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# To study the drug resistance pattern in cases of diabetes with pulmonary tuberculosis in Western UP

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**Abstract**

**Aim:** To evaluate the drug resistance pattern in cases of Diabetes with Pulmonary Tuberculosis in western UP.

**Material and Method:** The present hospital based study included 50 patients presenting to the Department of TB and Respiratory Diseases and Department of General Medicine at Chattrapati Shivaji Hospital of Subharti Medical College, Meerut, Uttar Pradesh between November 2018 to August 2020. Patients with DM and MDR-TB who were attending the OPD and admitted in IPD of Department were enrolled in the study. A good quality specimen, one with volume of 2-5 ml, preferably muco-purulent and not heavily blood stained or contaminated was collected from the patients after giving proper instructions. DST of Mycobacterium tuberculosis was performed using absolute concentration method on L-J media, and all procedures were carried out in accordance with the guideline of WHO.

**Results:** Multidrug resistant tuberculosis (MDR-TB) was reported among 47.62% of the subjects with HbA1c 7 to 9 and among 2.38% of the subjects with HbA1c >9. H mono resistance was revealed among 33.33% of the subjects with HbA1c 7 to 9 and among 13.33% of the subjects with HbA1c >9. Mortality was revealed among 4 subjects, out of which 25% were having HbA1c 7 to 9 and 75% were having >9 HbA1c.

**Conclusion:** From the results of our study, we suggest that each and every patient must be screened for diabetes before starting ATT.

**Keywords:** drug, resistance, diabetes, tuberculosis

## Introduction

Tuberculosis, the leading cause of death worldwide from an infectious disease among adults, has been considered global public health emergency for the past 25 years [1]. Drug resistant forms of tuberculosis are currently on course to be the world's deadliest pathogens and are responsible for a quarter of deaths due to anti-microbial resistance [2]. Global tuberculosis incidence is estimated to be slowly declining by 1·6% per year compared to 4–5% estimated to be required to reach WHO's End TB Strategy targets [3]. Tuberculosis is also a major public health problem in India. India is the highest TB burden country in the world having an estimated incidence of 26.9 lakh cases in 2019 (WHO) [4]. The impact of TB can be devastating, especially in developing countries suffering from high burdens of both TB and human immune-deficiency virus (HIV) infections [5]. There is a rising trend of drug-resistant TB in different parts of the world, India being next only to China, both contributing to more than 50% of global multi-drug resistant (MDR) TB cases. Frequency of MDR-TB is <3% in new cases and 12–50% among re-treatment cases as per the recent studies [6].

Increase in the burden of non-communicable diseases and aging populations are changing the importance of different risk factors for TB. The association of Diabetes and TB was confirmed by Root since 1934. Chronic hyperglycemia alters the treatment outcome and prognosis of TB to a great extent [7]. Diabetes is a known risk factor for the development of active TB, and an estimated 15% of patients with TB in countries with a high TB burden have diabetes [8].

It is commonly accepted that diabetes decreases the effectiveness of the cell-mediated immunity and makes individuals more vulnerable to MTB infection. Some animal studies have suggested that there may be a delay in immune recognition; however, a more recent study on humans advocates that epigenetic-reprogramming may be responsible for increasing inflammation thus causing individuals to become more susceptible to the infection. Researchers have shown that MTB infection can present itself differently amid diabetes co-morbidity [9].

The International Diabetes Federation (IDF) estimates that 46% of diabetes cases worldwide (around 175 million) are not diagnosed, with the highest proportions concentrated in Africa (62%) and south-east Asia (54%), coinciding with the greatest TB burden. Globally, 84% of all people with undiagnosed diabetes live in low-income and middle-income countries where the management of these people is rarely optimal [10]. DM could severely threaten TB control and may become most profound in resource-poor areas where TB thrives [11]. Hence the present study was planned to study the drug resistance pattern in cases of Diabetes with Pulmonary Tuberculosis in western UP.

## Material and Method

The present hospital based study included 50 patients presenting to the Department of TB and Respiratory Diseases and Department of General Medicine at Chattrapati Shivaji Hospital of Subharti Medical College, Meerut, Uttar Pradesh between November 2018 to August 2020. The study was initiated after taking approval from the

Institutional Ethical Committee. The patients were enrolled for the study after taking informed and written consent and after fulfilling the inclusion and exclusion criteria. Patients with DM and MDR-TB who were attending the OPD and admitted in IPD of Department were enrolled in the study. The subjects were recruited according to the following inclusion and exclusion criteria:

**Inclusion Criteria**

1. Patients who have symptoms suggestive of pulmonary tuberculosis e.g. fever, chronic cough, weight loss, haemoptysis, decreased appetite etc.
2. Positive sputum smear for acid fast bacilli.
3. Chest X ray with features suggestive of pulmonary tuberculosis.
4. Patients who are Sputum positive and CBNAAT resistant to rifampicin.
5. Patients with deranged Blood Sugar profile and positive on sputum examination or radiologically confirmed.

**Exclusion Criteria**

1. Critically ill patients.
2. Unwilling patients.

**Definitions**

Definitions of MDR-TB and diabetes as defined by the World Health Organization (WHO) were used for this project. MDR-TB is defined as infection with Mycobacterium tuberculosis with in-vitro resistance to at least isoniazid and rifampin. Drug-resistant TB was defined as M. tuberculosis with in-vitro resistance to any first-line anti-TB drug.

Patients identified as having diabetes in the medical records had their diabetes confirmed by any one of the following criteria: fasting plasma glucose >7.0 mmol/l (126 mg/dl), 2-h plasma glucose/random blood glucose >11.1 mmol/l (200 mg/dl), glycosylated hemoglobin (HbA1c) >7.0%, or treatment with insulin or oral hypoglycemic agents. Any values for HbA1c or urine glucose during the previous year before enrollment start date were also recorded.

**Procedure**

1. Patients were selected according to inclusion-exclusion criteria and subjected to sputum microscopy.
2. Sputum collection: A good quality specimen, one with volume of 2-5 ml, preferably muco-purulent and not heavily blood stained or contaminated was collected from the patients after giving proper instructions. Patients were advised to collect the specimen in a sterile container after thorough rinsing of the mouth with clean water. Container was then sent for ZN Staining to DOTS Centre, Subharti Medical College and Hospital, Meerut.
3. Two falcon tubes were provided to the patient from the DOTS Centre in which the patients were asked to collect a good quality sputum specimen which was at least 2 ml. These falcon tubes were then packed by triple packaging system, the steps of which were as follows:

Step 1: The falcon tube was tightly closed after the sample had been collected from the patient.
Step 2: Outer surface of the falcon tube was wiped with 5% phenol followed by absorbent tissues and allowed to air dry.
Step 3: The patient details were written on the opaque area (white area) of the Falcon tube using a permanent marker pen, clearly in capital letters.
Step 4: A parafilm strip was cut, one of the strips was wraped at the joint between the cap and the neck of the Falcon tube such that a secure seal could be formed. (Primary receptacle/ package)
Step 5: The falcon tube containing the sample was then rolled tightly in absorbent cotton such that the tube could be covered completely.
Step 6: This roll containing the Falcon tube was put into a Zip lock pouch which was rolled into a tight bundle ensuring no air in the pouch. This bundle was then secured with rubber bands. (Secondary receptacle/ package)
Step 7: Steps 5 -7 were repeated for the second sample of the patient.
Step 8: RNTCP Request Form for examination of Biological specimen for TB (15A) was the inserted in to the zip lock pouch after ensuring that the details on the form and the sample tubes matched, with the writing facing outside (details visible though the package). Zip lock on the pouch was then sealed.
Step 9: Cooled gel packs were placed into a thermocol box with the sample tubes packed in zip lock pouches on the frozen gel packs (frozen for 48hrs at -40°C) and also the pouch containing the RNTCP form (15 A) was kept on top. A BIOHAZARD and "From and To" stickers were stuck on the exterior of the thermocol box. The box was closed with a lid and wrapped tightly with brown duct tape. (Tertiary receptacle/ package)
Step 10: The 'From' and 'To' addresses on the stickers were completed using a permanent marker pen.

4. The boxes were then transported to PMDT Lab/DR-TB Centre, Pyare Lal Sharma District Hospital, Meerut. Of these, one falcon tube was used for CB-NAAT testing, reports of which were received after 2 days.
5. The second falcon tube with the sputum specimen was sent to Intermediate Reference Laboratory (IRL) Agra through for performing DST, reports of which were received after 42-45 days.
6. Patients were then followed-up and their data was analysed.

**DST**

DST of Mycobacterium tuberculosis was performed using absolute concentration method on L-J media, and all procedures were carried out in accordance with the guideline of WHO. The concentrations of first-line anti-TB drugs were as follows: 0.2 µg/mL (isoniazid, INH), 40 µg/mL (rifampicin, RFP), and 2 µg/mL (ethambutol, EMB) and the concentrations of Second line injectable anti-TB drugs were as follows: 4.0 µg/mL (streptomycin, S), 30.0 µg/mL (kanamycin, Km), 30.0 µg/mL (amikacin, Am) and 40.0 µg/mL (capreomycin, Cm). The concentrations of Fluoroquinolones were: 4.0 µg/mL (ofloxacin, Ofx), 2.0 µg/mL (levofloxacin, Lfx) and 1.0 µg/mL (moxifloxacin, Mfx).

**CB-NAAT**

One sputum sample of minimum 1 ml was collected in a sterile container and was analysed by CBNAAT on Xpert® MTB/RIF manufactured by Cepheid, endorsed by WHO (2010). The sample was diluted with three times the reagent, incubated at room temperature and loaded into the cartridge

for automated analysis with results in 100 minutes. Detection of mycobacteria and rifampicin resistance was carried-out in the same setting. Rifampicin resistant samples were further analysed by LPA. The three steps for LPA test included DNA extraction, multiplex polymerase chain reaction (PCR) amplification and reverse hybridisation.

**Statistical Analysis**

Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using chi square test and the level of significance was set at $p < 0.05$.

**Results**

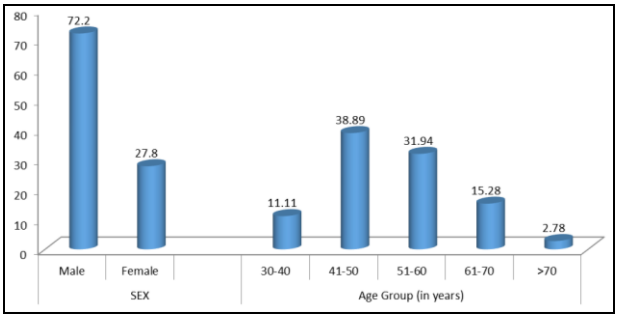
In our study male subjects (72.2%) were comparatively more as compared to female (27.8%). Maximum subjects belonged to age group of 41-50 years (38.89%) followed by 51-60 years (31.94%) while minimum subjects were in the age group of >70 years (2.78%) followed by 30-40 years (11.11%) as shown in graph 1. In our study, mean height (in cm) was 165.65, mean weight (In kgs) was 48.97 and mean BMI was 17.86.

Alcohol consumption was found among 37.5% of the subjects and 58.3% of the subjects were smokers. Hypertension was revealed among 18.1% of the subjects, COPD among 41.7% of the subjects and reactive HIV Status was revealed among 1.4% of the subjects (table 1).

In our study, mean RBS (MG/DL) was 310.17±110.56 with minimum 187 and maximum 655.2 and mean HbA1c was 9.02±1.52 with minimum 6.8 and maximum 14.7 (table 2). In our study, 58.3% of the subjects were having HbA1c 7-9 and 41.7% of the subjects had HbA1c >9.

As shown in table 3, in subjects with HbA1c 7 to 9, isoniazid resistance was observed in 28.57% (12 patients out of 42), rifampicin resistance in 69.05% (29 patients), pyrazinamide and ethambutol resistance in 0%, FQ in 11.90% (5 patients) and 2 patients had resistance to SLID (4.76%). In subjects with HbA1c >9, isoniazid resistance was observed in 13.33% (4 patients out of 30), rifampicin resistance in 63.33% (19 patients), pyrazinamide and ethambutol resistance in 0% and FQ in 6.67% (2 patients).

Multidrug resistant tuberculosis (MDR-TB) was reported among 47.62% of the subjects with HbA1c 7 to 9 and among 2.38% of the subjects with HbA1c >9. Pre extensively drug resistant tuberculosis (pre XDR-TB) was reported among 53.3% of the subjects with HbA1c 7 to 9 and among 6.67% of the subjects with HbA1c >9. H mono resistance was revealed among 33.33% of the subjects with HbA1c 7 to 9 and among 13.33% of the subjects with HbA1c >9. When MDR/XDR was compared according to HbA1c level, it was found to be statistically significant (table 4). 61.1% of the subjects are still undergoing the required treatment. 5 subjects were cured, out of which 80% of the subjects were having HbA1c 7 to 9 and 20% of the subjects were having HbA1c >9. Default treatment was reported more among subjects with >9 HbA1c level (54.54%) as compared to subjects with 7 to 9 HbA1c (45.46%). Mortality was revealed among 4 subjects, out of which 25% were having HbA1c 7 to 9 and 75% were having >9 HbA1c. Significant difference was found in relation to treatment outcome among the subjects according to HbA1c level as $p<0.05$ (table 5).




**Graph 1:** Gender and age distribution among the study subjects

**Table 1:** Alcohol, smoking and past history distribution among the study subjects

| Alcohol | N | % |
|---|---|---|
| No | 45 | 62.5 |
| Yes | 27 | 37.5 |
| Smoking | | |
| No | 30 | 41.7 |
| Yes | 42 | 58.3 |
| Past History | N | % |
| Hypertension | 13 | 18.1 |
| COPD | 30 | 41.7 |
| Reactive HIV Status | 1 | 1.4 |

**Table 2:** Mean RBS and HbA1c among the study subjects

| Variables | Minimum | Maximum | Mean | SD |
|---|---|---|---|---|
| RBS (MG/DL) | 187 | 655.2 | 310.17 | 110.56 |
| HbA1c | 6.8 | 14.7 | 9.019 | 1.52 |

**Table 3:** DST results according to HbA1c level

| DST | HbA1c level | | | | Total | |
|---|---|---|---|---|---|---|
| | 7 to 9 (N=42) | | >9 (N=30) | | N=72 | |
| | N | % | N | % | N | % |
| H: Resistance | 12 | 28.57 | 4 | 13.33 | 16 | 22.22 |
| R: Resistance | 29 | 69.05 | 19 | 63.33 | 48 | 66.67 |
| R: Sensitive | 12 | 28.57 | 10 | 33.33 | 22 | 30.56 |
| Z: Resistance | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| E: Resistance | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| FQ: Resistance | 5 | 11.90 | 2 | 6.67 | 7 | 9.72 |
| SLID: Resistance | 2 | 4.76 | 0 | 0.00 | 2 | 2.78 |
| SLID: Susceptible | 3 | 7.14 | 2 | 6.67 | 5 | 6.94 |
| O: Resistance | 0 | 0 | 0 | 0 | 0 | 0 |
| K: Resistance | 0 | 0 | 0 | 0 | 0 | 0 |
| CM: Resistance | 0 | 0 | 0 | 0 | 0 | 0 |
| LEV: Resistance | 0 | 0 | 0 | 0 | 0 | 0 |
| MOX: Resistance | 0 | 0 | 0 | 0 | 0 | 0 |
| AMK: Resistance | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 4:** MDR/XDR according to HbA1c level

| MDR/XDR | | HbA1c Category | | Total |
|---|---|---|---|---|
| | | 7 to 9 | >9 | |
| All Oral Longer | N | 3 | 0 | 3 |
| | % | 7.14% | 0% | 4.17% |
| H MONO | N | 14 | 4 | 18 |

| | | | | |
|---|---|---|---|---|
| | % | 33.33% | 13.33% | 25.0% |
| MDR | N | 20 | 16 | 36 |
| | % | 47.62% | 53.3% | 50.0% |
| PRE XDR | N | 1 | 2 | 3 |
| | % | 2.38% | 6.67% | 4.2% |
| SHORTER | N | 2 | 8 | 10 |
| | % | 4.76% | 26.67% | 13.9% |
| XDR | N | 2 | 0 | 2 |
| | % | 4.76% | 0.0% | 2.8% |
| Total | N | 42 | 30 | 72 |
| | % | 100% | 100% | 100.0% |
| Chi Square | | 14.02 | | |
| p value | | 0.02* | | |

*: statistically significant

**Table 5:** Treatment outcome according to HbA1c level among TB subjects

| Treatment Outcome | | HbA1c Category | | Total |
|---|---|---|---|---|
| | | 7 to 9 | >9 | |
| Cured | N | 4 | 1 | 5 |
| | % | 80% | 20% | 6.9% |
| Default | N | 5 | 6 | 11 |
| | % | 45.46% | 54.54% | 15.3% |
| Died | N | 1 | 3 | 4 |
| | % | 25% | 75% | 5.6% |
| On Going | N | 27 | 17 | 44 |
| | % | 61.36% | 38.64% | 61.1% |
| Switched To AOL | N | 1 | 2 | 3 |
| | % | 33.33% | 66.67% | 4.2% |
| Switched To AOL (BDQ) | N | 0 | 1 | 1 |
| | % | 0.0% | 100% | 1.4% |
| Switched To Modified Regimen | N | 1 | 0 | 1 |
| | % | 100% | 0.0% | 1.4% |
| Treatment Complete | N | 2 | 0 | 2 |
| | % | 100% | 0.0% | 2.8% |
| Chi Square | | 19.71 | | |
| p value | | 0.03* | | |

*: statistically significant

## Discussion

Along with the convergence of the diabetes mellitus (DM) and TB epidemics, the high prevalence of DM among MDR-TB patients is a serious cause for concern, with a range of 10–23% of MDR-TB patients having DM. Whether DM, usually accompanied with altered immunity, has an effect on MDR-TB transmission, as similar with other immunodeficiency related disease (e.g. HIV), is yet to be determined [12, 14]. Therefore this study was planned to study the drug resistance pattern in cases of diabetes with pulmonary tuberculosis in western UP.

In our study, male subjects (72.2%) were comparatively more as compared to females (27.8%). Maximum subjects belonged to age group of 41-50 years (38.89%) followed by 51-60 years (31.94%) while minimum subjects were in the age group of >70 years (2.78%) followed by 30-40 years (11.11%). Keshri Singh Yadav *et al.* [15] found that out of 200 patients, there were 160 (80%) males and 40 (20%) females. Fengling Mi *et al.* [16] revealed that there was a significantly higher proportion of males and persons aged >35 years.

In this study, alcohol consumption was found among 37.5% of the subjects and 58.3% of the subjects were smokers. The epidemics of tobacco smoking and tuberculosis (TB) are colliding and increasing evidence showed smoking was associated with an increased risk of active TB. An understanding of the epidemiological relationship between smoking and tuberculosis is important because both smoking and tuberculosis cause extensive morbidity and mortality worldwide. Compared with those who have never smoked, it is estimated that people who smoke have approximately twice the risk of active tuberculosis. Gajanan S. Gaude *et al.* [17] revealed smoking history and alcoholism among 11 (22.9%) and 21 (43.9%) subjects respectively. Dipali Gavali *et al.* [18] reported smoking habit in 4 (1%) subjects.

In subjects with HbA1c 7 to 9, isoniazid resistance was observed in 28.57% (12 patients out of 42), rifampicin resistance in 69.05% (29 patients), pyrazinamide and ethambutol in resistance 0%, FQ in 11.90% (5 patients) and 2 patients had resistance to SLID (4.76%). In subjects with HbA1c >9, isoniazid resistance was observed in 13.33% (4 patients out of 30), rifampicin resistance in 63.33% (19 patients), pyrazinamide and ethambutol resistance in 0% and FQ in 6.67% (2 patients). In our study, multidrug resistant tuberculosis (MDR-TB) was reported among 47.62% of the subjects with HbA1c 7 to 9 and among 2.38% of the subjects with HbA1c >9. H mono resistance was revealed among 33.33% of the subjects with HbA1c 7 to 9 and among 13.33% of the subjects with HbA1c >9 with statistically significant difference.

Diabetes was significantly associated with INH resistance among new cases in a study by A-H. Hsu *et al.* [19], with an OR of 1.88, implying that diabetic patients were more likely to be infected with INH-resistant TB through transmission than non-diabetics. Three potential mechanisms can result in a significant association between DM and INH resistance among previously treated cases: 1) DM patients primarily infected with INH-resistant strains were more likely to receive a retreatment regimen; 2) DM patients were more likely to acquire resistance to INH during treatment; and 3) DM patients were more likely to be re-infected with INH-resistant TB, compared to non-DM patients. The study concluded that DM patients were more likely to acquire resistance to INH during treatment.

A-H. Hsu *et al.* [19] in their study revealed that DM was significantly associated with INH resistance, but not MDR-TB, in both new and previously treated TB cases compared to susceptible TB cases. Two studies have reported a positive association between diabetes and MDR-TB [20, 21]. In a case-control study, Bashar *et al.* reported a relative risk of MDR-TB of 8.6 in the diabetic group compared to the control group[70]. M.J. Magee *et al*[39] in their study found that in patients without and with previous TB treatment, the prevalence of multidrug-resistant TB was 23% and 26%, respectively, among patients without diabetes, and 12% and 28%, respectively, among TB–DM patients. Among 149

TB–DM patients with DST results, 104 (69.8%) had drug-susceptible TB and 45 (30.2%) had drug-resistant TB, of whom 29 had multidrug-resistant TB. Fengling Mi *et al*. [22] found that prevalence of multidrug-resistant TB (MDR-TB) was 6.2% in new patients (N=422) and 62.3% in previously treated patients (N=199), with no significant differences between those with and without diabetes. In patients with diabetes, there was no association of drug resistance with diabetes duration or disease control. Balewgizie Sileshi Tegegne *et al*. [23] in their meta-analysis of 24 observational studies from 15 different countries revealed that DM has a significant association with MDR-TB (OR = 1.97, 95% CI = 1.58–2.45, I2 = 38.2%, P value for heterogeneity = 0.031). The significant positive association remained irrespective of country income level, type of DM, how TB or DM was diagnosed and design of primary studies.

Wan-mei Song *et al*. [24] in their study concluded that TB-DM groups had a higher proportion of drug resistance than TB groups.

In our study, default treatment was reported more among subjects with >9 HbA1c level (54.54%) as compared to subjects with 7 to 9 HbA1c (45.46%). Mortality was revealed among 4 subjects, out of which 25% were having HbA1c 7 to 9 and 75% were having >9 HbA1c. Significant difference was found in relation to treatment outcome among the subjects according to HbA1c level as $p<0.05$. M.J. Magee *et al*. [25] reported that there was no association between diabetes characteristics and drug resistant TB. Of 136 TB–DM patients with outcome information, 107 (78.7%) had a favorable TB outcome; active diabetes management was associated with a favorable outcome.

Clinicians and researchers should generate the necessary evidence for improvements to patient services and policies on combined TB and diabetes. Our study will clarify the existing controversies on whether DM puts the higher risk for MDR-TB. Hence, the results of this study will be helpful to remove confusions for policy-makers, clinicians and patients.

## Conclusion

From the results of our study, we suggest that each and every patient must be screened for diabetes before starting ATT because the control of resistance and blood sugar is very important not only to decrease morbidity but also helpful to prevent the propagation of resistant tuberculosis to society at large and these patients may be put on sensitive ATT regimen for complete cure from pulmonary tuberculosis especially resistant cases.

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