ORIGINAL ARTICLE

Incidence and Risk Factors of Tuberculosis among Patients with Type 2 Diabetes Mellitus Attending a Tertiary Care Hospital in Bhubaneswar, Odisha

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ABSTRACT

Background: Type 2 Diabetes mellitus (T2DM) and Tuberculosis (TB) often manifest together leading to complications at various levels.

Methods: In this prospective study**,** we determined the incidence of TB among 1200 patients with type 2 diabetes attending the Capital Hospital of Bhubaneswar. Various socio-demographic factors like age, gender, marital status, literacy status, locality, habits, etc. and clinical profile were assessed.

Results: Out of 1200 patients with type 2 diabetes mellitus, only 13 were having active TB disease, the incidence being 1.08%. Further, 12 were having pulmonary TB. More males with advancing age and sedentary life style were having Diabetes. About 23% of patients had familial history, high BMI levels, hypertension, high FBG levels, cholesterol and triglyceride levels. 30% of T2DM patients were having metabolic syndrome. In our study, age, literacy status, occupation, life style, familial history, habits and stress appeared to be significant risk factors among patients with diabetes. The HbA1C levels were higher among 51% of the diabetes patients. It was observed that while 84% of the patients were taking oral hypoglycemic drugs only 8% were taking Insulin injections. These patients were addicted to either smoking, drinking alcohol and/or chewing tobacco / gutka. The HbA1C levels were higher among 69% of the DM-TB patients indicating poorer glycemic control which is a proven risk factor for TBDM co-morbidity.

Conclusions: Screening for DM in TB patients could improve case detection of diabetes and early treatment, which in turn will lead to better TB-specific treatment outcomes and prevention of diabetes related complications.

Keywords: Incidence; TB; Diabetes patients; Bhubaneswar; Odisha

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) has become a pandemic and is in fact the bane of the modern times. At present, there are 300 million people affected with diabetes globally and the number is likely to rise two-fold/doubly in the future five years.[1] India has the highest burden of Tuberculosis (TB) and second highest burden of diabetes in the world, with annual TB incidence of 2.2 million cases (range 2.0-2.5 million) and around 63 million people living with diabetes. India has been dubbed the Diabetic Capital of the world with its huge diabetic population. India has the highest number of TB cases and also the highest number of dually infected individuals, in the world.[2,3] The association and synergistic role between T2DM and TB in causing human disease has been recognised since long back.[4-7] Globally, about 10% of TB cases are associated with diabetes. The linkage between T2DM and TB is a challenge for global tuberculosis control.[8, 9, 10] Improved understanding of the bi-directional relationship of the two diseases is necessary for proper planning and collaboration to reduce the dual burden of diabetes and TB. In people with TB, it may be appropriate to actively screen for DM. Prevention, screening, and treatment of both diseases together is more effective.[11-13] A model similar to the TB-HIV program may be the best approach.[14] Recognizing the serious threat posed by Diabetes-TB, the Revised National Tuberculosis Control Program (RNTCP) calls for strengthening collaboration between TB and Diabetes control programs for better management of Diabetic patients with TB and TB patients with Diabetes.[15] The Diabetes epidemic has a huge impact on the dynamics of

epidemiology of TB and poses several challenges to control of TB in a resource-poor country like India. Diabetes/TB burden can be brought under control by timely diagnosis of TB among Diabetics by intensified case finding, by adequate and effective treatment of detected cases and preventive therapy.[16-19] Diabetes epidemic poses a serious threat on control of TB, and the current gaps in knowledge related to diagnosis, prevention and treatment of TB among people with diabetes, this study was carried out to determine the prevalence of TB and risk factors among patients with Type 2 diabetes mellitus in an urban area of Bhubaneswar. In addition, the feasibility, results and challenges of screening patients with diabetes mellitus (DM) for tuberculosis (TB) within the healthcare settings of DM clinic in tertiary care hospital in Bhubaneswar were assessed.

METHODOLOGY

Ethical approval: The detailed plan of study was reviewed and approved by to the Institutional Ethics Committee as well as the Scientific Advisory Committee (SAC) of the ICMR-Regional Medical Research Centre, Bhubaneswar, Odisha. The study has been performed in accordance with the ethical standards.[20] The patients with Type 2 diabetes mellitus attending the Diabetes clinic of Capital Hospital in Bhubaneswar were enrolled after taking written informed consent.

Study Design: This was a prospective study among patients with Type 2 Diabetes mellitus to study the incidence of TB and to identify the risk factors like duration and severity (HbA1c level) of diabetes, socio-economic status, BMI, smoking, alcohol, history of contact with TB patient and Latent TB.

Study period: This study was conducted from Mar.,2015 to Mar.,2017 in the Dept. of NCDs, Regional Medical Research Centre, Bhubaneswar. Study subjects, were recruited from patients who attended the Diabetes clinic at the Capital Hospital, Bhubaneswar.

Capital Hospital in Bhubaneswar is the biggest peripheral public hospital in the State run by the Govt. of Odisha. It caters to the health needs of 1 million of people of Bhubaneswar, along with adjacent districts like Khurda, Nayagarh, Puri and adjoining areas.

Novo Nordisk Education Foundation runs the Diabetes clinic and about 20 patients attend the clinic per week, 80 per patients per month [960/year] and 1920/2 years.

Inclusion Criteria: Patients with Type 2 Diabetes Mellitus (T2DM) of >1 year duration, age 18 years and above, residing in and around the city of Bhubaneswar were included in the study.

Exclusion criteria: Patients below 18 years of age, pregnant or lactating women, patients terminally ill from TB, HIV-positive patients, Diabetic patients who are currently on ATT or with past history of TB, and patients suffering from other diseases like Psychiatric illness were excluded.

In all, 1200 patients with Type 2 diabetes mellitus attending the Diabetes clinic of Capital Hospital in Bhubaneswar were enrolled in the study. Socio-demographic and clinical data were collected from all using standardized forms. Blood samples for screening were collected from adults willing to participate in the study. In this study, the results of screening on the first visit have been described. In addition to a thorough clinical evaluation, following investigations were done. Blood glucose (fasting and post-prandial), HbA1c and lipid profile. Based on HbA1c levels (excellent control <7, good control 7-9, poor control >9), T2DM status was graded and this was compared with X-ray findings and chest symptoms. Classification of the patients' illness for further management was done based on results of sputum smears and chest X-ray.

Screening for active TB: The process of screening for TB was performed when each of the patient visited the clinic. For the purpose of this study, the results of screening on the first visit has been described.

The screening for active TB was followed as per the guidelines of Revised National TB Control Programme (RNTCP), which are based on WHO guidelines on identifying suspected active TB among persons seeking care (Central Tuberculosis Division, 2005; World Health Organization, 2009). For the screening of TB, all patients with diabetes attending the OPD were asked whether they had a history of TB diagnosis and treatment. The response was recorded and the patient was not asked again about TB until completion of TB treatment, if the answer was yes. In cases, where the answer was no, the patient was screened for symptoms by trained staff.

Patients with cough for ≥2 weeks or any suspicion of active pulmonary TB (PTB) or extra-pulmonary TB were categorised as having presumptive TB and were investigated to confirm the disease.

Two same-day sputum specimens from presumptive TB patients were collected in the DM clinic and given to the government-run microscopy centre for sputum smear microscopy by Ziehl-Neelsen staining. Patients with negative sputum smears or extra-pulmonary TB suspects underwent appropriate investigations such as chest radiography to confirm TB. Those diagnosed with TB were referred to the RNTCP for TB treatment. All the patient related da-

ta were recorded on treatment cards and also in an electronic database.[21, 22]

Diagnostic criteria for severity and duration of Diabetes : HbA1C was determined for all patients with type 2 Diabetes. HbA1c levels are routinely measured in the monitoring of people with type 2 diabetes and depend on the blood glucose concentration. Levels of HbA1c reflect the average glucose levels over the prior six to eight weeks and are not influenced by daily fluctuations in the blood glucose concentration. HbA1c is a useful indicator of the control of blood glucose levels in the recent past (over two to three months). The diagnostic criteria being, Normal - below 5.7 %, Pre-diabetes - 5.7% to 6.4% and Diabetes - 6.5% or greater.[23, 24, 25]

Diagnostic criteria for Cat-I and Cat-II : As per RNTCP guidelines and on the basis of the nature/severity of the disease and the exposure of the patients to previous anti-tubercular treatments, TB patients are categorized into two treatment categories, Category (Cat)-I and Category (Cat)-II. Newly diagnosed sputum positive pulmonary TB, Sputum negative pulmonary TB with extensive parenchymal involvement and Severe form of extra-pulmonary TB are included as Cat-1 patients with whereas Sputum smear-positive Treatment failure cases, Relapse cases and Return after interruption are included as Cat-2 patients.[26] Details about category of treatment, i.e., Cat-I or Cat-II and sputum status at the time of diagnosis, i.e., sputum positive, Sputum negative or extra-pulmonary TB were noted from the TB treatment card.

Table 1 depicts the socio-demographic profile of patients with Type 2 Diabetes mellitus (T2DM)

Parameters	Patients with T2DM (n = 1200) (%)	χ^2 (df), p value
Age (in years)		
<40	240 (20)	251.36 (4), p<0.0001
41 - 50	352 (29.33)	
51 - 60	354 (9.5)	
61 - 70	195 (16.25)	
>71	59 (4.91)	
Gender		
Male	813 (67.75)	150.52 (1), p<0.0001
Female	387 (32.25)	
Marital Status		
Married	1188 (99)	1152.48 (1), p<0.0001
Unmarried	12 (1)	
Illiterate	**188 (15.66)**	237.15(3), p<0.0001
Literacy Status		
Primary school	148 (12.33)	
Secondary school	414 (34.5)	
College & above	450 (37.5)	
Regular job	260 (21.66)	263.39 (5), p<0.0001
Retired	81 (6.75)	
Business	253 (21.08)	
House wife	296 (24.66)	
Students, Others, Laborer, etc.	294 (24.5)	
Nothing	16 (1.33)	
Life style		
Active	404 (33.66)	127.4 (1), p<0.0001
Sedentary	796 (66.33)	
Familiar history		
Yes	242 (20.16)	426.02 (1), p<0.0001
No	958 (79.83)	
Habits		
Smoking	74 (6.16)	891.67 (4), p<0.0001
Alcohol	37 (3.08)	
Gutka/Tobacco	603 (50.25)	
All	161 (13.41)	
None	325 (27.08)	
Reasons for Stress		
Professional / Occupational	451 (37.58)	76.46 (3), p<0.0001
Family	259 (21.58)	
Any other	490 (40.83)	

Statistical Analysis: SPSS version, 2017 was used for statistical analysis. Prevalences are reported with 95% confidence intervals calculated considering the design effect. Mean and standard deviation for continuous variables and proportions for categorical variables are reported. All variables were described as proportions, and differences between groups were compared for statistical significance using the Chi-Square ($\chi 2$) test and t test, as applicable. P values of < 0.05 were considered statistically significant.

RESULTS

Table 1 shows the socio-demographic profile of patients with Type 2 Diabetes mellitus. There is a clear gender bias in patients attending the Diabetes OPD. In all, 67% males and 32% female patients were enrolled in the study. 29% each were in the age group 41-50 and 51-60 years. 16% were in the age group 61-70 years.

Table 2 shows the anthropometric and clinical profile of the adults with Type 2 Diabetes mellitus

Parameters	Adults (n = 1200), (%)	p value
Body Mass Index		
Under weight	42 (3.5)	0.25 (3), p<0.0001
Normal weight	581 (48.4)	
Overweight	497 (41.41)	
Overweight Class I	80 (6.66)	
Hypertension		
Normal (90 - 119/60 - 79)	442 (36.83)	170.64(3), p<0.0001
Pre-hypertension (120 - 139/80 - 89)	359 (29.91)	
Stage 1 (140 - 159/90 - 99)	261 (22.33)	
Stage 2 (>160/>100)	138 (11.75)	
Blood glucose levels / Lipid profile		
IFG	883 (73.58)	141.56 (2), p<0.0001
Cholesterol	477 (39.75)	
Triglycerides	567 (47.25)	
HbA1C		
4 - 6.5	584 (48.66)	250.21 (2), p<0.0001
6.6 – 9	465 (38.75)	
9.1 – 16	151 (12.58)	
Medicine		
Oral Drugs	1016 (84.66)	1455.64 (3), p<0.0001
Insulin	101 (8.41)	
Both (Oral + Insulin)	55 (4.58)	
Ayurvedic/Homeopathy/alternative remedies	28 (2.33)	

Table 3: Profile of patients with diabetes diagnosed with tuberculosis

Variables	Cases (%)	p value
Diabetes patients diagnosed with TB (n=1200)	13 (1.08)	
Gender		
Male	11 (84.61)	$\chi^2 = 4.92$, p<0.027
Female	2 (15.38)	
Mean age of patients	51.307±10.819	$\chi^2 = 1.71$, p<0.191
HbA1C		
6.5 – 9	4 (30.7%)	$\chi^2 = 1.24$, p = 0.27
9.1 – 16	9 (69.2%)	
Type of TB		
Pulmonary	12 (1)	
Extra-pulmonary	1 (0.08)	
Category of treatment		
CAT-I	11 (0.91)	$\chi^2 = 4.92$, p = 0.0275
CAT-II	2 (0.16)	
Bacillary index (Sputum positivity)		
1+	7 (0.58)	$\chi^2 = 6.38$, p = 0.085
2+	3 (0.25)	
3+	1(0.08)	
Negative	2 (0.16)	

This shows that T2DM is more common with advancing age. Among the patients included in the study, 99% were married. About 34% people had studied in high schools and colleges. Thus, it appears that the prevalence of diabetes were more among the literate patients. 21% of these patients had either regular job, business and/or were housewives. Patients having specified jobs had Diabetes owing to desk job. 66% were sedentary whereas 33% were active. Being sedentary is a risk factor for developing Diabetes. 13% of patients were having habits of all types, namely chewing gutkha/tobacco, smoking and alcohol. 50% were addicted to chewing gutka/ tobacco. Around 6% were smokers and about 3% consumed alcohol regularly. More patients with diabetes were found to be addicted to either smoking, drinking alcohol and/or chewing tobacco/ gutkha which is a known risk factor for Diabetes. However, it is difficult to ascertain the number of people actually addicted physiologically to cigarettes and/or alcohol. Excessive alcohol intake reduces insulin sensitivity thereby increasing insulin resistance and the risk of diabetes. 20% of patients with Diabetes had familial history, i.e., at least one member in the family was having Diabetes.

40% of our study subjects were also having stress due to many reasons. While occupational stress appeared to be 37%, familial stress contributed to 21%. Stress is a known factor for many lifestyle diseases like Diabetes, BP, etc.Table 2 shows the anthropometric profile of patients with Type 2 Diabetes mellitus. With reference to BMI, 41% were overweight and 6% were obese. 48% were having normal weight whereas 3% of Diabetic patients were underweight. The variation in BMI levels in patients with Diabetes are highly significant, $p < 0.0001$.

Further, 29% of T2DM patients were having prehypertension, i.e., [120-139/80-89], while 11% were having stage 2 hypertension (>160/>100). Hypertension and Diabetes are common in most of the patients.

Fasting Blood Glucose (FBG) levels were high in 73% of T2DM patients, ranging from 145-250g/dl. Cholesterol and triglyceride levels were also high among 39% and 47% of the patients, respectively. These 3 entities are dangerous and may lead to serious conditions like stroke, heart attack, etc. About 30% of T2DM patients were having metabolic syndrome. Metabolic syndrome is becoming increasingly common. It occurs when a range of metabolic risk factors such as obesity and insulin resistance come together. Metabolic syndrome is a risk factor for diabetes. The HbA1C levels were higher among 51% of the patients, i.e., ranging from 6.6 - 15.

Thus, in our study, age, gender (males), literacy status, occupation, life style, familial history, habits and stress appeared to be significant risk factors among patients with diabetes. Increased BMI, hypertension, blood glucose levels, lipid profile and HbA1C were significant risk factors for TB. It was observed that while 84% of the patients were taking oral hypoglycemic drugs only 8% were taking Insulin injections. About 5% were on both oral hypoglycemic drugs and insulin.

Table 3 shows the profile of patients with diabetes diagnosed with tuberculosis. Out of 1200 patients with type 2 diabetes mellitus, only 13 were having active TB disease, the incidence being 1.08%. Based on the clinical, radiological and bacteriological findings, the diagnosis of active TB disease was confirmed. Among the TB patients, the predominant signs and symptoms were fever, cough, loss of weight, lethargy, pallor and hepatosplenomegaly which correlated with positive chest radiography and respiratory findings. 12 were having pulmonary and 1 was having extra-pulmonary type of TB. 11 were given Cat-I treatment while 2 were on Cat-II, Sputum examination revealed that 7 were having 1+ sputum positivity and 3 were 2+ sputum positivity. Chest X-ray PA (posterior-anterior) view indicated pulmonary involvement along with cavities in some of the patients.

DISCUSSION

In this study, we determined the incidence of Tuberculosis among 1200 patients with Type 2 Diabetes mellitus. More males with advancing age, sedentary life style and high BMI were having Diabetes. These patients were found to be addicted to either smoking, drinking alcohol and/or chewing tobacco / gutka. About 23% of patients with Diabetes had familial history, high BMI levels, hypertension, high FBG levels, cholesterol and triglyceride levels. In our study, age and gender were the strong determinants of TB, with the highest risks found in old people.[27] Several studies have reported that diabetes, smoking and alcohol abuse are the risk factors which can actually raise the risk of developing active TB twice or thrice. It was observed from a mathematical modeling analysis of the effects of smoking on TB infection and mortality that smoking might lead to an excess of 18 million TB cases and 40 million deaths from TB between 2010 and 2050. In India, a major portion of the TB burden can be attributed to smoking (40%) and DM (15%).[28, 29] Majority of the T2DM patients were having Metabolic syndrome. Many of the patients with both DM and TB were on combination therapy with both oral hypoglycemic drugs and insulin and duration of their disease was >10 years. In 69% of the TB-T2DM patients, the glycaemic control was poor as evident from significantly

higher HbA1C levels. Together, these data prove that severe and uncontrolled disease for a longer duration is a risk factor for TB among the diabetes patients with TB as reported in many studies. Only 13 were having active TB disease, the incidence being 1.08%. Some of the patients with TB identified during the study period were on treatment already as they had been diagnosed elsewhere. Good geographical coverage of the TB control programme in Odisha with emphasis on universal access to active TB case finding in the community is probably the reason. Several studies have reported that Diabetes makes a substantial contribution to incidence of TB.[30- 36] Our study shows that the screening of diabetes patients for TB for the first-time is feasible in a tertiary care hospital settings for DM in Odisha routinely. Over a period of 2 years, during which diabetes patients attending the clinic were screened, we detected 13 patients with TB, giving a case rate of 1083 per 1,00,000 screened patients. Moreover, 92% of the patients were highly infectious as they were diagnosed as having smear-positive disease. There is a need for further investigations to determine the relatively less number of new TB cases. TB control efforts might be benefited from active case finding and treatment of latent TB in people with diabetes and increased efforts to diagnose and treat diabetes in populations where diabetes affects the risk of TB to a larger extent.[37, 38] In India, the growing problem of diabetes in this high-risk group population could make prevention of tuberculosis, a priority area in the future.

The strengths of this study are that we could implement the screening process within the routine health care settings. A large number of diabetes patients were registered consecutively, in a robust manner and screened. The early identification of the newly diagnosed patients with co-morbidity helped us to refer these patients to proper care, leading to improved outcomes of TB treatment. Electronic database was used for the recording and reporting. There were a number of limitations and challenges. One limitation of our study was that we were not able to ascertain whether symptoms of other respiratory infections were present along with TB in T2DM. This requires periodic screening at intervals of 3 months, which was not the objective of this study. Further research is needed to determine this and ascertain the average timing of TB screening among diabetes patients. More research is warranted to investigate how the incidence of TB impacts diabetes control efforts in this state. Similarly, the investigations for estimation of HbA1C and lipid profile was done for patients which were costly. Another was few, 10% of patients with symptoms suggestive of TB were reluctant to give sputum specimens, the reason being stigma and/or denial that they might have TB. In India, the screening of TB patients for diabetes is relatively easy and a high rate of detection of DM, ranging from 10%-44% in TB patients has been observed in many studies in different states. However, screening for TB among diabetes patients is less easy, with several studies reporting challenges such as less registration of patients and reluctance to provide sputum specimens. The doctors and/or technical staff, on the other hand, are reluctant for this additional work and do not record the screening systematically.[39, 40] as observed in our study. This study shows the importance of good collaboration between communicable and non-communicable disease programmes.

CONCLUSIONS

Screening for TB among T2DM patients in diabetes clinics would lead to earlier detection of TB, which in turn, would help in early treatment while decreasing the risk of nosocomial transmission. It will further lead to better TB-specific treatment outcomes and prevention of diabetes complications. We, therefore, feel that screening T2DM patients, irrespective of their complaints and symptoms, at regular intervals, for signs and symptoms of TB would go a long way in early detection of the Tuberculosis.

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