Incidence of Tuberculosis in Diabetic patients in Kolkata, India – a pilot study

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Abstract: *Background & Objective – Tuberculosis (TB) and diabetes two of the most prevalent diseases worldwide and may occur concurrently. The association between TB & diabetes are known historically though from 18th century onwards it is being studied in a more scientific manner. The objective of this study is to determine incidence of TB in diabetic patients and also to understand comorbid correlation.*

Materials & Methods - This is a retrospective cross sectional study carried out at the Respiratory medicine department of Medical College between November 2017 and December 2017.

Results – Overall incidence of TB in diabetic patients was found to be 8.33%. Incidence rate of TB in Type I diabetes was 34.28% and in Type II diabetes was 8.49% (odds ratio 5.25). Fever as a presenting feature found to be more common in diabetic tuberculosis group (odds ratio 6.8333, 95% C.I 1.6535 to 28.2403, p = 0.0079). Diabetic tuberculosis group is more prone to develop cough in comparison to patients with only diabetes (Odds ratio 11.1724, 95% C.I 2.24 to 55.699, p= 0.0032). Chest pain, Respiratory distress and Haemoptysis are also more common in diabetic tuberculosis group (Odds ratio of 5.25, 153 and 6.66 respectively). Study results also showed that diabetic patient with TB have worse glycaemic control compared to patients suffering from only diabetes (Odds ratio 9.75, 95% C.I 1.9622 to 48.4476, p = 0.0054).

Conclusion – TB and diabetes are both prevalent in Kolkata. In our country, large scale prospective cohort studies are needed to understand this relationship more vividly to develop better management protocols in future.

Keywords – Tuberculosis, Diabetes, Incidence, Retrospective study, Type I diabetes, Type II diabetes

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I. Introduction

Diabetes and tuberculosis (TB) are considered two biggest public health problems across the world as well as in India. According to International Diabetes Federation (IDF), there are 72 million cases in India in 2017 [1]. Another country wide study involving 15 states done by ICMR found prevalence of diabetes mellitus in India is 7.3% [2]. India accounts for one fourth of the global TB burden.

In 2015, an estimated 28 lakh cases occurred and 4.8 lakh people died due to TB [3]. India is the country with the highest burden of TB. The World Health Organisation (WHO) TB statistics for India for 2016 give an estimated incidence figure of 2.79 million cases of TB for India [4].

Diabetes is a non-communicable disease whereas TB is a communicable disease. Diabetes involves multiple organ system of the body and infection is an important factor in the course of the disease. TB, when coexists with diabetes can cause serious complication and pose challenge to treat both the diseases successfully. Diabetes mellitus (DM) is a syndrome characterised by chronic hyperglycaemia and disturbance of carbohydrate, fat and protein associated with absolute or relative deficiency of insulin secretion/action. Tuberculosis is caused by mycobacterium tuberculosis and mostly involves lung though can affect other organs. Avicenna (980-1027 AD) first documented frequent association of DM & TB. It has been reported that presentation of TB in diabetics is different than in non-diabetics. One study in UK in Asian patients revealed that there is increase in cavitary lesion & sputum positivity in TB patients with diabetes [5]. In another study, an increase in lower lobe diseases was suggested [6].

II. Aims And Objective

- Incidence of Tuberculosis in diabetic patients.
- Difference in TB presentation in diabetic and non-diabetic.
- Association between diabetes and tuberculosis with respect to type and diabetic control
- To explore demographic variation between groups.

III. Materials And Methods

This is a retrospective cross sectional study carried out at the Respiratory medicine department of Medical College, Kolkata between November 2017 and December 2017.

Patient Inclusion criteria

- Age >20 years
- Diagnosed and confirmed cases of diabetes mellitus
- Not previously diagnosed and treated for tuberculosis

Total 120 patients admitted during the specified time period was randomly selected and included in the study. We planned to compare following parameters between two groups - 'Diabetic' and 'Diabetic tuberculosis'. The parameters that are looked into are Sex, Urban/Rural, Type of diabetes, Presenting signs & symptoms like fever, cough, chest pain, respiratory distress, weakness, loss of weight and haemoptysis. We also looked into diabetic control between both the groups. 10 patients were included in the diabetic tuberculosis group and 110 patient were included in the diabetic group. Detailed history and physical examination were carried out for each selected patients and documented for study purpose with the intention to treat.

Diabetes was diagnosed and confirmed by criteria set forth by American Diabetic Association (ADA) and World Health Organization (WHO) as given in Table 1 [7].

Table 1

Index	Value	Comment/Condition
HbA1C	≥6.5%	
FPG (Fasting plasma glucose)	≥126 mg/dl (7.0 mmol/l).	Fasting is defined as no caloric intake for at least 8 h
2-h Plasma glucose (post prandrial)	≥200 mg/dl (11.1 mmol/l)	The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l).		

Control of diabetes mellitus was defined by criteria given by ADA as in Table 2 [8].

Table 2

Index	Good control	Poor control
HbA1C	<7.0% (53mmol/L)	≥7.0% (53mmol/L)v
Preprandial capillary PG (FPG)	80-130 mg/dL (4.4-7.2 mmol/L)	≥130 mg/dL (7.2 mmol/L)
Peak postprandial capillary PG	<180 mg/dL* (<10.0 mmol/L)	≥180 mg/dL (10.0 mmol/L)

TB was diagnosed according to Revised National Tuberculosis Control Project guidelines by doing sputum smear microscopy [9]. Blood examination, Chest X-ray, sputum testing done for each selected patient for study purposes as well as treatment.

IV. Results

Total 120 patients included in the study. 10 patients were included in diabetic tuberculosis group and 110 patients was included in diabetic group. In our study, we found an incidence of 8.33% of tuberculosis in diabetic patients. Demographic distribution is given in Table 3 according to age, sex and area of residence.

Table 3: Demographic distribution of patients

Characteristics	Diabetic tuberculosis	% of patients	Diabetic	% of patients
21-30 years	2	20	1	0.9
31-40 years	0	0	12	10.90
41-50 years	7	70	28	25.45
51-60 years	1	10	42	38.18
>60 years	0	0	27	24.54
Male	6	60	72	65.45
Female	4	40	38	34.55
Urban	8	80	83	75.45
Rural	2	20	27	24.55

70% of diabetic tuberculosis group fall in 41-50 years age category whereas more than 60% patients in diabetic group are over 50 years of age.
Both Type I and II diabetic patients were included in the study as given in Table 4.

Table 4: Type of Diabetes

Type of diabetes	Diabetic tuberculosis	% of patients	Diabetic	% of patients
Type I	2	20	5	4.54
Type II	8	80	105	95.46

Incidence rate of TB in Type I diabetes was 28.57%% & in Type II diabetes was 7.08% as evident from table 4.
All the presenting symptoms were documented and categorized according to two groups and is given in table 5.

Table 5: Presenting symptoms of the patients

Symptoms	Diabetic tuberculosis	% of patients	Diabetic	% of patients
Fever	7	70	28	25.45
Cough	8	80	29	26.36
Chest pain	2	20	5	4.54
Resp. distress	4	40	0	0
Polyuria	0	0	25	22.72
Weakness	1	10	31	28.18
Weight loss	1	10	9	8.18
Haemoptysis	4	40	10	9.09
Skin infection	0	0	9	8.18
Anorexia	1	10	0	0

General survey findings and respiratory findings were also documented for research purposes as given Table 6 and 7.

Table 6: General survey findings

Survey findings	Diabetic tuberculosis	% of patients	Diabetic	% of patients
Fever	7	70	26	23.63
Clubbing	0	0	1	0.90
Oedema	1	10	0	0
Tachycardia	7	70	0	0
Tachypnoea	4	40	0	0
Cyanosis	0	0	0	0
Pallor	1	10	5	4.54

Table 7 : Respiratory system findings

Resp. findings	Diabetic tuberculosis	% of patients	Diabetic	% of patients
Crepitation	8	80	2	1.81
Bronchial breath sounds	1	10	1	0.90
Rhonchi	1	10	1	0.90
Hydropneumothorax	1	10	0	0
Pleural effusion	1	10	0	0
Pneumothorax	0	0	0	0

We could not find any statistical relationship between male and female comparing both the groups. The chi-square statistic is 0.1199. The p-value is .729165. This result is not significant at $p < .05$. There was no statistical association between urban and rural dwellers (The chi-square statistic is 0.1033. The p-value is .747852. This result is not significant at $p < .05$). Chi square test suggested an association between Type I diabetes and development of tuberculosis in comparison to Type II diabetes. The chi-square statistic is 3.9857. The p-value is .045887. This result is significant at $p < .05$. Type I are more prone to develop TB as odds ratio between two groups found to be 5.25 (95% C.I 0.8761 to 31.4605). As far as symptoms are concerned there are few positive findings in our study. Fever as a presenting feature found to be more common in diabetic tuberculosis group. Patients with both diabetes & tuberculosis are more prone to develop fever than patients with only diabetes (odds ratio 6.8333, 95% C.I 1.6535 to 28.2403, $p = 0.0079$). Diabetic tuberculosis group is more prone to develop cough in comparison to patients with only diabetes (Odds ratio 11.1724, 95% C.I 2.24 to 55.699, $p = 0.0032$). Chest pain also seems to occur more in diabetic tuberculosis group with odds ratio of 5.25 (95% C.I 0.8761 to 31.4605). Respiratory distress is also more common in diabetic tuberculosis group. These

patients are at much higher risk of suffering from respiratory distress than the patients having only diabetes (Odds ratio 153, 95% C.I 7.41 to 3157.16, p = 0.0011). Diabetic tuberculosis patients are also high risk of having complication like haemoptysis (6.6667, 95% C.I 1.61 to 27.65, p = 0.0089). Though in case of weakness and loss of weight there was no significant difference between the two groups. Looking into the treatment aspect, we found that diabetic tuberculosis group are more likely to have poor glycaemic control than the group having only diabetes (Odds ratio 9.75, 95% C.I 1.9622 to 48.4476, p = 0.0054).

V. Discussion

Historical perspective

Avicenna (980-1027) first documented frequent association of diabetes and pulmonary tuberculosis. Autopsy studies in 18th century found evidence of tuberculosis in 38% to more than 50% diabetics. Root also noted that pulmonary tuberculosis occurs at least 10 times more in case of diabetics [10]

Our pilot study revealed incidence of TB among diabetic patients to be 8.33%. Previous studies like Boukot K et al. in Philadelphia survey found it to be 8.4% and Lester FT et al. showed the incidence of TB in diabetic patients to be 16.5%. Other studies across the globe also showed prevalence of TB is 4 times greater in DM than general population [111, 12, 13]. A large prospective study carried out in Korea in a cohort of 331,601 DM patients showed TB case notification rates of 180 per 100,000 during a 3-year follow up [14], whereas a small cross-sectional study conducted in Nepal showed that 8 out of 100 DM patients were positive for pulmonary TB [15]. A retrospective study conducted in Pakistan found that the prevalence of TB in diabetic patients was 11.9%, 10 times higher than in non-diabetic patients (1.7%, p < 0.05) [16].Interestingly we also found that in Type I diabetes incidence rate is 34.28% but in Type II diabetes, it is 8.49% which is much closure to the overall incidence of 8.33%. Our result showed 5 times of higher risk of developing Tb in Type I patients compare to Type II DM patients. Similar results were corroborated in few other studies. In a cohort of 1529 diabetic individuals in Chile, who were followed prospectively from 1959 to 1982, the 10-year actuarial probability of developing tuberculosis was 24% in IDDM and 4·8% in NIDDM [17].In a prospective study of diabetic patients followed for 1–7 years in Tanzania, 9·0% of patients with IDDM and 2·7% of patients with NIDDM developed pulmonary tuberculosis [18]. Another large cohort study conducted in Australia found the crude RR of TB was 1.78 (95% CI 1.17 to 2.73) in all people with DM and 2.16 (95% CI 1.19 to 3.93) in people with DM using insulin. These studies showed evidence that insulin dependence may increase the risk of TB in DM patients.

Peak in incidence in diabetic tuberculosis group is a decade lower than patients having only diabetes. This is probably due to high prevalence of TB-DM comorbidity in Asian countries, especially in China and India, may be a result of the rapidly increasing prevalence of young-onset DM in these countries [19]. In southern India, from 2000 to 2006, the prevalence of DM in people younger than 44 years increased by 10.7% [20]. Data from China show an 88% increase in the prevalence of maturity-onset DM in the 35–44 years age group from 1994 to 2000, probably due to the rapid transition in dietary habits, reduced physical activity, longer working hours, and decreasing sleep hours [21]. Although the data does not provide concrete evidence, it has been shown that the relation between DM and TB is more prominent in younger people. A meta-analysis of 13 observational studies of association between DM and active TB identified 2 studies that presented age-stratified RRs (Risk ratios). They demonstrated stronger associations of DM and TB under the age of 40 and declining RR with increasing age in age groups over 40 years (trend pKim = 0.014, pPonce-de-Leon = 0.184) [20]. However, since many other studies found that TB-DM comorbidity was significantly more common in patients over 40 years [22, 23, 24], these results and the potential relation of young-onset DM and TB should be taken with caution.

Diabetic tuberculosis patients are much more prone to develop symptoms like fever, cough, respiratory distress and haemoptysis, as evident from our result. This is mostly due to comorbid TB in these patients and quite a few studies suggested a higher mycobacterial load in Tb patients with coexisting DM. The presentation of TB in diabetic subjects may not be always different as they may also manifest themselves with the common symptoms in diabetic subjects as in any other individual without DM. The DM–TB comorbidity introduces some peculiarities. In addition to the higher rates of poor outcome (in terms of mortality, relapse, etc.) [28,29], TB patients with DM also have worse clinical presentation, with more symptoms, in particular weight loss, fever, dyspnoea and night sweats [30]. The diabetic subjects with TB are more likely to have higher bacillary load. Three small retrospective studies suggest that baseline mycobacterial burdens might be higher in diabetic patients than in controls [25, 26, 27]. Diabetic treatment is hampered due to comorbid TB as evident from our result with diabetic tuberculosis group has much higher risk of poor control than the patients only suffering from diabetes. Poor glycaemic control in Asian populations represents a potentially important risk factor for TB [31]. Restrepo and colleagues conducted one of the first studies which revealed that persistent hyperglycaemia could play a key role in altering the immune responses to M. tuberculosis in diabetic patients [32]. The study showed that poor DM control (as indicated by HbA1c level) was associated with differences in the innate and cellular

cytokine responses to stimulation with purified protein derivative from M. tuberculosis, thus facilitating progression to active TB [32]. Another recent study, that recruited 4,690 elderly diabetic patients in Hong Kong, showed that the patients with greater HbA1c value (>7%) had a hazard risk of active TB that was 3 times increased compared with those who had HbA1c < 7% (HR 3.11; 95% CI 1.63–5.92, p < 0.01) [33]. A cohort study with 123,546 individuals performed in Taiwan found that, during a median follow-up period of 4.6 years, diabetic patients with poor glycaemic control had a significantly higher risk of TB (adjusted HR 2.21; 95% CI 1.63–2.99, p < 0.01) compared to those without DM [34].The evidence of poor glycaemic control in Indian patients call for further therapeutic actions in order to decrease TB-DM prevalence in India, knowing the fact that poor glycaemic control represents an important risk factor for TB.

VI.   Limitation Of The Study

Our study has few limitations. Firstly being a pilot study the sample size is small. Secondly it has innate problems of being a retrospective study. Third, no proper control group was selected to compare the results, especially no patients with only TB included in the study. Fourth, all patients recruited was over 20 years of age leading to much less number of Type I diabetes.

VII.   Conclusion

DM & TB are a heavy burden to Indian society and there is immense scope of further studies in future. Large scale prospective cohort studies as well as randomised controlled trials are needed to understand the disease interaction, clinical features, management options and drug-drug interaction in these comorbid conditions. More evidences will surely point us to the right direction in respect to manage both disease epidemic more efficiently in near future.

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