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ORIGINAL ARTICLE

Association between Diabetes Mellitus and Pulmonary Tuberculosis in Adults

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Abstract:

Background: *Tuberculosis (TB) and diabetes mellitus (DM) are national and global pandemic. Bangladesh is among the top ten countries for both diabetes and tuberculosis prevalence. The coexistence of both diabetes and tuberculosis has a greater impact on the disease process and treatment outcome. Hence bidirectional screening for this coexistence may have a positive role in the better management of both disease conditions.*

Methods and Materials: *A case-control study was conducted in the Department of Internal medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh among smear positive pulmonary TB patients as cases and non-TB controls. Participants were tested for fasting plasma glucose and glycosylated hemoglobin (HbA1c) for diagnosis of diabetes according to ADA guidelines.*

Results: *Among 142 cases and 142 controls the mean (SD) age was 40.48±14.17 and 42.70± 13.17 years. BMI was <18.5 kg/m² in most of the tuberculosis patients. Among 142 TB cases 45 (31.7%) were diabetic and 74(52.1%) were prediabetic. Tuberculosis was associated with prediabetes (OR 18.5, CI 5.6 – 60.9) and diabetes (OR 21.2, CI 4.4 - 100).Tuberculosis (TB) cases with Diabetes mellitus were more from urban areas. The previously diagnosed diabetic cases have poor glycemic control during diagnosis of tuberculosis.*

Conclusion: *In this case control study reconfirms the association of pulmonary tuberculosis and diabetes mellitus. The present study reveals risk of tuberculosis twenty one times more in diabetes mellitus cases and eighteen times more in prediabetes cases. This high frequency of diabetes mellitus suggest in adult patient should be tested for diabetes and patient with cough should be tested for tuberculosis.*

Key words: *Diabetes mellitus, tuberculosis.*

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Introduction:

Tuberculosis (TB) is a major cause of morbidity and mortality throughout the world. Bangladesh stands sixth among the 22 high TB burdened areas and the annual incidence of TB is 225/ 100000 per year in this country. The prevalence is estimated to be 434 per 100,000 populations. The estimated TB mortality is 45 per 100,000 populations per year[1]. Bangladesh, along with India, China and few other countries are also overburdened with both Tuberculosis and Diabetes Mellitus. Number of diabetic patients around the world is escalating in such a steep way that by the year 2030, DM will become the 7th leading cause of death around the world[2]. It is to be mentioned that, 80% of diabetic death in the world occurs in the low income countries like Bangladesh[3]. Bangladesh remains in the list of top 10 DM burdened countries around the world and by the year 2030 the ranking is expected to go up[4]. Both diabetes and tuberculosis are global and national concern.

Recent studies show prevalence of diabetes mellitus in Bangladesh community prevalence: 30-35% abnormal glucose tolerance of which diabetes is 8-12%[5]. Besides 1.75% of adult population (total 1.58 million) had Impaired Glucose Tolerance[6].

In Bangladesh almost all are type 2 diabetes; type 1 is rare. About half of all people with diabetes are unaware of their disease. 80% of people with diabetes live in low and middle income countries. Diabetic population shows 8.4% of all cause mortality. Health spending on diabetes accounts for 10.8% of total health expenditure worldwide (1).Co-existence of DM in TB has a greater impact on disease process and treatment outcome.

Diabetes contributes to the global increase in incidence of tuberculosis and may become a threat to the TB control program in coming days[7]. DM has been identified as an important risk factor for development of active TB[8]. The incidence of tuberculosis is 2 to 5 times higher in diabetic patients than the non-diabetic ones[8]. A screening program in China showed significant number of new cases (3%) of DM in TB patients. Total number of DM cases was also higher in this population. Moreover they were able to find 7.8% new cases of impaired fasting glucose which could significantly help in the primary prevention of diabetes[9]. Prevalence of DM in TB was found to be much higher in Kerala (44%), Mexico (36%) and Texas (39%)[10,11].

In China overall prevalence of DM in patients with TB was 12.4%. Health facilities serving urban populations and hospitals had a higher prevalence of DM compared with health facilities serving rural populations and clinics[9].

The innate and adaptive immune responses necessary for the prevention of tuberculous proliferation is hampered in diabetic patients[8]. TB patients with DM have different manifestations of the disease and unfavorable treatment outcome[12]. It has been found that these patients have more cavitatory lesions on chest x-ray, less sputum positivity and a paucity of clinical presentation[13]. Both treatment failure and number of death are high in this group of people. According to Baker et al they have a risk ratio (RR) for the combined outcome of failure and death of 1.69 (95% CI, 1.36 to 2)[14]. DM has a 2 fold higher risk of death[15]. Dooley et al also showed in the same study that the time for sputum culture conversion was longer in pulmonary TB cases with diabetes. Treatment failure among diabetic patients was also higher than the non-diabetic TB patients (4.1% vs. 6.7%)[15]. Diabetic patients are more prone to develop multidrug-resistant TB and they are more than 5 times likely to become infected with drug-resistant strains[16].

TB patients with anti-tuberculer drugs in diabetic patients can be troublesome as drugs like rifampicin can induce hyperglycemia directly or by indirect interaction with ongoing oral hypoglycemic agents[17,18]. TB infection is also responsible for reversible impaired glucose tolerance[19]. In diabetic patients the plasma concentrations of isoniazid and rifampicin is found to be lower[20].

This steep rise of the curve of diabetic prevalence will have an impact on the global prevalence of tuberculosis also. So detecting diabetes early in TB cases will be needed for better management of these "Tubercular diabetic" patients[7]. Extensive works have been done in China, India

and other countries where diabetes has been screened in TB patients and found to be higher[9,10,21]. Diabetic patients were also screened for TB in these countries and a higher prevalence was also evident there[22,23]. Bidirectional screening was also done for DM and TB in some places. Currently world health organization (WHO) also recommends for such bi-directional screening as detecting early the co-existence of these diseases can lead to better management of both cases[24].

Methods:

This study was conducted as a case-control study. Smear positive PTB patients were as cases, non TB patients were as controls. Cases were collected from DOTS corner and Outpatients Department (OPD) of BSMMU and 'TB control and training institute', Chankharpol, Dhaka. Controls were collected from Medicine OPD, BSMMU.

This study was carried out during a period of 1st Jan 2015 to 31st December 2015 in the Department of Internal Medicine, BSMMU, Dhaka. A total of 142 patients were cases and 142 were controls. Samples were collected by convenient sampling technique as per inclusion and exclusion criteria. PTB was diagnosed by history (fever, cough for 3 weeks or more, weight loss) & bacteriological confirmation by sputum for Acid Fast Bacilli & GeneXpert. TB was excluded by history (cough, low grade intermittent fever, night sweating in past 3 weeks and unexplained weight loss in the past month), physical examination and relevant investigations (CBC, CXR, FBS, HbA1c). Study purpose was explained to the patient and informed written consent was taken before collection of data. The findings were entered into the structured questionnaire and data sheet. Patient blood samples were obtained and sent to Biochemistry department to determine the FBS, HbA1C for both cases and controls. Complete blood count was done in hematology and chest x-ray was done in radiology department for only controls. Later reports were collected and entered into the data sheet. Persons fulfilling American Diabetes Association (ADA) diagnostic criteria 2014 for DM was enrolled as diabetic. For patients with self-reported DM, we also measured FBS, HbA1C level to see current glycaemic status. All available patients who fulfilled the inclusions criteria were selectedand analyzed. HbA1c was measured using the NGSP certified Bio-Rad D-10^{TM} Hemoglobin A_1C Program 220-0101, USA. All data were expressed as frequencies and mean (±SD or ± SE). Student's unpaired t- test for quantitative data and Chi-Square test for qualitative data were performed by using the statistical package for social science (SPSS) program[23]. Pearson's correlation test was used to see correlation among different variables. P values ≤0.05 was considered as significant. Multiple Logistic regression analysis was done to estimate the role of prediabetes and diabetes as a risk factor for tuberculosis.

Results:

A total of 284 subjects were enrolled in the study among which 142 were cases (smear positive pulmonary TB) and 142 were control. The age range of the subjects were between 18 and 70 years with the mean age of case group 40.48 ± 14.17 years and control group 42.70±13.17 (table i). Table I shows the baseline characteristics of the cases and controls.

There was no statistically significant difference between the duration of cough and weight loss among cases. Out of 142 cases previous history of pulmonary TB was present in 13 (4.6%).Among cases equal number were smoker and non-smoker (50%); Among controls non-smokers (58.50%) were more than smokers though the difference was not statistically significant. Most of the cases (60.6%) were under-weight while the participants of control group had normal weight (68.3%); differences in BMI among case and control groups were statistically significant (p value <0.001). (Table II).

Among 142 TB cases, DM was present in 45 (31.7%) (Previously known DM 32, newly diagnosed DM 13). 74(52%) cases were prediabetic. Normal fasting glucose was found in 23(16.2%). Among 142 controls, DM was found in 13(9.2%) (Previously known 5, newly diagnosed 8) and prediabetes was found in 30(21.1%), normal glucose tolerance in 99(69.7%) and were statistically significant (p<0.001).(Table III).

Table-I

Baseline characteristics of cases and controls

	Case (N=142)	Control (N=142)	P
Age (years)*	40.48±14.17	42.70±13.17	0.176
BMI kg/m² *	17.34±3.09	23.73±2.61	<0.001
Education**			
Illiterate	68 (47.9%)	34(23.9%)	<0.001
Primary	53 (37.3)	42 (29.6%)	
SSC/HSC	17 (12%)	53(37.3)	
Degree & above	4 (2.8%)	13 (9.2%)	
Occupation**			
Cultivator	4 (2.8%)	14(9.9%)	0.012
Service	41 (28.9%)	44(31%)	
Business	29 (20.4%)	28(19.7%)	
Housewife	35 (24.6%)	41(28.9%)	
Others(day labor)	33 (23.2%)	15(10.6%)	
Gender **			
Male	102 (71.8%)	94 (66.2%)	0.306*
Female	40 (28.2%)	48 (33.8%)	
Residence**			
Rural	22(15.5%)	44(31%)	
Urban	120(84.5%)	98(69%)	0.002

Table-II

BMI category of study subjects

BMI in Kg/m²	Case(N=142)	Control(N=142)	P
<18.5	86 (60.60%)	1 (0.70%)	
18.5-24.9	53 (37.30%)	97 (68.30%)	<0.001
25-29.9	2 (1.40%)	43(30.30%)	
>30	1 (0.70%)	1(0.70%)	

(Done by X^2 test)
(<18.5-under weight, 18.5-24.9-Normal, 25-29.9-Over weight,>30-Obese)
BMI-Body Mass Index)

Table-III

Distribution of NFG, Prediabetic, DM in case and control

	Case(N=142)	Control(N=142)	P
NFG	23 (16.2%)	99(69.7%)	<0.001
Prediabetic	74 (52.1%)	30(21.1%)	
DM	45(31.7%)	13(9.2%)	

The frequency of DM was higher in those aged 36 years or more. Patients with TB and DM were older than those with only TB. (Table IV)

Out Of 284 subjects mean fasting plasma glucose in cases were 6.77±2.98 and 5.42±1.58 in controls. HbA1c in cases were 7.15±2.28 and 5.724±1.52 among control. The difference was statistically significant (P value <0.001) (Table V)

In the study known diabetic cases were 32. Majority of patients' FPG (84.4%)& HbA1c (93.8%) were uncontrolled.

Multiple Logistic regression analysis showed odds ratio for the risk of tuberculosis associated with urban areas (5.0, CI1.7-14.7), history of smoking (2.8, CI 1.0 – 7.5), previous history of DM (12.4, CI 1.7- 88.4) prediabetes (18.5, CI5.6 – 60.9) and for diabetes (21.2, CI 4.4 - 100). (Table VI).

Table-IV

Age group distribution of DM & prediabetic cases

Age in years	NFG	Prediabetes	DM	P value
18-35	17(73.9%)	36(48.6%)	9(20.0%)	
36-50	5(21.7%)	23(31.1%)	18(40.0%)	<0.001
51-70	1(4.3%)	15(20.3%)	18(40.0%)	

(Done by x^2 test, NFG-Normal Fasting Glucose, DM-Diabetes Mellitus)

Table-V

FPG & HbA1c value in study subjects

	Case(N=142)	Control(N=142)	P value
FPG	6.77±2.98	5.42±1.58	<0.001
HbA1c	7.15±2.28	5.724±1.52	<0.001

(Done by student's t- test)

(FPG: Fasting plasma glucose, HbA1c: Glycosylated haemoglobin A1c)

Table-VI

Multiple analysis for association between Residence, Previous DM, Smoking, Prediabetes, Diabetes in cases (n=142) and controls (n=142)

Characteristic	Odds Ratio	95% Confidence Interval
Residence		
Rural	Ref	Ref
Urban	5.0*	1.7-14.7
No Pervious history of DM	Ref	Ref
Previous history of DM	12.4*	1.7 – 88.4
No H/O smoking	Ref	Ref
H/O smoking	2.8	1.0-7.5
Impaired Fasting Glucose	Ref	Ref
Prediabetes	18.5*	5.6 – 60.9
Diabetes	21.2*	4.4 – 100

DM - Diabetes mellitus, ref - Reference

*p value less than 0.05;

Done by- Multiple logistic regression analysis

Discussion:

The frequency of diabetes mellitus was higher among patients with active pulmonary TB, which was almost five times higher than the estimated population prevalence of DM in Bangladesh[5]. Our findings were in conformity with reports of high prevalence of DM in TB from Mexico, Tanzania, India, Pakistan, China, and Indonesia [25,26,27,28]. The wide range of prevalence of DM in different studies might be due to the socio-demographic characteristics of source populations in the localities. Previous literature supports that DM is an important risk factor for the occurrence of TB[8,29].

Although the direct mechanism has not yet been clearly identified, reduced immunity in diabetic patients might play a major role in increasing the risk of tuberculosis. People with diabetes have reduced chemotaxis and oxidative killing potential than those of non-diabetic control[30].

The overall presence of prediabetes among newly pulmonary TB cases in this study were higher than the report from Indonesia[28], India[10] and Guinea[31] Tanzania[21].This positive association may be due to stress-induced hyperglycemia caused by tuberculosis. Possible explanation of

high blood glucose level in tuberculosis is insulin resistance caused by severe infection[32].

This study also demonstrated that significant proportion of new cases of diabetes mellitus was detected in patients with pulmonary tuberculosis. These findings are an alarming signal that DM should be considered and investigated in all tuberculosis patients. These findings were similar in another study in India[33,10]. This high proportion of undiagnosed cases may indicate less awareness of DM by the public and lack of access to health care services for the diagnosis of DM[10, 34]. High prevalence of diabetes mellitus in developing countries may be also another cause.

High incidence of tuberculosis has been reported in diabetic patients. Tuberculosis increases the risk of diabetes; it is not clear. In general infection (tuberculosis) often worsens hyperglycemia[35]. Tuberculosis infection can stimulate free fatty acid synthesis and secretion[36], which mediates insulin resistance by elevating pro inflammatory cytokines, specifically tumor necrosis factor-±.

Some studies suggest that tuberculosis can cause diabetes, even in those not previously known to have diabetes mellitus[28]. However; it is unclear whether diabetes mellitus persists in these patients or whether diabetes is more prevalent with tuberculosis than with other infectious diseases.

In this current study patient those were previously diagnosed as DM, their FPG and HbA1c were uncontrolled and failed to reach target HbA1c level[37]. Diabetes was newly diagnosed in cases and their median HbA1c was significantly lower than those with previously diagnosed DM[38.] Previous diagnosed of diabetes mellitus patients have poorly controlled glycosylated haemoglobin levels.[10] The association between diabetes mellitus and TB reported in this and other case-control studies may reflect an elevated risk of TB among diabetes patients. Poorly controlled diabetes may impair the cell-mediated immune response and neutrophil function and hyperglycemia alone may provide a better environment for bacterial growth and increased virulence of various microorganisms[39].

In this study, most of cases were age over 35 years and whose was diabetics age also above 35 years. This may be related to the fact that Type 2 DM is seen more frequently in the higher age group. The mean age of the patients with TB and DM was higher than in those with tuberculosis alone. This is similar to the other study[21,40]. We assume that old age is acted as a confounding factor for this finding.

Greater number of men was diagnosed with tuberculosis than women. The finding is also compatible with other studies[40]. Male were more exposed, smoker, interpersonal and social interaction for socioeconomic and cultural reasons. In addition, men may delay seeking treatment at health clinics[41].

The body mass index was less in cases. This was true for both newly diagnosed and previously diagnosed diabetes mellitus cases. Our age group suggests more prevalent type 2 DM where we expect BMI to be higher, but coexistence with tuberculosis was probably the reason behind our findings of low BMI in TB-DM cases. Same result was matched in other study[40].

Illiterate subjects were more in our tuberculosis cases. Illiteracy is a risk factor for tuberculosis mortality and findings also pointed towards the vulnerability of uneducated persons to tuberculosis. Lack of education is correlated with poor social conditions, lower perception of health problems, less self-care, and delay in seeking health service.

The major part of the cases of this study was from urban areas. Rapid urbanization and overcrowded living conditions in urban areas are possible factors. The increased prevalence of diabetes in urban areas is responsible for the urban incidence of smear-positive tuberculosis greater than rural areas[42].

In this study odds ratio for the risk of tuberculosis associated with urban area, previous history of DM, prediabetes and for diabetes were higher than study in Indonesia[28].

The strength of study is that glycosylated haemoglobin levels & fasting plasma glucose levels were measured on all patients. HbA1C measurement provides blood glucose levels over a period 2–3 months and is not subject to the

rapid swings. Both were separately diagnostic criteria for diagnosis of diabetes mellitus[37].

Conclusion:

Diabetes is a risk factor for tuberculosis. The increasing diabetes prevalence may be a threat to TB control. So diabetes prevention and proper treatment may reduce TB mortality & drug resistance. Diabetes is an important co-morbid feature to be sought in patient with TB.

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