

## TO EVALUATE PREVALENCE OF DIABETES AND HIV IN NEWLY-DIAGNOSED MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS ADMITTED FOR PRETREATMENT EVALUATION IN DOTS PLUS CENTRE, THANJAVUR

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### ABSTRACT

#### BACKGROUND

More than 9 million people fall sick with tuberculosis every year in the world. People with weak immune system as a result of disease like diabetes and HIV are at high risk of developing MDR-TB infection. Proper monitoring and evaluation are needed to control MDR-TB in HIV and diabetes patients.

The aim of the study is to find the prevalence of diabetes and HIV among MDR-TB patients admitted for pretreatment evaluation in Dots Plus Centre, Thanjavur Medical College, Tamilnadu.

#### MATERIALS AND METHODS

The medical records with datas of 96 patients with MDR-TB who are having diabetes and HIV infection were examined. These cases were diagnosed and registered during January 2015 to December 2015. These patients had drug resistant to first line antituberculosis drugs (isoniazid and rifampicin). Duration of diabetes and HIV infection were noted. Age were categorised in to four groups- 20-29 years, 30-39 years, 40-49 years and above 50 years. The potential risk of association of diabetes, HIV or both with MDR-TB was evaluated by univariate conditional logistic regression model.

#### RESULTS

Out of 96 newly-diagnosed MDR-TB patients, prevalence of diabetes is about 34.37%, out of which (84.84%) were males and (15.15%) were females. Out of 34.37%, 38.54% of patients had controlled diabetes, 61.45% patients had uncontrolled diabetes. Nearly, more than half of diabetes patient falls under uncontrolled diabetes. More number of male patients had diabetes with MDR-TB when compared to females. 10.4% of these persons got oral hypoglycaemic agent and 6.3% got insulin as treatment for diabetes. 1% had irregular treatment with poor compliance. Prevalence of HIV is about 4.16% out of which 75% were males and 25% were females. One patient had both diabetes and HIV with MDR tuberculosis.

#### CONCLUSION

In our retrospective study, prevalence of diabetes in MDR-TB patients were more common in males than in females, most of them were in the age groups of 40 years and above, value shows statistical significance of <0.05. Association between diabetes and MDR-TB is the next challenge for global TB control. In patients with MDR-TB, it may be appropriate to actively screen for DM. Prevalence of HIV in MDR-TB patients was also more common in males. Association of HIV with MDR-TB need further evaluation since we had studied on less number of MDR-TB patients.

#### KEYWORDS

MDR Tuberculosis, HIV, Diabetes.

**HOW TO CITE THIS ARTICLE:** Kuppusamy N, Arjunan M, Nagarajan U, et al. To evaluate prevalence of diabetes and HIV in newly-diagnosed multidrug-resistant tuberculosis patients admitted for pretreatment evaluation in dots plus centre, Thanjavur. J. Evid. Based Med. Healthc. 2017; 4(60), 3619-3622. DOI: 10.18410/jebmh/2017/721

*Financial or Other, Competing Interest: None.*

*Submission 23-05-2017, Peer Review 30-05-2017, Acceptance 07-07-2017, Published 25-07-2017.*

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*DOI: 10.18410/jebmh/2017/721*



#### BACKGROUND

India is the country with highest TB burden in the world with estimated one-fifth of global TB cases worldwide. The WHO statistics for 2015 give an estimated incidence of 2.2 million cases of TB out of global incidence of 9.6 million. TB annually causes more deaths worldwide than HIV. About 2,80,000 people die from TB in India annually. Acquired immune deficiency syndrome, Tuberculosis (TB) and diabetes mellitus were individually one of top 10 cases of mortality all over the world.<sup>1</sup> There was an estimated 4,80,000 new cases of MDR-TB and an estimated 1,90,000 people died of MDR-

TB in 2014. MDR-TB (multidrug-resistant tuberculosis) is defined as isolates of mycobacterium tuberculosis resistant to isoniazid and rifampicin with or without resistance to other antituberculosis drugs. MDR-TB treatment is recommended for all patients with rifampicin-resistant tuberculosis regardless, if isoniazid resistance is confirmed or not. India has the second highest burden of MDR-TB in the world next to China. Drug resistance in tuberculosis is one of the major problems worldwide. The emergence and spread of MDR-TB is threatening to destabilise global TB control.<sup>2</sup> It is estimated that 0.5 million new cases of multidrug-resistant tuberculosis being diagnosed throughout the world. WHO estimate 60% cases are in India, China, Brazil and Russia. Globally in 2014, there was an estimated 3.3% of new cases and 20% of previously treated cases with MDR-TB. On an average, an estimated 9.7% of people with MDR-TB have XDR-TB. There are an estimated 99,000 annual incident cases of MDR-TB in India of which about 64,000 are from TB cases notified to the RNTCP. The proportion of MDR-TB is about 2.2% in new cases and 11-19% in retreatment cases. The incidence of MDR-TB is on the rise in India. MDR-TB poses therapeutic and infection control challenge with significantly higher rates of morbidity and mortality. To detect drug resistance, Drug Susceptibility Testing (DST) is done. DST is done on all retreatment cases at diagnosis, any sputum smear positive person during follow up, cases at diagnosis, contacts of confirmed MDR-TB cases and HIV associated TB. In 2013, 2,48,000 TB cases were tested for drug resistance and 35,400 were found to have either MDR/RR TB. However, only 20,700 received treatment. RNTCP is implementing DOTS PLUS facility in country to control MDR-TB burden since October 2007. Previous treatment for TB is the strongest risk factor for the development of MDR-TB. Naive patients are also at risk due to either spontaneous mutations or transmission of resistant strains. It is easy to prevent multidrug-resistant tuberculosis if the risk factors are known. By doing this study, we would be able to identify risk factors for MDR-TB, cause for failure, default and relapse identify at risk population, find methods to prevent transmission and control of MDR-TB.

**Age Wise Association of Diabetes in MDR-TB**

Karl Pearson’s coefficient correlation test.

**MATERIALS AND METHODS**

The medical records with datas of 96 patients with MDR-TB who are having diabetes and HIV infection were examined. These cases were diagnosed and registered during January 2015 to December 2015. These patients had drug resistant to first line antituberculosis drugs (isoniazid and rifampicin). Duration of diabetes and HIV infection were noted. Age were categorised into four groups- 20-29 years, 30-39 years, 40-49 years and above 50 years. The following signs are evaluated as treatment failure in MDR-TB. They include persistent positive smears or culture first month 8-10 of treatment, progressive extensive and bilateral lung disease on chest x-ray, overall deteriorating clinical conditions that usually include weight loss and respiratory insufficiency. Mode of TB diagnosis, treatment history in detail, initiation of ATT at private/DOTS centre, default statics during the course of treatment were assessed. Reason for default was noted. About the diabetes, duration level and mode of treatment status was noted. HbA1c level and admission RBS <200, >200 was used to classify the level of control of diabetes mellitus. About HIV, period of diagnosis, duration, level of control, CD4 level and treatment statics was assessed. Results of bioclinical analysis of blood for sugar, sputum AFB smear, sputum CBNAAT for MDR-TB diagnosis, AFB culture and sensitivity pattern were noted. Reports of chest x-ray and CT chest were analysed. Any associated immunological investigations were noted. The potential risk of association of diabetes, HIV or both with MDR-TB was evaluated by univariate conditional logistic regression model.

**RESULTS**

Out of 96 newly-diagnosed MDR-TB patient, the prevalence of diabetes and HIV were noted. The results were statistically evaluated. The univariate conditional logistic regression model was used. Karl Pearson’s coefficient correlation that was also used to conclude the incidence of DM, HIV in MDR-TB. The results are shown in table.

q10a-Comorbidi-ties, Diabetes (Duration of DM)	Age											Correlation Value	Statistical Inference	
	20 to 30 years		31 to 40 years		41 to 50 years		51 to 60 years		61 years and above		Total			
	(n=15)	(100%)	(n=21)	(100%)	(n=31)	(100%)	(n=18)	(100%)	(n=11)	(100%)	(n=96)			(100%)
Below 1 year	0	0.0%	3	14.3%	3	9.7%	1	5.6%	2	18.2%	9	9.4%	-0.233 (*)	0.022 <0.05 Significant
2 to 5 years	1	6.7%	6	28.6%	9	29.0%	4	22.2%	3	27.3%	23	24.0%		
6 to 10 years	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	9.1%	1	1.0%		
NA	14	93.3%	12	57.1%	19	61.3%	13	72.2%	5	45.5%	63	65.6%		

**Table 1**

\*Correlation is significant at the 0.05 level.

**MDR-TB with Control Level of Diabetes**

q11a-Comorbidities, Diabetes (Level of Control)	Age												Correlation Value	Statistical Inference
	20 to 30 years		31 to 40 years		41 to 50 years		51 to 60 years		61 years and above		Total			
	(n=15)	(100%)	(n=21)	(100%)	(n=31)	(100%)	(n=18)	(100%)	(n=11)	(100%)	(n=96)	(100%)		
Controlled <200	5	33.33%	9	42.85%	12	38.70%	5	27.77%	6	54.54%	37	38.54%	-0.234 (*)	0.022 <0.05 Significant
Uncontrolled >200	10	66.66%	12	57.14%	19	61.29%	13	72.22%	5	45.45%	59	61.45%		

**Table 2**

\*Correlation is significant at the 0.05 level.

**Treatment Status in Diabetes with MDR-TB**

q12a-Comorbidities, Diabetes (Treatment Status)	Age												Correlation Value	Statistical Inference
	20 to 30 years		31 to 40 years		41 to 50 years		51 to 60 years		61 years and above		Total			
	(n=15)	(100%)	(n=21)	(100%)	(n=31)	(100%)	(n=18)	(100%)	(n=11)	(100%)	(n=96)	(100%)		
Insulin	11	73.33%	11	52.38%	13	41.93%	10	55.55%	4	36.36%	49	51.04%	-0.233 (*)	0.022 <0.05 Significant
Insulin basal	0	0.0%	0	0.0%	2	6.5%	0	0.0%	0	0.0%	2	2.08%		
Insulin, OHA	0	0.0%	2	9.52%	1	3.2%	0	0.0%	1	9.09%	4	4.16%		
Irregular treatment with poor compliance	0	0.0%	0	0.0%	0	0.0%	1	5.6%	0	0.0%	1	1.0%		
Irregular (metformin)	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	9.1%	1	1.0%		
Overall irregular treatment	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	9.1%	1	1.0%		
OHA	4	26.66%	7	33.33%	10	32.25%	5	27.77%	4	36.36%	30	31.25%		
OHA (irregular treatment)	0	0.0%	1	4.8%	3	9.7%	2	11.1%	1	9.1%	7	7.29%		
OHA, insulin (irregular)	0	0.0%	0	0.0%	1	3.2%	0	0.0%	0	0.0%	1	1.0%		

**Table 3**

\*Correlation is significant at the 0.05 level.

q14a-comorbidities, HIV infection (duration)	Correlation value	Statistical inference
q16a-comorbidities, HIV infection (treatment status)	1.000 (**)	0.000<0.01 Significant

\*\*Correlation is significant at the 0.01 level.

Out of 96 newly-diagnosed MDR-TB patients, prevalence of diabetes is about 34.37%, out of which (84.84%) were males and (15.15%) were females. Diabetes has statistically significant association with MDR-TB. Out of 34.37%, 38.54% of patients had controlled diabetes, 61.45% patients had uncontrolled diabetes. Nearly, more than half of diabetes patient falls under uncontrolled diabetes. More number of male patients had diabetes with MDR-TB when compared to females. 10.4% of these persons got oral hypoglycaemic agent and 6.3% got insulin as treatment for diabetes. 1% had irregular treatment with poor complaints. Prevalence of HIV is about 4.16% out of which 75% were males and 25% were females. One patient had both diabetes and HIV with MDR tuberculosis.

**DISCUSSION**

Our study shows that diabetes and HIV are prevalent among MDR-TB patients. 34-37% showed diabetes mellitus along with TB. DM has been associated with a 3-fold risk of TB and it is hypothesised that TB may also increase the risk of developing DM. In comorbidity presentation of TB and DM, both disease outcomes are reported to worsen. Diabetes predispose to TB with some evidence that TB may also predispose to DM.<sup>3,4</sup> The link between TB and diabetes will pose a serious threat to public health. Our study results are similar to a study done by Fiona Young et al in Sub-Saharan Africa, which correlate with comorbidity between infections and chronic disease like TB, DM, HIV and metabolic syndrome.<sup>5</sup> Work done by Karachunskii et al shows that TB

patients develop changes in carbohydrate metabolism such as insulin deficiency and persistent hyperglycaemia.<sup>6</sup> A few studies shows there is increased level of IGT and diabetes in MDR-TB patients.<sup>7,8</sup> ATT medications like isoniazid have been shown to have hyperglycaemic effect and that maybe one of the reasons for diabetes in tuberculosis. Insulin resistance maybe produced by IL-6, TNF-2, which modulate the response to TB infections.<sup>9</sup> A study conducted in Texas border found that MDR-TB was associated with DM in a ratio of 2:1.<sup>10</sup> MDR-TB patients are thought to have impaired gastrointestinal uptake. They also have difference in metabolism and excretion of drugs. This poor intake of anti-TB drugs by DM patients could be a possible mechanism that leads to development of drug resistance. Diabetes may affect TB treatment outcome by delaying time to microbiological response.<sup>11,12</sup> In our study, prevalence of HIV is about 4.16%. One patient has both diabetics and HIV. A large proportion of the incident of TB seen in Africa is attributable to spread of HIV. In 2004, 34% of newly-diagnosed TB cases in Africa were estimated to be infected with HIV. The association between MDR-TB and HIV was described by other studies.<sup>13,14</sup> A study conducted in Portugal in 2009, HIV testing was performed on 87% of all TB patients and HIV coinfection prevalence was 15%.<sup>15</sup> The HIV-TB co-infected persons are 21-34 times more likely to develop active TB disease, than the persons without HIV.<sup>16</sup> The HIV infection can occur in person with latent TB and also HIV infected person acquire new TB infection.<sup>17</sup> A study done by Marta Gomes et al shows they did not find a significant association between HIV coinfection and drug resistance. More information about characteristic of HIV infected patients, namely mean of CD-4 count, antiretroviral therapy is needed to understand this result. The treatment of HIV-TB coinfection includes the concomitant administration of both Antituberculosis Therapy (ATT) and Antiretroviral Therapy (ART). Patient faces pill burden and overlapping toxic effects. This burden may lead to irregular treatment and drug resistance.

## CONCLUSION

In our retrospective study, prevalence of diabetes in MDR-TB patients was more common in males than in females, most of them were in the age groups 40 years and above. These values shows statistical significance of <0.05. Association between diabetes and MDR-TB, which is a great challenge for global TB control. It should be further explored. In patients with MDR-TB, it may be appropriate to actively screen for DM. Prevalence of HIV in MDR-TB patients was also more common in males. Association of HIV with MDR-TB need further evaluation since we had studied on less number of MDR-TB patients. Knowledge about coinfection of diabetes and HIV in TB permits identification of patients with a predisposition to drug resistance.

## REFERENCES

- [1] Sekar R, Mythreyee M. Tuberculosis HIV/AIDS and diabetes- is it time to think together? *Journal of Medical Microbiology & Diagnosis* 2012;1(1):2-4.
- [2] Gomes M, Correia A, Mendonca D, et al. Risk factors for drug-resistant tuberculosis. *Journal of Tuberculosis Research* 2014;2:111-118.
- [3] Jeon CY, Murray MB. Diabetes mellitus increase the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* 2008;5(7):152.
- [4] Stevenson CR, Forouhi NG, Roglic G, et al. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. *BMC Public Health* 2007;7:234.
- [5] Young F, Critchley JA, Johnstone LK, et al. A review of comorbidity between infectious and chronic disease in Sub-Saharan Africa: TB and diabetes, mellitus, HIV and metabolic syndrome, and the impact of globalization. *Global Health* 2009;5:9.
- [6] Karachunskii MA, Beglarian NR, Iakovleva OB. Clinical aspects of pulmonary tuberculosis in patients with borderline disorder of carbohydrate metabolism. *Probl Tuberk* 1993;(5):16-17.
- [7] Mugusi F, Swai AB, Albert KG, et al. Increased prevalence of diabetes mellitus in patients with pulmonary tuberculosis in Tanzania. *Tubercle* 1990;71(4):271-276.
- [8] Oluboya PO, Erasmus RT. The significance of glucose intolerance in pulmonary tuberculosis. *Tubercle* 1990;71(2):135-138.
- [9] Fisher-Hoch SP, Whitney E, McCormick JB, et al. Type 2 diabetes and multidrug-resistant tuberculosis. *Scand J Infect Dis* 2008;40(11-12):888-893.
- [10] Nijland HM, Ruslami R, Stalenhoef JE, et al. Exposure of rifampicin is strongly reduced in patients with tuberculosis and type 2 diabetes. *Clin Infect Dis* 2006;43(7):848-854.
- [11] Dooley KE, Chaisson RE. Tuberculosis and diabetic mellitus: convergence of two epidemics. *Lancet Infect Dis* 2009;9(12):737-746.
- [12] Oluboyo PO, Erasmes RT. The significance of glucose intolerance in pulmonary tuberculosis. *Tubercle* 1990;71(2):135-138.
- [13] Flora MS, Amin MN, Karim MR, et al. Risk factors of multidrug-resistant tuberculosis in Bangladeshi population: a case control study. *Bangladesh Medical Research Council Bulletin* 2013;39(1):34-41.
- [14] Wang K, Chen S, Wang X, et al. Factors contributing to the high prevalence of multidrug-resistant tuberculosis among previously treated patients: a case-control study from China. *Microb Drug Resist* 2014;20(4):294-300.
- [15] World Health Organization. Multidrug and Extensively Drug Resistant TB (M/XDR-TB)-2010. Global report on surveillance and response. Geneva 2010.
- [16] WHO TB/HIV facts World Health Organization 2011.
- [17] Chaisson RE, Martinson NA. Tuberculosis in Africa-combating an HIV-driven crisis. *N Engl J Med* 2008;358(11):1089-1092.