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Therapeutic Outcome of Pulmonary Tuberculosis in Type-2 Diabetes Patients

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ABSTRACT

Objective: Tuberculosis is a major cause of morbidity and mortality and diabetes is a leading risk factor of tuberculosis. Co-existence of tuberculosis and diabetes may increase the disease severity and worsen the treatment outcome. Therefore, objective is to find the anti-tuberculosis treatment outcome among pulmonary tuberculosis patients with or without diabetes mellitus; and to see the drug resistance pattern among treatment failure cases in both groups. **Methodology:** The cross-sectional study was carried out at PHRC Research Center FJMU Lahore in collaboration with PHRC TB Research Centre KEMU Lahore during the year 2013-14. The data of 268 patients including 187 pulmonary tuberculosis patients without diabetes and 81 with diabetes was analyzed. Anti-tuberculosis treatment according to current guidelines of Directly Observed Therapy (DOT) was provided to all patients; and were assessed for improvement of AFB smear; AFB culture and Chest X-Ray before and after four months of starting ATT. Data were analyzed by using Statistical Package for Social Sciences version 20. **Results:** Mean age of non-diabetic TB patients was 36±16 years; and of diabetic TB patients was 50±12 years. Mean duration of diabetes was 6±4 years. Other characteristics included 57.8% males, 42.2% females, and 53.7% had history of contact. Cough, expectoration, fever and weight loss were commonly occurring symptoms. Infiltration (76.1%) was the commonest type of lesion followed by consolidation (14.6%) and cavitation (9.3%). Findings of AFB Smear conversion, AFB Culture, and Chest X-ray were improved with time in both groups; and rates of improvement were significantly higher among non-diabetic TB patients ($p < 0.05$). The frequency of drug resistance was lower among non-diabetic TB patients (7.0% vs. 19.8%) but the difference was insignificant. The rates of drug resistance and MDR were considerably higher among patients with poor glycemic control (p 0.036). **Conclusion:** Therapeutic outcome of pulmonary tuberculosis was poor among diabetic TB patients as compare to non-diabetic TB patients. Therefore, along with anti-tuberculosis treatment, improvement of glycemic control must be considered among diabetic TB patients for better treatment outcome and reduced drug resistance rate.

Keywords: Therapeutics outcome, MDR, TB with diabetes, glycemic control.

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INTRODUCTION

Tuberculosis (TB) remained one of the major causes of mortality and morbidity. Approximately one-third of the world's population is currently infected with TB[1,2]. World Health Organization (WHO) suspects that TB control is being undermined by the growing number of patients with diabetes mellitus (DM) in the world[3]. Diabetes is a group of metabolic diseases characterized by hyperglycemia either due to insulin deficiency or insulin resistance[4]. Diabetic patients have compromised immunity, which renders them more susceptible to bacterial, viral, and fungal infections[5].

Pakistan ranks at5thamong countries with high burden of TB, worldwide; and at 8th among top ten countries with high prevalence of diabetes. It is estimated that Pakistan will be 4th with 14.5 million people suffering from diabetes in the year 2025[6]. With rising prevalence of diabetes in countries where TB is endemic, there has been renewed interest in the question of whether DM increases the risk of active TB and thus could significantly add to the worldwide burden of disease. In developing countries like Pakistan diabetic TB patients have weaker immune system and are at 2-3 times higher risk as compared to non- diabetic TB patients[7]. Prevalence of pulmonary tuberculosis among diabetics ranged from 7.5% to 10% in Pakistan.[7,8]

Diabetes is the leading risk factor for TB in Malaysia, and their co-existence increases the complications and cost of treatment[9]. Studies show 2-3 folds increased risk of TB among diabetics admitted in the hospitals.[10,11] Diabetes was a risk factor for death among TB patients in Maryland and there was a trend toward increased time to AFB culture conversion[12]. Globally about 10% of TB cases are linked with diabetes and a large proportion of TB patients with diabetes remain undiagnosed or diagnosed too late.[13] Therefore, the study was carried out to find the anti-tuberculosis treatment outcome among pulmonary tuberculosis patients with and without type-2 diabetes and to see the drug resistance pattern among treatment failure cases in both groups.

METHODOLOGY

Study Design: Cross-sectional study.

Place of Study: PHRC Research Center FJMU Lahore in collaboration with PHRC TB Research Centre KEMU Lahore

Duration of Study: One Year 2013 to 2014

Newly diagnosed sputum smear positive TB patients with or without type 2 diabetes; age ≥15 years; of both genders were included by non-probability convenient sampling technique. Total 287 patients participated but 19 patients were not available for follow up assessment and excluded from the study. Therefore, data of 268 patients including 187 pulmonary tuberculosis patients without diabetes and 81 with diabetes was analyzed. Informed written consent was obtained from all participants. A predesigned questionnaire was used to collect the data.

Tuberculosis was diagnosed by sputum smear microscopy and chest X-ray examination. Patients taking oral hypoglycemic or having random glucose level ≥200 mg/dl were diagnosed as diabetic[14]. Sputum smear microscopy, AFB culture and chest X-ray were performed in both groups at zero, two and four months. Glycosylated Hemoglobin was estimated before starting and after completion of treatment to assess glycemic control of diabetic TB patients. All patients were treated in accordance with current guidelines of Directly Observed Therapy (DOT) [15]and were followed for sputum smear and AFB culture conversion; and radiological improvement. After 4 months follow up, patients with AFB culture positive were subjected to drug sensitivity testing to see drug resistance pattern. Patients were followed till treatment completion as recommended by DOTS.

Patients were declared to have treatment success if results of both sputum smear and AFB culture were negative and patients were improved clinically and on chest X-ray; as treatment failure if results of both sputum smear and AFB culture were positive after four months of ATT and there was no clinical and radiological improvement.

Three sputum specimens, two spot and one morning, were taken from each patient. Smears were prepared by concentration method, stained by Ziehl Neelsen stain, and examined by trained microscopist. Internal quality assurance was done by using smear from known positive sample with each batch. External quality assurance was done by re-examination of smears in provincial reference lab of TB control program.

Three specimens of sputum smear positive patients were subjected to culture on Lowenstein Jensen medium by concentration method and were incubated at 37ºC for 6-8 weeks. The culture was declared as positive if one or more culture tubes showed growth of Mycobacterium tuberculosis. The organisms obtained were identified by Paranitrobenzoic acid test. For quality assurance, 5-7sputum smear positive and negative cases were subjected to culture. Moreover, a standard strain of Mycobacterium tuberculosis known as $H37_{RV}$ was inoculated. Sputum of treatment failure patients was subjected to Gene Xpert for the detection of rifampicin resistance. Plasma glucose level was measured by Oxidase method and HbA1c % was estimated by Ion Exchange Resin method. Data was analyzed by using Statistical Package for Social Sciences version 20.P-value ≤0.05 was considered as significant.

RESULTS

Out of total 268 pulmonary TB patients, 187 (69.8%) were non-diabetic TB patients and 81 (30.2%) were diabetic TB patients. Mean age of non-diabetic TB patients was 36±16 years; and of diabetic TB patients was 50±12 years. Mean duration of diabetes was 6±4 years. Other characteristics included 57.8% males, 42.2% females, 43.7% illiterate, 69.8% poor, and 53.7% had history of contact with TB patient. Commonly occurring signs and symptoms were cough (96.6%), expectoration and fever (95.1%) each, and weight loss (89.6%) with higher proportions among diabetic TB patients. Chest X-ray examination showed that patients having both lungs affected were 49.3%, right lung 30.2%, and left lung 20.5%. Analysis showed that infiltration (76.1%) was the commonest type of lesion followed by consolidation (14.6%) and cavitation (9.3%). Only 7.8% patients had extensive severe lesion. Relatively younger patients (age <45 years) and patients with less duration of diabetes showed better recovery than of elder patients (age >45 years) and patients with longer duration of diabetes.

Analysis showed that rates of improvement among non-diabetic TB patients were significantly higher than of diabetic TB patients ($p < 0.05$). The rates of all three lab variables improved with time at two and four months follow up. The rate of AFB Smear conversion (96.3%) was the highest followed by AFB Culture (93.0%) and Chest X-ray improvement (92.5%)among non-diabetic TB patients. At first follow up among non-diabetic TB patients; rate of AFB Smear conversion (83.4%) was higher than of AFB Culture improvement (69.5%) with a proportion difference of 13.9%. However, this difference was decreased to 3.3% by four months demonstrating higher AFB Culture improvement rate in second follow up. Similarly, among diabetic TB patients at first follow up; rate of AFB Smear conversion (66.7%) was also higher than of AFB Culture improvement (63.0%) with a proportion difference of 3.7%. But this difference was increased to 5.0% by four months demonstrating relatively low rate of AFB Culture improvement at second follow up. Overall, rates of AFB Smear conversion, AFB Culture, and Chest X-ray improvement were increased with time in both groups especially among diabetic TB patients at second follow up. Table 1

Total 29 patients showed growth of Mycobacterium tuberculosis on AFB culture and were subjected to drug resistance test. Though, the frequency of drug resistance was higher among diabetic TB patients (19.8%) as compared to non-diabetic TB patients (7.0%). But, no significant difference was obtained for any drug among both groups. Table 2

HbA1c levels after four months of starting ATT were significantly reduced in comparison to levels before starting ATT among diabetic TB patients. Also, the proportion of patients with good glycemic control at baseline (27.2%)was increased at second follow up (42.0%). There were 24(29.6%) patients who had poor glycemic control (HbA1c ≥8.5%) after four months of starting ATT. Comparison of lab findings revealed that frequencies especially of AFB Culture improvement were significantly lower among patients with poor glycemic control (p 0.046). The rates of drug resistance and MDR were also considerably higher among patients with poor glycemic control (p 0.036). Table 3

Table 1: Comparison of Lab Findings among Non-Diabetic and Diabetic TB Patients at Two and Four Months Follow Up

	Non-diabetic TB patients (n=187)		Diabetic TB patients (n=81)		Total (n=268)		
	n	%	n	%	n	%	p-value
Two Months Follow Up							
AFB Smear$_{Negative}$	156	83.4	54	66.7	210	78.4	0.002
AFB Culture $_{Negative}$	130	69.5	51	63.0	181	67.5	0.293
Chest X-ray $_{Improvement}$	164	87.7	55	67.9	219	81.7	0.001
Four Months Follow Up							
AFB Smear$_{Negative}$	180	96.3	69	85.2	249	92.9	0.001
AFB Culture $_{Negative}$	174	93.0	65	80.2	239	89.2	0.002
Chest X-ray $_{Improvement}$	173	92.5	60	74.1	233	86.9	0.001

Table 2: Comparison of Resistant Drugs among Non-Diabetic and Diabetic TB Patients

	Non-diabetic TB patients (n=13)		Diabetic TB patients (n=16)		Total (n=29)		
	n	%	n	%	n	%	p-value
MDR*	11	84.6	13	81.3	24	82.8	0.811
Rifampicin $_{R}$	11	84.6	14	87.5	25	86.2	0.822
Isoniazid $_{R}$	11	84.6	14	87.5	25	86.2	0.822
Streptomycin $_{R}$	08	61.5	08	50.0	16	55.2	0.534
Ethambutol $_{R}$	01	7.7	02	12.5	03	10.3	0.672

*MDR = Isoniazid and Rifampicin resistant

Table 3: Association of Glycemic Control with Lab Findings and Drug Resistance among Diabetic TB Patients

		Glycemic Control (n=81)				p-value
		HbA1c <8.5%		HbA1c ≥8.5%		
		n=57		n=24		
		n	%	n	%	
AFB Smear $_{Negative}$	**n=69**	51	89.5	18	75.0	0.094
AFB Culture $_{Negative}$	**n=65**	49	86.0	16	66.7	0.046
Chest X-ray $_{Improvement}$	**n=60**	44	77.2	16	66.7	0.323
Rifampicin $_{R}$	**n=14**	07	12.3	07	29.2	0.060
Isoniazid$_{R}$	**n=15**	07	12.3	08	33.3	0.025
Ethambutol$_{R}$	**n=07**	06	10.5	01	4.2	0.352
Streptomycin $_{R}$	**n=11**	05	8.8	06	25.0	0.051
MDR*	**n=13**	06	10.5	07	29.2	0.036

*MDR = Isoniazid and Rifampicin resistant

DISCUSSION

Co-existence of tuberculosis and diabetes may increase the disease severity and worsen the treatment outcome. About 70% patients of this study belonged to poor socioeconomic class. Similar findings were reported by Raghuraman et al that 95% TB patients and 70% diabetics live in poor or middle-class income countries[16]. In present study, 16% diabetic TB patients showed multi drug resistance (MDR) which was almost three times higher than resistance (5.9%) found in non-diabetic TB patients. These findings were comparable with high rates of MDR-TB among T2DM patients from Texas (31.6%) and Mexico (29.5%). It was also reported that T2DM had significant association with MDR-TB either in univariate analysis or age and gender binned analysis[17].

Association of TB with diabetes is an upcoming challenge for global TB control. Different findings have been reported regarding AFB smear conversion, some studies showed no association between diabetes and sputum smear conversion, while some reported delayed smear conversion among diabetics[18].Similar results can be seen in present study that rate of AFB Smear conversion was greatly improved in second follow up as compared to the first follow up.

Usually type 2 diabetes mellitus occur in elder people[19] and it is evidenced from the mean age 50±16 years of diabetic TB patients in comparison to 36±16 years of non-diabetic TB patients. Definitive cause of association of hyperglycemia with TB had not been identified yet however it is assumed that mechanisms like inflammation due to cytokines (like IL6 and TNFα) in response to TB infection attribute to insulin resistance and minimize its production which may lead to affect the treatment outcome[20].

Isoniazid and Rifampicin have definite hyperglycemic efficiency while Pyrazinamide may also cause problems in controlling DM. Rifampicin prompts metabolism thus increases the blood sugar levels[19] and this has already been studied the maximum effect one week after starting rifampicin and disappears two weeks after discontinuation [21]. It is obvious from Table 3 that Rifampicin resistance rate (12.3%) was lower among patients (HbA1c <8.5%) as compare to patients (HbA1c ≥8.5%). Best time for diagnosis and screening of TB among DM patients or vice versa is still controversial[18]. Rifampicin resistance using GeneXpert has been implemented by WHO to diagnose and initiating the treatment of MDR-TB in developing countries including Pakistan. Benefit of this technique is to diagnose TB and rifampicin susceptibility within two hours[22].

CONCLUSION

Therapeutic outcome of pulmonary tuberculosis was poor among diabetic TB patients as compare to non-diabetic TB patients. Therefore, along with anti-tuberculosis treatment, improvement of glycemic control must be considered among diabetic TB patients for better treatment outcome and reduced drug resistance rate.

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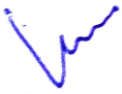
Dr. Muhammad Adnan Pakistan Health Research Council, Research Centre, Fatima Jinnah Medical University, Lahore.	Data Collection, Literature Search, Proof Reading	
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