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Original Research Article

Screening of diabetic respiratory symptomatics for pulmonary TB: a key to tackle another hurdle in patient care and TB control?

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ABSTRACT

Background: Association of diabetes and TB have been described in literature since ancient times. With the effective AIDS control programme, HIV related TB morbidity and mortality has decreased drastically, globally as well as in India. However with current life style, diabetes is increasing. And diabetes related TB, is one of the major hurdle in control of TB at both patient care to public health level. Bidirectional screening has been advocated by WHO and IUATLD. The purpose of this study is to revisit the problem of 'TB and DM duo'.
Methods: Hundred consecutive diabetic respiratory symptomatics, attending medical and chest outpatient department and referrals at ESI-post-graduate institute at a tertiary hospital, Mumbai, were enrolled as per inclusion and exclusion criteria and data was collected and analyzed. Data was compared with the similar studies in literature and final conclusion was drawn.
Results: From our experience, 15% diabetics having respiratory symptoms were diagnosed as PTB. Majority of patients had 'typical radiological findings '(i.e. upper zone predilection) and 50% of the diagnosed TB patients had +1 smear. Poor glycemic control was found to be associated with PTB (mean HbA1c -9.5%, S.D -1.866).
Conclusions: Diabetes possess a significant burden on pulmonary TB and a serious consideration and due priority should be given to screen diabetic respiratory symptomatics as part of collaborative diabetes TB management.

Keywords: Diabetic respiratory symptomatics, Screening

INTRODUCTION

'Diabetes – TB duo' is one of the major challenge. In the current scenario of global TB control**.** Vision of 'end TB strategy' is –"A world free of TB, zero deaths and suffering due to TB". Goal is to "end global TB epidemics. By 2025 targets are 75% reduction in tuberculosis deaths (compared with 2015), 50% reduction in tuberculosis incidence rate. No affected families facing catastrophic costs due to tuberculosis." (WHO -end TB strategy -2016). TB was one of the priorities included in the millennium development goals (MDGs) Goal 6, Target 8 (14). As per the MDG target, TB incidence has fallen by 1.5% from 2000 and by 2015 and deaths have been reduced by 47% (The Stop TB strategy-WHO). TB related deaths among PLWHIV (persons living with HIV) have fallen by 32% since 2004, and 2014. On the other hand, diabetes (Type2) is increasing in low middle income countries (LMICs), India alone has a prevalence of 65 million (aged 20-79) as per International Diabetes federation- Atlas, sixth edition, Brussels; 2013). The link between DM and TB is prominent in developing countries where TB is endemic and burden of DM is increasing. Association of diabetes with TB has been documented by Avicenna (980-1027) a thousand year ago.[1] Indian 'Sidhar' Yugimahamuni described symptoms of diabetes and correlation with TB in ancient time. [2] IDF's recent estimates indicate that 8.3% of adults – 382 million people – have diabetes. About 80% of these people live in low and middle income countries. TB is a

global health problem. Various studies have shown that approximately 15% diabetics suffer from TB showing that diabetes is "adding fuel to fire" to existing problem of TB.

HIV is the strongest risk factor for TB at an individual level, but DM may be more important from public health point of view. A study from India, estimated that DM accounts for 14.8% of pulmonary TB cases, and HIV accounts for 3.4% of cases indicating magnitude of diabetes related TB compared to HIV related TB.[3] Considering the fact, that TB related deaths among people living with HIV have fallen by 32% since 2004 and out of patients identified with HIV and TB, 77% of them have been put on ART (UNAIDS-2016). DM showing rising trends globally, and in India, it is the time to revisit 'DM and TB duo'.

Challenges in diagnosis and management of 'TB and Diabetes Duo'-(Framework for Care and Control of Tuberculosis and Diabetes. WHO and IUATLD) -

- To establish collaboration of DM and TB services.
- TB and diabetes treatment related issues.
- TB infection control.
- Lifestyle modification.

Aim of this study is not only to observe clinico-bacterio-radiological profile of diabetes related pulmonary TB, but it is to revisit and re-sensitize readers to take the cognizance of the problem of 'DM and TB duo'.

The objectives of the study was to determine the utility of screening of diabetic respiratory symptomatic for pulmonary TB, to observe the clinico-bacterio-radiological profile of tuberculosis in patients of diabetes mellitus with respiratory complaints and to study the correlation of glycosylated hemoglobin and pulmonary TB in diabetic respiratory symptomatic for TB.

METHODS

Hundred consecutive diabetic respiratory symptomatics, attending medical and chest outpatient department and referrals at ESI-post-graduate institute at MGM hospital (tertiary care) Mumbai, for respiratory complaints were enrolled as per inclusion and exclusion criteria. Study period was from January 2014 to September 2015.

Inclusion criteria were diabetic respiratory symptomatics and patients more than 12 years of age.

Exclusion criteria were pregnant women, patients less than 12 years of age, history of recent AMI, stroke, moribund patients, diabetic ketocidosis.

After obtaining approval from Institutional Ethics Committee, written informed consent was obtained from every patient who fulfilled the inclusion and exclusion criteria. A case study proforma was filled for each patient. Standard medical history and physical examination were undertaken for each enrolled patient. Diagnosis of tuberculosis was made as per standard guidelines. Investigations included complete blood count, fasting blood sugar, postprandial blood sugar, HbA1C measurement, FBS, Sputum examination for AFB (RNTCP), chest X-ray.

Diagnosis of diabetes mellitus was done as per guidelines by American Diabetes Association, 2011.

- Symptoms of diabetes with random blood glucose concentration more than or equal to 11.1 mmol/L (200 mg/dL) or
- Fasting plasma glucose more than or equal to 7 mmol/L (126 mg/dl) or
- HbA1C more than 6.5% or
- Two hour plasma glucose more than or equal to 11.1 mmol/L (200 mg/dl) during an oral GTT

Diagnosis of tuberculosis was done based on following criteria

- Sputum AFB smear and/or culture positivity as per RNTCP guidelines
- Radio diagnosis in form of a) X-ray b) HRCT wherever applicable
- Lymph node FNAC and histopathology
- Bronchoscopy and BAL examination.

Sputum smear examination was graded, as numerous (>10 bacilli/oil immersion field), less numerous (1-10 bacilli/oil immersion fields) and few bacilli (10–99 bacilli/100 oil immersion fields)

Statistical analysis

Data was analyzed using professional statistics package EPI info 7.0 versions for windows. Descriptive data represented as mean±SD for numeric variables, percentages and proportions for categorical variables. Appropriate tests of significance were used depending on nature and distribution of variables like independent t-test for numerical variables. Values of $p<0.05$ was considered statistically significant. This data was compared with the similar studies in literature and final conclusion was drawn.

RESULTS

Maximum numbers of patients (40) were from the age group 51 to 60 years of age and 31 were from the age group of 41-50 years in the diabetic (respiratory symptomatics) patients enrolled for the study. There were 60 males and 40 females (diabetic respiratory symptomatics patients enrolled for the study). 58% patients enrolled for the study had BMI in the range of-18.5-24.9. Nine patients enrolled for the study presented

with haemoptysis. 30% of the diabetics participated in the study had HbA1c between 8.0-8.9% (Table 1 and 2).

Table 1: Baseline characteristics of patients the enrolled in the study.

Characteristics	Number (n= 100)
Age distribution (years)	
31-40	07
41-50	31
51-60	40
61-70	15
71-80	07
Mean age group (years)	54.90; S.D.- 9.837
Gender distribution	
Males	55.42
Females	54.12
Male: Female	60:40
Symptoms profile	
Cough	99
Fever	47
Haemoptysis	09
BMI	
<18.5	02
18.5-24.9	58
25-29.9.	31
30-34.9.	09
Family history DM	53

Table 2: Clinical features.

Clinical features	Mean (SD)
Mean BMI patients with PTB	22.82 (4.56)
Mean BMI patients without PTB	24.79 (3.46)
Mean FBS	195.38 (66.38)
Mean PPBS	252.08 (89.90)
Urine sugar	**Number (n= 100)**
+1	09
+2	38
+3	20
Negative	33

Table 3: Mean fasting blood sugar level and postprandial sugar level of diabetics with tuberculosis and diabetics without tuberculosis.

	PTB	N	Mean	SD	P value
FBS	Yes	15	224.80	58.150	0.062
	No	85	190.19	66.698	
PPBS	Yes	15	290.47	68.209	0.073
	No	85	245.31	91.877	

Majority of diabetics (30%) from the study had HbA1C positive in the range of 8-8.9% (Figure 1). Out of 15 diagnosed diabetic PTB case 12 had positive AFB smear (Table 5). 50% patients had +1 AFB smear positivity (Table 6). Incidence of pulmonary TB was 15% (Table 7). 67% of PTB with Diabetes patients had upper zone involvement (Figure 2). Out of 15 patients 4 (26.67) had cavitatory lesions (Table 8).

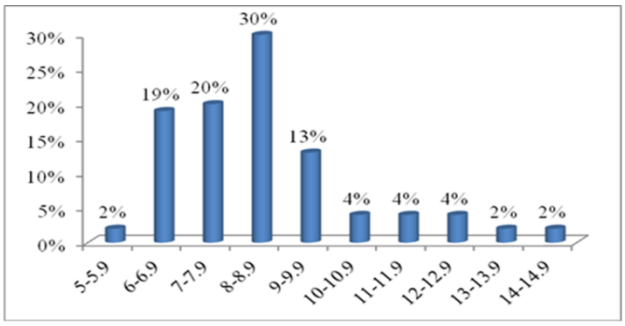

Figure 1: HbA1C of patients participated in study.

Table 4: Mean HbA1C level in patients participated in the study.

	PTB	N	Mean (%)	SD (%)	P value
HbA1C	Yes	15	9.50	1.86	0.004
	No	85	7.95	1.88	

Table 5: AFB smear in pulmonary TB in diabetic respiratory symptomatic in the study.

Sputum AFB smear	Count	Column N (%)
Positive	12	80
Negative	3	20
Total	15	100.0

Table 6: Grading of sputum AFB smear in sputum positive patients for AFB.

Grade	No of patients	Percentage (%)
1+	6	50.0
2+	2	16.7
3+	4	33.3
Total	12	100.0

Table 7: Incident tuberculosis in diabetic patients who were enrolled in the study.

PTB	No. of patients	Percentage (%)
Yes	15	15.0
No	85	85.0
Total	100	100.0

Table 8: Radiological presentation with cavitations (TB with DM).

Radiological presentations	No. of patients	Percentage
Cavitatory lesion	4	26.67%
Non cavitatory lesion	11	73.33%
Total	15	100.0

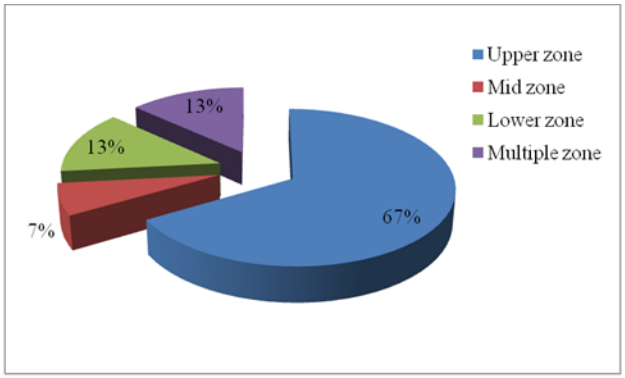

Figure 2: Radiological presentation in diabetics with tuberculosis.

DISCUSSION

Association between diabetes and tuberculosis is the next challenge for global TB control programme worldwide. With the effective collaborative HIV-TB programme, number of HIV related deaths are reduced (UNAIDS-2016) and now it is the time to tackle another interlinked problem of 'DM and TB'. Proper planning and collaboration are necessary to reduce the dual burden of diabetes and TB. A collaborative programme, similar to TB-HIV programme, can be one of the best approach to tackle another deadly duo of DM and PTB. WHO recommends bidirectional screening of diabetics and TB. Reviews about active screening of TB in diabetics, indicate overall quality of evidence is very low, but strength of recommendation is very strong. Collaborative framework for care and control of tuberculosis and diabetes i.e. "India tuberculosis-diabetes study group", worked on to assess feasibility of screening patients with tuberculosis (TB) for diabetes mellitus (DM) within the routine healthcare setting across the country at eight tertiary care hospitals and 60 peripheral health institutions in eight tuberculosis units . 8269 TB patients were diagnosed and started on treatment in existing facilities. This pilot project shows that it is feasible to screen patients with TB for DM in the routine setting. National programme for prevention and control of cancer, diabetes, cardiovascular diseases and stroke (NPCDCS) was implemented during the period 2010-2012 in 100 districts across 21 States. Purpose of integration of RNTCP with NPCDCS was to link a national strategy for management of tuberculosis and diabetes co morbidities in India.

In the current study, 15% of diabetic respiratory symptomatic (out of 100 randomly selected respiratory symptomatic diabetic patients) were diagnosed to have tuberculosis. Similar observation was observed in study done by Stevenson et al, that a substantial share of incident tuberculosis in India i.e. 14.8% of pulmonary tuberculosis was related to DM.[4] Two systematic reviews highlighted the risk that DM poses for the development of active TB, with cohort studies indicating a relative risk of 3.1 (95% CI 2.3 to 4.3) and case control studies indicating odds ratios of 1.2 to 7.8.[4,5] Jick and colleagues identified all cases of tuberculosis reported in UK general practice research database, which includes records from over 2 million patients, between 1990 and 2001 in and compared them with controls, and found that the adjusted odds ratio (adjusted for age, sex, and practice) for tuberculosis was 3.8 ($p<0.05$) for diabetic patients compared with those without diabetes.[6]

In our study, out of the 15 patients who were diagnosed to have pulmonary tuberculosis by different diagnostic methods, there were 8 males (53.3%) and 7 females (46.7%), indicating male: female ratio is 1.14:1. In a study by Pérez-Guzmán, the male: female ratio in TB group was higher than in the TBDM group ($p<0.05$). In the TB group male proportion was almost twice the female proportion (1.9:1), whereas in the TBDM group there was an almost equal proportion of men and women (1.1:1).[7] Singla et al, observed, in the PTB-DM group, the male: female ratio was 3.1:1 in DM-PTB group compared to 1.5:1 in the PTB group.[8]

In our study mean age of diabetics, who were found to have tuberculosis was 57.40 years with SD of 10.93. This is similar to observations in two case series by Deshmukh et al with 138 TB-DM patients revealed that 82.6% of the study population was above 45 years of age and there was a male preponderance.[9] Pérez-Guzmán found that the TB group were significantly younger than the TBDM patients ($p<0.001$).[7]

According to Ogbera et al, mean BMI between patients with DM with TB co morbidity and those without DM was comparable. Active TB disease and poor DM control both cause weight loss. The association between DM and BMI is not straightforward when associated with TB.[10] We observed that mean BMI in our study patient was found to be 22.82 kg/m^2 (S.D -4.56) in TB-DM group and the same in diabetes without TB was 24.79 kg/m^2 (S.D -3.46).

Out of 15 diabetics with tuberculosis, from this study, 13 patients (86.6%) had history of low grade fever, history of cough was present in 14 patients (93.33%) and history of hemoptysis was present in 3 patients (20%). Low-grade fever and productive cough were observed with equal frequency in both groups. Similar studies have reported no difference in the symptomatology between diabetic and non-diabetic TB patients.[11,12]

In this study, 12 TB DM patients were positive for sputum AFB smear (80%) whereas 3 were negative for sputum AFB smear (20%). Out of 3 sputum smear negative for AFB patients with diabetes mellitus diagnosis of PTB was made in 2 patients based on constitutional symptoms and HRCT findings (extensive tree in bud appearance) and in one patient diagnosis was made on the basis of constitutional features and BAL fluid positive for AFB. In twelve patients who were positive for sputum AFB smear, grading of 6 patients

(50%) was 1+ positive for sputum AFB smear, 4 patients (33.3%) were 3+ positive and 2 patients (16.7%) had 2+ positive grading of AFB smear. In a study done by Singla et al in the PTB-DM group, 65.2% of the patients had numerous AFB on sputum smear examination compared to 54.1% of the PTB group (p=0.008).[8] Alisjahbana et al reported that diabetic TB patients had more symptoms, but not a higher frequency of positive sputum smears for acid-fast bacilli (AFB).[13] Jiyani et al reported 40% of DM with TB**,** grading of AFB was 3+.[14] In another study by Shital et al in 2014, sputum smear examination for AFB was found positive in 98 (69.5%) cases in PTB DM group as compared to 96 (55.49%) cases in pulmonary TB without DM, p<0.015.[15]

Most of the diabetics had 3+ grade of sputum positivity in a study done by Nagaraju Boyilla and Swetha Madas.[16] In diabetic pulmonary tuberculosis patients, from our study chest X-ray upper zone involvement was noted in majority -10 patients(66.6%), mid zone and lower zone involvement was seen in one patient (6.6%), lower zone in 2 patients (13.3%) respectively. Multiple lobe involvement was observed in 2 patients (13.3%), and cavitations were seen in 4 patients (26.67%). In a large study done by Perenz-Guzman et al in Mexico, the radiological findings of pulmonary tuberculosis in 192 diabetic patients were compared with a control group of patients with pulmonary tuberculosis alone, it was observed that the TB-DM patients had a decreased frequency of upper (17% vs. 56%), and an increased frequency of lower (19% vs.7%) lung field lesions, and more TB-DM patients had cavitations (82% vs. 59%). In TBDM patients, 66% had these destructive lesions located in the upper lung fields.[17] Sossman and Steidl reported that "diabetic tuberculosis "patients had a special radiological pattern consisting of confluent, cavitatory wedge shaped lesions spreading from the hilum towards periphery, predominantly in lower zones.[18] Shital et al observed lower zone predominance in 24.11% and cavitatory pattern in 39.00% diabetic TB patients**.**[15]

Mean fasting blood sugar level in diabetics with tuberculosis in our study was found to be 224.80 mg% with SD of 58.15 and in diabetics without tuberculosis it found to be 190.19 mg% with SD of 66.69. In a similar study, mean FBS was 241 mg/dl and PPBS was 316 mg/dl.[19]

Lin et al found, fasting sugar (mg/dL) 146.18±51.79 in patients included in the study, while screening for pulmonary tuberculosis in type 2 diabetes elderly in across sectional study in a community hospital.[20]

Mean postprandial blood sugar level in diabetics with tuberculosis found to be 290.47 mg% with SD of 68.20and in diabetics without tuberculosis it found to be 245.31 mg% with SD of 91.87. As the P value is 0.07 this difference in both group, it is not statistically significant.

Mean HbA1C in diabetics with tuberculosis in the current study was found to be 9.5% with SD of 1.86 whereas in diabetics without tuberculosis was found to be 7.9% with SD of 1.88 with p value of 0.004. Webb and colleagues showed, that poor glycaemic control was significantly associated with prevalent TB disease (p<0.001).[21] Diabetic patients with HbA1C >9% had more symptom, i.e. hemoptysis, tiredness and weight loss in multivariate logistic regression models adjusted for age, sex, and smoking as compared with non-diabetic patients.[22] Chaya et al in a study on TB in diabetics, mean HbA1c was found to be with a range of 6.2-13.1 (mean±8.9-1.6).[19] In a study by Nagaraju Boyilla and Swetha Madas, HbA1c was elevated to >9% in the 35-64 age group and it was also high in the 35-44 and 55-64 age groups.[16] In a similar study, retreatment cases 22.7% were associated with higher mean HbA1C of 10.01 when compared to new cases 77.2% with HbA1C of 8.6.[23]

CONCLUSION

From our experience, 15% diabetics having respiratory symptoms diagnosis was TB, majority of patients had typical radiological findings (i.e. upper zone predilection) and 50% of the diagnosed TB patients had +1 smear. Poor glycemic control was found to be associated with PTB with HbA1c mean of 9.5%. Diabetes possess a significant burden on pulmonary TB and a serious consideration and due priority should be given to screen diabetic respiratory symptomatics. It can concluded that screening of "diabetic respiratory symptomatics for pulmonary TB useful for early detection and proper treatment of PTB in diabetics can be a key to overcome one of hurdle in TB control at patient care and public health level.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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