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Status of Vitamin D, Calcium and Parathyroid Hormone Levels & Hepatorenal Function in Untreated Pulmonary Tuberculosis: A Matched Case-Control Study

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ABSTRACT

Background & Objective: Tuberculosis (TB) remains an ongoing major public health problem in the world. In recent years, experimental evidenc suggests a link between TB and Vitamin (Vit) D. This study was conducted to determine serum Vit D, calcium (Ca), phosphorus (P), and parathormone (PTH) levels in untreated pulmonary TB (PTB) patients.

Materials & Methods: In this case control study, 50 outdoor PTB patients were selected with 50 gender- matched controls from April 2019 to March 2020. Controls were drawn randomly from general population. Body mass index (BMI), serum Vit D, PTH, Ca, P, Albumin (Alb), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total and direct bilirubin, blood urea nitrogen (BUN) and creatinine (Cr) levels were measured in the two study groups. The results were analyzed on SPSS version 25.

Results: Median [IQR] Vit D levels were 17.4 [14.0- 24.0] ng/ml in cases,and 23.0 [18.0- 27.0] ng/ml in controls (p=0.002). Median [IQR] serum corrected Ca value for the TB patients (8.91 [8.60- 9.15] mg/dL) was significantly lower than that of the healthy controls (9.60 [9.15- 9.89] mg/dL, P< 0.001). Median [IQR] PTH was 48 in TB patients [45- 52 pg/ml] and 38 in controls [28- 42 pg/ml] (p<0.0001).

Conclusion: BMI and uncorrected and corrected serum Ca, P, Vit D, Alb, and both two aminotransferases levels were significantly lower and serum PTH was significantly higher in patients with TB as compared to controls.

Keywords: Tuberculosis, Vitamin D, serum Calcium, Parathormone, Aminotransferase

Introduction

Tuberculosis (TB) remains a major public health problem in the world (1). Around a quarter of the world population is estimated to be infected with Myco-bacterium TB (MTB) (2, 3). Approximately 95% of TB cases occur in developing countries. According to the World Health Organization (WHO), 10 million incident cases of TB were estimated worldwide in 2017. In Iran, a Middle East country, because of a high frequency of TB, it has traditionally been a general public health concern. In 2015, the incidence rate of TB was sixteen cases per one hundred thousand people (4), and it is not clear why the occurrence of TB in Iran has not been on the decrease in recent years.

In recent years, experimental evidence suggests a link between TB and Vitamin (Vit) D (5-7). 1,25-dihydroxy-Vit D3 has been shown to inhibit growth of MTB through stimulation of cell- mediated immunity (activation of both macrophages and monocytes) (8).

In Qazvin, a temperate province in northern Iran, it has been lately shown that the prevalence of Vit D deficiency is high (9). Given the biologic link between immunity and Vit D, we hypothesized that TB patients had lower Vit D serum levels than healthy individuals. No research is yet carried out in Iran to determine the association between Vit D level together with corrected serum calcium (Ca), parathormone (PTH), phosphorus (P) and liver enzyme levels with TB. The purpose of this study was to assess the association of these elements in patients with pulmonary TB (PTB) in the Iranian population.

Materials and Methods

The study was a matched case control design, in which each PTB subject was matched with one age and sex matched healthy control without a TB history (matching ratio 1:1). This study was conducted from April 2019 to

March 2020 in Qazvin province, Iran. The cases were recruited from the provincial health center of Qazvin, which is a primary unit that specializes in anti-TB therapy. All PTB patients diagnosed during the study period, prior to starting of TB treatment, were invited to participate in the study.

Inclusion criteria contained the diagnosis of PTB by sputum smear microscopy. One positive Acid-Fast Bacillus (AFB) smear and chest radiography compatible with TB or a positive culture, and at least two positive AFB smears from two different sputum smears were considered as PTB diagnosis criteria. AFB was assessed using Ziehl-Neelsen staining method. Sequentially newly recognized PTB patients at our TB clinics were included. According to clinical information, patients with extra-PTB, having received prior Vit D supplementation for 3 months, chronic renal failure, those taking any immunosuppressive agents and corticosteroids, hepatic disease and human immunodeficiency virus (HIV) infection were excluded from the study. The anthropometric and demographic data such as age, sex, weight, height, job, alcohol intake and smoking were collected using a questionnaire. Body mass index (BMI) was then derived as the ratio of weight over height squared [weight (kg)/height (m^2)]. The research protocol and procedures were approved by the ethical committee of Qazvin University of Medical Sciences (QUMS) with assigned ethical code IR.QUMS.REC.1397.237. All participants were provided with full information about the study purpose and gave informed consent to participate in the study.

Before initiating anti-TB therapy, 25-hydroxy Vit D, total Ca, serum albumin (Alb), PTH, blood urea nitrogen, creatinine,and liver enzymes levels were measured in PTB patients. The same parameters were analyzed for healthy control subjects. Concentration of Vit D in serum was measured by the ELISA method using Euroimmun kit (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany). PTH measurement was performed according to the manufacturer's instructions. (Biomed Labordiagnostik, Oberschleißheim, Germany). Also, we used "modified" Orrell equation for calculation of corrected ca if the serum Alb level was lower than 4 g/dL (10): Corrected serum ca (mg/dL) = measured total ca (mg/dL) + 0.8 (4 – serum Alb g/dL). The normal range for serum PTH was 12–72 pg/dL. The normal ranges for serum Ca, P and Alb were considered 8.4–10.5 mg/dL, 1.9–2.5 mg/dL and 3.4 to 5.4 g/dL, respectively.

Nominal and ordinal data (categorical variable) in patient and control characteristics were described by frequency (percentage) and Chi square of statistical significance. Using Kolmogorov-Smirnov test, we assessed the normality assumptions of quantitative variables. Due to failing the normality test, these variables were expressed as median and interquartile [IQR] range and Mann-Whitney U tests were used to analyze data. The correlation between the results of the PTH level and corrected Ca, P and Vit D levels were tested using the Pearson's correlation coefficient. Pearson's correlation coefficients 0.10–0.30, 0.30–0.50 and >0.50 were considered as small, medium, and, large respectively, with respect to strength of association. Data were analyzed by Statistical Package for Social Sciences (SPSS, version 25). P value of <0.05 was considered to be statistically significant.

Results

A total of 100 individuals were investigated for this study, including 50 patients (31 men and 19 women) with TB and 50 healthy individuals as the control group (29 men and 21 women) referred to Qazvin Health Center.

Table 1 outlines characteristics of study participants. By design, there was no significant difference in age between TB and controls. The median age was 62 years in cases and 52 years in the control was which was not statistically different (p value=0.248). No significance was found while two groups were compared with respect to gender, marital status, job, smoking status, alcohol consumption and height (all p value>0.05). None of the participants used corticosteroids and all were HIV negative. Median weight and BMI were significantly lower in cases as compared to controls (p=0.001 and p<0.001 respectively).

Table 1. Baseline characteristics of study group

Valuable		Case	Control	P value
Age (Year)		62 [34- 74]	52 [36- 67]	0.248
Sex				
	Male	31 (62)	29 (58)	0.683
	Female	19 (38)	21 (42)	
Marital status				
	Single	11 (22)	10 (20)	0.188
	Married	32 (64)	38 (76)	
	Divorced/ Widowed	7 (14)	2 (4)	
Job				

Valuable	Case	Control	P value
Housekeeper	16 (32)	16 (32)	
Worker	8 (16)	14 (28)	
Farmer	6 (12)	4 (8)	
Jobless	6 (12)	1 (2)	0.101
Retired	6 (12)	3 (6)	
Student	2 (4)	8 (16)	
Other	6 (12)	4 (8)	
Smoker (%)	15 (30)	13 (26)	0.656
Alcohol Intake (%)	1 (2)	1 (2)	1
Height (cm)	169 [159- 173]	164 [161- 178]	0.471
Weight (kg)	56 [43- 65]	62 [58- 71]	0.001*
Body Mass Index (kg/m2)	19.78 [16.3- 22.4]	22.6 [21.9- 23.7]	<0.001*
median [IQR]			

median [IQR]

Median [IQR] Serum Ca levels were significantly lower in cases (8.91 [8.60- 9.15] mg/dl) as compared to controls (9.60 [9.15- 9.89] mg/dl, p<0.001). The median serum corrected Ca value for the TB patients (8.91 [8.60- 9.15] mg/dL) was significantly lower than that of the healthy controls (9.60 [9.15- 9.89] mg/dL, P< 0.001). Serum corrected Ca levels were higher than the normal range in 13 people in the control group, while hypercalcemia was only seen in three TB patients considered as statically, clinically significant.

The median serum Vit D levels of TB patients were significantly lower than those of controls. Median [IQR] were 17.4 [14.0- 24.0] ng/ml in cases, and 23 [18.0- 27.0] ng/ml in controls (p=0.002). Patients with TB had significantly lower PTH levels than those of controls. Median [IQR] PTH in TB patients was 48 [45- 52] pg/ml and 38 **[28- 42]** pg/ml in controls were (p<0.0001). There were no significant differences in serum P levels between the two study groups (3.28 [3.00- 3.40] vs. 3.20 [2.91- 3.40] mg/dL for the patient and control groups, respectively). (table 2)

Also, there were statically significant differences in median Alanine aminotransferase (ALT) and Aspartate Aminotransferase (AST) levels between the PTB patients and the controls (28 mg/dl vs. 48 mg/dl, P<0.0001 and 24 mg/dl vs. 48 mg/dl, P<0.0001; respectively). We found no clinically significant differences between the two groups in direct bilirubin, BUN and Cr (however, these differences were statistically significant). (Table 2).

Table 2. The results of measurement of serum Ca, Ph, Vit D, PTH levels and hepatic and renal tests among TB patients and the control group

Variable	Case	Control	P value
Calcium (mg/dl)	8.91 [8.60- 9.15]	9.60 [9.15- 9.89]	<0.001*
Corrected Calcium (mg/dl)	9.64 [9.32- 9.94]	10.12 [9.66- 10.54]	<0.001*
Phosphorus (mg/dl)	3.28 [3.00- 3.40]	3.20 [2.91- 3.40]	0.380
25 Vit D (ng/ml)	17.4 [14.0- 24.0]	23.0 [18.0- 27.0]	0.002*
Albumin (mg/dl)	3.10 [2.90- 3.40]	3.30 [3.01- 3.50]	0.023*
PTH (pg/ml)	48.00 [45.04- 52.00]	38.00 [28.00- 42.00]	<0.001*
ALT (mg/dl)	24 [18- 30]	47 [38- 61]	<0.001*
AST (mg/dl)	28 [20- 35]	48 [38- 54]	<0.001*
ALP (mg/dl)	180 [158- 226]	198 [185- 217]	0.112
Total Bilirubin (mg/dl)	0.90 [0.60- 1.08]	0.99 [0.90- 1.04]	0.108

Variable	Case	Control	P value
Direct Bilirubin (mg/dl)	0.30 [0.20- 0.40]	0.57 [0.36- 0.60]	<0.001*
BUN (mg/dl)	15.5 [12.0- 19.0]	13.1 [11.3- 17.1]	0.039*
Creatinine (mg/dl)	0.90 [0.70- 1.10]	0.96 [0.85- 1.13]	0.008*

median [IQR], PTH: parathyroid hormone, ALT: Alanine aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, BUN: Blood Urea Nitrogen

There was a significant negative correlation between serum PTH levels and serum corrected Ca levels (r=-0.305, P=0.031); a significant medium negative correlation between serum PTH levels and serum P levels in case group (r=-0.330, P=0.019); and a significant medium positive correlation between PTH and P in thecontrol group (r=0.385, P=0.006). (Table 3).

Table 3. Correlation between Serum corrected Ca, Serum Phosphorus, Vit D levels and PTH

PTH (pg/ml)		Corrected Ca (mg/dl)	Phosphorus (mg/dl)	Vit D (ng/ml)
Case	**r**	-0.305*	-0.330*	-0.183
	P value	0.031	0.019	0.204
Control	**r**	-0.216	0.385**	0.050
	P value	0.132	0.006	0.728

Discussion

In our study, low Vit D levels in TB patients and healthy individuals were detected. The observation in both groups could be due to nutritional factors. Low levels of Vit D are a common finding world over, especially prevalent in developing countries which varies depending on geographic location and season, the food fortification policies and demographic features **(11)**. In Iran, men and especially women usually wear long clothing which may limit their sunlight exposure **(12)**. It may also be that inactive lifestyles contribute to inadequate Vit D stores by limiting sunlight exposure. Most of Vit D is synthesized in the skin under the influence of sunlight, and only one tenth of it is obtained from food, mainly dairy products and salt-water fishes. In addition, quarantine strategy to control the Coronavirus Disease 2019 (COVID-19) outbreak may lead to longer deprivation of Vit D stores. In this study, we did not measure dietary Ca intake, but typical Iranian diets contain little dairy and very little salt-water fishes and thus have low Ca and Vit D. In a population-based study in Qazvin, none of the study population had Vit D sufficiency. All women and 81% of men had Vit D deficiency. Daily sun exposure of two-thirds of the study subjects was less than an hour **(13)**. In another previous population-based study in our province, Vit D ingestion among 95% of study population was less than minimum daily recommended amount of 10 µg/day **(9)**. In a meta-analysis, the overall prevalence of Vit D deficiency among Iranian population was reported as 0.56 (0.64 of women and 0.44 of men) **(14)**.

We have found a low median Vit D in our study population, most marked in TB patients. Our study population is representative of many Iranian TB clinics, where dairy products (such as milk, cheese, yogurt and butter) has not become a common ingredient in a regular meal, contributing to reduced serum Vit D concentrations. Furthermore, majority of the TB patients belonged to low socioeconomic class **(15)**. Thus, nutritional factors are likely to cause the lower level of Vit D in TB patients than the general population. Most studies have shown that TB patients had lower levels of Vit D than non-TB individuals **(16)**. However, there was no significant difference in Vit D levels between TB patients and controls in some other studies, for example, in Hong Kong and Indonesia **(17, 18)**. Nevertheless, a recent meta-analysis concluded that TB patients had lower Vit D concentration than non-TB individuals **(19)**. Thus, our finding is consistent with most previous studies.

The active form of Vit D boosts concentrations of cathelicidin in infected monocytes and neutrophils and consequently limits mycobacterial growth **(20, 21)**. In contrast to lines of in-vitro evidence, the in-vivo association between TB and Vit D status is still a contentious issue. In our study, serum Vit D level was lower in PTB patients than healthy individuals. This finding adds to the current evidence that Vit D plays a role in the response to MTB.

We have shown that serum PTH levels were significantly higher in PTB patients than healthy controls. Our observations of significant higher median serum PTH levels and lower median serum Vit D levels in TB patients than health individuals are probably not surprising. This finding is consistent with earlier results

that Vit D has a direct suppressive effect on PTH synthesis and secretion (22, 23).

We also found that BMI and serum levels of Alb were lower in PTB patients than in controls. Some studies have represented similar results. For instance, the research conducted by Matos E ,et al., on the relationship between PTB and nutritional status, the means of BMI, and Alb among the healthy controls, and HIV negative PTB patients were 19.6, and 18.5 kg/m2; and 4.1, and 3.6 g/dL, respectively. Similar to our study, both two parameters were significantly lower in PTB patients. Similarly, we found that reductions in serum Alb as well as wasting were significantly greater in PTB patients. Matos E ,et al., concluded that these changes may be attributable to acute phase reactant proteins, enteropathy and especially nutritional factors (24).

We also found that both serum levels of uncorrected and corrected Ca were lower in PTB patients than in controls although, most PTB patients like healthy controls- may have normal serum Ca levels. Also, measured Alb was lower in PTB patients. These finding are consistent with previous studies (25). This is consistent with the physiologic understanding that PTH and Vit D are the key regulators of serum Ca (22). A previous study suggested that TB patients had higher serum levels of Ca (26). We have seen only two PTB patients with hypercalcemia. In a prospective study Keleştimur et al., showed that TB patients are not at risk of hypercalcemia either before or during treatment (27). More studies in which TB was complicated by hypercalcemia were case reports or retrospective and therefore the other causes of hypercalcemia could not be excluded (28-30). In a recent study, the odds of developing hypercalcemia in the presence of renal failure, disseminated TB and diabetes were 7.33, 1.83 and 1.60, respectively (29). Also, in a previous population-based study in our province, Ca intake in three quarters of population was less than recommended daily allowance (800 mg/day) (9). Majority of TB patients belong to low socioeconomic class and thus, nutritional factors may have caused the lower level of serum Ca in PTB patients than general population (15).

In our study, serum P levels in PTB patients were not different from controls. A study has shown similar results (27) and two others have shown higher serum P levels in PTB patients (31) or lower serum P levels (32) than in controls. Our results suggest that factors other than PTH and Vit D may affect serum P levels including nutrition, hormonal factors and inflammation which can account for the varied results of serum P levels.

In our study, the medians of both serum aminotransferase levels of PTB patients were significantly lower than those of controls. The reason for this finding is not clear and could be a random occurrence but is in line with study of Quist etal. In this study, means of aminotransferase levels were significantly higher in patients with disseminated TB (DTB), bacterial pneumonia (BACT) and *pneumocystis carinii* pneumonia (PCP) than in patients with PTB (for both AST and ALT: PTB < PCP < BACT< DTB) (33).

The main strength of this study is the presence of a sex and age matched healthy control group that increases the reliability of effect size estimates.

Conclusion

In summary, there were significant differences between PTB patients and healthy individuals in serum corrected Ca, Vit D and PTH levels. BMI, serum Vit D, Alb, uncorrected and corrected Ca, and both two aminotransferases levels were significantly lower and serum PTH were significantly higher in PTB patients as compared to controls.

Limitations

Our study has several limitations. First, due to case-control design of the study, no causal inferences could be made for the observed associations and these deficiencies (low Vit D and Ca levels) could be a consequence of PTB disease. Second, 24 h urinary Ca levels lack, which are usually higher than normal in patients with granulomatous disorders (34). In PTB patients it has been shown that hypercalciuria may occur despite normocalcaemia (35). We could not perform this for technical reasons and non-adherence of patients and especially healthy participants in collection of urine for 24 h. To interpret our results more accurately, it would have been preferable to have measured urinary Ca levels. In spite of these limitations, we feel our results are of interest.

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Ethical considerations

The authors have observed ethical considerations in informed consent, double publication and/or submission and redundancy, plagiarism, misconduct, data fabrication and/or falsification.

Conflict of Interest

The authors declare no conflicts of interest.

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