Original Article

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25-hydroxy Vitamin D and Calcium Levels in Patients of Drug Resistant Tuberculosis: A Retrospective Study from a Tertiary Care Institute of Eastern India

Internal Medicine Section

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ABSTRACT

Introduction: Drug Resistant Tuberculosis (DR-TB) is a rapidly escalating problem. Vitamin D and calcium serum levels can be an important determinant of Multidrug-Resistant Tuberculosis (MDR-TB) infection, progression to disease. The link between the serum level of 25-hydroxy vitamin-D {25(OH) D and MDR-TB is an emerging area for conducting evidence-based research.

Aim: To assess the serum 25(OH)D and calcium levels and its deficiency in all the patients with drug resistant tuberculosis.

Materials and Methods: This retrospective, observational study was conducted in the Department of Pulmonary Medicine, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India, from October 2019 to October 2020, in the newly detected 100 patients experiencing DR-TB. Patients sputum/body fluid samples were subjected for GeneXpert/Line Probe Assay (LPA) examinations to confirm resistance to anti-tubercular drugs. The frequency and prevalence of mean serum vitamin D and mean serum calcium levels were recorded based on age and gender. DR-TB categorised into H-Mono resistance, MDR-TB, Pre-Extensively Drug Resistant (Pre-XDR) and Extensively Drug Resistance Pulmonary Tuberculosis (XDR-PTB), based on GeneXpert and LPA of sputum/body fluid. Descriptive statistics were used to determine the characteristics of all the patients. All the statistical analysis was done using the Statistical Software for Data Sciences (STATA) software.

Results: Mean age of study population was 31.12±15.49 years. Among them 63 were males and 37 were females. The mean serum vitamin D level of 10.87±8.49 ng/mL (deficient) and serum calcium level of 8.62±0.82 mg/dL (normal) was reported. Mean serum vitamin D levels were deficient in all the four types of DR-TB (p-value=0.04), while changes in mean serum calcium level was non significant (p-value=0.15).

Conclusion: All patients with DR-TB have significant propensity to vitamin D deficiency. While changes in mean serum calcium level was non significant.

Keywords: Hypocalcaemia, Pulmonary medicine, Therapy regime

INTRODUCTION

A survey on global burden of Tuberculosis (TB) 2020 by World Health Organisation (WHO) reported around 10 million cases of TB with 1.2 million TB deaths in Human Immunodeficiency Virus (HIV) negative patients and around 2,08,000 deaths among HIV positive patients. It also reported a staggering estimation of around 1.7 billion people being infected with latent TB among which 5-10% will develop active TB during their lifetime [1,2].

As the current Programmatic Management of Drug resistant Tuberculosis (PMDT) guideline, 2021, under Ministry of Health and Family Welfare, Government of India, strongly recommends administration of multiple antibiotics in combinational pattern for an extended period of time [3], any discrepancies in adherence of these guidelines can increase the risk for an individual to develop Drug Resistance Tuberculosis (DR-TB) [4,5]. DR-TB is a rapidly escalating problem globally and worsens the existing clinical and infrastructural challenges for eliminating TB [6]. The development of drug resistance from antitubercular agents is an outcome of multiple biological, clinical and microbiological reasons such as non adherence to the recommended therapy regimen [7], errors in physicians management of TB [8,9], poor vascularisation of granulomatous lesions leading to suboptimal drug concentration and genetic resistance [10,11] intrinsic resistance in bacilli [12-14], phenotypic resistance and due to acquired resistance by chromosomal mutations in *Mycobacterium tuberculosis (MTB)*.

In 2018, WHO, estimated 4,84,000 (approximately 0.5 million) new TB cases with resistance to the most effective 1st line drug Rifampicin (RIF) and of those, around 78% (3,78,000) were Multidrug Resistant Tuberculosis (MDR-TB) cases (MDR-TB: resistant atleast to isoniazid and rifampin). A 6.2% of the MDR-TB cases were Extensively Drug Resistant (XDR-TB) cases to a fluoroquinolone and a second line injectable drug (e.g., kanamycin, amikacin). Countries like India (27%), China (14%) and Russian Federation (9%) jointly accounted for 50% of the global burden of MDR/RR-TB [2]. India, with 27% incidence of MDR/DR-TB cases and approximately 25% of all unreported TB cases, emerges as the largest contributor to the global burden of TB [2].

Vitamin D and its active metabolites 1,25-hydroxy vitamin D (25(OH) D) primary function is to regulate calcium physiology in the body [15]. It is also a potent immunomodulator which effects both innate and adaptive immunity through its vital role on macrophages, dendrites, and T-cell function which subsequently restricts MTB growth [16-18]. The link between the serum level of 25(OH) D and MDR-TB is an emerging area for conducting evidence-based research. In the recent years, several studies have been conducted to explore the possible link between serum vitamin D deficiency and TB but reported conflicting results [19-21]. Reason for such conflict may be directed towards different population, socio-economic status of country, food fortification policies, demographic features, geographical location, and season. Most of the studies reported vitamin D deficiency being a risk factor of TB and correlated with developing MDR-TB [19,22,23]. Similarly, calcium abnormalities have been variedly reported in different studies conducted in TB patients, with some studies reporting hypocalcaemia [24-26] and few other reporting hypercalcaemia [27-30] as a major biochemical findings. However, there is a scarcity on data linking serum calcium levels and DR-TB.

The aim of this study was to determine the frequency and prevalence of patients with serum calcium and vitamin D deficiency within DR-TB patients.

MATERIALS AND METHODS

This retrospective, observational study was conducted in the Department of Pulmonary Medicine, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India, a tertiary care hospital, to assess the serum 25(OH)D and calcium levels in the newly detected patients experiencing DR-TB from October 2019 to October 2020 and analysis of data was done in April 2021 to May 2021. After the approval from Ethics Committee of the hospital (vide letter number: 208/IEC/IGIMS/2021). Before inclusion, all the clinical case sheets were reviewed against strict eligibility criteria.

Inclusion criteria:

- Participants aged between 1-85 years.
- Both genders receiving outpatient/inpatient treatment for DR-TB.
- DR-TB diagnosed using sputum/body fluid GeneXpert, Line Probe Assay (LPA), liquid culture and sensitivity.
- Participants having DR-TB along with their clinical laboratory data including serum vitamin D and calcium levels.

Exclusion criteria:

- Presence of secondary immunodeficiency due to use of corticosteroid or immunosuppressant's or cytotoxic chemotherapy.
- Pregnancy,
- Concurrent use of Vitamin D or calcium supplements.

Patients were on either all oral longer regimen in patients having Pre-extensively Drug Resistant TB (Pre-XDR TB), and Extensively Drug-Resistant Tuberculosis (XDR-TB), all oral longer regimen without new drug (bedaquiline/delamanid) where contraindications to newer drugs were present. Shorter regimen was given in newly diagnosed MDR-TB, and conventional regimen depending upon indications and contraindications as per Programmatic Management of Drug Resistant (PMDT) guideline in India 2019 under Ministry of Health and Family Welfare, Government of India [31].

Procedure

A total of 100 subjects were included in the study after strictly assessing the records against the eligibility criteria. The demographic details, socio-economic conditions, drug resistant types, treatment regimen used, and serum vitamin D and calcium levels were reviewed. The frequency and prevalence of mean serum vitamin D and serum calcium levels were recorded. DR-TB subcategorised into:

- H-Mono resistance based on specimen's LPA report for first line drugs,
- MDR-TB, based on GENE XPERT report and
- Pre-XDR-PTB, Extensively Drug Resistance Pulmonary Tuberculosis (XDR PTB), based on specimen's first- and second-line LPA report.

Standard serum concentrations of vitamin D and calcium range recommended by US National Institute of Health was followed as a reference. Normal serum 25-OH vitamin D reference range is 25-80 ng/mL and of serum calcium is 9-10.5 mg/dL [32-34]. The socio-economic status of all the participants was analysed with the help of Modified Kuppuswamy Scale, 2019 [35].

STATISTICAL ANALYSIS

Categorical variables were presented as frequencies and percentages while continuous variables were presented as mean±standard deviation. All the statistical analysis was done using the STATA software. Pearson Correlation was used to find the correlation between serum vitamin D level and serum calcium. Chi-square tests were applied to find the p-value. The p-value ≤0.05 was considered as significant.

RESULTS

Mean age of study population was 31.12±15.49 years. Among them 63 were males and the 37 were females. Out of these, 100 DR-TB patients an overall mean serum vitamin D level of 10.87±8.49 ng/mL (deficient) and serum calcium level of 8.62±0.82 mg/dL (normal) was reported. Clinical and demographic characteristics of the DR-TB subjects are given in [Table/Fig-1].

Variables	n, %
Age (years) (mean±SD)	31.12±15.49
Gender (n)	
Male	63
Female	37
Socio-economic condition	
Upper	4
Upper middle	14
Lower middle	21
Upper lower	29
Lower	32
Drug Resistant-TB (DR-TB)	
H-Mono	7
MDR-PTB	10
Pre-XDR-PTB	60
XDR-PTB	23
Treatment regimen	
All oral longer (18-20) Lfx Bdq $_{(6 \text{ months or longer})}$ Lzd Cfz Cs	71
Shorter regimen (4-6) Mfx^{h} Km/Am Eto Cfz Z Hh E/ (5) Mfxh Cfz Z E	10
All oral longer without new drugs (6-8) Lfx Lzd Cfz Cs Am/12 Lfx Cfz Lzd	12
Conventional regimen (6-9) Lfx Km Eto Cs Z E/ (18) Lfx Eto Cs E	7
Vitamin D (ng/mL)	10.87±8.49
Serum calcium (mg/dL)	8.62±0.82
Reports	
CSF GeneXpert	1
Sputum GeneXpert	9
Sputum line probe assay	90

[Table/Fig-1]: Clinical and demographic characteristics of DR-TB subjects. *MDR-EPTB: Multi drug resistant extra pulmonary tuberculosis; *MDR-PTB: Multi drug resistant pulmonary tuberculosis; *Pre-XDR-PTB: Pre-extensive drug resistance pulmonary tuberculosis; *XDR-PTB: Extensively drug resistance pulmonary tuberculosis; *Sputum LPA: Sputum line probe assay; *Bdq: Bedaquiline; Lzd: Linezolid; Cfz: Clofazimine; Lfx: Levofloxacin; Cs: Cycloserine; Am: Amikacin; km: Kanamycin; Eto: Ethionamide; Z: Pyrazinamide; Hh: High dose isoniazide; E: Ethambutol; Mfxh: Moxifloxacin high dose; *CSF GeneXpert: Cerebrospinal fluid genexpert

The mean values for serum 25(OH) vitamin D and serum calcium levels were reported based on age group [Table/Fig-2], gender [Table/Fig-3] and DR type as shown in [Table/Fig-4]. All the four categories of patients were found to have low mean serum vitamin D levels [Table/Fig-2]. Whereas, serum calcium levels were reported to be deficient only in patients above 60 years of age. In contrast, mean serum calcium levels were recorded to be normal in H-mono, Pre-XDR-PTB and XDR-PTB groups, whereas, MDR-TB patients had mean serum calcium deficiency [Table/Fig-4]. A positive correlation was found between calcium dysregulation and vitamin D deficiency, (r=0.197, p-value=0.05) [Table/Fig-2].

The mean serum vitamin D levels were reported to be deficient in both males and females with values of 10.92±6.80 (ng/mL) and 10.80±10.88 (ng/mL), respectively (p-value=0.05) [Table/Fig-3]. However, mean serum calcium levels were found to be

Parameters/Characteristics	Serum vitamin D (ng/mL) Mean±SD	Serum calcium (mg/mL) Mean±SD
Age (years)		
1-20 (n=29)	9.37±6.25	8.74±0.74
21-40 (n=49)	10.88±8.15	8.69±0.66
41-60 (n=18)	13.75±12.36	8.36±0.22
61-80 (n=3)	8.93±3.00	8.03±0.60
>80 (n=1)	8.50	7.90
p-value	0.045	0.34
Total (N=100)	10.87±8.49	8.62±0.82
r=0.197, p-value=0.05		

[Table/Fig-2]: Mean levels of serum vitamin D and calcium based on age group, and their correlation among study population.
p-value ≤0.05 is considered as significant

Parameters	Gender	
	Male (n,%)	Female (n,%)
Vitamin D (ng/mL)		
<12 ng/mL (deficiency)	39 (61.90%)	30 (81.08%)
12-20 ng/mL (Inadequate)	18 (28.57%)	4 (10.81%)
≥21 ng/mL	6 (9.53%)	3 (8.1%)
Mean±SD	10.92±6.80	10.80±10.88
p-value=0.05		
Serum calcium (mg/dL)		
<7 mg/dL (Severe deficient)	1 (1.59%)	1 (2.7%)
7-8.49 mg/dL (Deficient)	24 (38.10%)	18 (48.65%)
≥8.5 mg/dL	38 (60.31%)	18 (48.65%)
Mean±SD	8.74±0.70	8.40±0.95
p-value=0.25		

[Table/Fig-3]: Serum vitamin D and serum calcium levels based on gender.
p-value calculated by Chi-square test; p-value ≤0.05 is considered as significant

DISCUSSION

This study focused on the serum vitamin D, and calcium level, and the prevalence of vitamin D and calcium deficiency in patients with DR-TB. The results showed a significant decrease of serum vitamin D level in all the five groups of age, both genders, and all the four types of DR-TB. However, the serum calcium levels were decreased only in the patients age group ≥60 years, female gender, MDR-TB, which is also seen in normal population aged >60 years, and among female population.

It has been reported that vitamin D deficiency is associated with common cold and flu caused by rhinovirus and influenza virus and increased incidence of upper respiratory tract infection along with tuberculosis, HIV and sepsis [36-38]. Since a great deal of evidence verifies that vitamin D plays an essential role in macrophage activation and the subsequent restriction of mycobacterium tuberculosis growth [18-39], several studies have explored the role of its serum level among infected TB patients with their prognosis [40,41]. Although, the results of these studies indicated that the vitamin D deficiency is prominent in active-TB patients and its contribution as a major risk factor for the development of TB infection [42,43], very few data exists of its role in patients with DR-TB. The present study showed that across the various sub-types of DR-TB, vitamin D was universally deficient. In concordance with the findings of the present study, the mean serum vitamin D level was found to be deficient among MDR-TB patients of Pakistan [44]. The study by Rathored J et al., among an Indian cohort reported of 354 patients with MDR-TB, found an inverse association between serum 25(OH) vitamin D concentration and time to sputum smear conversion [45]. However, no specific studies have evaluated the serum vitamin D levels in patients experiencing DR-TB. Since vitamin D deficiency is related to calcium dysregulation [46], a similar correlation has been found in the present study (r=0.197, p-value=0.05) [Table/Fig-2]. Although the present study did not evaluate the outcome of MDR-TB patients upon supplementation of vitamin D, some studies argue

Parameters	Drug resistant tuberculosis				p-value
	H-Mono (n=7)	MDR-TB (n=10)	Pre-XDR-PTB (n=60)	XDR-PTB (n=23)	
Vitamin D (ng/mL)					
<12 ng/mL (deficiency)	5 (71.43%)	7 (70%)	40 (66.67%)	17 (73.91%)	0.04
12-20 ng/mL (Inadequate)	2 (28.57%)	1 (10%)	14 (23.33%)	5 (21.74%)	
≥21 ng/mL	0 (0.00%)	2 (20%)	6 (10%)	1 (4.35%)	
Mean±SD	8.6571±2.95232	11.4300±7.19599	11.0102±10.06746	10.9500±5.20491	
Serum calcium (mg/dL)					
<7 mg/dL (Negligible)	0 (0.00%)	1 (10%)	1 (1.67%)	0 (0.00%)	0.15
7-8.49 mg/dL (Deficient)	2 (28.57%)	5 (50%)	25 (41.67%)	10 (43.48%)	
≥8.5 mg/dL	5 (71.43%)	4 (40%)	34 (56.67%)	13 (56.52%)	
Mean±SD	8.9571±1.03095	8.1100±1.63330	8.6118±.61133	8.7478±.66802	

[Table/Fig-4]: Serum vitamin D and serum calcium levels based on DR-TB types.
*MDR-PTB: Multi drug resistant pulmonary tuberculosis; *Pre-XDR-PTB: Pre-extensive drug resistance pulmonary tuberculosis; *XDR-PTB: Extensively drug resistance pulmonary tuberculosis; p-value ≤0.05 is considered as significant

normal in males with reported values of 8.74±0.70 (mg/dL), while borderline deficiency was seen in females with 8.40±0.95 (mg/dL), (p-value=0.25), which was not significant. Moreover, 61.90% prevalence of serum vitamin D deficiency was reported in males, whereas, a higher prevalence of 81.08% was seen in female population. There was a significant decrease in vitamin D level across the DR-TB population (p-value=0.04), although serum calcium levels were deficient, but it was not significant (p-value=0.15) [Table/Fig-4]. Further, a prevalence of serum calcium deficiency was reported to be 38.10% in males, and 48.65% among female [Table/Fig-3].

Among various categories of DR-TB patients, most of the patients were reported to have Pre-XDR-PTB, followed by XDR-PTB. Mean serum vitamin D levels were deficient in all the four types of DR-TB [Table/Fig-4].

that some patients supplemented with cod liver oil show noticeable improvement in strength, appetite and wellbeing [47,48].

However, the serum calcium level was deficient mainly in the patients with MDR-TB with more than 50% of the patient showing deficiency, whereas, a total of 43.48% (10/23), 43.33% (26/60), and 28.57% (2/7) patients with XDR-PTB, Pre-XDR-PTB, and H-Mono had showed serum calcium deficiency, respectively [Table/Fig-4].

A deficiency of serum calcium level among TB patients has previously reported by several studies [26,49], though the results are conflicting and no sufficient data is available among DR-TB patients. Soeroto AY et al., reported that MDR-TB patients on kanamycin and capreomycin have significantly altered serum calcium levels [50]. In contrast to this, Gohel MG et al., suggested that this deficiency of serum calcium level

could be the result of the inflammatory process in TB resulting into hypoalbuminemia and pseudo hypercalcaemia [51].

In the index study, significant relationship was found between serum vitamin D level with age group, whereas, serum calcium levels were found more deficient in the older age (age≥60 years). This could be due to the decreased synthesis and dietary uptake [52]. Relating to the gender-wise association, a significant deficiency of serum vitamin D was found in females when compared to males. This was consistent with the several studies from Pakistan [38] and Ethiopia [53] reporting higher levels of serum vitamin D deficiency among female gender. The reason for this may be ascribed to the pregnancy and inadequate sunlight exposure. In contrast, a recent study from Iran reported no significant gender-wise difference of serum vitamin D [54]. Jolliffe DA et al., in their meta-analysis has shown vitamin D as a potential strategy for prevention and treatment of MDR-TB. Preliminary evidence also has suggested that vitamin D level is associated with duration to bacteriological conversion and may have association with the risk of acquiring MDR-TB [55].

So, this study hints towards universal screening of vitamin D especially in DR-TB patients and its supplementation which has the potential for prevention and treatment of the disease.

Limitation(s)

Though the study is the first of its kind to report the serum vitamin D and calcium levels in each of the sub-types of DR-TB and associate it with various predisposing factors like age, gender, and drug regimen, the sample size used was not large enough to develop definitive conclusions. Further, the study was planned only at a single centre unit. Therefore, a similar study with a larger sample size should be conducted to verify the present results, considering the limitations of this study.

CONCLUSION(S)

In conclusion, all patients with DR-TB have significant propensity to vitamin D deficiency and calcium deficiency with female gender, and increased age group showing greater risk. The MDR-TB and XDR-PTB also showed greater risk of deficiency. Based on our findings, vitamin D and calcium supplementation should be considered in patients undergoing DR-TB treatment. This study also warrants the need for serum vitamin D and calcium level monitoring and future studies with larger sample size to establish this association in DR-TB patients. A large sample sized prospective studies are further required to clarify the association between vitamin D and DR-TB.

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