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Original Research

To Study The Drug resistance Pattern In Cases Of Diabetes With Pulmonary Tuberculosis in F. H. Medical College

[1]Dr. Sanjeev Anand, [2]Dr. Abdul Rehman, [3]Dr. Rishi Yadav, [4]Dr. Deepak Sikarwar

[1]Professor, Department of TB and Chest, FH Medical College and Hospital, Etmadpur, Agra, U.P., India.
[2]Junior Resident, Department of TB and Chest F.H. Medical College and Hospital, Etmadpur, Agra, U.P., India.
[3]Assistant Professor, Department of TB and Chest F.H. Medical College and Hospital, Etmadpur, Agra, U.P., India.
[4]Assistant Professor, Department of TB and Chest F.H. Medical College and Hospital, Etmadpur, Agra, U.P, India

Corresponding Author
Dr. Abdul Rehman
Junior Resident, Department of TB and Chest F.H. Medical College and Hospital, Etmadpur, Agra, U.P., India

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ABSTRACT

Background: Drug Resistant tuberculosis is one of the most common barriers in treatment of tuberculosis. Diabetic patients have been identified to have an increased risk of drug resistance. The present study was conducted to assess drug resistance pattern, particularly MD-tuberculosis detected by CBNAAT/TRUENAAT in diabetic patients with pulmonary tuberculosis and to associate them with different clinicodemographic variables including blood sugar profile. **Materials & Methods:** A total of 157 diabetic patients with tuberculosis (aged 17-75 years) were enrolled in the study. Clinicodemographic assessment was done. CBNAAT/Truenat assessment was done for rapid assessment of drug resistance. Subsequently drug susceptibility test was also done. Diagnostic efficacy of CBNAAT/True NAT was assessed in terms of sensitivity, specificity, PPV, NPV and accuracy. **Results:** Mean age of patients was 49.76±14.05 years; 72.6% were males males; 51% urban residents, 53.5% unemployed/ retired or housewives. Smoking and alcohol use history was revealed by 42.7% and 32.5% patients. Prevalence drug resistance (rifampicin resistance) as revealed by TrueNAT-RR was 14.6%. On drug susceptibility test (DST), Rifampicin, isoniazid and pyrazinamide resistance was seen in 22 (14%), 2 (1.3%) and 1 (0.6%) patients respectively. DR-TB in diabetic patients with tuberculosis did not show a significant association with age, sex, place of residence, occupation, smoking and alcohol use. A significant association of DR-TB was seen with dyspnea, chest pain, duration of tuberculosis, duration of diabetes and level of glycemic control (HbA1c, fasting and post-prandial blood sugar). Sensitivity and specificity of TrueNAT against DST was 100% and 99.3% respectively for rifamipicin resistance. **Conclusion:** The findings of the study showed that CBNAAT/TrueNAT were useful modalities for evaluation of drug-resistant tuberculosis which showed a high correlation with diabetic factors.

Keywords: Tuberculosis, Drug resistant, Multidrug resistant, TrueNAT, CBNAAT, diabetes mellitus, Rifampicin resistant

INTRODUCTION

Tuberculosis is a huge global health problem for centuries and a global health priority since the establishment of World Health Organization in the year 19481. Despite concerted efforts on the part of healthcare planners, the global burden of tuberculosis is not still tamed. Each year nearly 6-7 million new cases of tuberculosis are reported across the world.[1] In the year 2019, a total of 7.1 new incident cases of tuberculosis were reported followed by a decline to 5.8 million during the year 2020 which was marked by global lock- downs restricting the person-to-person transmission of disease.[2] However, following relaxation of lockdowns and opening up of society and economy, this figure again showed an incremental trend to reach at 6.4 million in the year 2021 and 7.5 million in the year 2022. Tuberculosis is one of the commonest causes of mortality. In the recent years, while COVID-19 remained to be the most common cause of mortality, tuberculosis remained responsible for around 1.6 million deaths which is second only to the deaths due to COVID-19 during the year 20214. A little improvement in number of deaths was seen in the year 2022 when tuberculosis was responsible for 1.3 million deaths.[3]

Drug resistance is a major barrier in successful treatment and control of tuber culosis. Drug resistant tuberculosis patients are required to undergo alonger

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therapeutic course of antitubercular drugs with cautious monitoring andneed of special treatment strategies. Owing to resistance to drugs, the se patients are active carriers of tuberculosis for a long period thus placing the ircontactsatanincreasedrisk of beingtransmitted with aworse type of tuberculosis.[4] Multidrug resistant tuberculosis (MDR-TB) marked by resistance to atleast one of the two drugs from amongst the first line of antitubercular drugs, *viz.*, IsoniazidandRifampicin,isacauseofgreatconcernfromt hepublichealthpoint of view. In spite of the adaptation of various preventive and the rapeuticmeasures to reduce its prevalence, it still contributes to a sizeable proportionoftuberculosiscaseseachyear.Intherecentglo baltuberculosisdatareleasedby World Health Organization, it contributed to 3.6% of new diagnosed cases of tuberculosis.[5] The present study was conducted to assess drug resistance pattern, particularly MD-tuberculosis detected by CBNAAT/TRUENAAT in diabetic patients with pulmonary tuberculosis and to associate them with different clinicodemographic variables including blood sugar profile.

MATERIALS & METHODS

The study was carried out at Department of Tuberculosis and Respiratory Medicine, F.H. Medical College and Hospital (FHMCH), Etmadpur, Agra. The study protocol for all the described procedures was approved by the institutional review board for ethical clearance in accordance with the code of ethical of the world medical association according to the declaration of Helsinki of 1975, as revised in 2000.

Data such as name, age, gender etc. was recorded. The patients were interviewed for the demographic, socioeconomic status, medical history and previous history. Details related with intake of any medications and supplements, various co-morbidities like hypertension etc. were also recorded. Drug susceptibility testing was done at regional quality-assured culture and drug susceptibility testing (C-DST) laboratory using MGLT liquid culture for first as well as second line drugs, viz., Rifampicin., Isoniazid (inhA/0.1), Isoniazid (kat G/0.4), Streptomycin Ethambutol, Pyrazinamide, Kanamycin, Capreomycin, Amikacin, Levofloxacin, Moxifloxacin (0.5), Moxifloxacin (2), Fluoroquinolones Class, Ethionamide, p-aminosalicylic acid, Linezolid, Clofazimine, Clarithromycin, Azithromycin, Bedaquiline and Delamanid. Data thus obtained were subjected to statistical analysis. P value < 0.05 was considered significant.

RESULTS

Table: I Demographic profile(N=157)

Characteristics	Number	Percentage
AgeGroup		
≤25 years	10	6.4
26-35years	16	10.2
36-45years	25	15.9
46-55years	46	29.3
56-65years	42	26.8
66-75years	18	11.5
Meanage±SD(Range)inyears	49.76±14.05(17-75)	
Gender		
Female	43	27.4
Male	114	72.6
Place of living		
Rural	77	49.0
Urban	80	51.0
Occupation		
Farmer	32	20.4
Homemaker	40	25.5
Student	2	1.3
Trade worker	1	0.6
Other profession	38	24.2
Unemployed/Retired	44	28.0

Age of patients enrolled in the study ranged from 17 to 75 years, mean age was 49.76±14.05 years. Most common age group was 46-55 years (29.3%) followed by 56-65 years (26.8%). Only 6.4% of patients were aged ≤25 years and 11.5% were aged above 65 years. Rest of the patients fall in age group 26- 35 years (10.2%) and 36-45 years (15.9%). Out of 157 patients, approximately three fourth (72.6%) were males and rest were females (27.4%). Male gender was dominant, male: female ratio was 2.65. Study population was almost perfect mix of Rural and Urban population, 51.0% belonged to Urban areas while

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49% to Rural areas. Only 71/157 (45.2%) were in active professions (Farmer 20.4%, Trade worker 0.6% and other profession 24.2%), rest were Homemakers (25.5%), Students (1.3%), Unemployed/Retired (28.0%).

Table: II Tuberculosis investigations and treatment

Observation	No. of cases	Percentage
Sputum Examination		
Positive	157	100.0
CBNAAT/TRUENAT		
MTB	157	100.0
Rifampicinsensitive	134	85.6
Rifampicinresistant	23	14.6
Type of Regimen		
Shorter MDR	2	1.3
Longer MDR/ XD Rregimen	21	13.4
DSTB Regimen	134	85.4

Sputum examination of all the patients was positive. CBT/TRUENAAT diagnosed all the 157 cases as MDR, of these 23 (14.6%) cases were Rifampicin resistant mycobacterium tuberculosis (TB- DR), rest were Rifampicin sensitive mycobacterium tuberculosis (MTB). Majority of the patients were on DSTB Regimen (85.4%) rest were either on Longer MXDR regimen (13.4%) or on Shorter MDR regimen (1.3%).

Table: III Association of DR-TB with duration of tuberculosis

Duration of tuberculosis	Total(N=157)	DR-TB(n=23)		MTB(n=134)		Statistical significance
		No.	%	No.	%	
<6months	7	3	13.0	4	3.0	x^2=23.048;p<0.001
6-12months	145	16	69.6	129	96.3	
>12months	5	4	17.4	1	0.7	
Mean duration±SD		8.83±4.68		6.17±1.07		't'=5.823; p<0.01

Significantly higher proportion of DR-TB cases as compared to MTB cases had duration of diabetes >15 years (21.7% vs. 2.2%). On comparing the mean duration of tuberculosis of DR-TB and MTB cases (9.57±4.71 vs. 6.59±4.15 years) was found to be statistically significant.

Table: III Association of DR-TB with glycemic Levels

Glycemic levels	Total (N=157)	DR-TB(n=23)		MTB(n=134)		Statistical significance
		No.	%	No.	%	
HbA1c						
7.1-8.5%	82	2	8.7	80	59.7	x^2=15.834;p=0.001
>8.6%	75	21	91.3	54	40.3	
Mean HbA1c	8.05±0.70	9.32±0.48		8.36±0.63		't'=6.936;p<0.001
FBS						
≤170mg/dl	70	8	34.8	62	46.3	x^2=24.015;p<0.001
171-200mg/dl	83	11	47.8	72	53.7	
>200mg/dl	4	4	17.4	0	0.0	
Mean FBS±SD(mg/dl)	174.58± 17.20	183.87± 31.35		172.99± 12.93		't'=2.867;p=0.005
PP BS						
≤280mg/dl	87	9	39.1	78	58.2	x^2=11.060;p=0.004
281-300mg/dl	31	2	8.7	29	21.6	
>300mg/dl	39	12	52.2	27	20.1	
MeanPPBS±SD (mg/dl)	276.45± 39.04	300.13± 52.11		272.39± 34.99		't'=3.244;p=0.001

Mean HbA1c levels of DR-TB cases was found to be significantly higher than that of MTB cases (9.32±0.48 vs. 8.36±0.63%). DR-TB cases as compared to MTB cases had significantly higher Fasting blood sugar (183.87±31.35 vs. 172.99±12.93 mg/dl) and post-prandial blood sugar (300.13±52.11 vs. 272.39±34.39 mg/dl).

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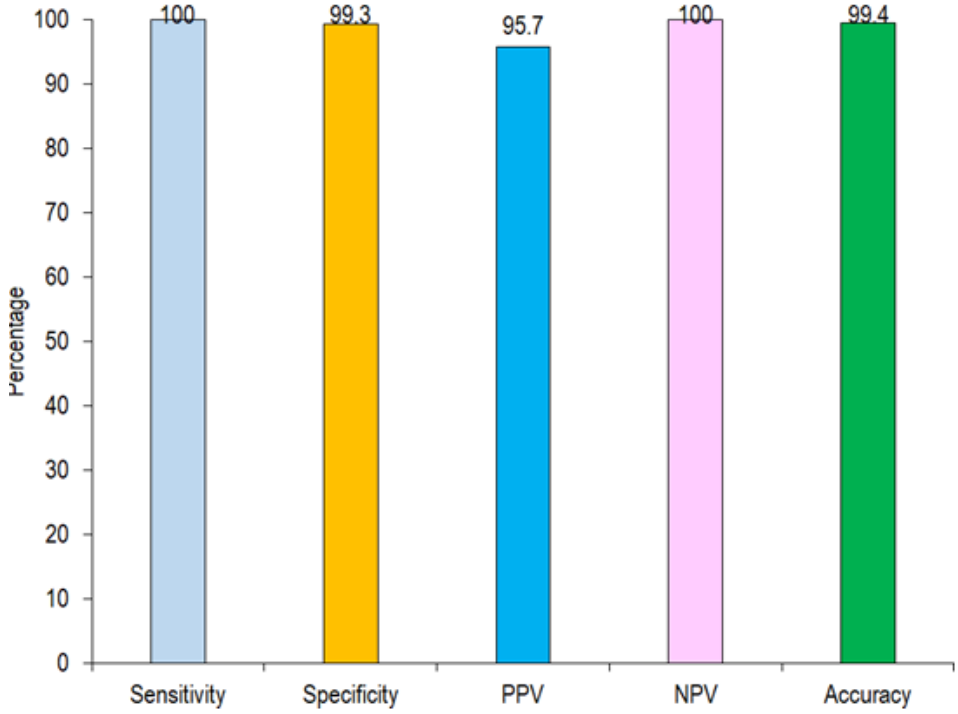
Table: IV Drug resistance pattern(DST)(N=157)

Drug	Resistant		Sensitive	
	No.	%	No.	%
Rifampicin	22	14.0	135	86.0
Isoniazid	2	1.3	155	98.7
Pyrazinamide	1	0.6	156	99.4
Ethambutol	0	0.0	157	100.0
Kanamycin	0	0.0	157	100.0
Capreomycin	0	0.0	157	100.0
Amikacin	0	0.0	157	100.0

Out of 157 patients enrolled in the study 22 (14.0%) were Rifampicin resistant, 2 (1.3%) were Isoniazid resistant, 1 (0.6%) was Pyrazinamide resistant. None was resistant for Ethambutol, Kanamycin Capreomycin and Amikacin.

Graph: I Diagnostic Accuracy of CBNAAT/TRUENAAT as compared to DST



DST diagnosed a total of 22 cases as Rifampicin resistant while CBNAAT/TRUENAAT diagnosed 23 cases as DR-TB, 22 true positive, 1 false positive, none false negative and 134 true negative. Correspondingly, CBNAAT/TRUENAAT had sensitivity, specificity, negative predictive, positive predictive and accuracy values of 100.0%, 99.3%, 95.7%, 100.0% and 99.4% respectively for diagnosis of Rifampicin resistance.

DISCUSSION

Diabetes mellitus (DM) significantly exacerbates the global burden of tuberculosis (TB) by increasing both susceptibility to TB infection andthe risk of developing multidrug-resistant tuberculosis (MDR-TB). Diabetic patients are not only more prone to TB but also more likely to have poorer treatment outcomes and higher mortality rates. The presence of DM complicates TB management due to immunosuppressive effects and altered pharmacokinetics, leading to challenges in achieving effective drug concentrations and optimal treatment responses.[6]

CBNAAT (Cartridge-Based Nucleic Acid Amplification Test) also known as Gene Xpert MTB/RIF and TRUENAT are the two rapid molecular tests that have revolutionized TB diagnosis and drug resistance detection. They are helpful in simultaneously detecting Mycobacterium tuberculosis and rifampicin resistance, providing results within hours. Owing to their rapidity in providing the results, they reduces diagnostic delays, allowing for timely intervention, which is particularly important for immunocompromised diabetic patient.[7] Both these tests, particularly TRUENAT are considered to be a boon as they are not only easy to perform but are also cost-effective and suitable for low-resource settings while at the same time being highly sensitive as well as specific. Truenat™ MTB (Mycobacterium tuberculosis) and Truenat™ MTB-RIF (rifampicin) is an indigenous chip-based real-time polymerase chain reaction (PCR) based test for detection of multidrug-

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resistant (MDR) TB71. In addition, use of TUENAT-INH also helps to detect MDR-TB by detecting mutations in the Mycobacterium tuberculosis (MTB) genome that cause resistance to isoniazid. [8]

We found that age of patients enrolled in the study ranged from 17 to 75 years, mean age was 49.76±14.05 years. Out of 157 patients, approximately three fourth (72.6%) were males and rest were females (27.4%). Male gender was dominant, male: female ratio was 2.65. Study population was almost perfect mix of Rural and Urban population, 51.0% belonged to Urban areas while 49% to Rural areas. Only 71/157 (45.2%) were in active professions (Farmer 20.4%, Trade worker 0.6% and other profession 24.2%), rest were Homemakers (25.5%), Students (1.3%), Unemployed/Retired (28.0%).Yadav et al[9]performed astudy on"200 newly diagnosedpulmonary tuberculosis patients who underwent oral glucose tolerance test(OGTT) and sputum culture sensitivity and divided into group A,(euglycemic),Bimpairedglucosetolerance(IGT)and C(diabetic)onthebasisofbloodsugarlevel. A total of 22.5% were in group B and 7.5% in group C. The development of multi drug 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%). The prevalence of frank diabetes and IGT in pulmonary tuberculosis was more than normal patients. MDR was more common in diabetic and impaired glucose tolerance patients.

We found that sputum examination of all the patients was positive. CBT/TRUENAAT diagnosed all the 157 cases as MDR, of these 23 (14.6%) cases were Rifampicin resistant mycobacterium tuberculosis (TB-DR), rest were Rifampicin sensitive mycobacterium tuberculosis (MTB). Majority of the patients were on DSTB Regimen (85.4%) rest were either on Longer MXDR regimen (13.4%) or on Shorter MDR regimen (1.3%).We found that significantly higher proportion of DR-TB cases as compared to MTB cases had duration of diabetes >15 years (21.7% vs. 2.2%).On comparing the mean duration of tuberculosis of DR-TB and MTB cases (9.57±4.71 vs. 6.59±4.15 years) was found to be statistically significant.Baghaei et al[10] carried out a case-control study on newly diagnosed pulmonary TB adult patients. A total of TB patients with diabetes were enrolled as cases and a total of 64 TB patients without DM were enrolled as controls. Mean age of diabetic TB patients was significantly higher (59 years) as compared to that of non-diabetic patients (43 years). Prevalence of MDR tuberculosis was 3.2% in cases as compared to nil in controls. Relatively higher proportion of TB-DM cases had isolates that were resistant to at least one drug (12.9% vs. 10.9%). On multivariate analysis presence of diabetes,age <40 years and history of TB contact emerged as independent risk factors significantly associated with any drug resistance.

We found that mean HbA1c levels of DR-TB cases was found to be significantly higher than that of MTB cases (9.32±0.48 vs. 8.36±0.63%). DR-TB cases as compared to MTB cases had significantly higher Fasting blood sugar (183.87±31.35 vs. 172.99±12.93 mg/dl) and post-prandial blood sugar (300.13±52.11 vs. 272.39±34.39 mg/dl).We found that out of 157 patients enrolled in the study 22 (14.0%) were Rifampicin resistant, 2 (1.3%) were Isoniazid resistant, 1 (0.6%) was Pyrazinamide resistant. None was resistant for Ethambutol, Kanamycin Capreomycin and Amikacin.Perez-Navarro et al[11] in an assessment of 507 individuals with pulmonary tuberculosis found 183 with coexisting type 2 diabetes mellitus. They found that "patients with TB-T2DM were more likely to remain positive for acid- fast bacilli after two months of anti-TB treatment RR = [2.01 (95% CI: 1.3, 3.1)], to have drug resistant (DR) [OR 3.5 (95% CI: 1.8, 6.7)] and multi-drug resistant (MDR) TB [OR 3.5 (95% CI: 1.8, 7.1)]. The Cohen's-d for DR or MDR in T2DMwas 0.69 when compared with non-DM subjects. The T2DM patients had higher odds of resistance to isoniazid (OR 3.9, 95% CI: 2.01, 7.9), rifampicin (OR 3.4,95% CI: 1.6, 7.2) and pyrazinamide (OR 9.4, 95% CI: 2.8, 25.6)".

The shortcoming of the study is small sample size.

CONCLUSION

The findings of the present study showed a significant association of drug resistance in diabetic patients was seen with duration of tuberculosis treatment and diabetic factors like duration of diabetes and level of glycemic control. This implies that poor glycemic control and longer duration of diabetes can be seen as factors influencing drug resistance in diabetic patients with tuberculosis. CBNAAT/ TRUENAT was found to be a highly sensitive and specific diagnostic test for evaluation of drug resistance in tuberculosis patients with diabetes. Further studies on a larger sample size relating the drugresistance pattern and treatment outcomes in diabetic tuberculosis patients are highly recommended to assess the clinical impact of these findings.

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