International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 03 Issue 07 July 2018, ISSN: 2455-8737, Imp. Factor - 4.102
Available online at - www.ijirms.in

Open Access Journal | Research Article | DOI: 10.23958/ijirms/vol03-i07/04

Vitamin and HbA1C Status in Tuberculosis Patients with Diabetes and its Association

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Abstract

Diabetes mellitus ***(DM)-tuberculosis*** is associated with poor glycemic control in **DM** patients. 2. **DM** is the most common risk factor associated with ***tuberculosis (TB); TB*** is also the third cause of death due to non-communicable disease (NCD).

Materials and Methods: Present study was conducted in Dept. of TB and Chest Vedanta Institute of Medical sciences, Vedanta Hospital. A total of 100 patients of Type 2 DM were enrolled in the study of which 60 were male and 40 were female. Written consent was obtained from each patient to participate in the study. The study will be conducted in the patients admitted in the Department of TB and Chest in collaboration with Dept. of Biochemistry, Intensive Coronary Care Unit at Vedanta Hospital. All patients of DM with TB infection are diagnosed by clinician and admitted in our hospital for treatment. Informed consent was taken from all patients, who participated in our study and the study was approved by the college ethics committee.

Blood pressure, height, body weight, and waist and hip circumferences of each patient were measured as an anthropometric and dietary measurement. Body mass index (BMI) and ratios of waist to hip circumference was calculated. Blood pressure of each patient was measured after giving rest for at least 5 min.

Results: HbA1C levels were higher in the selected group of DM + TB patients mean value being 8.1 ± 0.56 %. There was a significant difference in Vit. B12 levels between cases (218.15 ± 35.65) and controls (355.02 ± 23.39), where serum level was low in cases compared to control group. About 13(18.88%) patients had Vit. B12 level less than 150pg/ml and 28(40.58%) were lying in the intermediate level between 150pg/ml to 350pg/ml. Serum vit.B12 levels ranged from 118pg/ml to 315pg/ml. 25(OH) D3 levels were 17.09 ± 2.15 ng/ml in study group where as in control group the levels were found to be 22.88±4.01.The BMI was higher in those suffering from DM+TB (28.13± 3.24) in comparison to normal subjects (24.89 ± 3.95).

Conclusion: Our study has showed high prevalence of TB-DM co-burden of disease in our hospital settings and TB+DM TB-DM were significantly associated with age. Also it is concluded that vitamin D is a link between PTB and DM. Vitamin D levels are lower in patients with TB with DM. This study recommends the importance of performing diabetes screening among pulmonary TB patients and further similar studies needs to be done to determine the feasibility of TB-DM co-management.

Keywords: ***DM,TB, TB+DM, NCD, TIMP-4.***

Introduction

Tuberculosis is an infection caused by the Mycobacterium tuberculosis bacteria. While it can infect any part of the body, it is most commonly found in the lungs. Once in the lungs, it produces symptoms similar to a slowly progressive pneumonia. It breaks down the connections between the air sacs, leading to emphysema. Tuberculosis is an infectious disease that can be transferred from one person to another.

Diabetes is a chronic metabolic disorder which is linked to energy metabolism, particularly carbohydrate and fat. Obesity and physical inactivity are shown to be the major risk factors for type 2 diabetes (T2DM). Oxidative stress may also contribute to increase in blood glucose levels, thus contribute to the pathogenesis of T2DM by increasing insulin resistance or impairing insulin secretion.[1]The association between type-2 DM and TB is re-emerging. In developed countries type 2 DM will be increases, whereas TB is highly endemic.[2] As a result, a growing number of patients with TB worldwide will present with DM. Some recent studies showed that the 10%-30% of TB patients having DM.[3-5]

According to WHO DM as a global epidemic, mostly affecting low and middle income countries where 80% of all

deaths due to DM occur and about 10% of global TB cases are linked to diabetes.[6] In other hand TB has to be a major cause of death worldwide despite the fact that the epidemic appears to be on the verge of declining.[7] There were an estimated 285 million people living with DM in 2010. In 2011, as per the IDF worldwide, 366 million people had DM, in 2030 a number which will grow to 439 million, with approximately 4 million deaths. Near about 80% of peoples are highly prevalent by TB in low and middle income countries.[8] As per the report published by WHO 2009, in 2007, there were 14.4 million peoples living with TB, 9.2 million new cases were diagnosed and 1.7 million deaths accrued (WHO 2009).[9]

Exogenous and endogenous risk factors govern the risk of progression from exposure to the tuberculosis bacilli to the development of active disease. An exogenous factor makes the progression from exposure to infection more prominent among which the key factors are the bacillary load in the sputum and the proximity of an individual to an infectious TB case. And progression from infection to active TB disease is lead by endogenous factors. Emerging factors such as diabetes, indoor air pollution, alcohol, Immunosuppressive drugs, tobacco smoke also play a significant role along with well-established risk factors. Other key factors are 1) Socioeconomic and behavioral factors, 2) Demographic (ethnic) factors and 3) Health System Issues.[10]

A study in Ethiopia resulted in prevalence of smear positive Pulmonary TB was 6.2% in TB suspected diabetic patients, which is higher compared with the general population (0.39%). It was also found that Patients with a previous history of contact with TB patients, as well as those who had prolonged diabetes, were more prone to have PTB.[11]

A retrospective study in Texas and Mexico found 27.8% of Texan and 17.8% of Mexican TB patients suffered from Diabetes. It has been reported that patients with TB and diabetes were more likely to be smear positive at diagnosis, and remain positive at the end of the first or second month of treatment.[12]

The levels of leptin were significantly higher in TB patients than TB+T2DM. The level of ghrelin was significantly lower in TB and insignificantly lower in TB+T2DMPossible abnormalities in leptin and ghrelin regulation may be associated with the development of poor nutrition (low BMI) during the inflammatory response in TB patients with or without T2DM. TB patients with T2DM may have more complex and different pathogenesis compared to TB patients only.[13]

Individuals in lower income countries, where the majority of the world's TB burden is located, are more likely to report symptoms of active TB disease if they also reported a prior diagnosis of T2DM. At the population level, between the 1990s and early 2000s, TB prevalence and incidence were more likely to increase in countries in which diabetes prevalence increased, conditioning on base year, percapita gross domestic product (GDP).[14] It has been seen that patients with DM and severe vitamin D deficiency are more susceptible to develop PMT infection than those having normal or low vitamin D status.[15]

On the other hand, the increased prevalence of T2DM in countries endemic for TB poses a serious complication in the clinical management of this major infectious disease. Moreover, patients with coincident TB-T2DM exhibited increased plasma levels of tissue inhibitor of metalloproteinase-4 (TIMP-4) and elevated peripheral blood neutrophil counts which when considered together with heme oxygenase-1 (HO-1) resulted in increased power to discriminate diabetic from non-diabetic individuals with active TB [16].On the basis of recent study bi-directional screening and care of TB and DM patients, since both entities adversely affect one another and there is currently no plausible evidence supporting the strong association between DM and TB.[17] Diabetic patients suffering from cell-mediated immunity, renal failure, micronutrient deficiency and pulmonary microangiopathy, all there increases their propensity to develop TB.

Requirement of Some research as well as knowledge gap on the association between these two diseases has recently been shown in some studies.[9,18] The increasing co-occurrence of TB and DM is a clear case in point, especially in countries with rapidly emerging economies such as India and China, and that has resulted in the confluence of two pandemics-one communicable and another non-communicable.[19]

The union of these two epidemics may lead to an increased occurrence of TB, especially in low and middle-income countries with increasing numbers of people with DM and associated TB. DM almost triples the risk of developing TB[20] in areas such as the border population of South Texas and Mexico known for its high prevalence of DM, and where self-reported DM is the most common risk factor associated with TB development.[21]

Among patients afflicted with both TB and DM, diabetes is reported to be associated with poor TB treatment outcomes;[22] however, a systematic analysis to clarify and quantify the association between DM and TB outcomes, including persistence of sputum culture positivity, treatment failure, death and relapse, has not been performed.[18] This systematic review of the effect of DM on TB treatment outcomes has determined that DM increases the risk of death reported to be 6.5–6.7 times higher in TB patients with DM. The question of TB preventive therapy may only be answered with a randomized controlled trial, an expensive and difficult way to conduct proposal. A study from Kerala, India showed that non-drug resistant TB patients with DM were more likely to fail first-line TB

treatment when compared with patients without DM.[23] Screening and attention to better DM control might be a more cost-effective way of preventing TB and reducing other DM complications.[24] Routine screening of TB patients for DM using HbA1c yielded a large number of DM cases and offered earlier management opportunities that could improve TB and DM outcomes.

Materials and Methods

Present study was conducted in Dept. of TB and Chest Vedanta Institute of Medical sciences, Vedanta Hospital. A total of 100 patients of Type 2 DM were enrolled in the study of which 60 were male and 40 were female. Written consent was obtained from each patient to participate in the study. The study will be conducted in the patients admitted in the Department of TB and Chest in collaboration with Dept. of Biochemistry, Intensive Coronary Care Unit at Vedanta Hospital. All patients of DM with TB infection are diagnosed by clinician and admitted in our hospital for treatment. Informed consent was taken from all patients, who participated in our study and the study was approved by the college ethics committee.

Blood pressure, height, body weight, and waist and hip circumferences of each patient were measured as an anthropometric and dietary measurement. Body mass index (BMI) and ratios of waist to hip circumference was calculated. Blood pressure of each patient was measured after giving rest for at least 5 min.

Collection of Blood sample

5 ml fasting blood sample was collected in a dry, clean, plane tube from patients. After clotting of blood, it is centrifuged at 3000 r.p.m. for 10 minutes. Serum will separate for the analysis and fasting blood samples were collected in a tube with anticoagulant, centrifuged and serums were separated. Serum total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C), and high density lipoprotein-cholesterol (HDL-C) levels were measured using an automated biochemical analyzer. Serum levels of vitamin B-12 were measured by electro-chemi-luminescence immunoassay. Levels of 25-hydroxy vitamin D3 [25(OH) D3] were measured by radioimmunoassay (RIA). Levels of HbA1c were measured by high-performance liquid chromatography (HPLC)

Control Group:

Total 50 normal healthy 20-64 years adult, age & sex matched subject comprises for control group.

Data Analysis

Data were expressed as mean ±SD. Mean values were assessed for significance by unpaired student –t test. A statistical analysis was performed using the Stastical Package for the Social Science program (SPSS, 21.0). Frequencies and percentages were used for the categorical measures. Probability values $p < 0.05$ were considered statistically significant.

Table 1: Showed mean value of Age in patients with TB compared with control groups.

Age group	20-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	Above 60
No of Normal subjects	6	6	14	4	6	4	4	4	2
No of DM Patients	4	10	9	22	35	5	4	8	3
No of DM with TB Patients	0	1	1	2	13	3	3	3	1

Table 2: Showing sex wise distributions in TB patients and control group.

Age group	20-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	Above 60
Male	4	4	10	4	4	4	4	2	2
Female	2	2	4	0	2	0	0	2	0
Total Control	**6**	**6**	**14**	**4**	**6**	**4**	**4**	**4**	**2**
Male	3	7	5	14	21	1	3	6	0
Female	1	3	4	8	14	4	1	2	3
Total DM Patients	**4**	**10**	**9**	**22**	**35**	**5**	**4**	**8**	**3**
Male	0	1	1	1	9	1	2	2	0
Female	0	0	0	1	4	2	1	1	1
Total DM + TB Patients	**0**	**1**	**1**	**2**	**13**	**3**	**3**	**3**	**1**

Table no1 and 2 shows Patient group contains 60 (60%) males and 40 (40%) females. Sex-matched controls were selected from the hospital registry where 38 (76%) males and 12 (24%) females were included in group II. In patient group, mean ± SD age was 41.15 ± 11.52 years. Age-matched controls were selected as group II from the registry with a mean ± SD age of 38.8 ± 13.94 years. There was no statistically significant difference between the studied groups regarding age ($p = 0.30$). Patient group included 68 (68%) smokers and 32 (32%) non-smokers. Control included 29(58%) non-smokers and 21 (42%) smokers. The incidence of TB among DM patients is high about 27%.

Results and Discussion

Table 3: Shows HbA1C, Serum vitamin B-12, 25(OH)D3 levels and BMI in DM+ TB and control group.

Tests	DM + TB (n=69)	Control group (n=50)	P value
HbA1C (%)	8.1±0.56	5.2± 0.81	$p < 0.01$
Vit B12 (pmol/L)	218.15 ± 35.65	355.02 ± 23.39	$p < 0.01$
Vit D (ng/ml)	17.09± 2.15	22.88±4.01	$p < 0.01$
BMI	28.13± 3.24	24.89 ± 3.95	$p < 0.01$

HbA1C levels were higher in the selected group of DM + TB patients mean value being 8.1 ± 0.56 %.

There was a significant difference in Vit. B12 levels between cases (218.15 ± 35.65) and controls (355.02 ± 23.39), where serum level was low in cases compared to control group. About 13(18.88%) patients had Vit. B12 level less than 150pg/ml and 28(40.58%) were lying in the intermediate level between 150pg/ml to 350pg/ml. Serum vit.B12 levels ranged from 118pg/ml to 315pg/ml.

25(OH)D3 levels were 17.09 ± 2.15 ng/ml in study group where as in control group the levels were found to be 22.88±4.01.The BMI was higher in those suffering from DM+TB(28.13± 3.24) in comparison to normal subjects(24.89 ± 3.95).

The prevalence of diabetes mellitus has increased substantially worldwide, there is anestimate of about 415 million adults suffering from diabetes in 2015. The rates of type II diabetes is also increasinging in developing regions such as sub-Saharan Africa and India.[1] Patients with Tuberculosis and diabetes is associated with worse tuberculosis treatment outcomes, which includs delayed sputum culture conversion, relapse and recurrence and higher rates of treatment failure.[2,3] Also it is suggested that diabetes mellitus may also play a role in the development of drug resistant tuberculosis.[4]

In India estimated prevalence of DM ranges from 5.2% to 12.4%.[5,6] In our study patients with Tuberculosis and DM was 27%. Previous studies from three different Indian states observed prevalence of 19.6%, 29% and 25% in Kerala, Puducherry and Tamilnadu.[7,8,9]

Our study found that older TB patients had significantly higher incidence of having DM compared to younger patients (<40 years). This is in accordance with the cross-sectional study conducted by Geldsetzer et al. found that the prevalence of DM is highest in middle to older age patients across India.[10] Workneh et al. identified 22 studies which showed that the likelihood of TB-DM comorbidity increases with age.[11] Male patients had a higher prevalence of TB-DM than female patients similar results were shown by Patel et al.[12]

In our study TB-DM patients who hadundergone HbA1c test had poor glycemic control. In India tuberculosis and diabetes mellitus study shows that higher rates of DM were found among patients with a known history of TB, in South Indian[13] in our study also there was significant increase in the HbA1C levels in DM+ TB patients (8.1±0.56).

In our study there was a significant difference in the levels of vitamin D in TB+DM (17.09± 2.15) patients as compared to control group (24.89 ± 3.95), ($p < 0.01$). in a study by Wang Q et al. they observed 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 patients.[14] In a study by Zhao X et al they observed and concluded that serum vitamin D levels were lower in patients with TB with pre-DM and DM compared with those whose fasting blood glucose is normal.[15]

Conclusion

Our study has showed high prevalence of TB-DM co-burden of disease in our hospital settings and TB+DM TB-DM were significantly associated with age. Also it is concluded that vitamin D is a link between PTB and DM. Vitamin D levels are lower in patients with TB with DM. This study recommends the importance of performing diabetes screening among pulmonary TB patients and further similar studies needs to be done to determine the feasibility of TB-DM co-management.

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