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RESEARCH ARTICLE

VITAMIN D PROFILE OF TUBERCULOSIS PATIENTS AND ASSOCIATED FACTORS AMONG NEWLY DIAGNOSED TUBERCULOSIS PATIENTS AT A DOTS CENTRE OF DELHI

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ABSTRACT

Background: It is now generally accepted that Vitamin D Deficiency (VDD) is a worldwide health problem that affects not only musculoskeletal health but also a wide range of acute and chronic diseases. The role of VDD in predisposition of TB has been suspected since a long time.
Aim: The aim of the study was to assess the levels of Vitamin D, to find out the prevalence of VDD and the determinants associated with it among newly diagnosed tuberculosis patients attending Directly Observed Treatment Short-course (DOTS) center centre RHTC (Rural Health Training Centre) Najafgarh.
Methodology: A cross sectional DOTS center based study was conducted among 400 Tuberculosis patients. The study tool comprised of a pre-designed, pre-tested, semi-structured, interviewer administered questionnaire in Hindi. General physical examination and systemic examination was done for all the study participants.3 ml of blood was drawn from the ante-cubital vein using a 24G hypodermic needle and a 5cc plastic syringe. The Calbiotech, Inc. 25-hydroxy (25-OH) Vitamin D ELISA was used for quantitative determination of total 25-OH Vitamin D in human serum and plasma. The data was entered into Microsoft Excel after preparing a Master-chart. Data analysis was done using SPSS software licensed version 21. Chi-square test and Fischer exact test was used to determine the association.
Results: Out of 400 study participants, median age was 31 years ranged from a minimum of 7 years to a maximum of 90 years. Males were 66% and females were 44%. VDD was found in 90.5% patients and VDD was significantly associated with vegetarianism, inadequate consumption of dairy products, inadequate sun exposure and low BMI.
Conclusion: VDD was highly prevalent in Tuberculosis patients attending DOTS centre Najafgarh Delhi. Main contributing factors were inadequate sun exposure, vegetarianism, inadequate consumption of dairy products & low BMI.

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INTRODUCTION

Tuberculosis (TB) has existed for many years and still remains a major global health problem, particularly in the developing countries. The World Health Organization (WHO) estimates that 2 billion people have latent TB, while another 3 million people worldwide die each year due to TB (Herchline, 2017). India accounts for one fourth of the global TB burden. In 2015, an estimated 28 lakh cases occurred and 4.8 lakh people died due to TB (Programme. Annual Status Report. New Delhi: Central TB Division, 2017). In India, TB is mainly a disease of the poor as majority of its victims are migrant laborers, slum dwellers, those living in poor condition, residents of backward areas and slums (Hossein-nezhad and Holick, 2013). It is now generally accepted that Vitamin D Deficiency (VDD) is a worldwide health problem that affects not only musculoskeletal health but also a wide range of acute and chronic diseases. Vitamin D is best recognized as a regulator of calcium and bone homeostasis although it has diverse additional cellular functions, affecting differentiation, proliferation, activation, and death (Wallis and Zumla, 2016). The role of VDD in predisposition of TB has been suspected since a long time. Before the etiologic cause of TB was determined in 1903 by Sir Robert Koch, cod liver oil and sun exposure, both sources of Vitamin D, were commonly used in the treatment of TB in the pre-antibiotic era (Mastala *et al*., 2013; Ustianowski *et al*., 2005). The active form of Vitamin D is $1,25(OH)D_3$ and it has shown to inhibit growth of *Mycobacterium tuberculosis* through stimulating cell-mediated immunity (Nnoaham and Clarke, 2008). The biologically active form of vitamin D has been shown to affect innate immunity by modulating macrophage function; this may enhance protection against TB infection (Raja, 2004; Baeke *et al*., 2010).

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Vitamin D also up-regulates antimicrobial peptide cathelicidin and enhances killing of intracellular *M. tuberculosis*. There are few studies that have been done in India which have tried to address the issue of VDD and its association with TB but most of them were conducted in admitted patients (Selvaraj, 2011; Sly *et al*., 2001). There is paucity of studies on Vitamin D3 level among TB patients from out-patient facilities. Hence, the current study was planned against this background to find out the serum Vitamin-D status and various determinants of Vitamin D deficiency amongst the patients attending a Directly Observed Treatment Short-course (DOTS) center.

MATERIALS AND METHODS

The study was a cross-sectional study based at DOTS Centre located at RHTC, Najafgarh, New Delhi. It is located in the south-west district of Delhi, at latitude 28.61 degrees North and at a longitude of 76.89 degrees East. The study was carried out over a period of 18 months. The patients belonging to Category I, Category II and MDR who were attending DOTS, RHTC Najafgarh constituted the study population.

Sample size Estimation was done using the formula $n = 4\ pq/l^2$ where, p = known prevalence of the disease, q = 1 – p, l = error. For the purpose of sample size calculation p of 50% was considered due to paucity of studies in India on Vitamin D status of TB patients in DOTS centre. Hence, using p=50% with the absolute error of 5%, the total sample size was calculated to be 400. The study tool comprised of a pre-designed, pre-tested, semi-structured, interviewer administered questionnaire in Hindi. The questionnaire had questions pertaining to socio-demographic information, clinical features of Tuberculosis, history of substance abuse, average consumption of common dairy products such as milk, butter, ghee (clarified butter), paneer and curd in a week etc. General physical examination and systemic examination was done for all the study participants. All patients in whom VDD was detected were counselled about the diet, sun exposure and started on Vitamin D supplementation and further referred to the nearest government health facility.

Calculation of sun exposure: This was done by taking detailed history of exposure to the sun over the past two weeks, given that the half-life of Vitamin 25(OH) D is approximately 15 days. The daily average exposure to sunlight in minutes was noted by asking the duration of time that the participants spent outdoors at different times of the day, morning (sunrise till 10 am), afternoon (10 am till 2pm) and evening (2 pm onwards till sunset). The Body surface area (BSA) exposed to sunlight was documented by using the rule of nine. The surface area of the parts of the body on which the participant applied sunscreen (with SPF>8), and the parts of the body which were covered by the use of a *purdah* or *burkha* were deducted from the exposed BSA to yield the Net BSA exposed. For detailed comparison between different times of the day, the Sun Exposure Index (SEI) was calculated for morning (MSEI), afternoon (ASEI) and evening (ESEI). A daily 15 minutes of exposure to arms and face any time during the day is considered to produce adequate Vitamin D levels in Caucasians. Indian skin due to higher melanin content requires 2-4 times the exposure. (Holick, 1994) Adequate sun exposure was defined as one with any SEI equal to or above 16.875. This figure was derived by multiplying 22.5% net BSA (18% arms plus 4.5% face and neck) with 0.25 hours/day (15 minutes) and a multiplication factor of 3 (as Indians need thrice the exposure).

Blood sample collection: 3 ml of blood was drawnfrom the ante-cubital veinusing a 24G hypodermic needle and a 5cc plastic syringe.

Laboratory analysis: The Calbiotech, Inc. 25-hydroxy (25-OH) Vitamin D ELISA was used for quantitative determination of total 25-OH Vitamin D in human serum and plasma (Holick, 2009; Morris, 2005; Bikle, 2010; Zerwekh, 2008; Moyad, 2009).

Data analysis: was done using SPSS software licensed version 21. All the variables were analysed using descriptive statistics to calculate frequencies, mean, range etc. Bi-variate analysis was done using the Chi-square test and Fischer exact test, to determine the association between various socio-demographic variables, Vitamin D levels, diet, Body Mass Index (BMI), Sun Exposure Index (SEI) & sputum smear positivity. A p-value of less than 0.05 was considered as statistically significant. Approval from Institutional Ethical Committeeof VMMC and Safdarjung Hospital, New Delhi was taken before the start of the study. Written and informed consent were obtained from the study participants.

RESULTS

The age of the participants ranged from a minimum of 7 years to a maximum of 90 years. The median age was 31 years. 48 (12%) were illiterate and only 38(9.5%) had professional degree or honours. As per Modified B.G. Prasad's scale 194(73.5%) belonged to Socio economic classV.

Table 1. Distribution of study participants according to the Socio-demographic profile (N=400)

S. No.	Socio-demographic profile of study participants	Number (%)
I	Age groups (in completed years)	
1	0-14	14(3.5)
2	15-59	343(85.7)
3	≥60	43(10.8)
II	Sex	
1	Male	264(66)
2	Female	136(34)
III	Religion	
1	Hindu	386(96.5)
2	Muslim	12(3)
3	Others	2(0.5)
IV	Educational status	
1	Illiterate	48(12)
2	Primary school	80(20)
3	Middle school	68(17)
4	High school	50(12.5)
5	Higher secondary school	54(13.5)
6	Graduate/ post graduate	62(15.5)
7	Professional or Honours	38(9.5)
V	Type of Family	
1	Nuclear	300(75)
2	Joint / extended	100(25)
VI	Socio economic class (Modified B.G. Prasad's scale, May 2016)	
1	III	4(1.0)
2	IV	102(25.5)
3	V	294(73.5)

Table 2. Distribution of study participants as per category of TB at the time of diagnosis. (N=400)

S. No.	Category of TB	At the time of diagnosis, Number(%)
1	Cat I	306(76.5)
2	Cat II	86(21.5)
3	Cat IV	8(2)

Table 4. Distribution of study participants according to time & duration of sun exposure in past week (N=400)

S. No.	*Time of the day	Number of patients with exposure n (%)	Minimum (minutes) n (%)	Maximum (minutes) n(%)	Mean duration (minutes)
1.	Morning	370(92.5)	0(7.5)	120(2.0)	15.8
2.	Afternoon	104(26.0)	0(74.0)	180(1.0)	9.7
3.	Evening	124(31.0)	0(69.0)	180(0.5)	9.3
4.	No response	30	0	0	0

*Multiple Responses

Table 5. Distribution of study participants as per frequency of consumption of common dairy products in the past week (N=400)

S. No.	*Dairy Food source	5-7 days a week		2-4 days a week		Once a week or less		No consumption	
		No.	%	No.	%	No.	%	No.	%
1.	Milk	268	67	113	28.2	0	0	19	4.8
2.	Butter	153	38.3	227	56.8	4	1	16	4
3.	Ghee	189	47.3	189	47.3	5	1.3	17	4.3
4.	Curd	131	32.8	234	58.5	13	3.3	22	5.5
5.	Paneer/Cheese	11	2.8	146	36.5	206	51.5	37	9.3

*Multiple Responses

Table 6. Distribution of study participants according to level of Vitamin 25(OH)D. (N=400)

S. No.	Vitamin 25(OH)D levels	Cut-off (ng/mL)	Number (n)	Percentage (%)
1.	Normal Vitamin D levels	30-100	38	9.5
2.	Vitamin D insufficiency	10-29.9	266	66.5
3.	Vitamin D deficiency	<10	96	24

Table 7. Association between socio-demographic characteristics and insufficient/deficient levels of Vitamin D of study participants. (N=400)

S. No.	Characteristic	Insufficient/deficient levels of Vitamin D Number (%)		p-value
		Present	Absent	
1	Age group			0.365#
	0-14	14(100)	0(0)	
	15-59	311(90.7)	32(9.3)	
	>/=60	37(86)	6(14)	
2	Sex			0.293*
	Male	236(89.4)	28(10.6)	
	Female	126(92.6)	10(7.4)	
3	Religion			0.632#
	Hindu	350(90.7)	36(9.3)	
	Others	12(85.7)	2(14.3)	
4	Educational status			
	Illiterate	46(95.8)	2(4.2)	0.290#
	Literate	316(89.8)	36(10.2)	
5	Type of family			0.844*
	Nuclear	272(90.7)	28(9.3)	
	Joint/extended	90(90)	10(10)	
6	Socio economic class			0.321#
	III	4(100)	0(0)	
	IV	96(94.1)	6(5.9)	
	V	262(89.1)	32(10.9)	

'*' indicates Chi square test, '#' indicates 2 sided significance from Fisher's Exact Test, bold values indicates significant p-value.

Table 8. Association between tobacco and alcohol intake and insufficient/deficient levels of Vitamin D of study participants (N=400)

S. No.	Characteristic	Insufficient/deficient levels of Vitamin D Number (%)		p- value <0.05
		Present	Absent	
1.	Smoked form of tobacco			0.085*
	Never	137(93.8)	9(6.2)	
	Ever	225(88.6)	29(11.4)	
2.	Smoke-less form of tobacco			0.112*
	Never	143(93.5)	10(6.5)	
	Ever	219(88.7)	28(11.3)	
3.	Alcohol use			0.897*
	Never	185(90.7)	19(9.3)	
	Ever	177(90.3)	19(9.7)	

'*' indicates Chi-square Test.

There were 306 (76.5%) patients with Cat I, 86(21.5%) with Cat II and 8(2%) of them with Cat IV. There was no Cat III patient of TB. Out of the 400 study participants 309(77.2%) were vegetarian and 91(22.8%) were non- vegetarian.

less than 16.875, evening sun exposure index (ESEI) and Total sun exposure index (TSEI) of less than 16.875 had insufficient/deficient level of Vitamin D and the difference is statistically significant ($p<0.05$).

Table 9. Association between body surface exposed to sun and insufficient/deficient levels of Vitamin D of study participants (N=400)

S. No.	Characteristics of sun exposure	Insufficient/deficient levels of Vitamin D Number (%)		p- value <0.05
		Present	Absent	
1.	Net BSA (Body Surface Area)Exposed			0.404#
	<22.5%	324(90)	36(10)	
	≥22.5%	38(95)	2(5)	
2.	MSEI (Morning Sun Exposure Index)			
	<16.875	358(91.3)	34(8.7)	0.004#
	≥16.875	4(50)	4(50)	
3.	ASEI (Afternoon Sun Exposure Index)			0.047#
	<16.875	360(90.9)	36(9.1)	
	≥16.875	2(50)	2(50)	
4.	ESEI (Evening Sun Exposure Index)			0.010#
	<16.875	356(91.3)	34(8.7)	
	≥16.875	6(60)	4(40)	
5.	TSEI (Total Sun Exposure Index)			0.000*
	<16.875	352(95.1)	18(4.9)	
	≥16.875	10(33.3)	20(66.7)	

'#' indicates 2 sided significance from Fisher's Exact Test, '*' indicates Chi-square test and bold values indicate significant p-value

Table 10. Association between intake of common dairy products and insufficient/deficient levels of Vitamin D of study participants (N=400)

. No.	Vegetarian sources of Vitamin D	Insufficient/deficient levels of Vitamin D Number (%)		p- value <0.05
		Present	Absent	
1.	Vegetarianism			0.000#
	Present	307(99.4)	2(0.6)	
	Absent	55(60.4)	36(39.6)	
2.	Milk consumption			0.000#
	5-7 days/ week	234(87.3)	34(12.7)	
	2-4 days/ week	113(100)	0	
	No consumption	15(78.9)	4(21.1)	
3.	Ghee consumption			0.007#
	5-7 days/ week	162(85.7)	27(14.3)	
	2-4 days/ week	180(95.2)	9(4.8)	
	Once a week or less	4(80)	1(20)	
	No consumption	16(94.1)	1(5.9)	
4.	Butter consumption			0.188#
	5-7 days/ week	133(86.9)	20(13.1)	
	2-4 days/ week	211(93)	16(7)	
	Once a week or less	4(100)	0	
	No consumption	14(87.5)	2(12.5)	
5.	Paneer/Cheese consumption			0.001#
	5-7 days/ week	6(54.5)	5(45.5)	
	2-4 days/ week	127(87)	19(13)	
	Once a week or less	194(94.2)	12(5.8)	
	No consumption	35(94.6)	2(5.4)	
6.	Curd consumption			0.007#
	5-7 days/ week	109(83.2)	22(16.8)	
	2-4 days/ week	220(94)	14(6)	
	Once a week or less	13(100)	0	
	No consumption	20(90.9)	2(9.1)	

'#' indicates 2 sided significance from Fisher's Exact Test & bold values indicate significant p-value.

Table 11. Association between BMI and insufficient/deficient levels of Vitamin D of study participants (N= 400)

S. No.	Characteristic	insufficient/deficient levels of Vitamin D Number (%)		p-value
		Present	Absent	
1	BMI at the time of diagnosis			0.008*
2	Under weight	232(93.5)	16(6.5)	
3	Normal/Overweight/obese	130(85.5)	22(14.5)	

'*' indicates significant p-value, bold values indicate significant p-value.

Only 38(9.5%) of the study participants had Vitamin D levels in the normal range. There was no statistically significant association between Vitamin D insufficient/deficient level and tobacco use in any form and alcohol use ($p>0.05$).Higher proportion of those with Morning sun exposure index (MSEI) of less than 16.875, afternoon sun exposure index (ASEI) of

There was a higher proportion of participants with Vitamin D insufficient/deficient level and vegetarianism as compared to those without vegetarianism and the difference is statistically significant ($p<0.05$). Also there was a statistically significant association observed between consumption of Milk, Ghee, Paneer/cheese & Curd intake and Vitamin D level ($p<0.05$).

Higher proportion of those who were Underweight had Insufficient/deficient levels of Vitamin Das compared to those who were Normal/Overweight/ Obese, and this result was statistically significant ($p<0.05$).

DISCUSSION

The prevalence of VDD in present study was found to be 90.5%. This is similar to results of studies conducted by Ritu Karoli (Lucknow, 2012-2013) (Manhar, 2015), Sasidharan P K (Kerala, 1999-2000) (Sasidharan *et al*., 2002), Najeeha Talat (Karachi, 2001-2004) and Syed Fawad Mashhadi (Rawalpindi, 2013). Noemie Boillat Blanco (Tanzania, 2013) Conducted a case control study among 167 outdoor pulmonary tuberculosis patients where the prevalence of Vitamin-D Deficiency was reported to be 27.6%, Friis H (Tanzania, 2006-2009) conducted a cross-sectional study among 1250 PTB where 17.5% had VDD. That difference may be because of different cut off levels used for measuring Vitamin D levels in different studies. In the present study, there was a statistically significant association between body surface exposed to sun and insufficient/deficient levels of Vitamin D of study participants ($p<0.05$), which is similar to the study conducted by Nurbazlin (Malaysia, 2013), where vitamin D concentration was positively associated with the number of hours of sun exposure per week and the Sun Index, and negatively correlated with fraction of BSA exposed to the sun.

Intake of common dairy products was also found to be significantly associated in our study with insufficient/deficient levels of Vitamin D of study participants ($p<0.05$), which was also reported by Ritu (2014). In our study we observed a statistically significant association between low BMI & insufficient/deficient levels of Vitamin D levels. Majority of the TB patients were malnourished in our study. Similar association has been observed in study conducted by Lagunova (Norway, 2009), among 2,126 registered persons (1737 women, 389 men) where women with BMI less than 20 had lower serum Vitamin D level than women with normal BMI. Contrary to this many authors have found statistically significant association between high BMI & Vitamin D levels. Vimaleswaran (United Kingdom, 2013) in a Bi-directional Mendelian Randomization Analysis of 21 Cohorts(up to 42,024 participants) found that higher BMI lead to lower Vitamin D levels & Shah (Gujrat, 2016) in a case control study among 107 obese and 43 non-obese study participants also reported the similar results.

The main reason cited for low Vitamin D in obese is that Vitamin D deposited in fat tissue doesn't become available in obese population. In the present study, nearly half (46.3%) of the study participants were current smokers and 17.2% had quit smoking, whereas, 23% were current user of smoke-less form of tobacco and 38.7% quit the same. This result is similar to the studies conducted by Jethani S (Uttarakhand, 2010), Thakur R (Himachal Pradesh, 2009-2010) and Oliveira MG (Brazil, 2007-2012), where more than half of the TB patients were current or ex-smokers. In the present study, there is no statistically significant association between insufficient/ deficient level of Vitamin D and smoking practices ($p>0.05$). This result is similar to study conducted by Nnoahan K E (United Kingdom, 2007), however it differs from the study conducted by Arora (Noida, 2016).

The reason for this may be that the study participants in the latter study were not TB patients. This study addresses the status of Vitamin D among Tuberculosis patients in an outpatient setting. A pretested-predesigned & valid questionnaire was used for data collection. Sample size was adequate and scientifically calculated and interviews were conducted by single interviewer to eliminate interviewer bias. Since the study was a questionnaire based study, the effect of recall bias on the information provided by the study participants cannot be ruled out. Effect of skin pigmentation on Vitamin D level could not be assessed.

Conclusion

To conclude from our study, Vitamin D Deficiency was highly prevalent (90.5%) in Tuberculosis patients attending DOTS centre Najafgarh Delhi. Several factors such as inadequate sun exposure, vegetarianism, inadequate consumption of dairy products & low BMI showed a statistically significant association with Vitamin D Deficiency, hence Vitamin D supplements may be considered for those attending DOTS centre. IEC & dietary counselling about increased intake of dairy products and non-vegetarian food items, where possible is recommended.

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