

Original Research Article

Impact of diabetes mellitus on clinical presentation and treatment response of smear positive pulmonary tuberculosis patients

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ABSTRACT

Background: Diabetes mellitus (DM) is a known risk factor for tuberculosis (TB). The aim of this study was to evaluate the effect of DM on clinical presentation and treatment response of sputum positive pulmonary tuberculosis patients.

Methods: The present retrospective study was carried out in department of Pulmonary Medicine, Sree Gokulam Medical College and Research Foundation, Trivandrum, between January 2014 to December 2016.

Results: Out of 205 subjects enrolled for this study, 73 were diagnosed with DM and 132 patients had no history of DM and were having HbA1c less than 6.5%. Mean HbA1c in DM group at presentation was 10.5 and in patients without DM group was 5.6. Low BMI was more in DM patients. Clinical characteristics at presentation were similar in both the groups. Patients with DM presented after long duration of symptoms (>8 weeks duration) and also with more atypical symptoms. On radiological examination, lower zone involvement and cavity lesions were more in patients with DM which was statistically significant. Clinical picture at the end of 6 months showed improvement in both the groups but radiological improvement was more in patients without DM compared to the other group.

Conclusions: Uncontrolled DM is associated with high prevalence of Tuberculosis. Atypical symptoms and atypical radiological findings are more common in DM patients which lead to delayed presentation. Strategies are needed to ensure that optimal care is provided to patients with both diseases.

Keywords: Pulmonary tuberculosis, Diabetes mellitus

INTRODUCTION

Globally, tuberculosis (TB) is one of the leading infectious disease causes of death, responsible for more than 1.5 million deaths in 2013.¹ Tuberculosis remains a major challenge for healthcare workers throughout the world despite major progress in the development of new strategies for its diagnosis and treatment.² Although HIV is the strongest amplifier of TB disease worldwide, increasing attention has been given to the risk associated with DM.³ The WHO has identified 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.³ The prevalence of diabetes is increasing at an alarming rate and it could soon become one of the most important drivers of the global TB epidemic.^{4,5}

Worldwide, the International Diabetes Federation (IDF) predicts that the number of people with diabetes will rise by 55% in the next 20 years. In 2011, it was estimated that about 366 million people worldwide had DM, a number which is expected to grow to at least 439 million by the year 2030, with approximately 4 million deaths. Eighty percent (80%) of these people live in countries where tuberculosis (TB) is highly prevalent.⁶ The global

burden of disease due to DM and TB is immense. In 2007, there were an estimated 14.4 million people living with TB, 9.2 million new cases and 1.7 million deaths (WHO 2009).⁷ Already, the increase in diabetes prevalence in India seems to have contributed to the absence of a decrease in tuberculosis incidence between 1998 and 2008, despite improvement in tuberculosis treatment. The incidence of pulmonary TB has been reported to be higher in diabetics than non-diabetics. The higher incidence of TB amongst diabetics in India has also been reported by various studies.⁸⁻¹⁰

Diabetes mellitus is also risk factor for poor treatment outcomes of TB. A meta-analysis showed that diabetic patients were 3.1 times more likely to have tuberculosis than controls, and a prospective study in elderly subjects revealed that this increased risk is limited to those not so well-controlled diabetic patients with hemoglobin A1c $\geq 7\%$.^{11,12} Rawat et al. provide further evidence that DM modifies not only the clinical presentation but also the chest X-rays images of PTB.¹³

Aim of the study was to study the effect of Diabetes mellitus on presentation and treatment response of sputum positive Pulmonary Tuberculosis Patients.

METHODS

This was retrospective study a conducted in Sree Gokulam Medical College & Research Foundation which is a tertiary hospital in Kerala. We included all sputum positive pulmonary tuberculosis patients aged 18 years and above who were admitted or presented during the period of January 2014 to December 2016. We classified this patient into 2 groups depends on patients with DM and without DM. Patients with positive HIV result, patients on steroids or immunosuppressive therapy and incomplete records were excluded from this study. The medical records were reviewed for data collection. Information about demographic data, sputum positivity for acid fast bacilli staining, any history of DM, blood glucose level on admission, HbA1c result, duration of symptoms, and radiological findings, will be recorded. Their clinical details at presentation were noted and analyzed. Their body weight and height measured and BMI was calculated.

Table 1: Sputum microscopy grading.

Auramine O fluorescent staining grading (using 20 or 25x objective and 10x eye piece)	Reporting /Grading
>100 AFB/field after examination of 20 fields	3+
11-100 AFB/field after examination of 50 fields	2+
1-10 AFB/ field after examination of 100 fields	1+
No AFB per 100 fields	Negative

Diagnosis of TB was based on positive AFB staining, or positive culture for TB bacilli. Confirmation of Tuberculosis was done by Sputum smear microscopy (Fluorescence staining) and microscopic smear was graded into 3 categories based on severity (Table 1).

Patients were diabetic if they had a previous history of DM and were receiving anti-diabetic therapy at the time of presentation or screened them for diabetes (RBS, FBS, PPBS or HbA1C), presence or absence of diabetes was by ADA 2012 criteria and divided them into two groups whether they have diabetes or not. Comparison of clinical and microbiological parameters between patients with DM and without DM were done. All the patients had started anti tubercular treatment drugs.

Patients have been followed up during their treatment period and they were evaluated at 2months and 6 months' period in clinico-radiological and microbiological aspects. Their symptoms were analysed at followed up. Treatment which they were on noted during follow up (whether they were on intensive phase or continuation phase or completed both and stopped treatment). Patients with and without DM will be compared in clinical improvement, sputum conversion and treatment differences.

Statistical analysis will be performed using Statistical Package for Social Sciences (SPSS). Chi-square test will be performed to analyze the categorical variables, student's t-test will be used to analyze numerical variables for group differences. P-value of 0.05 or less will be considered of statistical significance.

RESULTS

Out of 205 subjects who were pulmonary tuberculosis proven by sputum positivity enrolled for this study, 73 were diagnosed with diabetes mellitus. 56 patients were previously diagnosed with diabetes and taking medication for it, and 17 patients without a prior diagnosis of diabetes who were found to have a HbA1c 6.5% (47.5 mmol/mol) or higher. 132 patients had no history of diabetes and were having HbA1c less than 6.5%.

Among the total patients 104 (50.7%) were females. Males are found more in Diabetic group than females who are more in non-diabetic group, with no gender difference in presentation among two groups of patients observed (Table 3). About 85% of the diabetic patients and 74% of the non-diabetic patients were married and 38% of the patients are smokers in both groups (Table 7). About 29% of the study population were unemployed, majority of whom comprised of women who were homemakers. Occupation-wise, the largest proportion consisted of farmers & unskilled workers in both groups (Table 8). Majority of patents were from rural area in both group (Table 4).

Table 2: Distribution of the sample according to age.

Age group	PTB with DM		PTB without DM		Total	
	n	%	n	%	N	%
18-30	1	1.4	20	15.2	21	10.2
30-40	2	2.7	27	20.5	29	14.1
40-50	10	13.7	23	17.4	33	16.1
50-60	18	24.7	17	12.9	35	17.1
>60	42	57.5	45	34.1	87	42.4

Table 3: Distribution of the sample according to sex.

Gender	PTB with DM	%	PTB without DM	%	Total	%
Male	33	45.2	68	51.5	101	49.3
Female	40	54.8	64	48.5	104	50.7

Table 4: Distribution of the sample according to residence.

Residence	PTB with DM	%	PTB without DM	%	Total	%
Urban	21	28.8	17	12.9	38	18.5
Rural	52	71.2	115	87.1	167	81.5

Table 5: Distribution of the sample according to education.

Education	PTB with DM	%	PTB without DM	%	Total	%
Illiterate	1	1.4	2	1.5	3	1.5
Primary	17	23.3	26	19.7	43	21.0
SSLC	21	28.8	52	39.4	73	35.6
Higher sec	19	26.0	44	33.3	63	30.7
Bachelors	13	17.8	7	5.3	20	9.8
masters	2	2.7	1	0.8	3	1.5

Education status of both groups was analyzed and there were no significant differences noted (Table 5). 20% patients with TB completed Bachelor's degree but only 6% from non-diabetic group which was statistically

significant. Monthly income of patients was compared, which showed higher income groups were more in TB with diabetes mellitus patients (Table 6). It is statistically significant with p value <0.05.

Table 6: Distribution of the sample according to monthly income.

Income	PTB with DM	%	PTB without DM	%	Total	%
<5000	20	27.4	45	34.1	65	31.7
5000-10000	18	24.7	62	47.0	80	39.0
10100-20000	17	23.3	12	9.1	29	14.1
20100-30000	11	15.1	8	6.1	19	9.3
>30000	7	9.6	5	3.8	12	5.9

Table 7: Distribution of the sample according to marital status.

Marital status	PTB with DM	%	PTB without DM	%	Total	%
married	62	84.9	98	74.2	160	78.0
single	8	11.0	21	15.9	29	14.1
divorced	1	1.4	4	3.0	5	2.4
widowed	3	4.1	9	6.8	12	5.9

Table 8: Distribution of the sample according to occupation.

Occupation	PTB with DM	%	PTB without DM	%	Total	%
Farmer	20	27.4	41	31.1	61	29.8
Merchant	8	11.0	13	9.8	21	10.2
Laborer	15	20.5	23	17.4	38	18.5
Govt employed	3	4.1	7	5.3	10	4.9
Private employed	4	5.5	7	5.3	11	5.4
Nil	22	30.1	41	31.1	63	30.7

16% of diabetic patients and 12% of non-diabetic patients had history of contact with smear positive TB. In each groups 5% of the patients had past history of pulmonary tuberculosis. Mean HbA1C in DM group at presentation was 10.5 and in patients without DM group was 5.6. Low BMI was more in DM patients, but there was no statistical significant difference (Table 10). Clinical characteristics at presentation were similar in both the

groups (Table 9). Most of the TB patients presented with fever and cough. Patients with DM presented with more atypical symptoms for tuberculosis like easy fatigability and chest pain (non-pleuritic) which was statistically significant (P value <0.05). Dyspnoea and hemoptysis were more in diabetic patients. Patients with Diabetes Mellitus presented after long duration of symptoms (>8 weeks duration) with significant P value (0.015).

Table 9: Distribution of the sample according to presenting symptoms.

Symptoms	PTB with DM	%	PTB without DM	%	Total	%
Cough	73	100.0	132	100.0	205	100.0
Fever	61	83.6	128	97.0	189	92.2
Chest pain	40	54.8	72	54.5	112	54.6
Dyspnoea	60	82.2	80	60.6	140	68.3
Hemoptysis	14	19.2	20	15.2	34	16.6
Atypical	32	43.8	49	37.1	81	39.5

Table 10: Distribution of the sample according to BMI.

BMI	PTB with DM	%	PTB without DM	%	Total	%
<18	54	74.0	87	65.9	141	68.8
18-24.99	14	19.2	36	27.3	50	24.4
25-29.99	4	5.5	7	5.3	11	5.4
>30	1	1.4	2	1.5	3	1.5

Sputum severity grading based on sputum microscopy was similar in both the groups at presentation which was not significant statistically (Table 11). Sputum was 1+ in 28% of patients in PTB group without DM compared to 34% in DM group. Sputum was 3+ in 13.7% of patients in DM group and 22% in group of patients without DM. On radiological examination, there was no difference

between two groups in upper zone involvement. Lower zone and mid zone involvement were more in patients with DM than in patients without DM which was statistically significant (p value of 0.009). Cavities noted higher in patients with DM, present in 39.7% of patients with DM and 29% of patients without DM. But Pleural effusion noted more in patients without DM (Table 12).

Table 11: Distribution of the sample according to sputum positivity.

Sputum status	PTB with DM	%	PTB without DM	%	Total	%
0	6	8.2	11	8.3	17	8.3
1	25	34.2	38	28.8	63	30.7
2	32	43.8	54	40.9	86	42.0
3	10	13.7	29	22.0	39	19.0

Table 12: Chest radiographic findings, comparing patients with diabetic and non-diabetic tuberculosis.

Radiological	PTB with DM	%	PTB without DM	%	Total	%
Cavity	29	39.7	38	28.8	67	32.7
Upper zone cons	64	87.7	120	90.9	184	89.8
Mid zone	60	82.2	71	53.8	131	63.9
Lower zone	21	28.8	15	11.4	36	17.6

At the end of 2 months' significant number of people (30%) in diabetes group still have symptoms compared with the other group without diabetes (16.3%), which are cough and expectoration in most of the patients (P value <0.05).

Among the 73 patients with diabetes, 81% converted their sputum smears at two months; by comparison, 89% of the 132 patients without diabetes converted sputum smears at 2 months. X-ray was normal at 2 months in 11% of patients with DM and 15% of patients without DM. Improvement of X-ray at 2 months was more in patients without DM. X-ray at the end of 2 months is still severe (Far advanced) in more number of patients with Diabetes Mellitus compared to the other group which is statistically significant (P value of 0.046). Cavity was persisting in 12% patients in DM group and 5% patients in without DM group at 2 months

Clinical picture at the end of 6 months showed improvement in both the groups; almost all the patients were asymptomatic in both groups except 2 patients. Only 2 patients in diabetes group still have persisting cough with expectoration and turned to be MDR TB. Improvement of X-Ray were more in patients without DM compared to the other group but it is not statistically significant.

DISCUSSION

In this study, the prevalence of diabetes in TB patients was found to be 35.6% (known DM cases-27.3%, new DM cases - 8.3%). Thus, the prevalence of diabetes in TB patients in this study is higher than the prevalence was reported by studies from Saudi Arabia and Tamil nadu.^{14,15} Another study of higher prevalence of 44% was also reported from Kerala, India.¹⁶ Studies from China and Indonesia have demonstrated a lower prevalence.^{17,18}

The present study has found a significantly higher prevalence of diabetes in older TB patients (Table 2). Similar findings have been reported by another study from India and other countries like Indonesia, Malaysia, Saudi Arabia, Taiwan and Mexico.^{15,18,19}

Routine screening of TB patients for DM will help detect cases of diabetes and pre-diabetes early, so that primary prevention methods may be initiated early and effectively. Government of India recommends that TB patients should be screened for DM immediately after the

diagnosis of TB, but can also be done at any time during the course of TB treatment. Most of the studies have demonstrated a higher association of diabetes with sputum positivity.^{15,18} Present study showed significant age difference between the two groups. This can be explained by high prevalence of type 2 DM in older age group and this was like other studies.^{15,18}

In present study, more number of patients presented after 8 weeks of onset of symptoms belong to diabetes group compared to patients without DM, this can be explained by more number of atypical symptoms in patients with DM which they might attribute to diabetes and thus delay their approach to healthcare center. Low grade fever and cough are the most common presenting symptoms which were almost similar in both the groups, correlating with studies done by Alisjhabana et al and shingla et al.^{15,18} No difference in number of patients with the habit of smoking were almost equal in both the groups, so effect of smoking on pulmonary tuberculosis was equal in both the groups. Sputum microscopy results of our patients at diagnosis in our study did not show any significant difference between the two group.

We have analyzed different radiological presentations in both groups and it showed lower zone and mid zone involvement were more in patients with DM than in patients without DM and cavities were also noted higher in patients with DM. Study by Qazi et al showed 20% of patients with DM had cavities.²⁰ Study by Shaik MA et al showed that PTB DM group of patients had significantly higher frequency of cavitory lung lesions compared to PTB without DM group (50.8% versus 39.0%, p=0.005).²¹ Study by Wang et al showed 19.2% of patients with DM had cavities and 10% of patients without DM had cavities, which was statistically significant with a P value of 0.015.²²

Study done by Shaikh MA et al, showed PTB DM group of patients had increased frequency of lung lesions confined to lower lung field compared to PTB group (23.5% versus 2.4%, p<10 (- 4)), this finding is correlating with present study.²¹ Study by Qazi et al showed 54% of lower zone involvement in patients with DM.²⁰ Study by Carriera et al also showed significant number of patients with DM had lower zone involvement than patients without DM.²³ Lesions confined to the lower lung field only can lead to the consideration of diagnostic possibilities other than TB, with consequent delay in diagnosis and institution of proper treatment

In our study treatment failure is noted in 2.7% in TB with DM group, and no failure was noted in TB without DM group. Alisjahbana et al study showed significant number of positive sputum culture results at the end of 6 months in DM group (22.2%), compared in patients without DM (9.6%) with P value of <0.05, diabetes remained as significant risk factor for sputum conversion even after adjusting for confounding factors with an adjusted OR of 2.69.¹⁸

CONCLUSION

Diabetes is one of the common co-morbidity in people with TB. Uncontrolled hyperglycemia is associated with high prevalence of Tuberculosis. Symptoms and radiological findings are more common in DM group which lead to delayed presentation. A diagnosis of TB should be considered in diabetics with an abnormal chest radiograph, in the presence or absence of specific clinical symptoms, in endemic regions. Strategies are needed to ensure that optimal care is provided to patients with both diseases. TB controls optimal care provided should consider targeting patients with diabetes for interventions such as active case finding and the treatment of latent TB and, conversely, that effort to diagnose, detect, and treat DM may have a beneficial impact on TB control.

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