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Title: Comparative Study of Diabetes Mellitus in Tuberculosis Patients in National Institute of Diseases of the Chest and Hospital, Dhaka

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Abstract**:** *The association between tuberculosis (TB) and Diabetes Mellitus (DM) has been established by multiple epidemiological studies worldwide. This study aims to find the prevalence of DM in TB patients in Bangladesh and attempts to investigate other factors associated to DM after a comparative analysis between TB and TB-DM groups. A descriptive cross sectional survey was done among 100 TB patients admitted in NIDCH, Dhaka using a structured questionnaire and interview, and data collected from their clinical records. Statistical analysis was carried out to find the association between TB and DM and other socio-demographic variables. Out of 100 patients admitted to NIDCH, 37% of the patients were diabetics. Majority of both groups had pulmonary TB and exhibited multi drug resistance. Amongst the TB-DM group, majority had Type 2 diabetes, poor glycemic control and reported having major complications of their co-morbidity. Males and middle aged (31-50) were more in TB-DM group while females and younger patients (<30) were prevalent in TB group. TB-DM group had a greater proportion of patients who drank alcohol while TB group had more smokers. Being married, higher income, occupation and greater age were found to have strong association with diabetes.*

Keywords: *Association, co-morbidity, diabetes, tuberculosis, prevalence*

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I. Introduction

Tuberculosis (TB) and Diabetes Mellitus (DM) have both become a global burden in recent years and the co-affliction with these two diseases has risen, which calls for renewed attention to this subject.[1]Literature has shown an association between diabetes and TB before the 1950's.However due to the emergence of widely available new drugs in both diseases, the association was nearly forgotten until the 1990s.[2]Multiple epidemiological studies investigated the relationship and presented a positive association between TB and DM.[3] Although the relationship reflected the effects of DM on TB, some controversy remains over the direction of the association due to the observation that TB induces hyperglycemia, transiently, which resolves with treatment.[3]

Diabetes Mellitus approximately triples the risk of active tuberculosis although the biological mechanism is still unclear. [2,4]It has been suggested that DM depresses immune system by affecting the macrophage and lymphocyte functions which can facilitate the progression to symptomatic disease.[5] The opposite might also be true that TB induces glucose intolerance which prevents good glycemic control in DM subjects.[5] It has been suggested that diabetic patients with impaired immune response suffer from more severe outcomes of active TB.[5,6]There are variable results with regards to how DM affects anti-tuberculosis treatment.[4] Some studies have reported that patients with DM and TB need more time to convert sputum cultures from positive to negative, are at increased chances of treatment failure, and have higher rates of death during anti-tuberculosis treatment.[4] However, other studies have not observed any notable differences between the TB and TB-DM groups. [4] It has also been suggested that DM might increase relapse rates in TB patients.[7]Apart from these, TB-DM patients were shown to have a greater tendency to develop MDR-TB when compared to their non- diabetic counterparts.[6]

Tuberculosis remains to be one of the conspicuous bacterial diseases worldwide. Globally, around 1.8 million people die from TB every year, a good proportion of which occurs in Bangladesh where there is hardly any significant trend in the prevalence of TB over the last couple of years.[6,8] Annual Global Tuberculosis Report by WHO from 2013 to 2015 has stated the prevalence to be 434, 402 and 404 per 100,000 respectively. The reports also mention that these figures are not the true representation due to lack of contribution of data.[6]Even then, these high prevalence rates should be seriously taken into account due to the cumbersome challenges posed by the TB burden.[6]

Diabetes Mellitus remains to be one of the major causes of mortality and disability globally.[9]In 2011,global prevalence was about 8% and it is expected to increase to 10% by 2030.[9]Past studies have shown a rise in prevalence of diabetes in Bangladesh from 2005 to 2011 (from 2 to 8% in rural and from 8 to 15% in urban areas).[6]According to the International Diabetes Federation, this prevalence is estimated to reach 13% by 2030.[9]This forecasted increase in such a short period of time incites huge concern as this also increases probability of higher prevalence of TB as diabetes makes an individual more susceptible to TB.[6]

Statistics have shown previously that 95% of people with TB live in the low and middle-income countries where prevalence of DM is escalating, especially in South Eastern Asian countries like Bangladesh, which is thus facing double burden of TB and DM.[10]With the current global increase in diabetes, the link between DM and TB does not bode well for the future and it is imperative to implement strategies to improve outcomes of both diseases and help Bangladesh tackle the challenges of TB control.[6] Screening for diabetes in TB patients will definitely identify undiagnosed diabetes and

indirectly improve TB treatment outcomes and reduce mortality. It is also important to delve into the differences between TB patients with and without DM to improve prognosis of patients with TB and DM.

II. Materials and Method

This study was conducted at the inpatient department of National Institute of Diseases of the Chest and Hospital, NIDCH, Dhaka, Mohakhali, central part of Dhaka city. A descriptive cross sectional survey was carried out using a structured questionnaire and interview with the TB patients. Data were also collected from the clinical records of the patients in the ward. A random group of 100 TB (with or without MDR-TB), both former and newly diagnosed, were included in the study undertaken between July-September 2015. Pregnant women and surgery patients were excluded from this study.

Patients were randomly interviewed face to face during the study period at NIDCH without taking into account whether or not they had pulmonary or extrapulmonary TB with or without complications. National TB control standardized guidelines were being used for the treatment of the patients. It was made sure that only the patients who gave verbal consent were included in the survey. Structured questionnaire was used to collect sociodemographic information of the patients like age, gender, marital status, education and employment status etc. Some clinical characteristics of TB namely type (whether pulmonary or MDR-TB), times of diagnosis of TB and signs and symptoms were recorded. Lifestyle factors such as smoking, alcohol intake and habituation to toxic substances like betel leaves, jorda and betel nuts were compared between TB-DM and TB groups. A comparison was made between the two groups to find out any significant association between diabetes and our study variables. All the data taken from the patients were confirmed by their clinical records. Moreover for diabetic patients, certain diabetes parameters were studied as discussed in results section.

Statistical Analysis

Data were entered into Microsoft Excel and then transferred to Statistical Package for Social Sciences (SPSS) version 17, where it was analyzed. Chi-square/Fischer's exact test was done to test the association between diabetes and the various study variables in our study.

III. Results

A total of 100 patients,(either newly diagnosed or former) were interviewed in the survey. Out of these patients,37% had diabetes, as shown in Table 1.Amongst the diabetic patients, 83.8% (31) had Type 2 diabetes, 8.1 %(3) had Type 1 diabetes, and the remaining 8.1 %(3) was not aware of the type and this information could not be retrieved from the clinical records as well. Majority of the diabetic patients, 75.7% (28), had diabetes for less than 5 years. Majority of them, 54.1 %(20), reported having poor control of blood glucose after being diagnosed with TB. 59.5% (22) TB-DM patients also reported of having major complications of TB-DM co-morbidity although these were not further delved into by the interviewer. When comparing the socio-demographic characteristics of TB and TB-DM group, as shown in Table 2, it was observed that there were more male patients than female patients in the TB-DM group, being 62.2%(23) and 37.8%(14) respectively. However, amongst the TB patients, there were slightly more female patients, 52.4 %(33), when compared to the males, being 47.6% (30).Majority of TB-DM patients were between the age (31-50), being 67.6 %(25). 54 %(34) of TB group patients was dominated by the age group <30.

Majority of both TB-DM and TB groups had married patients, being 83.8 %(31) and 63.5 %(40) respectively.40.5% (15) TB-DM patients went to college or were further qualified, the number being 34.9% (22), for TB patients. Amongst the TB patients, 58.7 %(37) had no income and on the other hand, 40.5 %(15) TB-DM patients were business holders. Majority of TB-DM patients, 45.9 %(17) had income $\leq$ 10,000. Most TB-DM and TB patients lived in semi-urban areas, numbers being 40.5 %(15) and 41.3 %(26) respectively.

From Table 3, it can be seen that 92.1 %(58) TB patients and 89.2 %(33) TB-DM patients had pulmonary TB whereas proportion of MDR-TB patients in the TB-DM and TB group was 62.2% (23) and 60.3 %(38) respectively.61% of overall population had MDR-TB which was also confirmed from their records. Table 3 also shows that 48.6 %(18) TB-DM patients had family history of diabetes compared to 30.2 %(19) TB patients. Most patients of both groups, TB-DM: 62.2 %(23) and TB: 54 %(34) were not diagnosed for the first time. Majority of patients in the TB-DM group, 62.16 %(23), and TB group, 68.25 % (43), were never smokers. However a slightly greater percentage, 14.29% (9) of TB patients were current smokers when compared to 10.81% (4) TB-DM patients. A greater number, 10.8 %(4), of TB-DM patients drank alcohol compared to 3.2 %(2) TB patients. The same scenario holds for habituation to toxic substances like betel leaves, nuts and jorda. 13.5 %(5) TB-DM patients and 1.6 %(1) TB patients had habituation to such toxic substances.

Fig. 1 shows the symptoms suffered by both TB and TB-DM groups. Majority of TB-DM and TB patients, 95% and 90% respectively, experienced cough as a symptom. Least number of both TB-DM and TB groups, 11% and 29% respectively, experienced haemoptysis as a symptom. From Chi-square test, occupation (P=0.001), income (P=0.008), being married (P=0.031) and greater age (P=0.001) were found to be associated with diabetes. We considered P values lesser than 0.05 to show significant association between the variable and diabetes. In cases of variables where more than one cell had expected value less than 5, Fisher's exact value was taken.

IV. Discussion

The dual burden of TB and DM has long been well recognized globally. However, very few studies have been done in Bangladesh regarding their link. This study, conducted during the time period (July-September) 2015, aimed to find the prevalence of DM in 100 TB patients who were admitted in NIDCH, Dhaka and investigate the factors associated with DM.37% of the patients had diabetes although it was unknown whether it was diagnosed before or after contracting TB. The factors significantly associated with TB-DM co-morbidity were occupation, being married and greater age.

The prevalence in this study was more than that found in the study by Sarker et al. (prevalence being 12.8%), where a community based cross-sectional study was conducted among 1910 tuberculosis patients enrolled in the Directly

Observed Treatment, short course program in selected areas in Bangladesh.[6] Although the diabetic status of the inpatients of our study was confirmed by clinical records, blood sugar tests were not carried out like the above study and the sample size of our study is also very small to give an exact prediction of the estimated prevalence value. It also must be kept in mind that there might be some patients with undiagnosed diabetes as blood sugar level was not checked for all patients. The prevalence reported is also higher than that reported in India in 2012 (prevalence being 25.3%) where a survey was carried out among a cohort of TB cases registered under Revised National Tuberculosis Control Program in selected TB units in Tamil Nadu, India.[10] A cross-sectional study in Kathmandu, Nepal conducted in 2015 estimated the prevalence of diabetes among National Tuberculosis Control Program registered TB patients to be 9.1%.[11]The estimated prevalence of DM in our study was much higher than the other studies probably due to having such a small sample of inpatients at NIDCH.

From this study, it was found that occupation was associated with TB-DM as P=0.001(Fishers exact test).Majority of TB-DM patients, 40.5% were business holders and on the other hand, majority of TB patients, 58.7% had no income. One of the reasons for this could be that people involved in business had better access to diagnostic facilities due to the nature of their work. A Peruvian study in Lima examined the relationship of diabetes characteristics with drug-resistant TB and its outcomes among adults during 2005-2008. [12] The percentage of employed patients was more than the unemployed patients in both the TB-DM and TB group. However there was no significant association.[12]There was also no significant association between occupation status and diabetes in a cross-sectional hospital based study which was carried out on 120 active pulmonary tuberculosis patients visiting St. Peter Specialized Hospital, Addis Ababa, Ethiopia.[13]It was found that income was significantly associated with TB-DM (P=0.008) as majority of TB-DM patients,45.9% had income ≤ 10,000, whereas most TB patients,58.7% had no income. This finding is similar to the study by Sarker et al., where the prevalence of diabetes was higher among individuals with monthly family income between 5000 to 10000 BDT compared to individuals with family income of less than 5000 BDT.A prospective community based study carried out from (2010-2012) on 6382 newly detected pulmonary TB patients in Linyi, China showed that higher yearly income ($10000 RMB yuan) was positively associated with DM.[5]A descriptive, cross-sectional study conducted on 407 TB patients in Kathmandu as mentioned above, also showed that high income status was positively associated with diabetes.[11] The reasons for this could be that higher income people have better access to diagnostic and medical facilities and also have greater chances of a higher BMI than normal, which is another risk factor for DM.

Our results show that diabetes is associated with marital status in tuberculosis patients as P=0.031 (Chi Square test).This is consistent with the study done by Sarker et al. where a regression model further determined that married TB patients were 2.66 times more likely to have diabetes than those who were never married.[6]It has also been found in the Peruvian study mentioned above that married or partnered people were more likely to have TB-DM.[12]However, results of our study are inconsistent with other studies where married people were not significantly likely to have greater chances of DM.[13,14]The association in our study could be due to the fact that married people are usually older than single people and diabetes is significantly associated with greater age as described below. This study has found a significant association between TB and older age as P=0.001(Chi Square test).This result has been consistent with the past study in Bangladesh[6] and other studies in India[1,7,10,], Nepal[11]and China[5].Age has been significantly linked to TB even in the Peruvian study discussed above[12] and another Brazilian study where the Brazilian national surveillance system compared socio-demographic and clinical differences in TB patients with and without DM.[15]The association between TB and DM in our study maybe due to the fact that Type II DM is mostly seen in older patients. It was also found that most of the patients (83.8%) had Type II DM in our study. With the increase in life expectancy and improved provisional health services, diabetes might also increase markedly in the future. Hence, screening for DM in TB patients at the right time is imperative for better health outcomes in both diseases.

In our study, both TB-DM and TB groups suffered from cough as a major symptom and haemoptysis as a minor symptom. However, a greater percentage of TB-DM patients suffered from cough and a greater percentage of TB patients suffered from haemoptysis. Similar results have been found from a study on subjects attending the outpatient department of tuberculosis and chest diseases in Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry from September 2002-July 2004[16].Out of 22 diabetic patients, 100% experienced cough and only 9.1% suffered from haemoptysis[16].Another study done in an urban Indonesian setting revealed that although DM-TB patients had more symptoms, they had no evidence of a more-severe TB[16].A prospective hospital based study in Thailand from April 2010-July 2012 which assessed the clinical and laboratory parameters in pulmonary TB patients with and without DM, revealed that a significantly greater proportion of patients without DM presented with cough.[14] However, a greater proportion of TB-DM experienced anorexia and haemoptysis.[14]More extensive studies must be carried out in the future to draw a conclusion on the effect of DM on TB symptoms.

Apart from the fact that the size of our population was very small and no blood sugar test was undertaken for any of the patients, we were also unaware whether diabetes was diagnosed before or after contracting TB. If TB patients are screened for DM, the time of screening is also crucial as literature shows that TB also induces hyperglycemia in non-diabetic patients.[17]Not only this, some TB drugs such as isoniazid may increase metabolism of anti-diabetic drugs and obstruct secretion of insulin in non-diabetics. [6, 17] In the future, hospital based studies must be carried out on a larger sample of population to get more precise results of prevalence and associated variables with DM.

The intersection of communicable diseases like TB and non-communicable diseases like diabetes poses a threat to both patient groups. It also underscores the need to implement effective strategies for screening of DM in TB population so that preventive measures can help manage the outcomes of both diseases.

V. Conclusion

According to this study, the prevalence of DM in TB patients is quite high. This not only necessitates the integration of diabetes screening and treatment in the national program of TB, but also poses great challenges for the said program. Further studies to uncover the underlying mechanisms are also of paramount importance and effective strategies need to be implemented to improve the prognosis of both diseases.

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Table 1 Diabetic Status In Study Population

Variables		Study population		
Category	Subcategory	All patients (n=100) number(%)	TB-DM number(%)	TB number(%)
Type of DM	None	63(63.0%)	0 (0.0%)	63(100.0%)
	Type 1	3(3.0%)	3(8.1%)	0 (0.0%)
	Type 2	31(31.0%)	31 (83.8%)	0 (0.0%)
	Don't know	3 (3.0%)	3(8.1%)	0 (0.0%)
Duration of Diabetes	Not applicable	63 (63.0%)	0 (0.0%)	63(100.0%)
	<5 years	28 (28.0%)	28(75.7%)	0(0.0%)
	6-9 years	4 (4.0%)	4(10.8%)	0(0.0%)
	>10 years	5(5.0%)	5(13.5%)	0(0.0%)
Control of blood glucose after being diagnosed with TB	Not applicable	63 (63.0%)	0 (0.05)	63(63.0%)
	Yes	6(6.0%)	6(16.2%)	0 (0.0%)
	No	20(20.0%)	20(54.1%)	0(0.0%)
	Don't know	11(11.0%)	11(29.7%)	0(0.0%)
Major Complications of having TB and DM comorbidity	Not applicable	63(63.0%)	0(0.0%)	63(63.0%)
	Yes	22(22.0%)	22(59.5%)	0(0.0%)
	No	15(15.0%)	15(40.5%)	0 (0.0%)

Table 2 Distribution Of Sociodemographic Characteristics Of Study Population

Variables		Study population			
Category	Subcategory	All patients (n=100)	TB-DM	TB	p value
		number (%)	number(%)	number(%)	
Gender	Male	53(53.0%)	23(62.2%)	30(47.6%)	0.159
	Female	47(47.0%)	14(37.8%)	33(52.4%)	
Age Group	≤30	40 (40.0%)	6 (16.2%)	34 (54%)	**0.001**
	31-50	48 (48.0%)	25(67.6%)	23 (36.5%)	
	>50	12 (12.0%)	6 (16.2%)	6 (9.5%)	
Marital Status	Single	29(29.%)	6(16.2%)	23(36.5%)	**0.031**
	Married	71 (71%)	31 (83.8%)	40 (63.5%)	
Educational Status	Illiterate	31(31.0%)	9 (24.3%)	22(34.9%)	0.365
	Primary	17(17%)	5(13.5%)	12(19.0%)	
	Secondary	15(15%)	8(21.6%)	7(11.1%)	
	College or more	37 (37%)	15 (40.5%)	22 (34.9%)	
Occupation	No income	47 (47.0%)	10(27.0%)	37 (58.7%)	**0.001***
	Business	21(21.0%)	15(40.5%)	6(9.5%)	
	Service Holder	16(16.0%)	8(21.6%)	8(12.7%)	
	Garments Worker	10(10.0%)	2(5.4%)	8(12.7%)	
	Farmer	6(6.0%)	2(5.4%)	4(6.3%)	
Income per month	No income	47 (47.0%)	10(27.0%)	37(58.7%)	**0.008**
	≤10,000	35(35.0%)	17(45.9%)	18(28.6%)	
	>10,000	18 (18.0%)	10(27.0%)	8(12.7%)	
Place of residence	Urban	24(24.0%)	9(24.3%)	15(23.8%)	0.997
	Rural	35(35.0%)	13(35.1%)	22(34.9%)	
	Semi-Urban	41(41.0%)	15(40.5%)	26(41.3%)	

Asterisk represents values from Fischer exact test
P<0.05 represents significance from Chi Square test (in bold)

Table 3 Distribution Of Tb Parameters, Lifestyle And Other Factors Among Study Population

Variables		Study population			
Category	Subcategory	All patients (n=100)	TB-DM	TB	p value
		number (%)	number(%)	number(%)	
Characteristics of TB					
Type of TB	Pulmonary TB	91(91.0%)	33(89.2%)	58(92.1%)	0.628
	Extrapulmonary TB	9 (9.0%)	4(10.8%)	5(7.9%)	
MDR-TB Patient	Yes	61(61%)	23(62.2%)	38(60.3%)	0.855
	No	39(39%)	14(37.8%)	25(39.7%)	
Diagnosed with TB for the first time	Yes	43(43.0%)	14 (37.8%)	29(46.0%)	0.424
	No	57(57.0%)	23 (62.2%)	34(54.0%)	
Family History of Diabetes	Yes	37 (37.0%)	18 (48.6%)	19 (30.2%)	0.06
	No	63 (63.0%)	19 (51.4%)	44 (69.8%)	
Smoking Status	Never a Smoker	66 (66%)	23(62.16%)	43(68.25%)	0.50*
	Past Smoker	21 (21%)	10(27.03%)	11(17.46%)	
	Current Smoker	13 (13%)	4 (10.81%)	9 (14.29%)	
Drinking Alcohol Status	Yes	6 (6.0%)	4(10.8%)	2 (3.2%)	0.19*
	No	94 (94.0%)	33(89.19%)	61(96.83%)	
Habituation of other toxic substances (betel leaves)	Yes	6 (6.0%)	5 (13.5%)	1 (1.6%)	0.05
	No	83 (83.0%)	29 (78.4%)	54 (85.7%)	
	Others	11 (11.0%)	3 (8.1%)	8(12.7%)	

Asterisk reprrsents values from Fischer exact test
P<0.05 represents significance from Chi Square test (in bold)

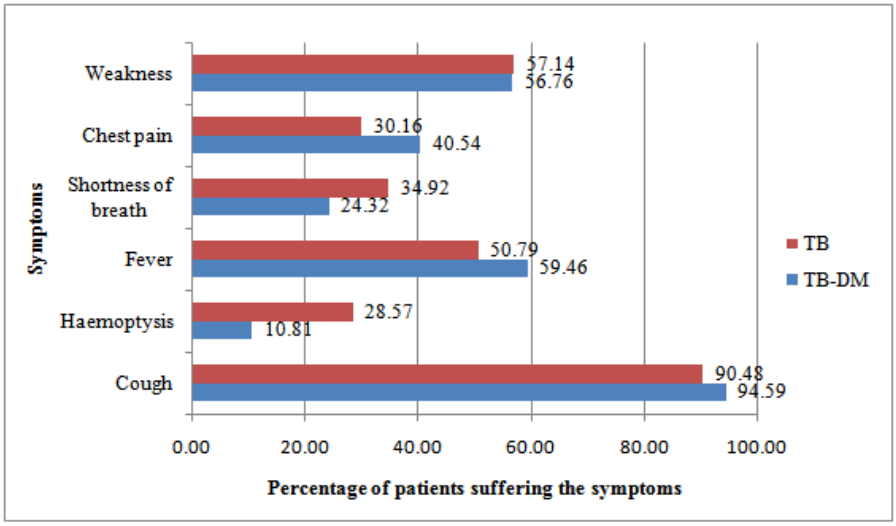

Figure 1 TB symptoms suffered by the TB and TB-DM groups