International Journal of Research in Medical Sciences
Karoli R et al. Int J Res Med Sci. 2020 Jan;8(1):239-243
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20195915

Original Research Article

Vitamin D deficiency in patients with tuberculosis and its correlation with glycemic status

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Received: 04 November 2019
Revised: 21 November 2019
Accepted: 05 December 2019

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ABSTRACT

Background: Comorbidity of diabetes and tuberculosis has serious health implications. Presence of diabetes at least three times increases the risk of tuberculosis which may be mediated by an abnormal innate immune response due to hyperglycaemia or low vitamin D levels.
Aim of the study- Present study was carried out to investigate whether lower serum 25(OH) D might be associated with higher prevalence of pulmonary or extra pulmonary tuberculosis which might provide an evidence for a role of vitamin D in the comorbidity of these two diseases and does it have any correlation with glycemic status.
Methods: In a hospital based cross sectional study, 264 patients with newly diagnosed tuberculosis were enrolled and according to glycemic status they were divided into three groups. They were assessed for vitamin D deficiency in addition to routine laboratory and biochemical parameters.
Results: The patients with diabetes had significantly lower vitamin D levels. The prevalence of severe vitamin D deficiency was highest in patients who had diabetes with tuberculosis. There was negative correlation between vitamin D levels and Hba1C and extensiveness of pulmonary tuberculosis
Conclusions: Serum vitamin D levels were significantly lower in tuberculosis patients with pre-diabetes and type 2 diabetes compared with those, who had normal glycemic status. We suggest that there is a need to pay more attention to vitamin D status in this country and if there is coexisting diabetes or impaired glucose intolerance, emphasis on vitamin D supplementation can be of utmost importance.

Keywords: Diabetes mellitus, Tuberculosis, Vitamin D

INTRODUCTION

In recent decades, there has been an exponential rise in patients with diabetes in developing countries. India is titled as the diabetes capital of the world, with an estimate of about 72.94 million diabetic patients in 2017 and the rising trends of type 2 diabetes in last few decades are due to increased life span, change in lifestyle, and genetic predisposition.[1]

Tuberculosis (TB) is a global epidemic and an important public health problem in India. In 2010, an estimated 8.8 million new cases were diagnosed worldwide (around 2 million in India).[2] Diabetes status affects the immunity of human body and responsible for increasing the burden of tuberculosis.[3] Presence of diabetes at least three times increases the risk of tuberculosis which may be mediated by an abnormal innate immune response due to hyperglycemia or low vitamin D levels.[4,5] Comorbidity of diabetes and tuberculosis has serious health implications.[6]

Pulmonary tuberculosis patients frequently suffer from deficiencies in antioxidant micronutrients and vitamins which are important for the integrity of the immune response, especially vitamin D which has been known for its role in bone and mineral metabolism but recent data suggests that it has effect on the host's immune response against mycobacterium tuberculosis.[7] Furthermore,

vitamin D plays an important role in glucose metabolism as well.[8] The studies have shown an association of vitamin D deficiency with both tuberculosis and diabetes.[9,10]

Present study was carried out to investigate whether lower serum 25(OH)D might be associated with higher prevalence of pulmonary or extra pulmonary tuberculosis which might provide an evidence for a role of vitamin D in the comorbidity of these two diseases and does it have any correlation with glycemic status.

METHODS

Study design was a cross sectional hospital-based study. The patients were enrolled between January 2018 to December 2018.

Study participants

Inclusion criteria

- The patients included were ≥18 years and newly registered with any type and category of tuberculosis. The diagnosis of TB was made in line with recommendations from RNTCP (Revised national Tuberculosis Control Program) guidelines. Patients with suspected pulmonary tuberculosis were investigated by sputum smear microscopy. If sputum specimens were smear positive for acid-fast bacilli, the patient was diagnosed as smear positive pulmonary tuberculosis. If sputum smears were negative, but the patient had tuberculosis-related symptoms and chest radiography that was compatible with active pulmonary tuberculosis, the patient was diagnosed as smear negative pulmonary tuberculosis. The consultations from respiratory physicians were sought whenever needed. Extra pulmonary tuberculosis was diagnosed on clinical grounds, using additional circumstantial evidence such as imaging studies and appropriate laboratory investigations according to the site of the lesion.

Exclusion criteria

- Pregnant or lactating women,
- Being positive for HIV,
- Having aspartate aminotransferase or alanine aminotransferase ≥3 times the upper limit of normal level as hepatic dysfunction may alter vitamin D metabolism,
- Receiving vitamin D or vitamin D analogues for any reason,
- Receiving corticosteroid treatment for any reason and
- Having cancer or receiving anticancer therapy.

Subjects with type 1 diabetes, trauma in the last three months, cancer, sever cardiac, hepatic and kidney diseases were excluded. Diagnosis of diabetes was based on ADA criteria for the classification of glucose tolerance based on Fasting Plasma Glucose (FPG) and/ or HbA1c (Glycosylated hemoglobin)

Structured questionnaires were used by 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 approved the present study and written informed consent was obtained from all the study participants.

Anthropometric measurements Height weight and waist circumference were measured by trained investigators using standard procedure. Body mass index (BMI, kg/m^2) was calculated by using the formula: BMI = weight (kg)/ $height^2$ (m^2),

Venous blood samples were also collected for fasting and post prandial blood glucose, HbA1c, 25-(OH) D3 complete blood counts, liver, lipid and renal profile in all the patients.

The samples were centrifuged within 2 hours to separate the serum and stored at -20◦ C until vitamin D analysis was undertaken.25-hydroxycholecalciferol [25-(OH)D3], was measured with the electrochemiluminescence (ECLIA) method that determines serum 25-(OH)D3 levels in a COBASE 601 Roche analyzer using a chemiluminescence immunoassay (CLIA).

Reagents were supplied by Roche (Switzerland) with a normal measurement range of 3-70 ng/ml. Vitamin D levels were classified according to the standard definitions of vitamin D status: 25-(OH)D3 ≥ 30 ng/ml = normal; 25-(OH)D3 between 20–29.9 ng/ml = insufficient vitamin D; 25-(OH)D3 between 10-19.9 ng/ml = vitamin D deficiency; 25-(OH)D3 between 0-9.9 ng/ml = severe vitamin D deficiency.[11]

Statistical analyses

Statistical Package for the Social Sciences (SPSS) software version 17.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Comparisons of characteristics of patients with TB between those with normal FBG, pre-DM and DM and categorical comparisons of various 25-(OH) D3 levels between patients with DM, pre-DM and normal FBG were carried out using the X2 test. For correlation analysis, Pearson's correlation test was used.

RESULTS

The present study included 264 newly diagnosed patients of tuberculosis. The baseline characteristics of the study population are displayed in Table 1. The patients with type 2 diabetes were significantly older and had higher levels of fasting glucose, HbA1c, cholesterol, LDL and triglycerides than the other groups.

Table 1: Clinical and biochemical characteristics of study participants(n=264).

Variable	Normal glycemic status	Prediabetes	Diabetes	p value
n	108(41%)	36(14%)	120(45%)	0.03*
Age(years)	35±12	45±14.2	50±16.5	0.01*
Male Sex	25(48%)	9(50%)	30(50%)	0.04*
Vitamin 25OHD (ng/ml)	18.4±4	12.6±3.4	8.2±2.5	0.001*
Glycosylated haemoglobin (%)	5.3±0.3	5.9±0.8	8.2±1.6	0.001*

Data is shown as Mean±SD (Standard deviation); *statistically significant

Out of these 264 patients with TB, 104 patients had pulmonary tuberculosis, 88 had pleural effusion and 72 were diagnosed to have extra pulmonary tuberculosis. As far as glycemic status was concerned, 108 (41%) had normal blood glucose, 36 (14%) had pre-diabetes and 120 (45%) had diabetes. Mean serum vitamin D levels were 18.4±4 ng/mL in patients with tuberculosis with normal fasting blood glucose, 12.6±3.4 ng/mL in patients with tuberculosis with pre-diabetes and 8.2±2.5 ng/mL in patients with tuberculosis with diabetes. The patients with diabetes had significantly lower vitamin D levels. The prevalence of severe vitamin D deficiency was highest in patients who had diabetes with tuberculosis as shown in (Table 2). In the subgroup analysis, in the patients with pulmonary tuberculosis, the prevalence of sputum positivity was higher in patients who had severe hypovitaminosis D. There was negative correlation between vitamin D levels and Hba1C and extensiveness of pulmonary tuberculosis as depicted in (Table 3).

Table 2: Vitamin D status in study participants of the three groups.

Vitamin D levels	Normal glycemic status(n=108)	Prediabetes (n=36)	Type 2 diabetes(n=120)	p value
Vitamin D sufficiency, n (%)	26	6	12	0.001*
Vitamin D insufficiency, n (%)	34	5	34	0.03*
Vitamin D deficiency, n (%)	30	14	36	0.01*
Severe Vitamin D deficiency, n (%)	18	11	38	0.001*

Table 3: Correlation analysis of hypovitaminosis D.

Variables	rho	p value
Prevalence of sputum positivity	-0.52	0.04
Extensive pulmonary parenchymal disease	-0.38	0.02
HbA1c	-0.46	0.02
Hypoalbuminemia	0.34	0.01
Hypocalcaemia	0.12	0.06

DISCUSSION

Developing countries are facing increasing burden of both diabetes and tuberculosis. Diabetes mellitus influences the development of tuberculosis through depressed cellular immunity, alveolar macrophages dysfunction, low interferon gamma level and becoming a risk factor for multi -drug resistant tuberculosis.[12,13]

Vitamin D also plays a key role in human innate and adaptive immunity, and assists mononuclear phagocytes to suppress the intracellular growth of Mycobacterium tuberculosis) after initial infection.[14,15] Herrera et al, have found type 2 diabetes patients with low serum vitamin D levels have impaired monocyte function and therefore reduced capacity to restrict the intracellular growth of mycobacterium tuberculosis and this may be one of the factors which can explain the link between diabetes and tuberculosis.[16] The evidence from another study has shown that vitamin D and its metabolites regulate the function of pancreatic ß-cells and influence insulin synthesis and secretion. Low levels of vitamin D are associated with insulin resistance and glucose intolerance.[17] Hypovitaminosis D increases the risk of both type 1 and type 2 diabetes mellitus, and vitamin D supplementation has been shown to be protective.[18,19]

In the present study, vitamin D status was estimated in patients of tuberculosis both pulmonary and extrapulmonary and correlation with their glycemic status was studied. Author found low vitamin D levels in patients with diabetes and tuberculosis both which is consistent with the findings of other studies.[20] A larger scale multi-center study in China that included 306 patients of pulmonary and extrapulmonary tuberculosis confirmed the findings of this study and reported that diabetes was a strong independent risk factor for vitamin D deficiency.[21]

A study in India by Choudhari et al, found no major differences in mean vitamin D levels between tuberculosis patients with diabetes and without diabetes, but showed

that the proportion of severe vitamin D deficiency was higher in patients with both tuberculosis and diabetes. Nearly 46.66% patients with diabetes plus pulmonary Koch's group were having vitamin D level <10 ng/ml in their study.[22]

This indicates that vitamin D might be a potential mediator of this relationship between diabetes and tuberculosis, thus, population-wide supplementation measures to prevent both diseases should be considered.

There are several limitations of this study. First is a relatively small sample size, second the cross-sectional design of this study, which pose difficulty to establish relation between outcome and exposure. Third limitation of this study was that we did not assess effect of vitamin D supplementation on glycemic status.

CONCLUSION

Serum vitamin D levels were significantly lower in tuberculosis patients with prediabetes and type 2 diabetes compared with those who had normal glycemic status. Hypovitaminosis D was also correlated with severity of tuberculosis and sputum positivity. Author suggest that there is a need to pay more attention to vitamin D status in our country and if there is coexisting diabetes or impaired glucose intolerance emphasis on vitamin D supplementation can be of utmost importance.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Karoli R, Shakya S, Singh PS. Vitamin D deficiency in patients with tuberculosis and its correlation with glycemic status. Int J Res Med Sci 2020;8:239-43.