Original Research Article

Study of rifampicin resistance among newly diagnosed pulmonary tuberculosis patients with type 2 diabetes mellitus: a prospective observational study

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ABSTRACT

Background: Rifampicin (RIF) resistance in new cases of pulmonary tuberculosis is a matter of concern. Diabetes Mellitus triples the risk of developing tuberculosis. Early detection of TB and its resistance status in diabetics can help in improving the care and treatment outcomes of both diseases.
Methods: It was a prospective study conducted from February 2019 to March 2020 in PGIMS, Rohtak on 50 patients of DM with newly diagnosed Pulmonary TB. Rifampicin resistance was detected by CBNAAT on sputum, induced sputum and BAL samples.
Results: Mean age of study subjects was 51.24±10.421 (in years) with M: F ratio of 3:1 and maximum patients in 50-59 age group. The average BMI in patients was 22.49±2.42 kg/m^2. The most common presenting complaint was cough (92%) followed by fever (68%). Mean serum HBA1c was 9.66±2.24 and mean FBS and PPBS was 195.81±59.08 and 302.02±99.01 mg/dl respectively. Out of 36 cases who gave sputum, 29 (80.55%) were detected rifampicin sensitive and 7 (19.44%) were rifampicin resistant whereas out of 11 who were induced, 9 (81.8%) were rifampicin sensitive and 2(18.18%) were rifampicin resistant. Out of 3 cases detected by BAL CBNAAT, 2 (66.6%) were rifampicin sensitive and 1 (33.33%) was rifampicin resistant. Overall, 10(20%) patients were detected Rifampicin resistant by CBNAAT.
Conclusions: We found that TB-DM patients had a higher proportion of drug resistance (20%), so DM should be considered as an independent risk factor for MDR-TB and effective measures are required for early diagnosis of MDR-TB.

Keywords: TB, DM, Rifampicin resistance, CBNAAT

INTRODUCTION

Tuberculosis (TB) is a major health problem with India being the highest tuberculosis burden country accounting for one fourth of the global incidence. About a quarter of the world's population is infected with M. tuberculosis with new infections occurring in about 1% of the population each year.[1] Most infections remain asymptomatic, in which case it is known as latent tuberculosis. Overall, about 10–15% of those infected will develop active disease at some later stage in life.[2] The most important risk factor globally is HIV; 13% of all TB patients are infected by this virus. Other disease states like diabetes mellitus also increase the risk of

developing tuberculosis (three-fold increase).[3] In 2018, an estimated 10 million people were diagnosed with tuberculosis (TB) worldwide and it was the leading cause of death worldwide from a single infectious agent.

Multi Drug Resistant TB (MDR TB) remains a major threat in the country with an estimated 84,000 MDR/Rifampicin-resistant TB cases in 2016.[4] Rifampicin resistance (RR) is resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR. Rifampicin resistance is due to genetic change in the beta subunit of bacterial RNA polymerase (RNAP) encoded by rpoβ gene which is detected by Gene Xpert testing. In 2018, globally there were about half a million new cases of rifampicin-resistant TB (of which 78% had multi drug resistant TB).The three countries with the largest share of the global burden were India (27%), China (14%) and the Russian Federation (9%). Globally, 3.4% of new TB cases and 18% of previously treated cases had multidrug resistant TB or rifampicin resistant TB (MDR/RR-TB).[1]

The treatment of patients infected with MDR-TB strains is extremely challenging due to the complexity of chemotherapy regimens and the toxicity of alternative drugs. Furthermore, treatment of MDR-TB imposes a huge financial burden on public health systems. Accordingly, identifying the risk factors associated with MDR-TB is of great significance, which may assist in the guidance of intervention measures, promote development of follow-up strategies in specific susceptible populations and help decision-making in terms of resource allocation. Several risk factors such as previous treatment, younger age, human immunodeficiency virus (HIV) infection and smoking have been identified. Recently, 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.[5, 6]

Diabetes mellitus (DM) is an endocrine disorder clinically characterized by abnormally high level of glucose in the blood. It is classified broadly into two types – diabetes mellitus type 1 (DM I) and diabetes mellitus type 2 (DM II). DM II, also known as non-insulin dependent, is the most common form of DM that results from a progressive defect in the secretion of insulin and/or resistance to the effects of insulin. Globally, an estimated 463 million adults are living with diabetes, according to the latest 2019 data from the International Diabetes Federation.[7] In India, 69.1 million people had diabetes and are estimated to have the second highest number of cases of DM in the world after China in 2015. More than 5 lakh cases of tuberculosis are attributable to diabetes. Diabetes increases the risk of developing TB by nearly three times. Moreover, diabetes can worsen the clinical course of TB and TB can worsen glycemic control in people with Diabetes.[8]

Mechanisms for increased development of TB/ increased severity of TB in diabetics are hyperglycemia which favors the growth of organisms in tissues, indirect effects on immune function, decreased activation of macrophages due to deposition of lipids , decreased IFN –Gamma levels, altered innate and type 1 cytokine expression, over synthesis of ACTH, vitamin A deficiency and over production of Glycerol.[9] Diabetes may also accelerate the emergence of drug-resistant TB, especially multidrug- resistant TB (defined as strains of TB resistant to both rifampicin and isoniazid) among those receiving TB treatment, although the evidence is limited.[10]

Rifampicin (RIF) resistance in Mycobacterium tuberculosis (MTB) bacilli is one of the key areas of research in the current scientific era and the resistance in new cases of pulmonary tuberculosis is a matter of concern. Chronic illnesses such as diabetes mellitus increase the risk of developing tuberculosis. Diabetes triples the risk of developing tuberculosis and 15% of TB cases may be linked globally to diabetes.[11] Therefore, study of Rifampicin resistance in new pulmonary tuberculosis patients associated with diabetes mellitus is important. Early detection of TB and its resistance status in diabetics can help in improving the care and treatment outcomes of both diseases in the patients. All high-risk people with diabetes should be systematically screened for TB and drug resistance for early detection and treatment of TB in a high prevalence country like India.

METHODS

It was a prospective study conducted from February 2019 to March 2020 in the Department of Respiratory Medicine and Microbiology at Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak. Approval from Institutional Ethics committee was obtained before the start of study. Study subjects were explained in detail regarding study objective in a language patient can understand and written informed consent was obtained.

Inclusion criteria

Diabetic patients with: symptoms suggestive of pulmonary tuberculosis example- cough with expectoration for >2 weeks, fever, weight loss, hemoptysis, decreased appetite, radiological findings suggestive of pulmonary tuberculosis.

Exclusion criteria

Previous history of Anti- tuberculosis treatment. Patients with co-morbid illnesses other than diabetes. Patients not willing to be assessed as per study protocol.

In all patients detailed history was taken followed by thorough clinical examination.

Patients were selected according to inclusion criteria and subjected to further procedures according to the flow chart (Figure 3).
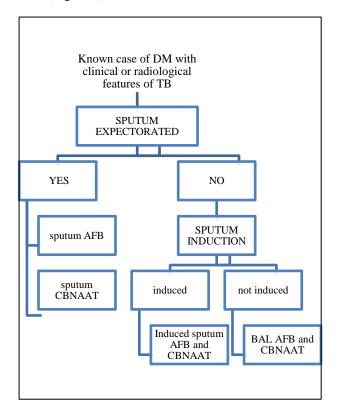

Figure 1: Algorithm for diagnosis.

Two sputum samples were collected from the patients who were expectorating- one on the spot and the other during next day early morning. For patients who were not expectorating, induced on-the-spot sputum was collected after 15 to 30 min of inhalation of 10 ml of 3% saline solution via a nebulizer in a well-ventilated isolated room. Sample collected was sent for direct smear and Cartridge Based Nucleic Acid Amplification Test (CBNAAT) in falcon tube to Microbiology department. Patients not expectorating even after induction or whose induced sputum was negative by CBNAAT were subjected to fiber optic bronchoscopy for collection of BAL. Sample was processed immediately and CBNAAT Test was done by Xpert MTB/RIF Cartridge (Cepheid) kit and Gene/Xpert system.

Gene Xpert test detects the DNA in tuberculosis bacteria. The Gene-Xpert System integrates and automates sample processing and nucleic acid amplification and detection of the target sequences in simple or complex samples using real-time PCR and reverse transcriptase PCR. The system consists of an instrument, personal computer, barcode scanner and preloaded software for running tests on collected samples and viewing the results. Disposable cartridges were used for the test. Xpert MTB/RIF includes reagents for the detection of tuberculosis and RIF resistance as well as a sample processing control (SPC) to control for adequate processing of the target

bacteria and to monitor the presence of inhibitors in the PCR reaction. The primers in the Xpert MTB/RIF assay amplify a portion of the rpoβ gene containing the 81 base pair "core" region. The probes are able to differentiate between the conserved wild-type sequence and mutations in the core region that associated with RIF resistance in 2 h.

RESULTS

Fifty patients of either sex, who fulfilled the inclusion and exclusion criteria were included in the study. The findings were filled up in the predesigned proforma and data was analyzed by appropriate statistical methods using Microsoft excel and statistical package for social sciences (SPSS) 20.
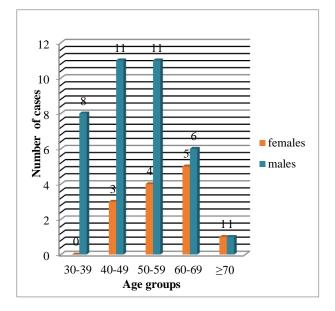

Figure 2: Age and gender based distribution of cases.

Table 1: Diabetes status of cases (n=50).

Cases		Diabetes status		
		Known diabetes	Recently diagnosed	Total
Male	N	23	14	37
	% within Sex	62.16%	37.8%	100%
Female	N	8	5	13
	% within Sex	61.5%	38.5%	100%
Total	N	31	19	50
	Percentage	62%	38%	100%

The males included in the study were of mean age 49.16±10.256 (in years). The mean age of females was 57.15±8.754 (in years). (Figure 2)

The mean weight of male and female patients was (52.54±8.7) versus (46.38±10.1) kg (p value=0.041 i.e. statistical significant) while the mean Body Mass Index

(BMI) of male and female cases was (22.92±2.33) versus (21.29±2.36) kg/m^2 (p=0.036 i.e. statistical significant). The average BMI in all study patients was observed to be 22.49±2.42 kg/m^2. Out of 50cases, 31 (62%) were known diabetic cases and 19 (38%) were diagnosed at the time of study (Table 1).

Table 2: Distribution of cases on the basis of sample taken to detect rifampicin resistance using CBNAAT.

	Frequency	Percentage
Sputum CBNAAT	36	72%
Induced Sputum CBNAAT	11	22%
BAL CBNAAT	3	6%

The most common presenting complaint among the patients was observed to be cough in 92% cases. The second most common complaint was fever (68%), followed by loss of appetite (62%), weight loss (56%), and shortness of breath (44%), chest pain (18%) and lastly hemoptysis (16%). The mean Hb of the patients was 11.51±1.74 gm/dl and the mean total leucocyte count was 9214.8±4036.77 and the mean platelet count of 2.916±0.90 lakhs. Mean serum HBA1c in study patients was 9.66±2.24. The mean fasting and postprandial blood sugar level of the cases was 195.81±59.08 and 302.02±99.01 mg/dl respectively. (Figure 3)

There were total 50 patients out of which 36 (72%) were expectorating and their sputum sample was sent for CBNAAT testing. Rest 14 (28%) patients had undergone for sputum induction after the result of which, 11 (22%) cases expectorated and rest 3 (6%) underwent fiberoptic bronchoscopy for bronchioalveolar lavage. (Table 2)
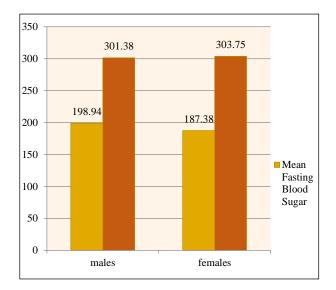

Figure 3: Comparison of mean fasting and postprandial blood sugar level in males and females.

Table 3: Distribution of cases detected by Sputum CBNAAT (n=36) on the basis of gender and Rifampicin (R) drug sensitivity.

Characteristics			Sputum CBNAAT		Total
			R. sensitive	R. resistant	
Sex	Male	Count	20	7	27
		% within Sex	74.1%	25.9%	100.0%
	Female	Count	9	0	9
		% within Sex	100.0%	0.0%	100.0%
Total		Count	29	7	36
		Percentage	80.6%	19.4%	100.0%
P value FE		0.156			

Table 4: Distribution of cases detected by induced Sputum CBNAAT (n=11) on the basis of their gender and Rifampicin (R) drug sensitivity.

Characteristics			Induced sputum CBNAAT		Total
			R. sensitive	R. resistant	
Sex	Male	Count	7	1	8
		% within Sex	87.5%	12.5%	100.0%
	Female	Count	2	1	3
		% within Sex	66.7%	33.3%	100.0%
Total		Count	9	2	11
		Percentage	81.8%	18.2%	100.0%
P value FE		0.491			

Out of 36 cases subjected to CBNAAT after positive smear, 27 were males and 9 were females. Out of 27

males, 20 (74.1%) were detected as rifampicin sensitive and 7 (25.9%) were rifampicin resistant. Rest 9 females

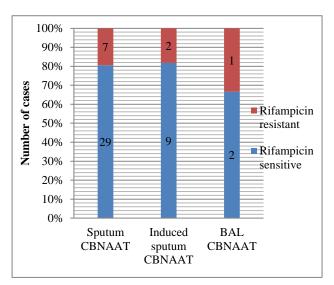patients all were detected as rifampicin sensitive. (Table 3)

Figure 4: Distribution of cases detected rifampicin resistant or sensitive by CBNAAT on various samples.
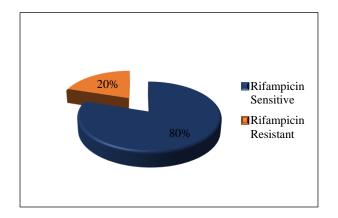

Figure 5: Rifampicin resistance in newly diagnosed pulmonary tuberculosis patients with diabetes mellitus.

Out of 14 cases, 11 patients expectorated after sputum induction. Out of those 11 patients subjected to induced sputum CBNAAT, 8 were males and 3 were females. In males, 7 (87.5%) were detected as rifampicin sensitive, 1 (12.5%) was rifampicin resistant and in 3 female patients, 2 (66.7%) were rifampicin sensitive and 1 (33.3%) was resistant to rifampicin. (Table 4)

Out of 3 cases detected by BAL CBNAAT, 2 were males and one was female. Out of those 2 males, 1 (50%) was detected as rifampicin sensitive and 1 (50%) was rifampicin resistant. Out of total number of cases, 37 were males and 13 were females. In those 37 male patients, 28 (75.7%) were rifampicin sensitive and 9 (24.3%) were rifampicin resistant. Out of 13 female patients, 12 (92.3%) were rifampicin sensitive and 1 (7.7%) was rifampicin resistant.

DISCUSSION

Diabetes triples the risk of developing tuberculosis (TB). Consequently, the prevalence of TB is higher in people living with diabetes than in the general population. Diabetes may also accelerate the emergence of drug-resistant TB, especially multidrug-resistant TB among those receiving TB treatment, although the evidence is limited.[10] There are not much evidences on the status of primary drug resistant TB in patients living with diabetes mellitus. The high prevalence of diabetes mellitus (DM) among multidrug resistant tuberculosis (MDR-TB) patients is a serious cause for concern. Studies are required to determine whether DM is an independent risk factor for MDR-TB.

The present study was conducted in the Department of Respiratory Medicine in collaboration with the Department of Microbiology, Pt. B.D. Sharma PGIMS Rohtak to detect rifampicin resistance in newly diagnosed pulmonary tuberculosis patients with type 2 Diabetes mellitus. The observations recorded during the study were compared with other studies to draw the objective comparisons.

In the present study, mean age of the study population was found to be 51.24±10.4 years. Mean age of male patients was 49.16±10.25 years and the mean age of female patients was 57.15±8.75 years. Overall majority of cases were in the age group of 50-59 years of age group (30%). This matches the results of study by Nissapatorn et al who reported the mean age of DM-TB patients to be 51.5 years versus 37.5 years in non-DM TB patients.[12] Similarly Ponce-de-Leon et al in his study found that DM-TB patients' mean age was 53 years vs 44 years in non-DM TB patients.[13] Manjareeka et al in the study 'Diabetes mellitus among newly diagnosed tuberculosis patients in tribal Odisha: an exploratory study' found the average age of the patients to be 46.7 years of which the mean age (53.8 years) of TB-DM patients was higher than that of the isolated TB patients (45.9 years) with a statistically significant difference.[14] Similar findings were reported by Rawat et al who found that the patients in the PTB-DM group were significantly older (53.34±14.06 years) in comparison to PTB group (44.35±18.14 years).[15] This can be accounted to the reason that older age group had a significantly higher prevalence of diabetes compared to the younger age group.

In the present study, out of total 50 patients, there were 37 (74%) males and 13 (26%) females. The present study showed male: female ratio of approx. 3:1. The male preponderance in this study is in accordance with the global tuberculosis report 2019 which states that the incidence of pulmonary tuberculosis is more in males as compared to females.[1] Khalil et al in the 'Study of risk factors for pulmonary tuberculosis among diabetes mellitus patients' also noticed male predominance, as in DM-TB group there were 56 males versus 24 females.[16]

This is observed that the rate of TB is higher among men than women, beginning in the young adult years and persisting throughout life. This is a longstanding observation thought to reflect more frequent tuberculosis exposure in the community among men than women.[17]

In the present study, mean body weight of cases was 50.94 ± 9.4 kg and mean Body Mass Index (BMI) was 22.49 ± 2.42 kg/m^2. Magee et al in his study 'Clinical characteristics, drug resistance and treatment outcomes among tuberculosis patients with diabetes in Peru' found that TB–DM patients with no previous history of TB treatment had body mass index (BMI) >18.5 kg/m^2.[18] There are similar findings in the study by Kikvidze et al, as the mean BMI of TB-DM cases in his study was 23.44 (SD-3.78).[19]

We found that the most common clinical symptom was cough. It was found in 92% of the patients. The second most common complaint was fever (68%), followed by loss of appetite (62%), weight loss (56%), shortness of breath (44%), chest pain (18%) and hemoptysis (16%). There were similar findings in the study by Manjareeka et al which also found that the most common symptom in their study population was cough (87.1%) followed by weight loss (80.2%), digestion related problems (60.4%), night sweat (46.5%) and hemoptysis (10.9%).[14] Studies had shown that the clinical characteristics of TB do not differ among diabetics and non-diabetics. Singla et al found the prevalence of cough in a comparative study between DM-TB patients and non-DM TB patients to be 98.9% versus 97.8%.[20]

The present study shows that of all the cases included in the study, there were 31 known diabetic cases (62%) and 19 were diagnosed at the time of study only (38%). The mean fasting and postprandial blood sugar level of the study patients was found to be 195.81 ± 59.08 and 302.02 ± 99.01 mg/dl respectively. The mean serum HBA1c in study patients was 9.66 ± 2.24. Result matches with the study by Alisjahbana et al in which the mean fasting blood glucose level among DM-TB was 215 mg/dl.[21] Khalil et al in the study found that fasting blood sugar in DM-TB group was 214 ± 67.43 mg/dl, postprandial blood glucose was 319.01 ± 85.01 mg/dl and mean theHbA1c in DM-TB group was 9.88 m$\pm$2.03 mmo1/L which are very similar to the observations of the present study.[16] These results show a poor glycemic control in TB.

In the present study, out of total 50 numbers of cases, 10 (20%) were found to be rifampicin resistant and rest 40 (80%) were rifampicin sensitive. Out of 37 male patients under study, 28 (75.7%) were rifampicin sensitive and 9 (24.3%) were rifampicin resistant and out of 13 female patients, 12 (92.3%) were rifampicin sensitive and 1 (7.7%) was rifampicin resistant. Out of total female patients, 7.7% were diagnosed rifampicin resistant compared to 24.3% of males with a p>0.05 i.e.

statistically insignificant. Hence, no gender predilection was seen for rifampicin resistance in cases.

The present study concludes that 10 (20%) out of 50 cases who attended the tertiary care hospital in Haryana in 2019 were found to be rifampicin resistant. The prevalence rate observed is much higher compared to the primary rifampicin resistant cases seen among non diabetics, given in the other studies conducted in India and outside. This might be due to small number of cases and selection bias since only few cases consulted at tertiary level hospital.

Magee et al found that in the patients without DM, prevalence of multidrug-resistant TB was 23% and 26% among new and previously treated patients respectively.[18] Whereas among TB–DM patients the prevalence of multidrug-resistant TB was 12% and 28%, respectively among new and previously treated patients. Baghaei et al in the study found that two new TB–DM patients had multidrug resistant TB (MDR-TB) (4.4%) compared with zero cases of MDR-TB in the control group.[22]

Chang et al in their study effect of type 2 diabetes mellitus on the clinical severity and treatment outcome in patients with pulmonary tuberculosis: a potential role in the emergence of multidrug-resistance found that DMTB patients had more severe infections, higher mycobacterial loads, higher treatment failure rates and longer delayed clearance of mycobacteria than did the TB patients.[23] After one year, three DMTB patients and one TB patient had MDR-TB (5.0% versus 0.8%, p=0.056). Sinha et al in the study 'prevalence of multi-drug resistant tuberculosis among new culture- positive pulmonary tuberculosis patients in tertiary care center of North India' found that out of a total of 713 patients with culture-positive results, there were a total of 683 new cases. Of these 683 patients, 62 (9.1%) were resistant to Rifampicin, 75 (11%) were resistant to Isoniazid and 60 (8.7%) patients were resistant to both drugs.[24] Gautam et al found that out of total rifampicin resistant cases, 7.6% cases were treatment naive patients.[25] Study by Charan et al showed a prevalence of 3% and 28% MDR-TB in new and previously treated TB cases respectively, similarly to the national survey of India which reported the prevalence of MDR-TB in new cases as 2.8%.[26] Similar results by Lohiya et al who found that the prevalence of MDR, any drug resistance and extensive drug resistance was 3.5%, 24.9% and 0.06% among new PTB cases.[27] All above mentioned studies were conducted in India while Arega et al in the study conducted in Ethiopia found that the prevalence of rifampicin resistant TB among new and previously treated was 7.6 and 27.4% respectively.[28]

In a study done by Mehta et al sputum and blood samples were collected from 304 adult patients in rural Andhra Pradesh. Rifampin resistance was assessed by Xpert MTB/RIF (Xpert), and diabetes status was based on self-report. They found that in patients with confirmed TB

(n=194), diabetes was associated with 3.0-fold higher risk of rifampin resistance (95 % CI 1.3–6.7). They concluded that increased risk of rifampin resistance in patients with diabetes highlights the need for integrated diabetes surveillance in TB programs, particularly in settings undergoing the epidemiological transition.

However, Mi et al did a cross-sectional and retrospective study involving record reviews.[29] There were 621 patients with culture-positive TB, of whom 187 (30%) had previously known or new type 2 diabetes. 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. They suggested that further prospective studies are needed to confirm these findings.

Song et al assessed the clinical characteristics, drug-resistance profile, and increased risk of resistance among TB-DM patients across China from 2004 to 2017.[30] They found that out of 7223 newly diagnosed TB patients, 426 (5.90%) were TB-DM cases. TB-DM cases were more likely to be older, accompanied by higher body mass index (BMI) than TB-no DM cases (refers to TB patients without diabetes). The rates of DRTB (21.83% vs 16.96%), polydrug resistant TB (PDR-TB, 6.10% versus 3.80%), isoniazid (INH) +streptomycin (SM)-resistant TB (4.93% versus 3.13%), and SM-resistant TB (16.20% versus 11.7%) among TB-DM group were higher than TB-no DM group, $p<0.05$. DM was significantly associated with any DR-TB compared with pan-susceptible TB patients ($p<0.05$). They concluded that TB-DM groups had a higher proportion of drug resistance than TB groups and diabetes was identified as a risk factor of total DR, PDR, SM resistance and INH+SM resistance among newly diagnosed TB cases.[31] However, previous researches had produced inconsistent results on the association between increased prevalence or risk of primary DR-TB with diabetes.[32,33]

CONCLUSION

Few previous published studies have examined the risk factors and primary drug-resistant profile of TB-DM cases. Our study indicated that TB-DM patients had a higher proportion of drug resistance (20%) compared to the primary rifampicin resistant cases seen among non diabetics, given in the other studies conducted in India and outside. So, DM should be considered as an independent risk factor for MDR-TB, especially for primary MDR-TB. In patients with DM-TB co-morbidity, effective measures need to be implemented to promote early diagnosis of MDR-TB followed by intensive treatment and follow-up.

REFERENCES

1. Global tuberculosis report 2019. World Health Organization, Geneva. 2019. Available at: https://www.who.int/tb/publications/global_report/en/. Last accessed 10 May 2021.
2. Maher D. The natural history of Mycobacterium tuberculosis infection in adults. In: Schaaf HS, Zumla A, editors. Tuberculosis: A Comprehensive Clinical Reference. 1st Edition Elsevier Health Sci. 2009;129-32.
3. Restrepo BI. Convergence of the tuberculosis and diabetes epidemics: renewal of old acquaintances. Clin Infect Dis. 2007;45(4):436-8.
4. Global tuberculosis report 2017. World Health Organization, Geneva. 2017. Available at: https://www.who.int/tb/publications/global_report/gtbr2017_main_text.pdf?ua=1. Last accessed 10 May 2021.
5. Singh R, Gothi D, Joshi J M. Multidrug resistant tuberculosis: Role of previous treatment with second line therapy on treatment outcome. Lung India. 2007;24:54-7.
6. Aragon J., Litonjua A., Tupasi T., Quela I. Prevalence of type 2 diabetes among multi-drug resistant tuberculosis (MDR-TB) patients seen in Makati Medical Center under the directly observed therapy plus (DOTS PLUS) program. Philippine Journal of Internal Medicine. 2003;41:7-10.
7. Williams R, Colagiuri S, Chan J, Gregg EW, Ke C, Lim LL, et al. IDF Atlas 9th Edition 2019. International Diabetes Federation 2019. Available at https://www.diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf. Last accessed 10 May 2021.
8. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R, et al. Prevalence of diabetes and pre-diabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian Council of Medical Research-INdia DIABetes (ICMR-INDIAB) study. Diabetologia. 2011;54(12):3022-7.
9. Vellalacheruvu BN, Bekur R, Mapakshi H. Effect of type 2 diabetes mellitus on presentation and treatment response of sputum positive pulmonary tuberculosis. Int J Sci R Pub. 2015;5(9).
10. Fisher-Hoch SP, Whitney E, McCormick JB, Crespo G, Smith B, Rahbar MH, et al. Type 2 diabetes and multidrug-resistant tuberculosis. Scand J Infect Dis. 2008;40(11-12):888-93.
11. Tuberculosis and Diabetes. World Health Organization, Geneva. 2016. Available at: http://www.who.int/tb/publications/global_report/e. Last accessed 10 May 2021.
12. Nissapatorn V, Kuppusamy I, Jamaiah I, Fong MY, Rohela M, Anuar AK. Tuberculosis in diabetic patients: a clinical perspective. Southeast Asian J Trop Med Public Health. 2005;36(4):213-20.
13. Ponce-De-Leon A, Garcia-Garcia Md Mde L, Garcia-Sancho MC, Gomez-Perez FJ, Valdespino-

Gomez JL, Olaiz-Fernandez G, et al. Tuberculosis and diabetes in southern Mexico. Diabetes Care. 2004;27(7):1584-90.

14. Manjareeka M, Palo SK, Swain S, Pati S, Pati S. Diabetes Mellitus among Newly Diagnosed Tuberculosis Patients in Tribal Odisha: An Exploratory Study. J Clin Diagn Res. 2016;10(10):LC06-8.

15. Rawat J, Sindhwani G, Biswas D. Effect of age on presentation with diabetes: Comparison of non diabetic patients with new smear-positive pulmonary tuberculosis patients. Lung India. 2011;28:187-90.

16. Khalil N, Ramadan RA. Study of risk factors for pulmonary tuberculosis among diabetes mellitus patients. Egypt J Chest Dis Tuberc. 2016;65:817-23.

17. Comstock GW. Epidemiology of tuberculosis. Am Rev Respir Dis. 1982;125(3P2):8-15.

18. Magee MJ, Bloss E, Shin SS, Contreras C, Huaman H, Ticona J, et al. Clinical characteristics, drug resistance, and treatment outcomes among tuberculosis patients with diabetes in Peru. Int J Infect Dis. 2013;17:404-12.

19. Kikvidze M, Mikiashvili L. Impact of diabetes mellitus on drug-resistant tuberculosis treatment outcomes in Georgia - Cohort study. Eur Respir J. 2013;42(57):2826.

20. Singla R, Khan N, Al-Sharif N, Ai-Sayegh MO, Shaikh MA, Osman MM. Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. Int J Tuberc Lung Dis. 2006;10(1):74-9.

21. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, Ottenhoff TH, et al. The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Clin Infect Dis. 2007;45(4):428-35.

22. Baghaei P, Tabarsi P, Moniri A, Marjani M, Velayati A. Impact of diabetes mellitus on tuberculosis drug resistance in new cases of tuberculosis. Int J Mycobact. 2015;4:128.

23. Chang JT, Dou HY, Yen CL, Wu YH, Huang RM, Lin HJ, et al. Effect of Type 2 Diabetes Mellitus on the Clinical Severity and Treatment Outcome in Patients with Pulmonary Tuberculosis: A Potential Role in the Emergence of Multidrug-resistance. J Formos Med Assoc. 2011;110:372-81.

24. Sinha S, Gupta K, Kohli M, Myneedu VP, Pandey RM, Singh PP. Prevalence of Multi-Drug Resistant Tuberculosis among New Culture- Positive Pulmonary Tuberculosis Patients in Tertiary Care Center of North India. J Tuberc Ther. 2018; 3(2):116.

25. Gautam PB, Mishra A, Kumar S. Prevalence of rifampicin resistant mycobacterium tuberculosis and associated factors among presumptive tuberculosis patients in eastern Uttar Pradesh: a cross sectional study. Int J Community Med Public Health. 2018;5(6):2271-6.

26. Charan J, Tank N, Reljic T, Singh S, Bhardwaj P, Kaur R, et al. Prevalence of multidrug resistance tuberculosis in adult patients in India: A systematic review and meta-analysis. J Family Med Prim Care. 2019;8:3191-201.

27. Lohiya A, Suliankatchi Abdulkader R, Rath RS, Jacob O, Chinnakali P, Goel AD, et al. Prevalence and patterns of drug resistant pulmonary tuberculosis in India-A systematic review and meta-analysis. J Glob Antimicrob Resist. 2020;22:308-16.

28. Arega B, Menbere F, Getachew Y. Prevalence of rifampicin resistant Mycobacterium tuberculosis among presumptive tuberculosis patients in selected governmental hospitals in Addis Ababa, Ethiopia. BMC Infect Dis. 2019;19:307.

29. Saurabh M, Yu EA, Fazil AS, Wesley B, John K. Rifampin resistance and diabetes mellitus in a cross-sectional study of adult patients in rural South India. BMC Infectious Diseases. 2015;15:451.

30. Mi F, Jiang G, Du J, Li L, Yue W, Harries AD et al. Is resistance to anti-tuberculosis drugs associated with type 2 diabetes mellitus? A register review in Beijing, China. Global Health Action. 2014;(7)1:24022.

31. Wanmei S, Yang S, Jinyue L, Ningning T, Yao L, Qianyun Z et al. Primary drug resistance among tuberculosis patients with diabetes mellitus: a retrospective study among 7223 cases in China. Infection and Drug Resistance. 2019;12:2397-407.

32. Perez-Navarro LM, Restrepo BI, Fuentes-Dominguez FJ. The effect size of type 2 diabetes mellitus on tuberculosis drug resistance and adverse treatment outcomes. Tuberculosis. 2017;103:83-91.

33. Liu Q, Li W, Xue M. Diabetes mellitus and the risk of multidrug resistant tuberculosis : a meta-analysis. Sci Rep. 2017;7(1):1090.