Journal of Tuberculosis Research, 2018, 6, 251-269
http://www.scirp.org/journal/jtr
ISSN Online: 2329-8448
ISSN Print: 2329-843X

Vitamin D: Level of Vitamin D3 in AFB Positive PTB Patients in Initial Diagnostic Phase

Anwar Ali Jamali[1*], Jawaid Hussain Lighari[2], Shamasddin Shaikh [1], Ghulam Mustafa Jamali[1], Bhojo Mal Tanwani[3], Muhammad Aslam Channa[4], Ameer Ali Jamali[5], Muhammad Ali Suhail[6]

[1]Department of Medicine, Peoples University of Medical and Health Sciences, Nawabshah, Pakistan
[2]Department of Community Medicine, Peoples University of Medical and Health Sciences, Nawabshah, Pakistan
[3]Department of Physiology, Peoples University of Medical and Health Sciences for Women, Nawabshah, Pakistan
[4]Department of Anatomy, Gambat Institute of Medical Sciences, Khairpur, Pakistan
[5]Department of Peadiatrics, Peoples University of Medical and Health Sciences for Women, Nawabshah, Pakistan
[6]Department of Surgery, Peoples University of Medical and Health Sciences for Women, Nawabshah, Pakistan
Email: *jamalianwarali@gmail.com

How to cite this paper: Jamali, A.A., Lighari, J.H., Shaikh, S., Jamali, G.M., Tanwani, B.M., Channa, M.A., Jamali, A.A. and Suhail, M.A. (2018) Vitamin D: Level of Vitamin D3 in AFB Positive PTB Patients in Initial Diagnostic Phase. *Journal of Tuberculosis Research*, **6**, 251-269.
https://doi.org/10.4236/jtr.2018.64023

Received: September 16, 2018
Accepted: October 12, 2018
Published: October 15, 2018

Abstract

Background: A relationship among vitamin D and pulmonary tuberculosis. **Objective:** To conclude the occurrence of Vitamin D insufficiency in subjects suffering from pulmonary TB. **Design:** This was a cross sectional study. **Setting:** Current study was performed at department of medicine, Peoples Medical College Hospital Nawabshah starting from January 2017 to December 2017. **Samples: 385** AFB positive subjects of pulmonary tuberculosis after achieving the criteria of selection were recruited. **Material and Methods:** After a brief discussion, the patients were characterized for variable evaluation such as age, gender, sputum AFB and duration of disease and presence of low vitamin D levels. Sputum AFB criterion was used for Data collection. Fasting blood samples were collected for analysis of vitamin D levels in all subjects of AFB positive pulmonary tuberculosis. **Results:** In **385** diagnosed patients with smear positive PTB, 273 (70.9%) males and 112 (29.1%) were female. Vitamin D levels were within normal or sufficient range in 134 (34.8%), below normal range in 251 (65.2%) cases (insufficient in 09.56% (24/251) and deficient in 90.43% (227/251) cases). **Conclusion:** Decreased levels of vitamin D were common in subjects with AFB smear Positive PTB cases.

Keywords

Pulmonary Tuberculosis, Vitamin D, Vitamin D Insufficiency, 25-Hydroxyvitamin D.

1. Introduction

Tuberculosis (TB) is the most important community health issue worldwide.

In 2011 it was assessed that about 8.7 million new cases of tuberculosis were reported and about 1.4 million deaths was related to this disease [1]. Association of vitamin D deficiency/insufficiency as a cause of Tuberculosis or its manifestations as malnutrition is still undetermined. Incidence and progression of tuberculosis had been related with many factors and vitamin D deficiency is considered as one of them [2]. Low levels of vitamin D were noted in subjects with Tuberculosis in comparison to controls. Vitamin D deficiency had been related with higher risk of Tuberculosis, also increased risk of developing active tuberculosis in subjects with latent tuberculosis infection had been noted [3]. The chief source of vitamin D in humans remains the sun exposure. The conversion of 7-dehydrocholesterol to vitamin D3 via pre-vitamin D3 in human derma is induced by sun exposure. Liver and kidneys play essential role in the activation of vitamin D3 from 25-hydroxyvitamin D (25(OH)D) to bioactive form 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) [4]. In a meta-analysis on relationship among vitamin D deficiency and tuberculosis, increased risk of active tuberculosis was observed in subjects with decreased levels of this vitamin [5]. The bioactive form of vitamin D3 binds with receptors of vitamin D (VDR), activation of VDR signaling and induction of mitochondrial response series leads to autophagy, fusion of phagolysosome, cathelicidin release and activation, and intracellular death of Mycobacterium Tuberculosis bacilli [4] [6] [7].

Studies had been conducted throughout the entire world on tuberculosis and vitamin D levels but no study had been carried out here in our setup. Vitamin D deficiency and pulmonary tuberculosis are the major issues of our population. This study will elaborate the association of vitamin D in subjects with AFB positive tuberculosis because both of these issues are linked with morbidity and mortality as reported all over the globe.

This study will help in making the public health policies keeping in view with vitamin D levels and tuberculosis. This study will determine the frequency of decrease levels of vitamin D in subjects with different gender groups in tuberculosis and to find out whether vitamin D has any protective role in the tuberculosis.

The rationale behind current study was that there is paucity of such type of researches in our population and on other hand most of the previous studies were done on retrospective data. Further research on association of vitamin D with pulmonary tuberculosis in Pakistan is needed. This study estimates the risk of acquiring tuberculosis in relation to different levels of vitamin D in Pakistani population.

Operational Definitions

PTB: Pulmonary tuberculosis is a commonailment of lungs results due to infectious agent mycobacterium tuberculosis, a small rod shaped bacilli causing dis-

eases in mankind.

Sputum AFB: This is a laboratory investigation also known as acid-fast bacillus (**AFB**) stain or a tuberculosis (TB) smear and accomplished on a sample of sputum from subjects suspected for tuberculosis to conclude if a subject has tuberculosis or other category of mycobacterial infection [8].

Vitamin D Deficiency: Levels of serum 25(OH) D3 > 30 ng/ml are considered normal, levels > 20 and <30 ng/ml are insufficient and levels below < 20 ng/ml are labeled as deficiency [9].

2. Material and Methods

Inclusion criteria: All male and female patients with clinical history of pulmonary tuberculosis and smear positive sputum for AFB were included.

Exclusion Criteria: Patients not willing for taking part in study, known cases of respiratory diseases other than PTB.

2.1. Ethical Consideration

Approval of study was sought from the hospital ethics committee PMCH Nawabshah. Permission for data collection will be taken from the head of department of the Medicine. Written informed consent will be obtained from adult subjects while ensuring that the data will be kept confidential. People will be thoroughly informed about the objectives and methods of the study.

2.2. Data Collection

After a brief discussion, the patients were characterized for variable evaluation such as age, gender, sputum AFB and duration of disease and presence of low vitamin D levels. Sputum AFB criterion was used for Data collection. Fasting blood samples were collected for analysis of vitamin D levels in all subjects of AFB positive pulmonary tuberculosis. Data were collected through interview based questionnaire. Sample size was calculated used 95% level of confidence and margin error of 5%, from 1.6 million populations with 50% distribution response rate through the Rao-software. Sample size included **385** participants. Subjects grouping were done with positive sputum AFB for tuberculosis to analyze the frequency of low levels of vitamin D levels and AFB positivity.

Sputum examination was done after preparation of the sputum slide for ZN staining for proper microscopic examination of AFB.

Collected blood samples were stored before to examination. Total serum levels of vitamin D were analyzed by automatic analyzer. Convenience sample procedure was performed.

This Current study was hospital based, subjects aged more than 20 years and diagnosed cases of PTB with sputum AFB positive were included.

2.3. Statistical Analysis

SPSS version 20.0 was used for collected data analysis. Frequencies & percentag-

es were calculated for variables such as sex, Sputum AFB & vitamin D levels. Quantitative variables as age were calculated for mean and standard deviation. Importance of vitamin D was observed in subjects with pulmonary TB with relation to age, sex, and sputum positive for AFB and PTB duration to conclude the effect on consequences.

3. Results

A total of 1245 subjects suspected of Pulmonary Tuberculosis who presented with different symptoms like cough, fever, and weight loss, loss of appetite, body ache, and difficulty in breath were included. They were advised sputum for AFB and 385 cases with AFB positive were included. In parallel to this 144 healthy controls were selected in respect to age and gender for vitamin D levels.

The average ages of patients were 37.80 years with SD of 15.05 years. The age ranged between 21 and 85 years. The mean age of healthy controls was 36.70 years with standard deviation was 14.14 years ranging between 20 and 78 years. Male to female ratio was 2.43/1 (273/112) in patients and in healthy control group it was 2.27/1 (100/44) out of 144. The mean serum vitamin D3 level of patients was 26.98 with SD 22.10 ng/ml. The mean vitamin D3 levels of healthy controls were 34.46 with SD 44.4 ng/ml (Table 1).

In Table 2 it is observed that 273 (70.9%) males and 112 (29.1%) were female. Out of all study subjects, 242 (62.9%) from young age, 101 (26.2%) from middle age and 42 (10.9%) were from old age group. There were 361 (93.8%) married patients while 24 (6.2%) were unmarried. Patients from rural setup were 209 (54.3%) while 176 (45.7%) belonged to urban areas. There were 202 (52.5%) subjects with primary to matriculation, 60 (15.6%) were intermediate to graduate and 123 (31.9%) uneducated. Socioeconomic class had shown dominant ratio of lower economic class 351 (91.2%), while 23 (6.0%), 11 (2.9%) belonged middle and upper class respectively. By occupation, 98 (25.5%) house wives, 146 (37.9%) manual workers, 55 (14.3%) were office workers and remaining 86 (22.3%) claimed no occupation. History of sun exposure < 01 hour was noted in 228 (59.2%), 2 hours in 68 (17.7%), 3 hours in 46 (11.9%), 4 hours in 21 (5.5%) and 5 hours in 22 (5.7%) subjects. Vitamin D levels were within normal or sufficient range in 134 (34.8%), below normal range in 251 (65.2%) cases, while insufficient in 09.56% (24/251) and deficient in 90.43% (227/251) cases. BCG vaccination history was negative 318 (82.6%), while positive in 67 (17.4%) cases. Family history of PTB was positive in 37 (09.6%) while negative in 348 (90.4%).

History of fever in 318 (82.6%) cases, cough in 348 (90.4%), heamoptysis 62 (16.1%), loss of appetite in 309 (80.3%), weight loss in 68 (17.7%), night sweats in 291 (75.6%), body ache 240 (62.3%) chest pain in 26 (6.8%), shortness of breath in 87 (22.6%), headache in 324 (84.2%) and joint pain in 47 (12.2%) was present respectively (Table 3).

Out of 273 male patients of different age groups 170 (62.3%) were vitamin D deficient, while out of 112 female patients 81 (72.3%) were vitamin D deficient.

Table 1. Statistics of Vitamin D in patients and control Group.

		Patients		Control	
		age in years	vitamin D level	age in years	vitamin D level
N	Valid	385	385	144	144
	Missing	0	0	0	0
Mean		37.80	26.98	36.70	34.46
Std. Deviation		15.050	22.10	14.14	44.4
Range		64	123.00	62	130.00
Minimum		21	7.00	20	20
Maximum		85	130.00	78	140

Table 2. Frequency and percentage of different variables and non parametric test N = 385.

				Non-parametric test		
variable		**Frequency**	**Percent**	**Chi square**	**df**	**p-value**
Age Groups	20 - 40 years young age	242	62.9	164.577[a]	2	0.000
	41 - 60 years middle age	101	26.2			
	>60 years old age	42	10.9			
gender	male	273	70.9	67.327[b]	1	0.000
	female	112	29.1			
marital status	married	361	93.8	294.984[b]	1	0.000
	unmarried	24	6.2			
address	rural	209	54.3	2.829[b]	1	0.093
	urban	176	45.7			
education level	un-educated	123	31.9	78.894[a]	2	0.000
	primary to matriculation	202	52.5			
	intermediate to graduate	60	15.6			
economical class	lower class	351	91.2	580.073[a]	2	0.000
	middle class	23	6.0			
	upper class	11	2.9			
occupation	no occupation	86	22.3	44.517[c]	3	0.000
	house wife	98	25.5			
	manual worker	146	37.9			
	office worker	55	14.3			
vitamin D Deficiency	>30 ng/dl normal	134	34.8	160.930[a]	2	0.000
	20 - 30 ng/dl insufficient	24	6.2			
	<20 ng/dl deficiency	227	59.0			
vitamin D Deficiency	yes	251	65.2	35.556[b]	1	0.000
	no	134	34.8			

Continued

sun exposure	1 hour/24 hours	228	59.2	389.662[d]	4	0.000
	2 hours/24 hours	68	17.7			
	3 hours/24 hours	46	11.9			
	4 hours/24 hours	21	5.5			
	5 hours/24 hours	22	5.7			
BCG Vaccination	no	318	82.6	163.639[b]	1	0.000
	yes	67	17.4			
family History of TB	no	348	90.4	251.223[b]	1	0.000
	yes	37	9.6			

Table 3. Frequency and percentage of different symptoms of PTB and non parametric test N = 385.

				Non-parametric test		
		Frequency	Percent	Chi square	df	p-value
Fever	yes	318	82.6	163.639[a]	1	0.000
	no	67	17.4			
Cough	yes	348	90.4	251.223[a]	1	0.000
	no	37	9.6			
Heamoptysis	no	323	83.9	176.938[a]	1	0.000
	yes	62	16.1			
Loss of Appetite	yes	309	80.3	141.010[a]	1	0.000
	no	76	19.7			
Weight Loss	no	317	82.3	161.042[a]	1	0.000
	yes	68	17.7			
Night Sweets	yes	291	75.6	100.803[a]	1	0.000
	no	94	24.4			
Body Ache	yes	240	62.3	23.442[a]	1	0.000
	no	145	37.7			
Chest Pain	no	359	93.2	288.023[a]	1	0.000
	yes	26	6.8			
Shortness of Breath	no	298	77.4	115.639[a]	1	0.000
	yes	87	22.6			
Headache	yes	324	84.2	179.660[a]	1	0.000
	no	61	15.8			
Joint Pain	no	338	87.8	219.951[a]	1	0.000
	yes	47	12.2			

Young age group males were 104 (38.6%), females 52 (46.4%), while middle age group males were 51 (18.7%), females 17 (15.2%) and old age group male were

15 (5.5%), old age females were 12 (10.7%) were vitamin D deficient.

The different statistical values for male and females like chi-square, df, asymp. Sig. (2-sided), Likelyhood ratio, Linear by linear association, Interval by interval pearsons R value, Ordinal by ordinal Spearman correlation and Approx. Sig. are described in Table 4.

A total of 251 different age group subjects were directly related to sun exposure in context of vitamin D deficiency, patients with sun exposure up-to 01 hour were 213 (93.4%), 2 hours 25 (36.8%), 3 hours 10 (21.7%), 4 hours 2 (9.5%) and 5 hours 1 (4.5%) were vitamin D deficient.

Out of 273 male patients of different age groups 170 (62.3%) were vitamin D deficient, while out of 112 female patients 81 (72.3%) were vitamin D deficient.

The different statistical values for vitamin D, age group and sun exposure like chi-square, df, asymp. sig. (2-sided), Likelyhood ratio, Linear by linear association, Interval by interval pearsons R value, Ordinal by ordinal Spearman correlation and Approx. Sig. are described in Table 5(a) & Table 5(b).

Vitamin D deficiency was observed in 65.5% (230/351) belonging to lower socioeconomic class, 65.2% (15/23) from middle and 54.5% (906/11) belonging to upper socioeconomic class. Chi-square tests and Symmetric measures are shown in Table 6.

Table 4. Vitamin D, Age Group and Gender.

gender				Age Groups			Total
				20 - 40 years young age	41 - 60 years middle age	>60 years old age	
male	vitamin D Deficiency	yes	Count	104	51	15	170
			% of Total	38.1%	18.7%	5.5%	62.3%
		no	Count	63	28	12	103
			% of Total	23.1%	10.3%	4.4%	37.7%
	Total		Count	167	79	27	273
			% of Total	61.2%	28.9%	9.9%	100.0%
female	vitamin D Deficiency	yes	Count	52	17	12	81
			% of Total	46.4%	15.2%	10.7%	72.3%
		no	Count	23	5	3	31
			% of Total	20.5%	4.5%	2.7%	27.7%
	Total		Count	75	22	15	112
			% of Total	67.0%	19.6%	13.4%	100.0%

Chi-Square Tests

gender		Value	df	Asymp. Sig. (2-sided)
male	Pearson Chi-Square	0.694[a]	2	0.707
	Likelihood Ratio	0.685	2	0.710
	Linear-by-Linear Association	0.115	1	0.735

Continued

female	N of Valid Cases	273			
	Pearson Chi-Square	1.046[b]	2		0.593
	Likelihood Ratio	1.080	2		0.583
	Linear-by-Linear Association	0.985	1		0.321
	N of Valid Cases	112			

Symmetric Measures

gender			Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
male	Interval by Interval	Pearson's R	0.021	0.061	0.339	0.735[c]
	Ordinal by Ordinal	Spearman Correlation	0.011	0.061	0.177	0.859[c]
	N of Valid Cases		273			
female	Interval by Interval	Pearson's R	−0.094	0.088	−0.992	0.323[c]
	Ordinal by Ordinal	Spearman Correlation	−0.097	0.089	−1.018	0.311[c]
	N of Valid Cases		112			

Table 5. Vitamin D, Age Group and sun exposure.

(a)

sun exposure				Age Groups			Total
				20 - 40 years young age	41 - 60 years middle age	>60 years old age	
1 hour/24 hours	vitamin D Deficiency	yes	Count	138	53	22	213
			% of Total	60.5%	23.2%	9.6%	93.4%
		no	Count	9	5	1	15
			% of Total	3.9%	2.2%	0.4%	6.6%
	Total		Count	147	58	23	228
			% of Total	64.5%	25.4%	10.1%	100.0%
2 hours/24 hours	vitamin D Deficiency	yes	Count	9	12	4	25
			% of Total	13.2%	17.6%	5.9%	36.8%
		no	Count	29	10	4	43
			% of Total	42.6%	14.7%	5.9%	63.2%
	Total		Count	38	22	8	68
			% of Total	55.9%	32.4%	11.8%	100.0%
3 hours/24 hours	vitamin D Deficiency	yes	Count	7	3	0	10
			% of Total	15.2%	6.5%	0.0%	21.7%
		no	Count	24	7	5	36
			% of Total	52.2%	15.2%	10.9%	78.3%

Continued

	Total		Count	31	10	5	46
			% of Total	67.4%	21.7%	10.9%	100.0%
4 hours/24 hours	vitamin D Deficiency	yes	Count	1	0	1	2
			% of Total	4.8%	0.0%	4.8%	9.5%
		no	Count	12	5	2	19
			% of Total	57.1%	23.8%	9.5%	90.5%
	Total		Count	13	5	3	21
			% of Total	61.9%	23.8%	14.3%	100.0%
5 hours/24 hours	vitamin D Deficiency	yes	Count	1	0	0	1
			% of Total	4.5%	0.0%	0.0%	4.5%
		no	Count	12	6	3	21
			% of Total	54.5%	27.3%	13.6%	95.5%
	Total		Count	13	6	3	22
			% of Total	59.1%	27.3%	13.6%	100.0%

(b)

Chi-Square Tests

sun exposure		Value	df	Asymp. Sig. (2-sided)
1 hour/24 hours	Pearson Chi-Square	0.630[a]	2	0.730
	Likelihood Ratio	0.622	2	0.733
	Linear-by-Linear Association	0.004	1	0.950
	N of Valid Cases	228		
2 hours/24 hours	Pearson Chi-Square	6.391[b]	2	0.041
	Likelihood Ratio	6.436	2	0.040
	Linear-by-Linear Association	4.702	1	0.030
	N of Valid Cases	68		
3 hours/24 hours	Pearson Chi-Square	1.803[c]	2	0.406
	Likelihood Ratio	2.835	2	0.242
	Linear-by-Linear Association	0.490	1	0.484
	N of Valid Cases	46		
4 hours/24 hours	Pearson Chi-Square	2.551[d]	2	0.279
	Likelihood Ratio	2.339	2	0.311
	Linear-by-Linear Association	0.892	1	0.345
	N of Valid Cases	21		
5 hours/24 hours	Pearson Chi-Square	0.725[e]	2	0.696
	Likelihood Ratio	1.085	2	0.581
	Linear-by-Linear Association	0.571	1	0.450
	N of Valid Cases	22		

Continued

Symmetric Measures						
sun exposure			Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
1 hour/24 hours	Interval by Interval	Pearson's R	0.004	0.061	0.063	0.950[c]
	Ordinal by Ordinal	Spearman Correlation	0.015	0.065	0.229	0.819[c]
	N of Valid Cases		228			
2 hours/24 hours	Interval by Interval	Pearson's R	−0.265	0.119	−20.232	0.029[c]
	Ordinal by Ordinal	Spearman Correlation	−0.288	0.117	−20.447	0.017[c]
	N of Valid Cases		68			
3 hours/24 hours	Interval by Interval	Pearson's R	0.104	0.110	0.696	0.490[c]
	Ordinal by Ordinal	Spearman Correlation	0.065	0.132	0.431	0.668[c]
	N of Valid Cases		46			
4 hours/24 hours	Interval by Interval	Pearson's R	−0.211	0.288	−0.942	0.358[c]
	Ordinal by Ordinal	Spearman Correlation	−0.155	0.269	−0.683	0.503[c]
	N of Valid Cases		21			
5 hours/24 hours	Interval by Interval	Pearson's R	0.165	0.085	0.748	0.463[c]
	Ordinal by Ordinal	Spearman Correlation	0.176	0.090	0.800	0.433[c]
	N of Valid Cases		22			

Table 6. Vitamin D, Age Group and economical Class.

economical class				Age Groups			Total
				20 - 40 years young age	41 - 60 years middle age	>60 years old age	
lower class	vitamin D Deficiency	yes	Count	142	63	25	230
			% of Total	40.5%	17.9%	7.1%	65.5%
		no	Count	77	30	14	121
			% of Total	21.9%	8.5%	4.0%	34.5%
	Total		Count	219	93	39	351
			% of Total	62.4%	26.5%	11.1%	100.0%
middle class	vitamin D Deficiency	yes	Count	9	4	2	15
			% of Total	39.1%	17.4%	8.7%	65.2%
		no	Count	6	1	1	8
			% of Total	26.1%	4.3%	4.3%	34.8%
	Total		Count	15	5	3	23
			% of Total	65.2%	21.7%	13.0%	100.0%

Continued

upper class	vitamin D Deficiency	yes	Count	5	1	6
			% of Total	45.5%	9.1%	54.5%
		no	Count	3	2	5
			% of Total	27.3%	18.2%	45.5%
	Total		Count	8	3	11
			% of Total	72.7%	27.3%	100.0%

Chi-Square Tests

economical class		Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
lower class	Pearson Chi-Square	0.283[a]	2	0.868		
	Likelihood Ratio	0.285	2	0.867		
	Linear-by-Linear Association	0.024	1	0.877		
	N of Valid Cases	351				
middle class	Pearson Chi-Square	0.664[b]	2	0.717		
	Likelihood Ratio	0.707	2	0.702		
	Linear-by-Linear Association	0.245	1	0.621		
	N of Valid Cases	23				
upper class	Pearson Chi-Square	0.749[c]	1	0.387		
	Continuity Correction[d]	0.034	1	0.853		
	Likelihood Ratio	0.754	1	0.385		
	Fisher's Exact Test				0.545	0.424
	Linear-by-Linear Association	0.681	1	0.409		
	N of Valid Cases	11				

Symmetric Measures

economical class			Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
lower class	Interval by Interval	Pearson's R	−0.008	0.054	−0.155	0.877[c]
	Ordinal by Ordinal	Spearman Correlation	−0.014	0.053	−0.255	0.799[c]
	N of Valid Cases		351			
middle class	Interval by Interval	Pearson's R	−0.106	0.206	−0.486	0.632[c]
	Ordinal by Ordinal	Spearman Correlation	−0.131	0.203	−0.603	0.553[c]
	N of Valid Cases		23			
upper class	Interval by Interval	Pearson's R	0.261	0.290	0.811	0.438[c]
	Ordinal by Ordinal	Spearman Correlation	0.261	0.290	0.811	0.438[c]
	N of Valid Cases		11			

Vitamin D deficiency was significantly associated with education, occupation, sun exposure and family history of pulmonary tuberculosis. There was signifi-

cant association between gender and address of patients. Marital status and BCG vaccine status were statistically significant. Sun exposure was significantly related to education, occupation and family history of tuberculosis. Educational status was statistically related to vitamin D deficiency and sun exposure. Economical class was statistically related to marital status, BCG vaccination status and family history of PTB. Occupation of patients was directly related to vitamin D deficiency and sun exposure. While the relationship of vitamin D deficiency with age group, gender, marital status, address, economical class and BCG vaccination was not significant statistically (Table 7).

Vitamin D deficiency and different symptoms of tuberculosis were related statistically like cough, loss of appetite, chest pain and headache. While fever, heamoptysis, weight loss, night sweats, bodyache, shortness of breath and joint pain did not show significant statistical relation. Different symptoms were interrelated and shown significant relation like fever, cough, heamoptysis, chest pain, and shortness of breath, headache and joint pain were interrelated with significant statistical relation (Table 8).

The paired sample testing and paired samples correlation were analyzed and found statistically significant. Various means and standard deviations with standard error of mean were checked in parallel to correlations and significance as shown in the p-value that was statistically significant vitamin D level with occupation (<0.000), sun exposure (<0.000) and family history of tuberculosis (<0.003). While age group (<0.828), gender (<0.060), address (<0.874), education (<0.032), economical class (<0.533) and BCG vaccination was statistically insignificant in paired sample testing and paired correlations (Table 9).

In relation to tuberculosis parameters and vitamin D levels paired sample test was performed with mean and SD, upper and lower limits, with 95% confidence interval as shown in Table 10, the p-value was statistically significant vitamin D level with pair of vitamin D and age group < 0.002, address < 0.002, economical status < 0.000, occupation < 0.000, sun exposure < 0.000, BCG vaccination < 0.000 and family history of PTB < 0.000.While there was insignificant statistical relation of gender 0.105 and education 0.629 (Table 10).

Table 7. Correlations of vitamin D and different variables of study N = 385.

		vitamin D Deficiency	Age Groups	gender	marital status	address	education	economical class	occupation	sun exposure	BCG Vaccination	family History of TB
vitamin D Deficiency	Pearson Correlation	1	−0.011	−0.096	0.082	0.008	0.109*	0.032	0.231**	0.679**	0.053	0.150**
	Sig. (2-tailed)		0.828	0.060	0.107	0.874	0.032	0.533	0.000	0.000	0.300	0.003
Age Groups	Pearson Correlation	−0.011	1	−0.015	−0.024	0.003	−0.012	−0.044	0.036	0.031	−0.012	−0.010
	Sig. (2-tailed)	0.828		0.766	0.638	0.949	0.812	0.391	0.484	0.549	0.815	0.844
Gender	Pearson Correlation	−0.096	−0.015	1	0.048	0.101*	−0.027	0.027	−0.055	−0.050	−0.038	−0.034

Continued

	Sig. (2-tailed)	0.060	0.766		0.350	0.048	0.595	0.594	0.285	0.323	0.462	0.503
marital status	Pearson Correlation	0.082	−0.024	0.048	1	−0.021	0.046	0.193**	−0.093	0.060	0.108*	0.062
	Sig. (2-tailed)	0.107	0.638	0.350		0.682	0.367	0.000	0.067	0.241	0.034	0.227
Address	Pearson Correlation	0.008	0.003	0.101*	−0.021	1	−0.028	0.045	−0.014	−0.027	0.033	0.055
	Sig. (2-tailed)	0.874	0.949	0.048	0.682		0.586	0.382	0.780	0.596	0.523	0.285
education	Pearson Correlation	0.109*	−0.012	−0.027	0.046	−0.028	1	−0.055	0.058	0.184**	−0.048	−0.006
	Sig. (2-tailed)	0.032	0.812	0.595	0.367	0.586		0.286	0.253	0.000	0.351	0.912
economical class	Pearson Correlation	0.032	−0.044	0.027	0.193**	0.045	−0.055	1	0.099	0.020	0.106*	0.103*
	Sig. (2-tailed)	0.533	0.391	0.594	0.000	0.382	0.286		0.052	0.696	0.038	0.044
occupation	Pearson Correlation	0.231**	0.036	−0.055	−0.093	−0.014	0.058	0.099	1	0.249**	−0.032	0.024
	Sig. (2-tailed)	0.000	0.484	0.285	0.067	0.780	0.253	0.052		0.000	0.535	0.643
sun exposure	Pearson Correlation	0.679**	0.031	−0.050	0.060	−0.027	0.184**	0.020	0.249**	1	0.022	0.120*
	Sig. (2-tailed)	0.000	0.549	0.323	0.241	0.596	0.000	0.696	0.000		0.661	0.019
BCG Vaccination	Pearson Correlation	0.053	−0.012	−0.038	0.108*	0.033	−0.048	0.106*	−0.032	0.022	1	0.129*
	Sig. (2-tailed)	0.300	0.815	0.462	0.034	0.523	0.351	0.038	0.535	0.661		0.011
family History of TB	Pearson Correlation	0.150**	−0.010	−0.034	0.062	0.055	−0.006	0.103*	0.024	0.120*	0.129*	1
	Sig. (2-tailed)	0.003	0.844	0.503	0.227	0.285	0.912	0.044	0.643	0.019	0.011	

*Correlation is significant at the 0.05 level (2-tailed); **Correlation is significant at the 0.01 level (2-tailed).

Table 8. Correlations of vitamin D and different symptoms of PTB, N = 385.

		vitamin D Deficiency	fever	cough	heamoptysis	loss of appetite	weight loss	night sweats	body ache	chest pain	shortness of breath	headache	joint pain
vitamin D Deficiency	Pearson Correlation	1	0.053	0.150**	0.066	0.144**	0.062	0.029	0.028	0.151**	0.048	0.116*	−0.023
	Sig. (2-tailed)		0.300	0.003	0.199	0.004	0.225	0.571	0.577	0.003	0.343	0.023	0.658
fever	Pearson Correlation	0.053	1	0.129*	0.954**	0.134**	0.991**	0.170**	0.591**	0.095	0.850**	0.082	0.812**
	Sig. (2-tailed)	0.300		0.011	0.000	0.009	0.000	0.001	0.000	0.063	0.000	0.107	0.000
cough	Pearson Correlation	0.150**	0.129*	1	0.145**	0.657**	0.126*	0.574**	0.110*	0.825**	0.161**	0.751**	0.067
	Sig. (2-tailed)	0.003	0.011		0.004	0.000	0.013	0.000	0.030	0.000	0.002	0.000	0.191
heamoptysis	Pearson Correlation	0.066	0.954**	0.145**	1	0.138**	0.946**	0.195**	0.564**	0.107*	0.811**	0.061	0.765**
	Sig. (2-tailed)	0.199	0.000	0.004		0.007	0.000	0.000	0.000	0.035	0.000	0.229	0.000
loss of appetite	Pearson Correlation	0.144**	0.134**	0.657**	0.138**	1	0.130*	0.371**	0.113*	0.543**	0.122*	0.482**	0.114*

Continued

	Sig. (2-tailed)	0.004	0.009	0.000	0.007		0.011	0.000	0.027	0.000	0.017	0.000	0.025
weight loss	Pearson Correlation	0.062	0.991**	0.126*	0.946**	0.130*	1	0.165**	0.582**	0.092	0.841**	0.097	0.805**
	Sig. (2-tailed)	0.225	0.000	0.013	0.000	0.011		0.001	0.000	0.070	0.000	0.056	0.000
night sweats	Pearson Correlation	0.029	0.170**	0.574**	0.195**	0.371**	0.165**	1	0.082	0.474**	0.213**	0.482**	0.102*
	Sig. (2-tailed)	0.571	0.001	0.000	0.000	0.000	0.001		0.107	0.000	0.000	0.000	0.045
body ache	Pearson Correlation	0.028	0.591**	0.110*	0.564**	0.113*	0.582**	0.082	1	0.069	0.503**	0.088	0.480**
	Sig. (2-tailed)	0.577	0.000	0.030	0.000	0.027	0.000	0.107		0.180	0.000	0.083	0.000
chest pain	Pearson Correlation	0.151**	0.095	0.825**	0.107*	0.543**	0.092	0.474**	0.069	1	0.127*	0.620**	0.058
	Sig. (2-tailed)	0.003	0.063	0.000	0.035	0.000	0.070	0.000	0.180		0.013	0.000	0.258
shortness of breath	Pearson Correlation	0.048	0.850**	0.161**	0.811**	0.122*	0.841**	0.213**	0.503**	0.127*	1	0.106*	0.690**
	Sig. (2-tailed)	0.343	0.000	0.002	0.000	0.017	0.000	0.000	0.000	0.013		0.038	0.000
headache	Pearson Correlation	0.116*	0.082	0.751**	0.061	0.482**	0.097	0.482**	0.088	0.620**	0.106*	1	0.055
	Sig. (2-tailed)	0.023	0.107	0.000	0.229	0.000	0.056	0.000	0.083	0.000	0.038		0.278
joint pain	Pearson Correlation	−0.023	0.812**	0.067	0.765**	0.114*	0.805**	0.102*	0.480**	0.058	0.690**	0.055	1
	Sig. (2-tailed)	0.658	0.000	0.191	0.000	0.025	0.000	0.045	0.000	0.258	0.000	0.278	

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed).

Table 9. Vitamin D and demographic variables (paired statistic and correlations).

		Mean	Std. Deviation	Std. Error Mean	Correlation	Sig.
Pair 1	vitamin D Deficiency	1.3481	0.47697	0.02431	−0.011	0.828
	Age Groups	1.4805	0.68485	0.03490		
Pair 2	vitamin D Deficiency	1.3481	0.47697	0.02431	−0.096	0.060
	gender	1.2909	0.45477	0.02318		
Pair 3	vitamin D Deficiency	1.3481	0.47697	0.02431	0.008	0.874
	address	1.4571	0.49881	0.02542		
Pair 4	vitamin D Deficiency	1.3481	0.47697	0.02431	0.109	0.032
	education	1.3325	0.47171	0.02404		
Pair 5	vitamin D Deficiency	1.3481	0.47697	0.02431	0.032	0.533
	economical class	1.1169	0.40098	0.02044		
Pair 6	vitamin D Deficiency	1.3481	0.47697	0.02431	0.231	0.000
	occupation	2.4416	0.99076	0.05049		
Pair 7	vitamin D Deficiency	1.3481	0.47697	0.02431	0.679	0.000
	sun exposure	1.8078	1.18780	.06054		
Pair 8	vitamin D Deficiency	1.3481	0.47697	0.02431	0.053	0.300
	BCG Vaccination	1.17403	0.379625	0.019347		
Pair 9	vitamin D Deficiency	1.3481	0.47697	0.02431	0.150	0.003
	family History of TB	1.0961	0.29512	0.01504		

Table 10. Vitamin D and different parameters (paired sample tests).

		Paired Differences					t	df	Sig. (2-tailed)
					95% Confidence Interval of the Difference				
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper			
Pair 1	vitamin D Deficiency – Age Groups	−0.13247	0.83890	0.04275	−0.21653	−0.04841	−3.098	384	0.002
Pair 2	vitamin D Deficiency – gender	0.05714	0.68985	0.03516	−0.01198	0.12627	1.625	384	0.105
Pair 3	vitamin D Deficiency – address	−0.10909	0.68735	0.03503	−0.17797	−0.04022	−3.114	384	0.002
Pair 4	vitamin D Deficiency – education	0.01558	0.63309	0.03227	−0.04785	0.07902	0.483	384	0.629
Pair 5	vitamin D Deficiency – economical class	0.23117	0.61328	0.03126	0.16972	0.29262	7.396	384	0.000
Pair 6	vitamin D Deficiency – occupation	−1.09351	0.99561	0.05074	−1.19327	−0.99374	−21.551	384	0.000
Pair 7	vitamin D Deficiency – sun exposure	−0.45974	0.93210	0.04750	−0.55314	−0.36634	−9.678	384	0.000
Pair 8	vitamin D Deficiency – BCG Vaccination	0.174026	0.593674	0.030256	0.114537	0.233515	5.752	384	0.000
Pair 9	vitamin D Deficiency – family History of TB	0.25195	0.52182	0.02659	0.19966	0.30424	9.474	384	0.000

4. Discussion

Pulmonary tuberculosis including extra-pulmonary tuberculosis is general health issue in Pakistan. List of factors are accountable to the development of tuberculosis. Vitamin D is also labeled as one of the risk agents for the occurrence and progress of tuberculosis. Worldwide studies are available on different health issues and role of vitamin D, but our setup lacks that. Nawabshah is located in Sindh Pakistan a hot area in summer the temperature reaches at the world record temperatures. Inspite of sunny environment our controls and patients are vitamin D deficient. Nowadays vitamin D is blamed for a list of problems all over the world as reported. Here our setup is also one of the victims out of them.

The hazard of tuberculosis (TB) infection is related to the decreased levels of vitamin D [10] [11]. Current research also declares the low levels of vitamin D in subjects who were suffering from the pulmonary tuberculosis.

Subjects with vitamin D deficiency had increased vulnerability to acquire the tuberculosis [12] and worse progression of disease in tuberculosis subjects [12] [13]. Although the current study was not focusing the before analysis of vitamin D levels in subjects who are at increased risk level for the development of pulmonary tuberculosis.

Receptor for vitamin D (VDR) is polymorphic nuclear receptor which con-

trols the expression of genes responsible for immune function. The process by which tuberculosis infection may be limited or prevented is through the binding of bioactive form of vitamin D binds with VDR [14] [15] [16]. The role of vitamin D after development of Pulmonary TB needs randomized control trials to check out the effect after therapy.

Vitamin D deficiency is associated with list of problems as reported and Vitamin D deficiency had been labeled for many diseases. Naveed and Anwar concluded that chronic kidney disease is a chief contributing cause of vitamin D deficiency which was observed in about 83% of subjects [17].

Jamali A.A. *et al.* found that considerably low levels of vitamin D3 were seen in (62.1%) of patients suffering from parkinsons disease and in second study they found low levels were associated with primary infertility as compared to controlled population [18] [19].

In Pakistan Najeeha Talat *et al.* determined the serum levels of vitamin D on subjects with tuberculosis and their contacts; they observed that 79% subjects were vitamin D deficient (<20 ng/ml), 14% with insufficient and 07% had sufficient vitamin D levels [12]. The results of current research are also at match able position to Najeeha study as low serum vitamin D levels were seen in 60.00% AFB positive PTB patients in our study.

There is 5 fold augmented risk for tuberculosis progression in subjects with vitamin D deficiency. Sutaria *et al.* [20] observed the association among deficient vitamin D status and tuberculosis, relationship among VDR polymorphism and vulnerability of tuberculosis and also evaluated part of vitamin D supplements in the prevention and treatment of tuberculosis. They concluded that subjects with tuberculosis had low vitamin D in comparison to healthy age and sex matched controls [21], subjects with convinced VDR polymorphisms (BsmI and FokI) were found to have high vulnerability for tuberculosis and subjects who were given supplementary vitamin D showed the enhanced results in most of studies [20]. The needs of retrograde studies are essential here to look in this regard.

Significant decreased levels of vitamin D were observed in subjects with tuberculosis in comparison to healthy controls and lack of vitamin D was related with amplified hazard of tuberculosis but subjects of the African populations with tuberculosis and HIV infected were lacking such association. Decreased levels of vitamin D were analyzed in subjects co-infected with tuberculosis and HIV on antiretroviral treatment with immune reconstitution inflammatory syndrome vs. those co-infected subjects who did not develop Tuberculosis related immune reconstitution syndrome. Subjects with latent tuberculosis infection with decreased vitamin D levels had increased risk to develop the active tuberculosis vs. those subjects with sufficient levels of vitamin D, also high risk of conversion of tuberculin skin test/tuberculosis infection, decreased levels of vitamin D in active tuberculosis subjects vs. latent tuberculosis infection did not achieve the statistical significance, thus representing that vitamin D deficiency expected as a risk agent rather than a result of tuberculosis. Further researches are required to analyse that either vitamin D supplements are helpful in preven-

tion and treatment of tuberculosis [3].

In present study male patients of different age groups 170 (62.3%) were vitamin D deficient, while out of 112 female patients 81 (72.3%) were vitamin D deficient. The majority of population belonged to young age group and HIV is not a common risk factor here for tuberculosis in our setup.

Nnoaham *et al.* in a meta-analysis on the relationship among vitamin D and tuberculosis had observed decreased levels of vitamin D in subjects with tuberculosis vs. controls and vitamin D deficiency confidently related with high risk of tuberculosis [5]. In current research the mean serum vitamin D3 level of patients was 26.98 with SD 22.10 ng/ml. The mean vitamin D3 levels of healthy controls were 34.46 with SD 44.4 ng/ml these results are matchable with the meta-analysis by Nnoaham *et al.*

Supplements of vitamin D were not significantly beneficial in tuberculosis subjects on treatment as denoted by Xia *et al.* in 2012, their analysis did not discourse the query whether it could be beneficial in prevention of tuberculosis. More controlled studies are further required to conclude about the beneficial effects of supplement vitamin D in tuberculosis patients [22].

Levels of bioactive form of vitamin D (1,25(OH)D3) were higher in tuberculosis subjects in comparison to controls without tuberculosis [4].

Selvaraj *et al.* suggested that such rise in 1,25(OH)2D3 may be due to CYP27B1 expression up regulation that led to augmented transformation of 25(OH)D to 1,25(OH)2D3, that can be the reason for 25(OH)D lack since of its amplified use [23].

The role of vitamin D in prevention and treatment of pulmonary tuberculosis still needs much more clarifications in future. The test availability at government setup is not available at large scale. There should be vitamin D screening in general population throughout the nation for to address the exact levels of deficiency and future plan to manage it properly. Early identification and diagnosis of vitamin D deficiency may prevent the burden of some morbid diseases which may result in morbidity and mortality.

Limitations

In current study there are certain restrictions and strengths. Current study demonstrates completely most features of association of vitamin D and tuberculosis, and solved the query about vitamin D deficiency was cause or sequel of tuberculosis. Current analysis was based on most of the available quality data to ensure the outcomes. Certain limits are also concerned with this study such as number of related studies was restricted with small sample size that indeed may have certain effects on study outcomes. Moreover inconsistency in VDD definition was seen due to the different standards for VDD in different studies that could affect our study outcomes.

5. Conclusion

Current study had shown an association between serum levels of vitamin D and

tuberculosis. Vitamin D deficiency is probably a risk factor for tuberculosis than its consequence. Further studies are required to conclude about the beneficial effects with vitamin D supplementations in treatment and prevention of tuberculosis.

Acknowledgements

We gratefully acknowledge Dr Bhojo Mal Tanwaniand Dr Ghulam Mustafa Jamaliand for their excellent support.

We also thank Mr Parkashkumar and staff of Jholylal Diagnostic Lab for their positive role and cooperation in this research.

Funding

This study was not supported financially by any institutional/governmental and nongovernmental organization.

Conflicts of Interest

There is no conflicting interest as declared by the authors for this research.

References

[1] Kim, J.H., Park, J.S., Cho, Y.J., *et al.* (2014) Low Serum 25-Hydroxyvitamin D Level: An Independent Risk Factor for Tuberculosis? *Clinical Nutrition*, **33**, 1081-1086. https://doi.org/10.1016/j.clnu.2013.11.014

[2] Chocano-Bedoya, P. and Ronnenberg, A.G. (2009) Vitamin D and Tuberculosis. *Nutrition Reviews*, **67**, 289-293. https://doi.org/10.1111/j.1753-4887.2009.00195.x

[3] Huang, S.-J., Wang, X.-H., Liu, Z.-D., Cao, W.-L., Han, Y., Ma, A.-G. and Xu, S.-F. (2017) Vitamin D Deficiency and the Risk of Tuberculosis: A Meta-Analysis. *Drug Design, Development and Therapy*, **11**, 91-102. https://doi.org/10.2147/DDDT.S79870

[4] Realegeno, S. and Modlin, R.L. (2011) Shedding Light on the Vitamin D-Tuberculosis-HIV Connection. *Proceedings of the National Academy of Sciences of the United States of America*, **108**, 18861-18862. https://doi.org/10.1073/pnas.1116513108

[5] Nnoaham, K.E. and Clarke, A. (2008) Low Serum Vitamin D Levels and Tuberculosis: A Systematic Review and Meta-Analysis. *International Journal of Epidemiology*, **37**, 113-119. https://doi.org/10.1093/ije/dym247

[6] Liu, P.T., Stenger, S., Li, H., *et al.* (2006) Toll-Like Receptors Triggering of a Vitamin D Mediated Anti-Microbical Response. *Science*, **311**, 1770-1773. https://doi.org/10.1126/science.1123933

[7] Adams, J.S., Ren, S., Liu, P.T., *et al.* (2009) Vitamin D Directed Rheostatic Regulation of Monocyte Antibacterial Responses. *The Journal of Immunology*, **182**, 4289-4295. https://doi.org/10.4049/jimmunol.0803736

[8] A National Clinical Guideline (2018) Diagnosis and Management of Drug Susceptible Tuberculosis. Pakistan Chest Society, 4-19.

[9] Shen, L. and Ji, H.F. (2015) Associations between Vitamin D Status, Supplementation, Outdoor Work and Risk of Parkinson's Disease: A Meta-Analysis Assessment. *Nutrients*, **7**, 4817-4827. https://doi.org/10.3390/nu7064817

[10] Holick, M.F. (2006) High Prevalence of Vitamin D Inadequacy and Implications for Health. *Mayo Clinic Proceedings*, **81**, 353-373. https://doi.org/10.4065/81.3.353

[11] Wilkinson, R.J., Llewelyn, M., Toossi, Z., Patel, P., Pasvol, G. and Lalvani, A. (2000) Influence of Vitamin D Deficiency and Vitamin D Receptor Polymorphisms on Tuberculosis among Gujarati Asians in West London: A Case-Control Study. *The Lancet*, **355**, 618-621. https://doi.org/10.1016/S0140-6736(99)02301-6

[12] Talat, N., Perry, S., Parsonnet, J., Dawood, G. and Hussain, R. (2010) Vitamin D Deficiency and Tuberculosis Progression. *Emerging Infectious Diseases Journal*, **16**, 853-855. https://doi.org/10.3201/eid1605.091693

[13] Sita-Lumsden, A., Lapthorn, G., Swaminathan, R. and Milburn, H.J. (2007) Reactivation of Tuberculosis and Vitamin D Deficiency: The Contribution of Diet and Exposure to Sunlight. *Thorax*, **62**, 1003-1007. https://doi.org/10.1136/thx.2006.070060

[14] Lemire, J.M. (1992) Immunomodulatory Role of 1,25-Dihydroxyvitamin D3. *Journal of Cellular Biochemistry*, **49**, 26-31. https://doi.org/10.1002/jcb.240490106

[15] Reichel, H., Koeffler, H.P., Tobler, A. and Norman, A.W. (1987) 1 Alpha, 25-Dihydroxyvitamin D3 Inhibits Gamma-Interferon Synthesis by Normal Human Peripheral Blood Lymphocytes. *Proceedings of the National Academy of Sciences of the United States of America*, **84**, 3385-3389. https://doi.org/10.1073/pnas.84.10.3385

[16] Rachez, C. and Freedman, L.P. (2000) Mechanisms of Gene Regulation by Vitamin D_3 Receptor: A Network of Coactivator Interactions. *Gene*, **246**, 9-21. https://doi.org/10.1016/S0378-1119(00)00052-4

[17] Shaikh, N.S., Jamali, A.A., Jamali, G.M., Jamali, N.H., Rajput, A.A. and Jamali, A.A. (2018) Frequency of Vitamin D Deficiency in Patients with Chronic Kidney Disease Presenting at Siut Karachi. *IAJPS*, **5**, 3525-3532.

[18] Jamali, A.A., Jamali, G.M., Tanwani, B.M., Jamali, N.H. and Bhatia, M.R. (2018) Frequency of Low Vitamin D3 Levels in Subjects with Parkinson's Disease. A Study Conducted at PMCH, a Tertiary Care Hospital, Nawabshah. *Advances in Parkinson's Disease*, **7**, 7-18. https://doi.org/10.4236/apd.2018.71002

[19] Jamali, A.A., Tanwani, B.M., Jamali, G.M., *et al.* (2018) Vitamin D3: Association of Low Vitamin D3 Levels with Semen Abnormalities in Infertile Males. *Advances in Sexual Medicine*, **8**, 39-59.

[20] Sutaria, N., Liu, C.-T. and Chen, T.C. (2014) Vitamin D Status, Receptor Gene Polymorphisms, and Supplementation on Tuberculosis: A Systematic Review of Case-Control Studies and Randomized Controlled Trials. *Journal of Clinical & Translational Endocrinology*, **1**, 151-160. https://doi.org/10.1016/j.jcte.2014.08.001

[21] Lips, P. (2001) Vitamin D Deficiency and Secondary Hyperparathyroidism in the Elderly: Consequences for Bone Loss and Fractures and Therapeutic Implications. *Endocrine Reviews*, **22**, 477-501. https://doi.org/10.1210/edrv.22.4.0437

[22] Xia, J., Shi, L., Zhao, L. and Xu, F. (2014) Review Impact of Vitamin D Supplementation on the Outcome of Tuberculosis Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Chinese Medical Journal*, **127**, 3127-3134.

[23] Selvaraj, P., Prabhu Anand, S., Harishankar, M. and Alagarasu, K. (2009) Plasma 1,25Dihydroxy Vitamin D3 Level and Expression of Vitamin D Receptor and Cathelicidin in Pulmonary Tuberculosis. *Journal of Clinical Immunology*, **29**, 470-478.