuberculosis | 65 | Male | 3+ | 34.30 | 34.30 | Sufficient | Sufficient | 13.80 | Sufficient | 4.90 | 6.90 | No | Hindu |
| 16 | 572353 | Tuberculosis | 55 | Female | 1+ | 18.70 | 10.00 | Deficient | Low | 13.90 | Insufficient | 3.50 | 5.90 | Yes | Hindu |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 17 | 528338 | Tuberculosis | 62 | Female | 1+ | 47.00 | 47.00 | Sufficient | Sufficient | 6.60 | Sufficient | 3.50 | 7.20 | Yes | Hindu |
| 18 | 576515 | Tuberculosis | 25 | Female | 2+ | 8.00 | 8.00 | Deficient | Low | 11.40 | Deficient | 4.00 | 7.00 | Yes | Hindu |
| 19 | 596929 | Tuberculosis | 27 | Female | 1+ | 12.90 | 9.90 | Deficient | Low | 17.70 | Insufficient | 3.00 | 5.20 | Yes | Hindu |
| 20 | 593140 | Tuberculosis | 25 | Female | 2+ | 18.40 | 9.00 | Deficient | Low | 9.30 | Insufficient | 3.40 | 5.50 | Yes | Hindu |
| 21 | 566264 | Tuberculosis | 52 | Female | 3+ | 19.60 | 9.60 | Deficient | Low | 8.60 | Insufficient | 4.60 | 7.40 | Yes | Hindu |
| 22 | 591027 | Tuberculosis | 65 | Male | 2+ | 34.00 | 34.00 | Sufficient | Sufficient | 14.90 | Sufficient | 4.40 | 8.90 | No | Muslim |
| 23 | 582183 | Tuberculosis | 50 | Male | 1+ | 18.00 | 8.00 | Deficient | Low | 14.60 | Insufficient | 5.00 | 6.65 | Yes | Hindu |
| 24 | 624426 | Tuberculosis | 62 | Male | 2+ | 11.50 | 10.00 | Deficient | Low | 12.20 | Insufficient | 4.10 | 5.30 | Yes | Hindu |
| 25 | 556682 | Tuberculosis | 28 | Male | 1+ | 96.00 | 96.00 | Sufficient | Sufficient | 9.60 | Sufficient | 3.70 | 9.00 | Yes | Hindu |
| 26 | 558466 | Tuberculosis | 65 | Male | 3+ | 17.20 | 10.00 | Deficient | Low | 10.60 | Insufficient | 3.60 | 5.20 | Yes | Hindu |
| 27 | 575724 | Tuberculosis | 27 | Male | 1+ | 26.60 | 20.00 | Insufficient | Low | 8.10 | Sufficient | 4.60 | 6.40 | Yes | Hindu |
| 28 | 666534 | Tuberculosis | 27 | Male | 2+ | 18.10 | 9.80 | Deficient | Low | 9.60 | Insufficient | 4.40 | 6.30 | Yes | Hindu |
| 29 | 612704 | Tuberculosis | 60 | Male | 2+ | 32.20 | 32.20 | Sufficient | Sufficient | 12.70 | Sufficient | 4.80 | 8.90 | Yes | Muslim |
| 30 | 613752 | Tuberculosis | 65 | Male | 3+ | 28.00 | 19.00 | Insufficient | Low | 14.50 | Sufficient | 2.60 | 7.00 | Yes | Hindu |
| 31 | 616920 | Tuberculosis | 75 | Male | 3+ | 22.00 | 18.00 | Insufficient | Low | 13.70 | Sufficient | 3.50 | 6.00 | No | Hindu |
| 32 | 558466 | Tuberculosis | 56 | Male | 2+ | 90.60 | 90.60 | Sufficient | Sufficient | 4.80 | Sufficient | 3.40 | 12.50 | Yes | Hindu |
| 33 | 561500 | Tuberculosis | 63 | Male | 3+ | 44.00 | 44.00 | Sufficient | Sufficient | 14.10 | Sufficient | 4.20 | 9.00 | Yes | Hindu |
| 34 | 568066 | Tuberculosis | 44 | Male | 2+ | 54.00 | 54.00 | Sufficient | Sufficient | 10.00 | Sufficient | 0.90 | 9.20 | Yes | Hindu |
| 35 | 570190 | Tuberculosis | 57 | Male | 3+ | 32.00 | 32.00 | Sufficient | Sufficient | 9.00 | Sufficient | 3.70 | 8.50 | Yes | Hindu |
| 36 | 578759 | Tuberculosis | 72 | Male | 1+ | 27.00 | 19.00 | Insufficient | Low | 8.60 | Sufficient | 3.90 | 8.00 | No | Muslim |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 37 | 582183 | Tuberculosis | 50 | Male | 3+ | 42.50 | 42.50 | Sufficient | Sufficient | 14.90 | Sufficient | 4.40 | 8.20 | Yes | Hindu |
| 38 | 602585 | Tuberculosis | 70 | Male | 1+ | 18.00 | 10.00 | Deficient | Low | 10.80 | Insufficient | 5.30 | 5.00 | Yes | Hindu |
| 39 | 621756 | Tuberculosis | 70 | Female | 1+ | 24.00 | 19.00 | Insufficient | Low | 5.40 | Sufficient | 4.80 | 6.40 | Yes | Hindu |
| 40 | 589032 | Tuberculosis | 64 | Male | 2+ | 17.00 | 9.00 | Deficient | Low | 15.10 | Insufficient | 3.80 | 6.60 | Yes | Muslim |
| 41 | 628515 | Tuberculosis | 75 | Female | 2+ | 26.00 | 18.00 | Insufficient | Low | 13.00 | Sufficient | 4.00 | 7.90 | Yes | Hindu |
| 42 | 626499 | Tuberculosis | 68 | Female | 2+ | 19.00 | 10.00 | Deficient | Low | 14.20 | Insufficient | 3.00 | 8.50 | Yes | Hindu |
| 43 | 627996 | Tuberculosis | 32 | Male | 2+ | 29.00 | 20.00 | Insufficient | Low | 9.70 | Sufficient | 3.20 | 9.00 | Yes | Hindu |
| 44 | 629256 | Tuberculosis | 46 | Female | 1+ | 8.00 | 8.00 | Deficient | Low | 7.70 | Deficient | 4.30 | 6.00 | Yes | Hindu |
| 45 | 607643 | Tuberculosis | 36 | Female | 1+ | 7.90 | 7.90 | Deficient | Low | 9.40 | Deficient | 4.90 | 6.10 | Yes | Hindu |
| 46 | 617935 | Tuberculosis | 50 | Female | 2+ | 22.00 | 20.00 | Insufficient | Low | 14.50 | Sufficient | 4.50 | 8.20 | Yes | Hindu |
| 47 | 627556 | Tuberculosis | 60 | Male | 1+ | 24.00 | 20.00 | Insufficient | Low | 11.00 | Sufficient | 3.60 | 7.80 | Yes | Hindu |
| 48 | 626526 | Tuberculosis | 55 | Male | 2+ | 36.00 | 36.00 | Sufficient | Sufficient | 10.60 | Sufficient | 3.50 | 8.20 | Yes | Hindu |
| 49 | 575724 | Tuberculosis | 24 | Male | 3+ | 18.00 | 8.00 | Deficient | Low | 8.10 | Insufficient | 3.40 | 7.00 | Yes | Hindu |
| 50 | 572286 | Tuberculosis | 65 | Male | 2+ | 24.00 | 20.00 | Insufficient | Low | 12.20 | Sufficient | 3.00 | 7.00 | Yes | Hindu |
| 51 | 579482 | Tuberculosis | 40 | Male | 1+ | 54.00 | 54.00 | Sufficient | Sufficient | 13.10 | Sufficient | 4.70 | 8.45 | Yes | Hindu |
| 52 | 584514 | Tuberculosis | 75 | Male | 2+ | 16.00 | 6.00 | Deficient | Low | 12.30 | Insufficient | 4.40 | 6.00 | Yes | Hindu |
| 53 | 591027 | Tuberculosis | 65 | Male | 3+ | 8.20 | 8.20 | Deficient | Low | 8.60 | Deficient | 3.30 | 5.00 | Yes | Hindu |
| 54 | 597009 | Tuberculosis | 60 | Male | 2+ | 19.80 | 9.80 | Deficient | Low | 9.40 | Insufficient | 3.60 | 7.00 | Yes | Muslim |
| 55 | 605356 | Tuberculosis | 75 | Male | 1+ | 45.00 | 45.00 | Sufficient | Sufficient | 10.00 | Sufficient | 3.90 | 9.00 | Yes | Hindu |
| 56 | 630103 | Tuberculosis | 70 | Male | 1+ | 33.70 | 33.70 | Sufficient | Sufficient | 8.80 | Sufficient | 3.80 | 9.00 | Yes | Hindu |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 57 | 411493 | Tuberculosis | 40 | Male | 3+ | 17.80 | 7.80 | Deficient | Low | 10.80 | Insufficient | 3.30 | 7.20 | Yes | Hindu |
| 58 | 637625 | Tuberculosis | 65 | Male | 1+ | 14.50 | 10.00 | Deficient | Low | 10.80 | Insufficient | 4.40 | 8.40 | Yes | Hindu |
| 59 | 633659 | Tuberculosis | 28 | Male | 2+ | 19.40 | 10.00 | Deficient | Low | 16.40 | Insufficient | 4.90 | 5.60 | Yes | Hindu |
| 60 | 696454 | Tuberculosis | 37 | Male | 3+ | 26.00 | 20.00 | Insufficient | Low | 14.60 | Sufficient | 4.70 | 9.00 | Yes | Hindu |
| 61 | 407167 | Tuberculosis | 75 | Male | 2+ | 17.00 | 7.00 | Deficient | Low | 9.80 | Insufficient | 4.80 | 9.00 | Yes | Hindu |
| 62 | 420505 | Tuberculosis | 60 | Female | 3+ | 19.00 | 9.00 | Deficient | Low | 8.90 | Insufficient | 5.50 | 8.00 | Yes | Hindu |
| 63 | 420255 | Tuberculosis | 45 | Female | 2+ | 26.00 | 20.00 | Insufficient | Low | 10.20 | Sufficient | 5.10 | 8.20 | Yes | Hindu |
| 64 | 423015 | Tuberculosis | 70 | Female | 2+ | 29.00 | 20.00 | Insufficient | Low | 15.50 | Sufficient | 1.70 | 8.30 | Yes | Hindu |
| 65 | 538171 | Tuberculosis | 60 | Male | 2+ | 55.00 | 55.00 | Sufficient | Sufficient | 14.00 | Sufficient | 4.60 | 7.50 | Yes | Hindu |
| 66 | 526823 | Tuberculosis | 40 | Male | 2+ | 25.00 | 18.00 | Insufficient | Low | 9.30 | Sufficient | 4.20 | 6.60 | Yes | Hindu |
| 67 | 521984 | Tuberculosis | 30 | Female | 3+ | 16.00 | 6.00 | Deficient | Low | 11.00 | Insufficient | 4.30 | 6.90 | Yes | Hindu |
| 68 | 499655 | Tuberculosis | 60 | Male | 3+ | 9.00 | 9.00 | Deficient | Low | 14.30 | Deficient | 3.70 | 7.00 | Yes | Hindu |
| 69 | 497275 | Tuberculosis | 45 | Male | 2+ | 25.00 | 20.00 | Insufficient | Low | 9.80 | Sufficient | 3.30 | 6.50 | Yes | Hindu |
| 70 | 486554 | Tuberculosis | 33 | Male | 2+ | 23.40 | 19.80 | Insufficient | Low | 7.10 | Sufficient | 5.30 | 6.70 | Yes | Hindu |
| 71 | 344848 | Non tuberculosis | 55 | Male | Negative | 67.00 | 67.00 | Sufficient | Sufficient | 9.00 | Sufficient | 3.40 | 9.00 | Yes | Hindu |
| 72 | 270123 | Non tuberculosis | 60 | Female | Negative | 54.00 | 54.00 | Sufficient | Sufficient | 9.20 | Sufficient | 3.00 | 9.20 | Yes | Hindu |
| 73 | 401166 | Non tuberculosis | 41 | Male | Negative | 23.00 | 18.90 | Insufficient | Low | 5.60 | Sufficient | 3.20 | 10.00 | Yes | Hindu |
| 74 | 401181 | Non tuberculosis | 60 | Female | Negative | 78.00 | 78.00 | Sufficient | Sufficient | 8.90 | Sufficient | 4.50 | 10.30 | Yes | Hindu |
| 75 | 33486 | Non tuberculosis | 60 | Male | Negative | 136.00 | 136.00 | Sufficient | Sufficient | 14.00 | Sufficient | 4.20 | 8.50 | Yes | Hindu |
| 76 | 401179 | Non tuberculosis | 43 | Male | Negative | 18.00 | 8.00 | Deficient | Low | 13.20 | Insufficient | 2.90 | 8.40 | Yes | Hindu |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 77 | 401095 | Non tuberculosis | 50 | Male | Negative | 35.00 | 35.00 | Sufficient | Sufficient | 12.90 | Sufficient | 3.30 | 9.20 | Yes | Hindu |
| 78 | 112262 | Non tuberculosis | 40 | Female | Negative | 47.00 | 47.00 | Sufficient | Sufficient | 14.60 | Sufficient | 2.90 | 9.50 | Yes | Muslim |
| 79 | 401150 | Non tuberculosis | 70 | Male | Negative | 24.00 | 17.00 | Insufficient | Low | 11.10 | Sufficient | 3.30 | 8.40 | Yes | Hindu |
| 80 | 395943 | Non tuberculosis | 42 | Male | Negative | 36.00 | 36.00 | Sufficient | Sufficient | 12.30 | Sufficient | 4.30 | 8.50 | Yes | Hindu |
| 81 | 309956 | Non tuberculosis | 60 | Female | Negative | 89.00 | 89.00 | Sufficient | Sufficient | 13.10 | Sufficient | 4.20 | 9.20 | Yes | Hindu |
| 82 | 400853 | Non tuberculosis | 53 | Male | Negative | 56.00 | 56.00 | Sufficient | Sufficient | 12.50 | Sufficient | 3.90 | 10.00 | Yes | Hindu |
| 83 | 400856 | Non tuberculosis | 47 | Female | Negative | 65.00 | 65.00 | Sufficient | Sufficient | 11.00 | Sufficient | 2.45 | 9.90 | Yes | Hindu |
| 84 | 348747 | Non tuberculosis | 61 | Male | Negative | 23.00 | 19.00 | Insufficient | Low | 7.00 | Sufficient | 2.20 | 7.60 | Yes | Hindu |
| 85 | 315663 | Non tuberculosis | 45 | Male | Negative | 72.50 | 72.50 | Sufficient | Sufficient | 8.00 | Sufficient | 3.90 | 10.00 | Yes | Hindu |
| 86 | 369843 | Non tuberculosis | 46 | Male | Negative | 75.00 | 75.00 | Sufficient | Sufficient | 8.90 | Sufficient | 3.40 | 9.60 | Yes | Hindu |
| 87 | 327342 | Non tuberculosis | 70 | Female | Negative | 76.00 | 76.00 | Sufficient | Sufficient | 9.80 | Sufficient | 1.90 | 8.90 | Yes | Hindu |
| 88 | 327463 | Non tuberculosis | 65 | Male | Negative | 34.00 | 34.00 | Sufficient | Sufficient | 10.00 | Sufficient | 2.60 | 8.40 | Yes | Hindu |
| 89 | 159166 | Non tuberculosis | 52 | Female | Negative | 32.00 | 32.00 | Sufficient | Sufficient | 10.00 | Sufficient | 3.60 | 6.70 | Yes | Hindu |
| 90 | 167659 | Non tuberculosis | 63 | Female | Negative | 27.00 | 20.00 | Insufficient | Low | 4.60 | Sufficient | 4.30 | 6.30 | Yes | Hindu |
| 91 | 290533 | Non tuberculosis | 62 | Male | Negative | 23.00 | 20.00 | Insufficient | Low | 13.00 | Sufficient | 4.30 | 6.20 | Yes | Muslim |
| 92 | 285035 | Non tuberculosis | 40 | Female | Negative | 21.00 | 19.80 | Insufficient | Low | 12.67 | Sufficient | 4.50 | 6.10 | Yes | Muslim |
| 93 | 375728 | Non tuberculosis | 60 | Male | Negative | 89.00 | 89.00 | Sufficient | Sufficient | 11.50 | Sufficient | 3.50 | 10.40 | Yes | Hindu |
| 94 | 34000 | Non tuberculosis | 80 | Male | Negative | 75.00 | 75.00 | Sufficient | Sufficient | 13.00 | Sufficient | 2.60 | 9.75 | Yes | Hindu |
| 95 | 173281 | Non tuberculosis | 60 | Male | Negative | 54.00 | 54.00 | Sufficient | Sufficient | 12.50 | Sufficient | 2.75 | 9.00 | Yes | Hindu |
| 96 | 188275 | Non tuberculosis | 57 | Male | Negative | 33.00 | 33.00 | Sufficient | Sufficient | 15.00 | Sufficient | 5.00 | 8.70 | Yes | Hindu |

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| 97 | 187538 | Non tuberculosis | 60 | Female | Negative | 12.00 | 8.90 | Deficient | Low | 7.40 | Insufficient | 3.20 | 6.00 | Yes | Muslim |
| 98 | 335931 | Non tuberculosis | 65 | Male | Negative | 28.00 | 20.00 | Insufficient | Low | 9.00 | Sufficient | 2.90 | 7.80 | Yes | Hindu |
| 99 | 400893 | Non tuberculosis | 65 | Male | Negative | 24.00 | 19.80 | Insufficient | Low | 13.00 | Sufficient | 3.20 | 7.00 | Yes | Hindu |
| 100 | 375732 | Non tuberculosis | 50 | Male | Negative | 35.00 | 35.00 | Sufficient | Sufficient | 8.00 | Sufficient | 3.10 | 6.50 | Yes | Hindu |
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