

Original Article

Is low serum 25-hydroxyvitamin D level a possible link between pulmonary tuberculosis and type 2 diabetes?

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Background and Objectives: Although vitamin D is implicated in the generation of anti-microbial peptide cathelicidin, which plays a key role against pulmonary tuberculosis (PTB), and may have an inverse association with the risk of type 2 diabetes (DM), its role in the co-existence of these two diseases (PTB-DM) is still uncertain. This study explored the association of vitamin D status with prevalent PTB, PTB-DM and DM. **Methods and Study Design:** We randomly selected 130 PTB patients, 90 PTB-DM, 91 DM and 134 controls. Serum 25(OH)D levels were determined. A structured questionnaire and anthropometric measurements were administered. **Results:** Serum 25(OH)D levels in PTB and PTB-DM were 12.2±2.2 ng/mL and 12.9±2.5 ng/mL, respectively, which were lower than those in DM and control groups. Odds ratios of PTB and PTB-DM comparing extreme quartiles of 25(OH)D (lower than 8.6 ng/mL versus ≥26.6 ng/mL) were 3.26 and 2.27, respectively. These associations remained after adjustment for possible risk factors [OR (95% CI)=4.73 (2.04-10.9) and 2.50 (1.04-6.02), respectively]. A synergistic interaction was observed between low 25(OH)D and underweight in respect to prevalent PTB-DM [OR=24.6 vs 2.50 for lowest quartile of 25(OH) D and 4.59 for underweight]. **Conclusions:** Odds ratios of low serum 25(OH)D levels for PTB and PTB-DM were greater than 1.0, and were even much greater when combined with underweight. However, since the association of serum 25(OH)D levels with PTB was stronger than with PTB-DM, we could not draw the conclusion that vitamin D is a link between PTB and DM.

Key Words: 25-hydroxyvitamin D, pulmonary tuberculosis, link, type 2 diabetes, body mass index

INTRODUCTION

The co-morbidity of pulmonary tuberculosis (PTB) and type 2 diabetes (DM) represents a double burden with significant public health implications.¹ With increasing global prevalence of DM that is anticipated to reach 552 million by 2030,² and the continued high rates of tuberculosis in developing countries, the number of individuals with both diseases will increase markedly in the coming decades. Until now, the mechanisms that might underlie this association are still uncertain.

Vitamin D, which is mainly derived from endogenous synthesis after exposure of the skin to solar ultraviolet radiation, has been proven to have more functions in the body than the classical effects on calcium metabolism. Receptors for its active form, 1,25-dihydroxyvitamin D₃, are widely expressed in human cells, including pancreatic β-cells as well as numerous cell types of the immune system such as monocytes and macrophages, dendritic, T cells, B cells, and natural killer cells.^{3,4}

Epidemiologic studies have shown a higher incidence of TB disease in populations with diminished 25-hydroxyvitamin D [25(OH)D] levels.⁵ It is hypothesised

that vitamin D is closely associated with the onset and treatment of active tuberculosis. Sufficient vitamin D can decrease the risk of infection with MTB and the progression of active tuberculosis from latent TB, and may decrease the duration and improve the treatment outcome.⁶⁻⁹ Vitamin D was also discovered to mediate the important innate antimicrobial immune response against MTB in vitro.¹⁰

At the same time, the associations between vitamin D and DM have been reported recently. Cross-sectional studies showed that 25 (OH)D concentration was lower in individuals with DM and impaired glucose tolerance than in those with normal glucose tolerance.¹¹ A prospective study¹² in 1080 subjects of 5 year follow-up suggested

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that participants with 25(OH)D deficiency had an increased risk of DM, and the supplementation may be protective.^{13,14} Associations of 25(OH)D with insulin resistance and β cell function were reported by some authors,¹⁵ whereas others did not find an association.¹⁶

It was supposed by Handel et al that Vitamin D may be the missing link between TB and DM.¹⁷ However, there were hardly any related epidemiological reports. The current case control study was carried out to investigate whether lower serum 25(OH)D might be associated with higher prevalence of PTB, PTB-DM and DM, which might provide evidence for a role of vitamin D in the comorbidity of these two diseases.

METHODS

Study Population

The subjects were randomly selected from a previous large scale community based study of the prevalence of DM in active PTB patients and non-TB subjects in rural area in China.¹⁸ The investigation study was registered in the Chinese Clinical Trial Registry (No. ChiCTR-OCC-10000994, URL: <http://www.chictr.org/cn/proj/show.aspx?proj=411>). Briefly, newly-diagnosed PTB patients, 18 to 85 years of age, who registered for Directly Observed Treatment, Short Course (DOTS) were recruited consecutively from 7 TB clinics (Yishui TB clinic, Yanan TB clinic, Lanshan TB clinic, Cangshan TB clinic, Tancheng TB clinic, Feixian TB clinic and Pingyi TB clinic) in Linyi area (Linyi, China) from September 2010 to December 2012. PTB was diagnosed by chest radiography followed by sputum smear examination or sputum culture for those with a suspicious TB symptoms and shadow on chest X-ray. Diagnosis of diabetes was based on WHO criteria for the classification of glucose tolerance based on fasting plasma glucose (FPG). HIV-positive patients as well as subjects with type 1 diabetes, trauma in the last three months, cancer, sever cardiac, hepatic and kidney diseases were excluded. Cluster random sampling was used to recruit non-TB subjects from the same communities as TB cases, using the same exclusion criteria. Stratification was performed based on economic level (low/middle/high). Fasting blood samples were obtained from the participants for screening of DM. According to the DM screening results, the subjects were divided into four groups including PTB patients with DM (PTB-DM) and without DM (PTB), non-TB subjects with DM (DM) and without DM (NON). Finally, the study comprised 130 PTB, 90 PTB-DM, 91 DM and 134 NON.

Structured questionnaires were used by trained interviewers to collect information on demographic variables, medical history, medications, dietary and lifestyle habits. 24-hour dietary recall and food frequency questionnaire were used concerning the dietary habit together with the information of vitamin and mineral supplements. The Ethics Committee of Qingdao Disease Prevention and Control Centre approved the present study (No. 200904), and written informed consent was obtained from each subject.

Laboratory analyses

Serum 25(OH)D was measured by using a radioimmunoassay (RIA) kit from DiaSorin Inc (DiaSorin, USA) in

Beifang Institute of Biotechnology (Beijing, China). The sensitivity of the assay was 1.5 ng/mL. The interassay variability was 10.5% and the intraassay variability was 8.2%. Lipid indexes including total cholesterol (TC), triglyceride (TG) and high density lipoprotein cholesterol (HDL) were estimated by enzymatic procedure.

Anthropometric measurements

Height and weight were measured by trained investigators using standard procedure. Body mass index (BMI, kg/m²) was calculated by using the formula: BMI = weight (kg)/height² (m²), and the cut-off value for Chinese population was used, as described previously.¹⁸

Statistical analyses

Serum 25(OH)D levels exhibited a lognormal distribution, and data were therefore transformed (log₁₀) before logistic regression analysis and Pearson's correlation analysis. Subjects were divided into quartiles based on their serum 25(OH)D levels. Multiple logistic regression analysis was used to evaluate the association(s) between serum 25(OH)D levels and PTB, PTB-DM or DM, with appropriate adjustment for covariates, including age [(years) (categorized in 3 units: <30, 30-49, \geq 50)], sex, BMI [(kg/m²) (categorized as <18.5, 18.5-23.9, \geq 24.0)], family history of DM and former smoking (smoking index, package per year multiplied with smoking year was used and categorized in 4 units: 0, <15, 15-29, \geq 30). The model fit was significant ($\chi^2=203.15$, $p<0.001$) and the fit was good (Pearson $\chi^2=448$, $p=0.12$). All probability values were derived from 2-tailed analyses, and those below 0.05 were considered to be of statistical significance. Analyses were performed with SPSS version 21.0 software (IBM SPSS Statistics 21).

RESULTS

Characteristics of the study population

The general characteristics of the study population are displayed in Table 1. Patients with PTB-DM were older than PTB and NON ($p<0.05$). Male proportion was highest in PTB. And BMI in PTB and PTB-DM was lower than in the other two groups ($p<0.05$). There existed a difference in the lipid profile among these groups. Former smoking, evaluated by smoking index (SI) of package per day multiplied with smoking years, was more common among PTB cases and heavy smoking (SI \geq 30) was more common in PTB-DM and PTB groups. Patients with PTB-DM and DM were more likely to have a family history of diabetes. Serum 25(OH)D concentrations were significantly lower in PTB and PTB-DM groups than in DM and controls ($p<0.05$).

Most of the subjects were peasants, with an educational level lower than college. Occupation, education level and alcohol drinking history were distributed equally in the four groups, as also were the seasons in which the blood samples were collected.

Determinants of PTB-DM

After adjustment for potential confounders including sex, age, DM family history, BMI and smoking index, log serum 25(OH)D levels showed a protective association with PTB-DM (adjusted OR 0.37, 95% CI 0.15-0.92).

Also, this association was observed with PTB (adjusted OR 0.22, 95% CI 0.09-0.52). A clear association of serum log 25(OH)D with DM was not observed ($p>0.05$) (see in Table 2).

Relationship between vitamin D levels and PTB-DM

The relationship between serum 25(OH)D levels and the presence of PTB, PTB-DM and DM is presented in Table 3. Subjects in the lowest quartile of 25(OH)D levels were about 3 times more likely to have PTB than those in the highest quartile (OR 3.26, 95%CI 1.56-6.82). This relationship was maintained after adjustment for other possible confounders, including age, sex, body mass index, family history of DM and former smoking (adjusted OR 4.73, 95% CI 2.04-10.9). An decreased association was

observed between 25(OH)D and PTB-DM. Subjects in the lowest quartile of 25(OH)D levels ($<25^{\text{th}}$) were 2 times more likely to have PTB-DM than those in the highest quartile (OR 2.27, 95% CI 1.05-4.92) and the adjusted OR was 2.50 (95% CI 1.04-6.02). There was no significant association between 25(OH)D and the prevalence of DM.

Synergistic association of 25(OH)D and BMI on the potential risk of PTB-DM

A synergistic association was observed when the lowest quartile of 25(OH)D and the underweight category (BMI <18.5) were considered together. After adjustment for the possible confounders, the odds ratio of having PTB in subjects with both characteristics was 14.1 (1.56-128).

Table 1. Basic characteristics of the subjects ($\bar{x} \pm \text{SD}$)

	PTB	PTB-DM	DM	NON	<i>p</i> value
N	130	90	91	134	
Age	45.6 \pm 18.7*	56.9 \pm 14.5***	55.8 \pm 13.8**	51.7 \pm 15.8	<0.001
Men, n (%)	102 (77.3)	54 (61.4)	55 (61.1)	60 (44.4)	<0.001
BMI	20.3 \pm 2.83*	20.9 \pm 3.32*	22.9 \pm 2.61	22.1 \pm 2.79	<0.001
SBP(mmHg)	120 \pm 12.7	119 \pm 14.0	124 \pm 13.3**	121 \pm 11.5	0.033
DBP(mmHg)	75.7 \pm 8.14	78.0 \pm 6.60**	79.8 \pm 10.0**	79.5 \pm 6.85**	<0.001
Hypertension, n(%)	14 (10.8)	10 (11.1)	22 (24.2)	20 (14.9)	0.030
FPG, (mmol/L)	4.66 \pm 1.19	7.22 \pm 1.25	7.15 \pm 1.21	4.59 \pm 1.17	<0.001
TC(mmol/L)	4.11 \pm 1.17	5.03 \pm 1.32**	4.68 \pm 1.01**	4.78 \pm 1.27**	<0.001
TG(mmol/L)	0.95 \pm 0.49	1.23 \pm 0.67***	1.25 \pm 0.54***	0.85 \pm 0.58	<0.001
HDLC(mmol/L)	1.52 \pm 0.66*	1.67 \pm 0.59*	1.69 \pm 0.49*	1.99 \pm 0.73	<0.001
Vitamin D(ng/mL) [†]	12.2 \pm 2.15*	12.9 \pm 2.51*	17.86 \pm 1.98**	16.69 \pm 2.02**	0.014
SI					
0	75 (59.1)	59 (67.8)	70 (80.5)	94 (73.4)	<0.001
<15	16 (12.6)	2 (2.3)	4 (4.6)	18 (14.1)	
15~	17 (13.4)	6 (6.9)	5 (5.7)	12 (9.4)	
\geq 30	19 (15.0)	20 (23.0)	8 (9.2)	4 (3.1)	
DM Family history	10 (7.8)	19 (21.2)	22 (24.2)	6 (4.5)	<0.001

PTB: pulmonary tuberculosis patient without diabetes; PTB-DM: pulmonary tuberculosis patient with diabetes; DM: non-TB subjects with diabetes; NON: non-TB subjects without diabetes; BMI: body mass index; FPG: fasting plasma glucose; TC: total cholesterol; TG: triglyceride; HDLC: high density Lipoprotein Cholesterol; SI: smoking index.

[†]Log10 transformed, then back-transformed for presentation.

* $p<0.05$ compared to NON group; ** $p<0.05$ compared to PTB group.

Table 2. Multivariate logistic regression analysis of odds ratios on PTB, PTB-DM, and DM

Variables	PTB		PTB-DM		DM	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Men	2.76 (1.46-5.19)	0.002	1.60 (0.80-3.22)	0.185	2.34 (1.21-4.51)	0.011
Age						
<30	1.00	--	1.00	--	1.00	--
30~	0.43 (0.19-0.98)	0.045	4.68 (1.12-19.5)	0.034	2.75 (0.72-10.5)	0.139
\geq 50	0.36 (0.16-0.78)	0.010	7.64 (1.90-30.8)	0.004	7.69 (2.09-28.3)	0.002
DM family history	0.90 (0.28-2.86)	0.857	6.62 (2.21-19.8)	0.001	7.91 (2.73-22.9)	<0.001
BMI						
18.5~23.9	1.00	--	1.00	--	1.00	--
<18.5	1.88 (0.87-4.09)	0.109	4.73 (2.06-10.9)	<0.001	0.41 (0.11-1.55)	0.187
\geq 24	0.37 (0.16-0.83)	0.016	1.29 (0.60-2.75)	0.508	2.09 (1.06-4.12)	0.033
SI						
0	1.00	--	1.00	--	1.00	--
<15	0.68 (0.29-1.58)	0.365	0.12 (0.02-0.57)	0.008	0.28 (0.08-0.90)	0.033
15~	1.31 (0.52-3.30)	0.565	0.35 (0.11-1.16)	0.086	0.30 (0.09-0.99)	0.049
\geq 30	3.91 (1.15-13.3)	0.029	4.20 (1.20-14.7)	0.025	1.26 (0.33-4.84)	0.734
LogVD [†]	0.22 (0.09-0.52)	<0.001	0.37 (0.15-0.92)	0.032	1.30 (0.50-3.37)	0.585

PTB: pulmonary tuberculosis patient without diabetes; PTB-DM: pulmonary tuberculosis patient with diabetes; DM: non-TB subjects with diabetes; BMI: body mass index; SI: smoking index.

[†]Log10 transformed

Table 3. Odds ratios for PTB, PTB-DM, DM by quartiles of serum 25(OH)D (ng/mL)

VitaminD	≥26.62	15.40~26.61	8.58~15.39	≤8.57
N	111	112	111	111
PTB				
N (%)	23 (17.7)	32 (24.6)	30 (23.1)	45 (34.6)
Crude OR	1.00	1.32 (0.65-2.67)	1.11 (0.55-2.26)	3.26 (1.56-6.82)*
Adjusted OR [†]	1.00	1.64 (0.74-3.59)	1.35 (0.61-2.97)	4.73 (2.04-10.9)*
PTB-DM				
N (%)	22 (24.4)	18 (20.0)	20 (22.2)	30 (33.3)
Crude OR	1.00	0.77 (0.36-1.68)	0.78 (0.36-1.65)	2.27 (1.05-4.92)*
Adjusted OR [†]	1.00	0.97 (0.42-2.27)	0.79 (0.34-1.83)	2.50 (1.04-6.02)*
DM				
N (%)	31 (34.1)	25 (27.5)	20 (22.0)	15 (16.5)
Crude OR	1.00	0.76 (0.38-1.54)	0.55 (0.27-1.13)	0.81 (0.36-1.83)
Adjusted OR [†]	1.00	0.79 (0.36-1.72)	0.58 (0.26-1.29)	0.86 (0.34-2.16)

PTB: pulmonary tuberculosis patient without diabetes; PTB-DM: pulmonary tuberculosis patient with diabetes; DM- non: TB subjects with diabetes.

[†]Adjusted for age (categorical), sex, BMI (categorical), family history of DM, SI (categorical).

* $p < 0.05$ compared to the highest quartile (≥26.62 ng/mL).

This association was enhanced with a nearly 2-fold increased odds ratio of 24.6 (95% CI 2.55-242) with prevalent PTB-DM compared with persons with highest quartile of 25(OH)D and normal weight, while the odds ratio was 2.50 (95% CI 1.04-6.02) for lowest quartile of 25(OH)D and 4.59 (95% CI 1.98-10.6) for underweight separately.

DISCUSSION

Lower serum 25(OH)D levels were significantly associated with higher prevalence of PTB and PTB-DM after adjustment for confounders. A synergistic interaction was observed between underweight (BMI <18.5) and low 25(OH)D.

It has been indicated by several case-control studies and large scale longitudinal cohort studies that DM will increase the risk of active TB.¹⁹ However, the link behind the association is not fully understood. Several studies have suggested that DM depresses the immune response through effects on macrophage and lymphocyte function, which in turn facilitates active TB disease. Conversely, it is also possible that TB induces glucose intolerance and deteriorates glycemic control in subjects with DM.^{19,20}

It has been indicated that vitamin D is associated with antimicrobial immune activity of human macrophages.²¹ In vitro, the actions of monocytes and macrophages on *Mycobacterium tuberculosis* (MTB) are heavily dependent on vitamin D concentrations,¹³ and the antimicrobial peptide cathelicidin was induced by the increased expression of the vitamin D receptor and the vitamin D-1-hydroxylase genes in human macrophages, which may play a key role in killing of intracellular MTB.¹⁰ Also, a growing body of evidence from observational studies suggests an association between low 25(OH)D and increasing DM risk²² with impaired pancreatic β cell function being the possible mechanism.²³

The present study, therefore, compared the odds ratio of prevalent PTB, PTB-DM and DM in individuals with lower levels of serum 25(OH)D to that in individuals with higher levels, to check for evidence that vitamin D might be a link that explain part of the association between these two diseases.

We found a negative association between 25(OH)D

and prevalent PTB, which was in accordance with other reports.^{5,6,25} However, the odds ratio was clearly lower for the association between 25(OH) D and prevalent PTB-DM. Till now, the association of vitamin D level and the prevalence of PTB-DM has not been reported. The lowered odds ratio compared with PTB alone indicates that vitamin D may not be a link between PTB and DM.

Given the association of BMI with 25(OH)D in PTB-DM, it might be that combined lower 25(OH)D and underweight reflects a heightened potential risk that is associated with or drives the progress of PTB-DM. Moreover, it might therefore be possible to use the combined information of these factors to better estimate an individual's possible risk of having PTB-DM, and combined low 25(OH)D and underweight may be a possible link between PTB and DM. As we have discussed in our former study,²⁰ the association for BMI in the setting of comorbid DM and TB is complex. While increasing the risk of DM, increased BMI is a protective factor against developing TB.²⁴ Weight loss due to poorly controlled DM and metabolic de-compensation takes away this protection, and would result in significant weight loss in patient with combined TB and DM.²⁵ Similarly, a study carried out in Tanzania²⁶ reported severe underweight (BMI <16 kg/m²) among male TB patients was associated with DM. However, the number of subjects with both characteristics was relatively small (n=23), which may explain partly the wide confidence interval: 2.55-242. Therefore, the precise evaluation of the possible synergistic effect of low vitamin D level and underweight and its possible link of PTB and DM should be investigated in studies of larger sample size preferably prospective.

Other than what had been expected, low 25(OH)D levels were not significantly associated with the prevalence of DM. Similarly, a 5-year follow-up study found that low 25(OH)D status was not significantly associated with incident diabetes but it was indicated that low vitamin D status could be related to deterioration of glucose homeostasis.²⁷ However, Pittas et al reported that the relative risk of type 2 diabetes was 0.87 (95% CI 0.75-1.00; p for trend=0.04) comparing the highest with the lowest category of vitamin D intake from supplements.¹⁴ Hitherto, strong epidemiological evidence of a link between vita-

min D deficiency and increased risk of type 2 diabetes has been limited, since most studies were cross sectional.²⁸ Therefore, more longitudinal studies are needed to get a full insight into the association.

In conclusion, we observed an inverse correlation between circulating levels of vitamin D and the prevalence of PTB-DM, while we did not find any evidence that low vitamin D was a link between PTB and DM. It was also indicated that low 25(OH)D and underweight might cooperate in the co-occurrence of PTB and DM. The precise mechanisms underlying the relationship need further investigation.

Limitations

A major limitation of our study is that it may not allow causal inference. Vitamin D status might be a consequence of the disease status instead of a cause. Furthermore, despite adjustment for confounders, residual confounding cannot be completely ruled out. Most of the DM patients in this community based study were non-insulin dependent diabetes mellitus (NIDDM), the severity of DM with PTB and the role of vitamin D could not be analyzed. Nevertheless, the evidence with respect to the association of vitamin D with PTB and PTB-DM based on our study are worthy of further investigation.

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AUTHOR DISCLOSURES

None.

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