Drug Susceptibility Pattern of Mycobacterium tuberculosis among Type II Diabetes Patients

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AA SZ conceived idea, SZ drafted the study, IS SR collected data, SR MAM SK did statistical analysis & interpretation of data, AA SZ critical reviewed manuscript, All approved final version to be published.

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The Authors declares that there is no conflict of interest.

Abstract

Background: Prevalence of diabetes is on the rise in TB endemic countries. Co-existence of TB and diabetes increase the complications as well as cost of treatment with bad therapeutic outcomes, further drug resistance TB has frightened the world.

Methodology: Present study was undertaken to see the patterns of drug susceptibility and to compare the drug resistance patterns among patients of TB with and without type II diabetes mellitus.

Results: A total of 268 subjects with mean age of 40±16 years were included for final analysis. Mean age of TB group was 36±16 years while mean age of TB&DM group was 50±12 years. Frequency of MDR TB, Rifampicin, Isoniazid and streptomycin resistance was significantly high among TB&DM group compared to TB group (p-value <0.05). Insignificant difference (p-value >0.05) was observed regarding resistant to ethambutol.

Conclusion: Patients suffering from DM are at higher risk of getting primary Drug resistant TB as compared to non-diabetics, however various underlying disorders and comorbidities also effect the drug resistance pattern of patients having TB with DM. Integrated approach of diabetes and TB control programs is necessary for prevention and control of drug resistance TB.

Key Words: Tuberculosis; Drug Resistance; MDR TB; Diabetes Mellitus

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Introduction

Tuberculosis (TB) is notorious but common, lethal infectious disease occurs due to Mycobacterium tuberculosis (MTB) and a major health delinquent in developing and developed countries.[1] Mainly TB involves the lungs but can invade in each and every tissue of human body therefore called pulmonary and extra-pulmonary TB respectively. World Health Organization (WHO) has estimated 10 million new active TB cases during 2017 comprising 3.2 million females, 5.8 million males and 1 million children. Moreover, Pakistan ranked 5th highest Tb burden country and comprises 5% TB cases all alone among total TB cases in the world.[2]

Prevalence of diabetes is on the rise in TB endemic countries which has up surged the interest to question whether diabetes mellitus (DM) escalates risk of active TB, ultimately increase the global burden of diseases at significant level.[3] Risk of TB has been reported to be 3 times higher among diabetics as

compared to non-diabetics in most of the developing countries including Pakistan.[4] Patients with diabetes have compromised immune system which exposes them as more vulnerable to viral, fungal and bacterial infections including MTB.[5] Association of diabetes with TB has been reported to be 10% globally and most of which remain undiagnosed for a long time.[6]

Co-existence of TB and diabetes increase the complications as well as cost of treatment with bad therapeutic outcomes, further drug resistance TB has frightened the whole world.[7] Impact of multi-drug resistant (MDR) TB is exorbitant in its management. Simultaneous resistance to isoniazid (INH) and rifampicin (RIF) with or without resistance to other anti TB drugs in any strain infecting patients is called MDR TB. This resistance develops due to number of known reasons contributing mortality and morbidity throughout the world.[8] Pakistan is at fifth position and solely bears 4% global MDR TB burden. Global decline of TB incidence as 1.5% during 2014-15 remained remarkably below the target and requires major enhancement of >5% annual decline till 2020 for achieving primary landmark of end TB strategy.[9]

Existence of MDR and or drug resistant TB has developed as major challenge over the few decades which generated uncertainty among TB physicians and ambiguity in such patients due to limited choice of anti TB treatment (ATT). Management of drug resistant TB becomes worse when few strains of MTB also show resistance against second choice broad spectrum drugs. Once MDR TB strains also show resistance against fluoroquinolones along one of three injectable including amikacin, kanamycin and capreomycin is known as extensively drug resistant (XDR) TB.[10]

Both TB and DM are big challenges for the community and occurrence in single individual creates many problems in disease management and treatment outcome. Onset of TB infection is very slow and sometimes delay in diagnosing also especially in DM patients. Pattern of drug resistance in TB patients has already been studied extensively[8,11] which is helpful in management of disease. Patients co-infected with TB and DM on the other hand have different scenario and need to explore further for batter management and treatment outcome. Keeping in view present study was undertaken to see the patterns of drug susceptibility and to compare the drug resistance patterns among patients of TB with and without type II DM.

Methodology

This cross sectional study was undertaken in Department of Pathology, Quaid-e-Azam Medical College, Bahawal Victoria Hospital, Bahawalpur from June 2017 to December 2108. A sample size of 268 patients was calculated in two groups. Group 1 comprising 81 patients of TB with DM and group 2 was consists of 187 patients of TB without DM by taking expected proportion of prevalence of TB with DM as 22.% and TB without DM as 9.6% and level of

Table 1: Demographic Characteristics of Study Subjects

Characteristics		Groups					
		TB (n=187)		TB & DM (n=81)		Total (n=268)	
		n	%	n	%	N	%
Gender	Male	108	57.8%	47	58.0%	155	57.8
	Female	79	42.2%	34	42.0%	113	42.2
Education	Illiterate	74	39.6	43	53.1	117	43.7
	Primary	71	38.0	29	35.8	100	37.3
	Secondary	42	22.5	8	9.9	50	18.7
	Above Secondary	0	0.0	1	1.2	1	0.4
Socio Economic Status	Poor	142	75.9	45	55.6	187	69.8
	Middle	40	21.4	34	42.0	74	27.6
	Upper Middle	5	2.7	2	2.5	7	2.6
History of Contact		99	52.9	45	55.6	144	53.7

significance as 5%. Non probability convenient sampling technique was used to collect samples from all newly registered TB patients with and without DM aged 15 years and above however treatment defaulters, failure and relapse cases were excluded from the study.

A semi structured questionnaire was designed to collect data including demographic characteristics like age, gender, education, marital status and socioeconomic status of patients. Further history of diabetes, TB contacts and diagnosis of TB was noted. Patients who did not report DM were screened by measuring random blood sugar for confirmation. Groups of patients were named as 1-"TB& DM" and 2-"TB" accordingly. All the patients were asked to provide two sputum specimens (one first morning and other spot specimen).

Direct and concentrated smears were prepared and stained by Auramine stain to observe under fluorescent microscope. A 4% NaOH was used for decontamination and emulsification of sputum specimens then phosphate buffer with PH 6.8 was added to neutralize the effect of NaOH. Centrifugation at 3000 rpm for 15 minutes was done to concentrate the TB bacilli. Supernatant was discarded and sediment was re-suspended to inoculate in duplicate on the pre labeled Lowenstein Jensen (LJ) media slants. Inoculated LJ media slants were incubated at 37 °C for isolation of TB bacilli in 4-8 weeks.

Standard drug proportion method was used for drug susceptibility testing of after primary isolation of TB bacilli from specimens. Rifampicin, isoniazid, streptomycin and ethambutol were tested with final concentrations of 40, 0.2, 4 and 2µg/ml respectively as prescribed in previous study[8]. Para-nitro benzoic acid test was done on all specimens to differentiate MTB from Mycobacteria other than tuberculosis. Standard strain of Mycobacterium tuberculosis known as H37RV was also inoculated for quality assurance. Data was entered and analyzed by using statistical package for social sciences (SPSS) software. Qualitative variables were presented as number and percentages while quantitative variables were reported as mean±standard deviation. Paired t-test and chi square were used for comparison and p-value <0.05 was considered as significant.

Results

A total of 50 participants took part in the activity. This included 10 (20%) respiratory therapists, 15 (30%) doctors and 25 (50%) nurses. All the participants (100%) returned the questionnaire. The mean percent score of all the participants before the activity was 36.7±12.84% and after the activity 73.6±10.6% (p=0.005) (table.1). all the three categories of participants made significant improvement after the educational activity. Doctors scored a mean of 37.6 ± 11.15% and 77.0 ± 9.0% (p=0.003) before and after the programme respectively. Similarly nurses improved their score from 36.2 ± 14.08% to 75.2 ± 9.8% (p=0.005) and respiratory therapists from 36.5 ± 13.1 % to 64.5 ±10.39% (p=0.002) (table.1).

Table 2: Diabetic complications and Comorbidities in both groups

Diabetic Complication and Comorbidities	Groups					
	TB (n=187)			TB & DM (n=81)		
	M n (%)	F n (%)	Total n (%)	M n (%)	F n (%)	Total n (%)
None	90 (83.3)	70 (88.6)	160 (85.6)	27 (57.44)	13 (38.24)	40 (49.38)
Micro Vascular		-	-	1 (2.12)	3 (8.82)	4 (4.94)
Macro vascular	-	-	-	7 (14.89)	4 (11.76)	11 (13.58)
Micro Vascular & Macro Vascular	-	-	-	0	1 (2.94)	1 (1.23)
Others	18 (16.7)	9 (11.4)	27 (14.4)	12 (25.53)	13 (38.24)	25 (30.86)
Hypertension*	12 (66.7)	3 (33.3)	15 (55.6)	9 (75.0)	10 (76.92)	19 (76.0)
Anti HCV*	5 (27.8)	-	9 (33.3)	1 (8.33)	1 (7.69)	2 (8.0)
HBsAg*	1 (5.6)	1 (11.1)	2 (7.4)	1 (8.33)	0	1 (4.0)

*Frequency percentages calculated from row showing others.

The mean score on the knowledge part of the questionnaire was 25.5 ± 13.5% before the educational activity and 74.8 ± 9.3 % after the activity (p=0.002). Similarly, there was a significant difference between the mean score for the practice part before and after the educational activity for all the participants (26.7 ± 13.07% and 76.5 ± 10 % respectively, (p=0.003) (Fig. 1 and 2).

Cough, expectoration, fever and weight loss are the predominant sign and symptoms in both groups. Symptoms were more commonly seen in patients with diabetes and TB as compared to TB only. Table II shows the diabetic complications and comorbidities among both groups. The most common diabetic complication among TB & DM group was found to be macro vascular disease. Frequency of hypertension was higher in TB&DM group; and frequency of anti-HCV and HBsAg were in TB group.

Table 3: Comparison of drug resistance pattern in Both Groups

Drugs	Group						P-Value
	TB (n=187)		TB & DM (n=81)		Total (n=268)		
	n	%	n	%	N	%	
MDR*	11	5.9	13	16.0	24	8.9	0.007*
Rifampicin (R)	11	5.9	14	17.3	25	9.3	0.003*
Isoniazid (R)	11	5.9	14	17.3	25	9.3	0.003*
Streptomycin (R)	8	4.3	8	9.8	16	5.8	0.075
Ethambutol (R)	1	0.5	2	2.5	3	1.1	0.163

*MDR = INH + Rifampicin resistant simultaneously, R = Resistant

Discussion

An overall prevalence of MDR was found to be 8.9% in present study was in agreement with a recent study which reported prevalence of MDR among new TB patients as 8.2%8 however remained high from recent report of WHO showing an incidence of 4.2% MDR TB among new patients[2]. Results are not comparable with previous studies which reported a high MDR rates among new TB patients as 12.8% and 12.3% respectively.[11,12] Most of the studies from Pakistan[8,11] and WHO[2] show acquired MDR TB rate around 20% due to the previous history of treatment however a wide range of primary MDR TB has also been reported as 5.4% - 28.3%.[13]

Prevalence of MDR TB remained significantly high (p-value <0.05) as 16% in TB &DM group as compared to 5.9% in normal TB in this study. Much higher rates of MDR TB among type 2 diabetes patients have been reported in studies from Texas (31.6%) and Mexico (29.5%) which expounded significant association of type 2 DM with occurrence of MDR TB in each of both univariate analysis or gender and age binned analysis.[14] A study in 2013 reported as, DM and its association with TB has been reflected as an imminent problem for global TB control programs in coming years.[15] A follow up study about treatment outcome of TB among diabetics has also revealed low sputum conversion rate among diabetics as compared to non-diabetic TB patients.3 Although opinion exists that there is no association of DM as independent risk factor in sputum conversion, though a study undertaken Qatar on 134 adult patients presented 53% culture positivity among DM patients as compared to non-diabetics (27%) having TB.16 Similarly, another study concluded significant association of DM with adverse drug reactions and poor treatment outcomes among pulmonary TB patients and observed lower sputum conversion at two months' treatment and poor outcomes at treatment completion among diabetics as compared to non diabetics.[17]

Various factors have been reported to acquire drug resistance among patients infected with susceptible strains of TB some of which include poor quality of drugs, under dose, poor compliance to treatment, absence of laboratory infrastructure for prompt diagnosis, insufficient supply of drug and different programmatic challenges to set length of requisite treatment period.[18] DM on the other hand is proving itself as a higher risk factor of not only contracting TB but also acquiring high proportion of primary MDR TB as explored by the present study. Higher mean age of 50±12 was observed among diabetic as compared to non-diabetic TB patients as 36±16 in present study, further it was also revealed that diabetics acquire TB infection in 6±4 years after onset of type 2 DM. These

facts are in agreement to the studies which validated that type 2 diabetes occurs in older age and that patients obtain TB infection over diabetes.[15,19]

Isoniazid and rifampicin resistance simultaneously characterize MDR TB and are important anti TB agents. These anti TB drugs have been proved to enhance hyperglycemic efficiency thus elevate blood glucose levels and has been proved by various studies.[19,20] Similarly a recent study has reported low rifampicin resistance of 12.28% among diabetic Tb patients with good glycemic control (HBA1c <8.5%) as compared to 29.2% with poor glycemic control (HBA1c ≥8.5%)3. Patients with DM are difficult to diagnose at times due to certain number of underlying conditions and delayed appearance of symptoms therefore controversial.[15] Advancement in technology on the other hand has made it easy to diagnose and find rifampicin resistance in only two hours using GeneXpert MTB Rif Assay which ultimately remained helpful in achieving such challenges especially in Pakistan and can be useful in diabetic group also.[21]

Various macro and micro vascular disorders were noted among TB and diabetes group are not very well evaluated regarding drug resistance in present study while others have revealed that metabolic disorders describe diabetes including hyperglycemia, insulin resistance and high free fatty acid levels etc. trigger molecular signals which cause vascular dysfunction.[22]

In conclusion patients suffering from DM are at higher risk of getting primary MDR TB as compared to non-diabetics. Response to anti TB treatment is also compromised in TB and DM group and association of poor glycemic control has been revealed with poor treatment outcomes. However various underlying disorders and comorbidities also effect the drug resistance pattern of patients having TB with DM. Integrated approach of diabetes and TB control programs is necessary for prevention and control of drug resistance TB particularly in high burden countries which will ultimately improve early detection and batter management of both diseases.

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