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A Study on Vitamin D Levels in Tuberculosis Patients

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Abstract
INTRODUCTION*: In TB patients and population controls multiple studies demonstrated contradictory findings in vitamin D intake. Moreover the prevalence of vitamin D in household TB contacts in India has not been examined in any previous study.* ***MATERIAL & METHODS****: It was a Hospital based comparative, Case control study conducted From June 2019 to October 2020. Group 1: Newly confirmed cases of tuberculosis (Pulmonary and Extra Pulmonary) in wards and OPD of Department of General Medicine, King George hospital, Visakhapatnam. Group 2: Apparently healthy attenders of non-Tuberculous patients in wards and OPD of Department of General Medicine, King George hospital, Visakhapatnam. Total sample size is 74 with 37 each in cases and control arms. Serum 25 hydroxy cholecalciferol were done by using chemiluminescent immunometric assay (CLIA). Deficiency is considered if value < 20 ng/ml* ***RESULTS****: The mean age of Cases was 40.35 ± 12.23, and for Controls was 40.89 ± 13.7 years. Majority participants belonged to 41 to 50 years age group in cases and 51 to 60 years age group in controls. Majority participants belonged to male gender in both cases and controls. Among cases majority participants were found to be Vitamin-D Deficient (37.8%) followed by Vitamin D insufficient (35.1%) and Vitamin D sufficient category (27%).* ***CONCLUSIONS****: There was difference between cases and controls distribution in terms of vitamin D levels which was found to be statistically significant. Mean Vitamin-D level of cases was significantly lower than controls.*
Key Words*: Tuberculosis, vitamin D levels, deficiency*

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I. Introduction

Tuberculosis is the leading cause of death of HIV-positive people and also contributes strongly to antimicrobial resistance. Most people who suffer from TB live in countries with low and middle income, but there is TB worldwide. It is estimated that nearly one fifth of the world population is contaminated with TB bacteria. Just 5-15% of those who suffer from active TB disease will get sick. The others are infected with TB, but not sick and are not likely to spread the disease [1,2].

TB susceptibility depends on diverse associations between host, bacterial and environmental influences such as poverty, malnutrition, overcrowding and other pathogenic exposures [3,4]. Host susceptibility Genetic factors such as interleukin1 (IL-1) polymorphisms have shown to affect the host response to TB in addition to environmental factors [5]. In the host defence against mycobacteria infection cell mediated immunity is essential [6]. Concurrently along with TB, the problem of Vitamin D deficiency (VDD) is a large global problem with high regional variability; adult prevalence of VDDs in North America ranges from 10 percent to 80 percent in Asia [7,8].

1,25 dihydroxy vitamin D is the major steroid hormone involved in regulation of mineral ion homeostasis. In response to UV radiation of the skin, a photo chemical cleavage results in the formation of vitamin D from 7- dehydrocholesterol. Cutaneous production of vitamin D is decreased by high solar protection factor sun blocks, which effectively impair skin penetration by ultraviolet light. Vitamin D from plant sources is in the form of vitamin D2 whereas that from animal sources is vitamin D3. Vitamin D enters circulation whether absorbed from the intestine or synthesized cutaneously bound to Vitamin D-binding protein, an alpha globulin synthesized in the liver. Vitamin D is subsequently hydroxylated in the liver by a cytochrome P450 oxidase in the mitochondria and microsomes. 25(OH)D is the major circulating and storage form of vitamin D. It circulates bound to vitamin D- binding protein. Half- life is 2-3 weeks. The second hydroxylation required for formation of mature hormone occurs in the kidney by 1alpha hydroxylase enzyme in the proximal convoluted tubule.

When exposed to ultraviolet light Vitamin D is synthesized in the skin and is also present in the diet primarily from food (Fish)[9]. By enhancing the phagocytic potential of monocyte and macrophage and increasing the development of peptides such as cathelicidin and also by immunomodulation Vitamin D was found to have an important role in the host immune defence against TB [10-13]. In animal studies when mice have been deficient in vitamin D Mycobacterium bovis replication was increased[14]. Studies have also shown that vitamin D causes a blast of superoxide and improves the MTB-infecting phagolysosome fusion [15-18]. Some experiments have also shown that vitamin D receptor polymorphisms impair the TB sensitivity of the host[5].

In TB patients and population controls multiple studies demonstrated contradictory findings in vitamin D intake [19-24]. In newly diagnosed TB patients, there are no preceding data indicating vitamin D deficiency prevalence and related factors compared with seemingly stable population controls in the region of the research. Moreover the prevalence of vitamin D in household TB contacts in India has not been examined in any previous study. Therefore in comparison with household contacts and community controls in Visakhapatnam Andhra Pradesh India, this study aims to determine the prevalence and related factors of vitamin D deficiency among newly diagnosed TB patients.

II. Material & Methods

This current study is Hospital based comparative, Case control study conducted From June 2019 to October 2020 in the Department of Medicine, Andhra Medical College, Visakhapatnam, Andhra Pradesh, India.

STUDY POPULATION: Group 1: Newly confirmed cases of tuberculosis (Pulmonary and Extra Pulmonary) in wards and OPD of Department of General Medicine, King George hospital, Visakhapatnam.

Group 2: Apparently healthy attenders of non-Tuberculous patients in wards and OPD of Department of General Medicine, King George hospital, Visakhapatnam.

Inclusion Criteria

1. Newly diagnosed pulmonary and Extra-pulmonary tuberculosis (CNS tuberculosis, abdominal tuberculosis and pleural effusion) patients of all ages.
2. Apparently healthy attenders of non-tuberculosis patients.

Exclusion criteria:

a) The patients and healthy attenders who are not willing to participate in the study.
b) Patients with chronic kidney disease, diabetes, hypertension, chronic liver disease and malabsorption syndromes.
c) Patients and healthy attenders who are smokers and alcoholics.
d) Patients who are HIV, HCV & HBsAg Positive.
e) Patients and healthy attenders who are on vitamin D medication and on immunosuppressive drugs.
f) Post-transplantation period (renal, cardiac).

Total sample size is 74 with 37 study subjects each in cases and controls arms.

METHOD OF COLLECTION OF DATA: This study was conducted at King George hospital, Visakhapatnam after taking written informed consent from the study participants and after getting approval from the ethical committee. Proforma was filled up during inclusion of patients (cases and controls) which contained epidemiological information (Age, sex, occupation and place) and questionnaires for risk factors evaluation for pulmonary Tuberculosis (smoking, alcohol, hypertension, diabetes, CKD, CLD, HIV and malabsorption) and information of clinical presentation. The following set of investigations are asked for the study population (cases and controls) in the study: Complete blood picture, Renal function tests, Liver function tests, Viral markers (HIV, HCV, HBsAg), Vitamin D levels, Chest X ray, Sputum for CBNAAT, Pleural fluid, Ascitic fluid and CSF with ADA levels and Fasting blood glucose levels.

Serum 25 hydroxy cholecalciferol levels were estimated by using chemiluminescent immunometric assay (CLIA). Deficiency is considered if value < 20 ng/ml. Insufficiency is considered if value lies between 21.0 - 30.0 ng/ml. Sufficiency is considered if value lies between 31.0 -100.0 ng/ml. Toxicity is considered if value > 100.1 ng/ml.

DATA ANALYSIS: Data was entered in MS-excel 2007 and data was analysed using IBM SPSS (Statistical Package for the Social Sciences) software trail version 22. Relevant statistical tests (chi-square test, Yates corrected chi-square test, pearsons correlation, point biserial test, T test) were applied and $p<0.05$ is considered as Statistical significance. Results were expressed in numbers and frequencies.

III. Results:

In this present study, among cases majority participants belong to 41 to 50 years age group (35.1%) with mean age being 40.35 years and among controls majority participants belong to 51 to 60 years age group (27%) with mean age being 40.89 years.

TABLE NO.1: AGE DISTRIBUTION AMONG STUDY PARTICIPANTS

AGE CATEGORIES	CASES		CONTROLS	
	FREQUENCY	PERCENTAGE	FREQUENCY	PERCENTAGE
<20	2	5.4%	3	8.1%
21 TO 30	8	21.6%	8	21.6%
31 TO 40	6	16.2%	6	16.2%
41 TO 50	13	35.1%	8	21.6%
51 TO 60	7	18.9%	10	27.0%
ABOVE 60	1	2.7%	2	5.4%
TOTAL	37	100.0%	37	100.0%
MEAN $\pm$ SD	40.35 $\pm$ 12.23		40.89 $\pm$ 13.7	
CHI-SQUARE VALUE:2.253, P VALUE: 0.8				

Gender distribution showed that among cases majority participants were belonging to male gender (59.5%) followed by females (40.5%); and among controls males were (56.8%) and females (43.2%). More than half the proportion were urban residents both in cases (59.5%) and controls (59.5%). Three fourth (75.7%) were literate among cases compared to controls where 56.8% were literate. Majority participants from both cases and controls belonged to employed category (81.1% and 75.7% respectively).

TABLE NO.2: GENDER DISTRIBUTION AMONG STUDY PARTICIPANTS

GENDER	CASE		CONTROL	
	FREQUENCY	PERCENTAGE	FREQUENCY	PERCENTAGE
FEMALE	15	40.5%	16	43.2%
MALE	22	59.5%	21	56.8%
TOTAL	37	100.0%	37	100.0%
CHI-SQUARE VALUE: 0.5, P VALUE: 0.8				

With regards to BCG scar, majority participants from both cases and controls were having BCG scar (83.8% and 89.2% respectively). Study participants with BMI < 18.5 are considered to be malnourished. Malnutrition with TB (13.5%) were more when compared to healthy controls (8.1%) and this difference between cases and controls was found to be statistically significant (P Value 0.04).

TABLE NO.3: BMI DISTRIBUTION AMONG STUDY PARTICIPANTS

BMI CATEGORIES	CASE		CONTROL	
	FREQUENCY	PERCENTAGE	FREQUENCY	PERCENTAGE
<18.5	5	13.5%	3	8.1%
18.5 TO 24.9	30	81.1%	20	54.1%
<25-29.9	2	5.4%	9	24.3%
>30	0	.0%	5	13.5%
TOTAL	37	100%	37	100%

Mean Hemoglobin of cases was 10.9 ± 2.2 and for controls 11.3 ± 1.8(MEAN ± SD). It shows that those who contracted disease are having slightly lesser Mean HB than those who did not contract TB. And this difference was not found to be statistically significant (P Value 0.3).

Mean WBC of cases was 7845 ± 1399, and for controls 5774 ± 1234 (MEAN ± SD). It shows that those who contracted disease are having higher Mean WBC than who did not. And this difference between mean WBC of cases and controls was found to be highly statistically significant (P Value 0.0001).

Mean Albumin level of cases was 4.35 ± 0.64 and for controls 4.46 ± 0.65 (MEAN ± SD). It shows that those who contracted disease are having slightly lesser Mean Albumin level than who did not contract TB. But this difference was not found to be statistically significant (P Value 0.4).

In this present study among the cases arm majority participants belonged to Vitamin-D Deficient category (37.8%) followed by Vitamin-D Insufficient (35.1%) and Vitamin-D Sufficient category (27%).

Among the controls majority participants were found to be Vitamin-D Sufficient (59.5%) followed by Vitamin-D Deficient (21.6%) and Vitamin-D Insufficient category (18.9%). The above difference between cases and controls distribution in terms of vitamin D levels was found to be statistically significant.

TABLE N0.4: VITAMIN D LEVELS DISTRIBUTION AMONG STUDY PARTICIPANTS

Vitamin D	**Cases**		**Controls**	
	Count	Column N%	Count	Column N%
Deficient	14	37.8	08	21.6
Insufficient	13	35.2	07	18.9
Sufficient	10	27.0	22	59.5
Total	37	100.0	37	100.0

Chi-square: 7.9 P value 0.01

Mean Vitamin-D level of cases was 24.8 ± 28.5 and for controls 34.2 ± 13.6 (MEAN ± SD). It clearly shows that those who contracted disease are having lesser mean Vitamin-D level than who did not have TB. And this difference between mean Vitamin-D level of cases and controls was found to be highly statistically significant (P value 0.0007)

TABLE NO.5: MEAN VITAMIN D LEVELS AMONG STUDY PARTICIPANTS

	CASES		CONTROLS	
	MEAN	SD	MEAN	SD
VIT-D LEVEL	24.8	8.5	34.2	13.6
UN-PAIRED T TEST, P VALUE 0.0007				

IV. Discussion

Age difference between cases and controls was not found to be statistically significant (P Value 0.8). Cases and controls were comparable in terms of age. A similar descriptive cross sectional study in south India by Vandana Balgi et al[25] in 80 tuberculosis (extrapulmonary and pulmonary) to estimate vitamin D levels had mean age of 42.34 ±14.65 year. The mean age of their study is comparable with present study mean age of cases. Another recent study done in 2019 by Sharma P et al[26] in North India on the Epidemiological profile of tuberculosis showed highest (72.2%) TB disease burden was seen in 20–60 year age group in their study. Their study finding of were also similar to the present study finding.

Gender distribution between cases and controls was not found to be statistically significant (P Value 0.8). Cases and controls were comparable in terms of gender distribution. A recent similar study done by Belay Tessema et al[27] from Ethiopia had male predominance (59.4%) which is almost similar to present study findings. Another recent study done by V Ramkumar et al[28] in 2019 showed male: female ratio as 1.27: 1 which is coinciding with the present study findings.

Literacy level distribution between cases and controls was not found to be statistically significant (P Value 0.8). Cases and controls were comparable in terms of Literacy level. It is surprising to see the high incidence TB among literates, which shows non-awareness of Tuberculosis spread among literates. This finding

in the present study is supported by Meseret Workineh et al[29] research work where they had 70% of literates in their TB population. By above findings it is suggested that awareness programs should be aimed at everyone irrespective of literacy level.

Though controls were slightly more in having BCG Scar compared to cases, BCG Scar distribution between cases and controls was not found to be statistically significant (P Value 0.7). In India, BCG vaccination usually administered in the early days of life, that does not protect the adults in contracting TB disease. Under universal immunization schedule BCG is administered to all children. Though above finding indicates nearly 90 percent of successful immunization in the past, it realizes the fact that at least 10% of the people were missed in the past. Another similar study done by Elisangela B. Maceda et al[30] from Brazil showed, 83% BCG Scar in Cases and 94% in controls. In their study controls were having more BCG scar than cases but it was not found to be statistically significant.

Malnutrition plays a major role in the pathogenesis of Tuberculosis. It can be better explained by vicious cycle of malnutrition and infection. A similar study done by Meseret Workineh et al[29] showed17.4 ± 2.25 mean BMI of cases, whereas in matched controls it was 21.4 ± 2.84. In their study cases mean BMI way lower than healthy controls, and the difference was statistically significant (0.001), which is supporting present study. Elisangela B. Maceda et al[30] study also showed Cases with 22.6 ± 26.0 mean BMI and Controls with 26.0 ± 3 mean BMI, which is almost similar to present study.

Among cases majority participants were belonging to Vitamin-D Deficient category (37.8%) followed by Vitamin-D insufficient category (35.1%) and Vitamin-D sufficient category (27%). Among controls majority participants were belonging to Vitamin-D Sufficient category (59.5%) followed by Vitamin-D deficient category (21.6%) and Vitamin-D insufficient category (18.9%). This difference between cases and controls distribution in terms of vitamin D levels was found to be statistically significant. Mean Vitamin-D level of cases was significantly lower than controls.

A study by Vandana Balgi et al[25] showed the Vitamin D mean levels in Tuberculosis cases were significantly lower (24.8±12.3) than healthy controls (34.4±6.1). These results are almost similar to present study mean values of vitamin D in cases and controls. Another similar study by Samah Sidahmed M.S Elsafi et al[31] had significantly smaller mean amount of Vitamin D in TB patients (26.7 ± 1.6) than in the non-TB controls (117.3 ± 3.2). Mean value of cases was similar to present study whereas controls mean values were way higher than present study.

Nouri-Vaskeh M et al[32] study also showed significantly lower mean serum levels of vitamin D in patients with TB than healthy subjects (22.66 ± 15.17 vs. 73.03±25.6 ng/mL; P<0.001). Mean value of cases was similar to present study whereas controls mean values were way higher than present study.

CONCLUSION:

The mean age of Cases was 40.35 + 12.23 and for Controls was 40.89 + 13.7 years. Majority participants belonged to 41 to 50 years age group in cases and 51 to 60 years age group in controls. Majority participants belonged to male gender followed by females in both cases and controls. Cases have higher mean WBC count compared to Controls which was statistically significant. Cases have slightly lower mean Albumin level compared to Controls and was not statistically significant. Among cases majority participants were found to be Vitamin-D deficient (37.8%) followed by Vitamin D insufficient (35.1%) and Vitamin D sufficient category (27%). In the control arm majority participants were found to be Vitamin-D Sufficient (59.5%) followed by Vitamin D deficient (21.6%) and Vitamin D insufficient category (18.9%). This difference between cases and controls distribution in terms of vitamin D levels was found to be statistically significant (chi square 7.9, P value 0.01). Mean Vitamin-D level of cases was significantly lower than controls (P value 0.0007).

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