ASSOCIATION OF MULTIDRUG RESISTANT PULMONARY TUBERCULOSIS AND DIABETES MELLITUSSujit Kumar¹, Shailendra Kumar Yadav², AD Shukla³, Adesh Singh⁴¹Associate Professor, Department of Internal Medicine, MLN Medical College, Allahabad, Uttar Pradesh, India.²3rd Year Junior Resident, Department of Internal Medicine, MLN Medical College, Allahabad, Uttar Pradesh, India.³Associate Professor, Department of Respiratory Medicine, MLN Medical College, Allahabad, Uttar Pradesh, India.⁴Assistant Professor, Department of Internal Medicine, MLN Medical College, Allahabad, Uttar Pradesh, India.**ABSTRACT****BACKGROUND**

Multidrug Resistant Tuberculosis is a form of tuberculosis, which is caused by resistance for rifampicin and/or isoniazid. Diabetes increases the chances of emergence of resistance in tuberculosis patients. So, the aim of this study is to evaluate the association of diabetes mellitus in the emergence of resistance in tuberculosis patients.

Aims and Objectives- To study the association of multidrug resistant pulmonary tuberculosis and diabetes mellitus.

MATERIALS AND METHODS

218 patients of pulmonary tuberculosis taken in this study who presented to SRN Hospital, over a period of one year from September 2016 to August 2017. Patients were investigated for FBS, PPBS and A1c and Gene-Xpert test was done to find drug resistance among tubercular patients.

Study Design- A cross-sectional observational study.

RESULTS

Out of 218 patients, 108 were of MDR-TB and 110 were of drug sensitive TB on the basis of Gene-Xpert test. That means, 49.5% were of MDR-TB and 50.5% were drug sensitive TB. Out of 108 patients of MDR-TB, 33 (30.60%) were diabetic and among 110 patients of drug sensitive TB, 19 (17.03%) were diabetic. After using Chi-square test, p value was found to be 0.0210 which was statistically significant.

CONCLUSION

Prevalence of diabetes mellitus was higher in patients suffering from tuberculosis and even greater in patients of multi-drug resistant pulmonary tuberculosis, so it can be concluded that diabetes mellitus may be one of the risk factors for emergence of resistance in the patients having pulmonary tuberculosis.

KEY WORDS

Diabetes Mellitus, Multidrug Resistant Pulmonary Tuberculosis, Gene-Xpert Test.

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BACKGROUND

India is the second most populous country in the world and is ranked first among the 22 high burden countries, which accounts for 80% of all estimated incident cases of TB worldwide.¹ An important cause of TB epidemic is the emergence of multi-drug resistant (MDR) strains of Mycobacterium tuberculosis. Globally, an estimated 3.3% of new TB cases and 20% of previously treated cases have MDR-TB (Global Tuberculosis Report 2015). This translates into an estimated 480,000 people having developed MDR-TB in 2014.¹ If all notified TB patients (6.1 million, new and previously treated) had been tested for drug resistance in 2014, an estimated 300,000 cases of MDR-TB would have been detected, more than half (54%) of these in three countries alone: India, China and the Russian Federation.

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India, Indonesia and China alone accounted for 23%, 10% and 10% of total cases, respectively. The Revised National TB Control Program (RNTCP), based on the internationally recommended Directly Observed Treatment Short-course (DOTS)² strategy was launched in India in 1997. Data from studies conducted by NIRT and NTI have found MDR-TB levels of less than 1% to 3% in new cases and around 12% in re-treatment cases. Diabetes Mellitus (DM) was a known risk factor for TB in the past, but this was mostly neglected during the second half of the 20th century with the advent of widely available treatment for both diseases.³ In recent decades with the increasing prevalence of TB, particularly Multi-Drug Resistant TB and DM cases in the world. The relationship is re-emerging as a significant public health problem. The link of DM and TB is more prominent in developing countries, where TB is endemic, and the prevalence of diabetes is rising. The association between DM and TB has been known for centuries and in the 1950s the DM patient not dying from a diabetic coma was likely to do so from TB. This association was reduced with the advent of insulin for DM and antibiotics to treat TB, but in the 1980s the co-occurrence began to re-emerge as a consequence of the DM 'pandemic' which is predicted to reach 439 million patients by 2030 and is primarily attributed to type 2 DM.⁴

Aims and Objectives

To study the association of multidrug resistant pulmonary tuberculosis and diabetes mellitus.

MATERIALS AND METHODS

The cross-sectional study was conducted in Moti Lal Nehru Medical College, Allahabad and its associated hospital Swaroop Rani Nehru Hospital from September 2016 to August 2017.

Patients Selection

Pulmonary TB patients as diagnosed by sputum examination aged > 18 years attending the Medicine and Pulmonary Department (indoor patient and outdoor patient).

Inclusion Criteria

All individuals aged > 18 years of either sex with MDR pulmonary TB and drug sensitive pulmonary tuberculosis were included in the study.

Exclusion Criteria

1. Patients with extrapulmonary tuberculosis.
2. Pregnancy.
3. HIV patients.
4. Connective tissue disorder.
5. Chronic liver disease.
6. Chronic renal failure.
7. Malignancy.
8. Patients on immunosuppressive therapy.
9. Chronic alcoholics.

Methodology

The study protocol was explained to all participants and written informed consent was taken in both English and Hindi. Approval for the study was obtained from the Ethics Committee in the institution. All patients were assessed clinically by detailed history taking and general physical examination that included and body mass index also. Height and body weight were measured using a digital scale and body mass index (BMI) was calculated as $BMI = \text{body weight (kg)} / \text{height}^2 (\text{metre})$.

The Study Population was investigated for the following Parameters-

- FPG.
- PPBG.
- HbA1c.

CBNAAT- Gene-Xpert Test

The Gene-Xpert MTB/ RIF assay is a nucleic acid amplification (NAA) test that uses a disposable cartridge with the Gene-Xpert Instrument System. Sputum sample taken for Gene-Xpert test by this resistance was seen for Rifampicin only. And those patients who were resistant for Rifampicin were considered as MDR-TB and patients who were sensitive were considered as drug sensitive TB patients. Venous blood was collected from all patients for FPG, PPBG, HbA1c and the patients who were having FPG ≥ 126 mg/dL or PPBG ≥ 200 mg/dL or HbA1c $\geq 6.5\%$ were considered as diabetic.

Statistical Analysis

This study is a cross-sectional observational study. Chi-square test was applied for finding significant association between the categories of variables- that is to find association of MDR-TB and Type 2 DM. Unpaired t-test was applied for finding the significant difference between mean values of variables. SPSS version 19 was used to analyse the data. The numerical data was compared using unpaired t-test for independent variables. The level of significance was considered at $p < 0.05$.

RESULTS

218 patients of pulmonary tuberculosis were taken in this study who presented to SRN Hospital over a period of one year from September 2016 to August 2017. Out of them 108 were of MDR-TB and 110 were of drug sensitive TB on the basis of Gene-Xpert test. That means 49.5% were of MDR-TB and 50.5% were of drug sensitive TB.

Flow Chart showing Status of Drug Resistance and Diabetes

Characteristics	MDR-TB (n= 108)	Drug Sensitive TB (n= 110)	P
Mean Age and S.D.	41.50±11.91	45.60 ± 12.99	p=0.9580
Age Group (30-60 years)	94 (87.04%)	72 (65.45%)	p=0.0005
Male patients	87 (80.55%)	90 (81.81%)	p=0.867
Female patients	21 (19.44%)	20 (18.18%)	
BMI- <18.5	21 (64%)	42 (57%)	p=0.5543
18.5 - 24.99	10 (31%)	28 (37%)	
>25	2 (5%)	05 (06%)	
FBS	176.27 ± 22.40	164.63 ± 10.00	p=0.037
PPBS	230.18 ± 33.87	205.42 ± 46.64	p=0.032
HbA1C	11.1152 ± 1.3271	9.6579 ± 1.7179	p=0.0030
Diabetes Mellitus	33 (30.60%)	19 (17.30%)	p=0.0210

Table 1. Comparison of Characteristics between MDR Tuberculosis and Drug Sensitive Tuberculosis

Patient's Categories	Frequency	Percentage (%)
MDR-TB	108	49.50
Drug Sensitive TB	110	50.50
Total	218	100

Table 2. Frequency of Patients among MDR-TB and Drug Sensitive TB

Mean age for the patients of MDR-TB is 41.50 ± 11.91 and for drug sensitive TB is 45.60 ± 12.99 .

Patient's Category	Number of Patients	Mean Age $\pm$ S.D.	P
MDR-TB	108	41.50 $\pm$ 11.91	p=0.9580
Drug Sensitive TB	110	45.60 $\pm$ 12.99	

Table 3. Mean Age and Standard Deviation of Patients of MDR-TB and Drug Sensitive TB

Mean value of FBS in diabetic patients in MDR-TB and drug sensitive TB categories was found to be 176.27 $\pm$ 22.40 and 164.63 $\pm$ 10.00 respectively. Both category of patients are having higher values of FBS, which is statistically significant too (p= 0.037).

TB	No. of Diabetic Patients	FBS (mg/dL)	P
MDR (n= 108)	33	176.27 $\pm$ 22.40	P=0.037
Drug sensitive (n= 110)	19	164.63 $\pm$ 10.00	

Table 4. FBS of Diabetic Patients with MDR-TB and Drug Sensitive TB Patients

In MDR-TB category 33 patients having FBS in diabetic range and in drug sensitive TB patients 19 patients were having FBS in diabetic range. On application of student t-test, p value was found to be 0.037 which is statistically significant.

Mean PPBS of diabetic patients in MDR-TB categories was found to be 230.18 $\pm$ 33.87 mg/dL and in drug sensitive TB categories was 205.42 $\pm$ 46.64 mg/dL. After applying student's t-test, p-value was found to be 0.032 which is statistically significant.

TB	No. of Diabetic Patients	PPBS (mg/dL)	P
MDR (n= 108)	33	230.18 $\pm$ 33.87	p= 0.032
Drug Sensitive TB (n= 110)	19	205.42 $\pm$ 46.64	

Table 5. PPBS among Diabetic Patients of MDR-TB and Drug Sensitive TB

Diabetic patients among MDR-TB is having higher values of HbA1C than in drug sensitive TB patients. It indicates that the patients of tuberculosis those who have high values of HbA1C may have higher chances of developing MDR-TB. On statistical analysis, data was found to be statistically significant (p= 0.0032).

Patients	Diabetic	HbA1C (Mean)	P
MDR-TB (n= 108)	33	11.11 $\pm$ 1.3271	p= 0.0032
Drug Sensitive TB (n= 110)	19	9.65 $\pm$ 1.7179	

Table 6. HbA1C of Diabetic Patients of MDR-TB and Drug Sensitive TB

Among 108 patients of MDR-TB, 33 (30.60%) were having diabetes mellitus and 75 were non-diabetic.

DM Status	No. of MDR-TB Patients	% of MDR-TB Patients
Diabetic	33	30.60%
Non-Diabetic	75	69.40%

Table 7. Distribution of Diabetes in MDR-TB Patients

Figure 1. Distribution of DM in MDR-TB Patients

Among 110 drug sensitive TB patients, 19 patients were diabetic, and 91 patients were non-diabetic.

DM Status	No. of Drug Sensitive TB Patients	% of Drug Sensitive TB Patients
Diabetic	19	17.30%
Non-Diabetic	91	82.70%

Table 8. Distribution of DM in Drug Sensitive TB

Figure 2. Distribution of DM in Drug Sensitive TB Patients

In this study total patients were 218 and out of 108 patients of MDR-TB 33 (30.60%) were diabetic and in drug sensitive TB categories 19 (17.03%) were diabetic.

After applying chi-square test, p value was found to be 0.0210 which was statistically significant.

Diabetic Status	MDR-TB Patients (n=108)	Drug Sensitive TB Patients (n=110)	P
Diabetic	33 (30.60%)	19 (17.30%)	p= 0.0210
Non-Diabetic	75 (69.40%)	91 (82.70%)	

Table 9. Distribution of Diabetes Mellitus among 218 Patients

Figure 3. Distribution of Diabetes Mellitus among MDR-TB and Drug Sensitive TB Patients

DISCUSSION

In this study, 218 patients of PTB were included. On the basis of FPG, PPG and A1C patients were separated into diabetic and non-diabetic group, whereas on the other hand on the basis of CB-NAAT- Gene-Xpert test patients were separated into MDR-TB and drug sensitive TB group. Following were the findings in the study. In this study, the prevalence of diabetes in MDR-TB patients was 30.6%. And in drug sensitive TB, prevalence was 17.03%. A study done by Mohammad Zaeem Khan et al,³ Haryana, India 2017 also found significant association between diabetes mellitus and MDR group ($p = .0017$). In MDR group 45% ($n = 9$) had diabetes mellitus, whereas in non-MDR group 14% ($n = 11$) had diabetes mellitus. In India, the overall prevalence⁵ of diabetes mellitus is 8.7%. Another study done by Keshri Singh Yadav et al⁶ 2016 studied- The Pattern of Drug Resistance in Patients of Pulmonary Tuberculosis having Diabetes Mellitus. They found that development of multidrug resistance (MDR) tuberculosis accounted for nearly 37.5% in diabetics, which was significantly greater in comparison to IGT (33.3%) and non-diabetics (1.2%). Saurabh Mehta et al⁷ 2015 studied Rifampin resistance and diabetes mellitus in a cross-sectional study of adult patients in rural South India. Among patients with confirmed TB ($n = 194$), diabetes was associated with 3.0-fold higher risk of rifampin resistance. Another study done by Alejandro Gomez- Gomez et al⁸ 2015 found that MDR-TB and DM are associated in 47.2% of MDR-TB cases. Another study done by Baodong Yuan et al⁹ in January 2017 in China on effect of type 2 diabetes mellitus on sputum negative conversion and treatment effects of multidrug-resistant tuberculosis. A total of 359 MDR-TB patients for comparing the sputum negative conversion rates at 2, 6 and 12 months after initiating treatment and the recovery (Treatment Success) rates after completion of treatment for patients with T2DM versus those without T2DM. A total of 20.6% of the patients (74/359) had T2DM. Guadalupe Delgado-Sánchez et al¹⁰ found that 53.87% patients of MDR-TB have diabetes and 39.03% were without diabetes. The p -value was < 0.001 , which was significant. Matthew J Magee et al¹¹ found that tuberculosis patients who have DM had more cavitation, higher smear positive rates and more MDR-TB as compared to patients without DM (28.1% vs. 23.6%). Another study done by Marta Gomes et al¹² found that Diabetes Mellitus, intravenous drug use and

previous TB treatment were risk factors for drug-resistant disease development. Another study done by Fengling Mi et al¹³ found that prevalence of multidrug-resistant TB (MDR-TB) was 6.2% in new patients (N422) and 62.3% in previously treated patients (N199) with no significant differences between those with and without diabetes. Parvaneh Baghaei et al¹⁴ also concluded that TB patients with DM are at increased risk of anti-TB drug resistance. Maria-Eugenia Jimenez-Corona et al¹⁵ found that the prevalence of DM among 1262 patients with pulmonary TB was 29.63% ($n = 374$) and patients with DM and pulmonary TB had more severe clinical manifestations. A-H Hsu et al¹⁶ found that 4% new TB cases and 15.7% among previously treated cases in Eastern Taiwan were MDR-TB. Tiyas Sen et al¹⁷ 2009 found that 36% of the patients with diabetes and TB had MDR-TB, compared to only 10% in the drug sensitive TB patients. Mona Bashir MD et al¹⁸ found that 36% (18 cases) of the patients with diabetes and tuberculosis had multidrug-resistant tuberculosis (MDR-TB) compared to only 10% (10 cases) in the control group ($p < 0.01$). A study done by Bokam et al reported 44% prevalence of diabetes among PTB patients in 2016. Hardy Kornfeld et al¹⁹ reported 54.1% had associated diabetes out of 209 PTB patients from south India in 2016. Park et al²⁰ showed increasing prevalence of TB in DM patients in developing countries like India.

In our study MDR-TB and drug sensitive TB, maximum number of patients were in between 30 and 60 years. In MDR-TB 87.04% and in drug sensitive TB group 65.45% patients were in between 30 - 60 years.

A study done by Jagadish Rawat et al,²¹ which showed the mean age of the patients PTB-DM as 53.3 ± 14.06 . A study done by Bokam et al, which showed the mean age of the patients PTB-DM as 52.13 ± 10 . There were more male patients in both the categories. There were 80.55% in MDR-TB categories and 80.81% males in drug sensitive TB categories and female patients were 19.44% and 18.18% respectively. A study done by Bokam et al, which showed 52.3% were males and remaining 47.7% were females with mean A1C of 8.5. A study done by Rawat et al, which showed 53.7% were males and remaining 46.3% were females. In both categories, patients were having HbA1C in the higher range. Mean of HbA1C in MDR-TB DM patients was 10.02 ± 1.49 and in drug sensitive TB DM patients mean of HbA1C was 11.03 ± 2.12 . A study done by Chen-Yuan Chiang et al,²² which showed 88.8% had A1C more than 7 and 11.2% had A1C less than 7. A study done by Payam Tabarsi et al²³ reported 40% of their study population had normal glycaemic control of less than 7.

CONCLUSION

Diabetes mellitus was more prevalent in patients of multi-drug resistant pulmonary tuberculosis, who were having lower body mass index. FPG was more in diabetic patients of multi-drug resistant pulmonary tuberculosis than diabetic patients of drug sensitive pulmonary tuberculosis. PPG was more in diabetic patients of multi-drug resistant pulmonary tuberculosis than diabetic patients of drug sensitive pulmonary tuberculosis. A1c was more in diabetic patients of multi-drug resistant pulmonary tuberculosis than diabetic patients of drug sensitive pulmonary tuberculosis. Prevalence of diabetes mellitus was higher in patients suffering from tuberculosis and even greater in patients of multi-drug

resistant pulmonary tuberculosis, so it can be concluded that diabetes mellitus may be one of the risk factors for emergence of resistance in the patients having pulmonary tuberculosis.

Limitations of Study

This study was done in small group of population so cannot be compared with national data. In this study, patients only taken from government hospital, patients attending private health facilities are not included in the study. So, this study is biased. Duration of study was only 1 year, and study was cross-sectional study, so natural history and impact of diabetes cannot be exactly known in this short period of time and in this small study group.

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