Proportion of Rifampicin Resistance in Sputum Smear Positive Pulmonary Tuberculosis with Diabetes Mellitus in Urban Bengaluru - A Cross-Sectional Study

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ABSTRACT

BACKGROUND

Pulmonary tuberculosis (PTB) still remains a global public health problem. Diabetes along with poor glycaemic control leads to an immune compromised state. Type 2 diabetes (DM) is a strong risk factor for tuberculosis (TB) and is associated with a slower response to TB treatment and a higher mortality rate. Objective of the study was to determine the prevalence of rifampicin resistance in pulmonary tuberculosis in patients with DM.

METHODS

The study was conducted in General Medicine Department, Dr. B.R. Ambedkar Medical College, Bengaluru, Karnataka, from July 2018 to December 2019. Sputum was collected from a total of 100 patients who were sputum smear positive for acid fast bacilli (AFB). Sample was collected and was subjected to GeneXpert testing for the evaluation of resistance against rifampicin.

RESULTS

In our study the incidence of rifampicin resistance was 45.16 % in diabetes and 5.79 % in non-diabetes which was statistically significant (χ^2-1.1; p-0.01) between rifampicin resistance and diabetic patients' status with active TB in South Karnataka, India. This result supports previous research showing a higher multidrug-resistant tuberculosis risk in tuberculosis & diabetes patients relative to those with no diabetes. Additionally, correlation of other findings between type 2 diabetes & multidrug-resistant tuberculosis as well as delayed time to sputum smear conversion were confirmed.

CONCLUSIONS

The results showed correlation between diabetes & rifampicin resistance and probably suggest the necessity of integrated diabetes and tuberculosis surveillance programs in South Karnataka, India.

KEYWORDS

Rifampicin, Tuberculosis, Diabetes Mellitus

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BACKGROUND

Pulmonary tuberculosis caused by *Mycobacterium tuberculosis* (MTB) still remains a considerable global public health concern, mainly affecting vulnerable population.[1] India, the world's second most populous country, accounts for a quarter of the world's annual incidence of TB. Every year around two million people develop TB in India and 300,000 die of TB.[2] India accounts for 25 % of the global burden of tuberculosis and 29 % of global TB mortality.[3] India is the highest TB burden country in the world having an estimated incidence of 26.9 lakh cases in 2019 (WHO).[4] India has the highest number of patients with tuberculosis and multi drug-resistant tuberculosis in the world.

An association between HIV and TB is already known.[5] But similar association may exist between DM and TB. Diabetic patients are at a higher risk of developing new as well as reactivation of old TB disease.[6] The synergistic interactions between tuberculosis & diabetes are recognized widely.[7] Findings among TB subjects reported co-relations between diabetes & unfavourable consequences, which includes mortality, failure & amp relapse in treatment of TB.[8] Furthermore, diabetes is linked with threefold increased active tuberculosis risk, as per a systematic assessment.[9] Patients with this dual disease may be more contagious at diagnosis, may remain infectious for longer period and uncontrolled and undiagnosed diabetes may lead to poor TB treatment outcome.[10,11]

Available evidence and modelling studies indicate that nearly 20 % of all TB cases in India also suffer from DM. Diabetes triples the risk of TB. Diabetes can worsen the clinical course of TB, and TB can worsen blood sugar control in people with diabetes. The National TB Elimination Programme (erstwhile Revised National TB Control Programme) and the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) have jointly developed a 'National Framework for Joint TB-Diabetes Collaborative Activities' in 2017. The framework aims to reduce morbidity and mortality due to TB and diabetes through prevention, bi-directional screening for early diagnosis and prompt management of TB and diabetes. Accordingly, all TB patients need to be screened for diabetes by testing for blood sugar, and diabetic patients attending diabetic clinics should be asked for symptoms of tuberculosis during each visit.[4]

Globally, drug resistance to tuberculosis is a challenge to improve control of tuberculosis 2013 statistics indicate 480,000 cases of MDR-TB (multidrug-resistant tuberculosis). More than fifty per cent of MDR-TB cases were recorded in the year 2013 in India, China, & the Russian Federation. In 2015, the World Health Organization (WHO) estimated 480,000 incident of multidrug resistant TB (MDR-TB; resistance of both isoniazid and rifampicin) cases globally. With an estimated 79,000 MDR-TB cases, India along with the Russian Federation and South Africa accounted for 45 % of the total notified combined MDR-TB and rifampicin-resistant (RR-TB) cases in 2015.[4]

The treatment success rate of multi drug-resistant tuberculosis worldwide is forty eight percent which is considerably lower compared to that of new cases of tuberculosis which is of eighty six percent.[12] Preliminary evidence from research on pharmacokinetics indicates that the association between tuberculosis drug resistance & diabetes is biologically plausible. One analysis revealed reduced rifampicin exposure in subjects suffering from co infections with tuberculosis - diabetes relative to subjects with tuberculosis.[13] One more research showed low absorption of anti-tuberculosis treatment was linked with greater resistance to drugs.[14] Furthermore, literature study evidenced among subjects affected with tuberculosis & diabetes mellitus both, diabetes is stated to be linked to outcomes of poor tuberculosis treatment.[15,16]

Prevention and control of drug resistance is therefore strongly recommended by the WHO through implementation of routine surveillance systems driven by systematic DST. As reported by Stephanie Law et al. in their study published in The Lancet, if tuberculosis management practices across sectors in India remain unchanged over the next 20 years, we estimated a 47 % increase in the incidence of isoniazid resistance, a 152 % increase in multi drug-resistant tuberculosis incidence, a 242 % increase in prevalent untreated multi drug-resistant tuberculosis, and a 275 % increase in the risk of multi drug-resistant tuberculosis infection. By 2032, an estimated 85 % of multi drug-resistant tuberculosis will be primary multi drug-resistant tuberculosis compared with only 15 % in 2012.[17]

There are many challenges for TB control in India. Prompt, accurate diagnosis and effective treatment of TB are not only essential for good patient care, but they are also the key elements in the public health response to tuberculosis and the cornerstone of any initiative for tuberculosis control. The private sector holds a factual predominance of health care service delivery in India. There is very little information about the TB patient from the private sector available to the programme and little is known about their quality of treatment, including treatment outcomes. Engaging the private sector effectively is the single most important intervention required for India to achieve the overall goal of universal access to quality TB care.[2]

Key research gaps included the determination of the clinical significance of possible effects of diabetes on drug resistance to TB, especially in epidemiological transition settings.[18] During the shift from infectious to chronic illnesses, some geographical areas might still have a higher TB prevalence & at the same time a growing incidence of diabetes.

As prevalence of both TB and DM is increasing in India, this association of PTB and DM may prove a threat to TB control program. Various studies have been carried out to determine the prevalence of DM in TB patients, but only limited studies are available on prevalence of TB in DM cases. Hence this study was undertaken to detect prevalence of pulmonary tuberculosis in patients with DM and lower respiratory tract infection (LRTI).

Our primary goal was therefore to evaluate the link between DM & rifampicin resistance in subjects suffering from active tuberculosis in South Karnataka.

METHODS

This cross-sectional study was carried out in General Medicine Department, Dr. B. R. Ambedkar Medical College, Bengaluru, Karnataka from July 2018 to December 2019 after obtaining Institutional ethics committee permission. A total of 100 study subjects diagnosed with sputum positive pulmonary TB were selected for study purpose irrespective of any gender, duration of diabetes, antidiabetic treatment. The demographic details viz. age, gender, and patient history of diabetes, its duration, treatment were collected. Informed written consent was taken from patients about the participation in present study.

Sample Size and Sampling

Sample size was calculated using estimation technique. The prevalence of rifampicin resistance among pulmonary TB diabetics was 29.17 %,[19] with 95 % confidence interval and absolute error of 10 %, the sample size calculated as 79 and inflated to 100. We used simple random sampling for selection of cases.

Study Protocol

The sputum was collected from total of 100 patients who were admitted and on outpatient basis with sputum smear positive for AFB were included in the study. Sample was collected and was subjected to GeneXpert testing for the evaluation of resistance against rifampicin. All processing was carried out in Bio Safety Cabinet (BSC) class 2 and level 2 bio safety practices were followed. Two sputum specimens of minimum 2 ml quantity were collected in sterile container from each patient of which one was early morning specimen. Direct microscopy by Ziehl Neelsen (ZN) staining was carried out on both the specimens. Early morning specimen was tested by Xpert MTB/RIF assay (Xpert assay). These patients were divided into two groups as diabetes and non-diabetes based on history and blood investigations according to ADA criteria.

Those who were diagnosed with diabetes, a detailed history of duration of diabetes, anti-diabetic treatment was taken. All these subjects were examined for the presence of diabetic complications. Among the two groups of diabetes and non-diabetes further statistics was collected for presence and absence of rifampicin resistance. On confirmation of resistance to rifampicin further the type of anti-diabetic treatment was compared with presence of rifampicin resistance. Ethical clearance from institution ethical committee was taken.

Statistical Analysis

The data was recorded in Microsoft excel sheet & amp was evaluated with the use of software SPSS (Statistical Package for Social Sciences) version 22. The representation of categorical data was in the frequency & percentage form. Chi-square test was applied to test the importance for qualitative data. Continuous data was represented as mean & standard deviation. P - value & < 0.05 was deemed as significant.

RESULTS

In our study, majority of the subjects diagnosed with TB & DM were in the range of 21 to 40 years of age group (39 %) trailed by 41 to 60 years (35 %), & 21 % of study subjects fallen in less than 20 years of age. The female preponderance (57 %) was observed among the study subjects as compared to males (43 %). (Table 1)

	Characteristics	No. of Cases	Percentage
Age in Years	<20	21	21.00
	21-40	39	39.00
	41-60	35	35.00
	>60	05	05.00
Gender	Male	43	43.00
	Female	57	57.00

Table 1. Demographic Profile of Cases Enrolled in the Study

The mean weight of the diabetic and non-diabetic study subjects was 51.06 ± 11.97 and 46.09 ± 12.11 respectively (Figure 1). The results of rifampicin resistance among study subjects diagnosed with diabetes mellitus revealed 31 out of 100 subjects were diabetic and 69 out of 100 were non-diabetic. Cross-tabulation results depicted that out of 31 diabetic patients, 10 were rifampicin resistant and 21 were non-resistant. Chi-square statistical analysis revealed considerable correlation between rifampicin resistance & diabetic status of subjects (χ^2-1.1; p-0.04) (Table 2).

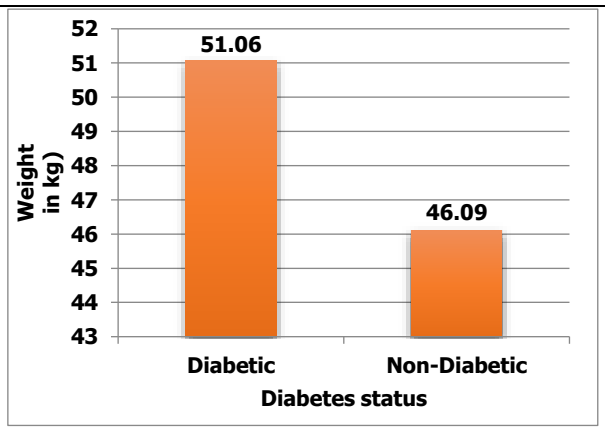

Figure 1. Mean Weight Distribution of Study Subjects Based on Diabetic Status

Diabetes Status		Rifampicin Resistance: Resistance	Rifampicin Resistance: Non-Resistance	Total
Diabetic	Count	14	17	31
	%	45.16	54.83	100.00
Non-diabetic	Count	4	65	69
	%	5.79	94.2	100.00
Total	Count	18	82	100
	%	18.00	82.00	100.00
		Chi-square value-3.916 p-value-0.01		

Table 2. Diabetic Status of Patients and Rifampicin Resistance

The results on association of anti-diabetic drugs and rifampicin resistance revealed that, out of 100 study subjects, 20 were on OHA and 11 were on insulin. Out of 20 study subjects on OHA, 7 subjects were resistant to rifampicin. Similarly, out of 11 study subjects on insulin, 3 subjects were resistant to rifampicin. Chi-square test showed significant association between anti-diabetic drugs and rifampicin resistance (χ^2 - 0.009; P - 0.92). (Table 3)

Anti-Diabetic Drugs	Description	Rifampicin Resistance		Total
		Resistance	Non-Resistance	
OHA	Count	7	13	20
	%	35	65	100
Insulin	Count	3	8	11
	%	27.27	72.72	100
Total	Count	10	21	31
	%	32.25	67.74	100.00
		Chi - square value - 3.916 P – value - 0.01		

Table 3. Anti-Diabetic Drugs and Rifampicin Resistance

The results of association between complications and rifampicin resistance revealed significant association between neuropathy and rifampicin resistance (P < 0.001). 12 out of 20 patients (60 %) study subjects had neuropathy followed by 5 out of 20 patients had retinopathy, and 3 out of 20 patients had nephropathy (Table 4).

Complications	Description	Rifampicin Resistance		Fischer Exact Test Statistic
		Resistance	Non-Resistance	
Neuropathy	Present	9	3	P < 0.001
	Absent	1	18	
Retinopathy	Present	3	2	P = 0.29
	Absent	7	19	
Nephropathy	Present	2	1	P = 0.24
	Absent	8	20	

Table 4. Complications and Rifampicin Resistance

DISCUSSION

Diabetes mellitus has emerged as a growing worldwide chronic health condition, as a consequence of obesity, changing patterns of diet, physical inactivity and aging populations. The epidemic growth of DM has occurred in developing countries where TB is highly endemic. Diabetes can worsen the clinical course of TB, and TB can worsen glycaemic control in people with diabetes.

Individuals with both conditions thus require careful clinical management. Strategies are needed to ensure that optimal care is provided to patients with both diseases. TB must be diagnosed early in people with diabetes for eliminating disease and move to "End TB".

Altered pulmonary physiology and defects in the immune function of diabetics may account for the predisposition to infections in which intact cell-mediated immunity is necessary as in TB. Diabetes is listed as an indication for TB testing because of the increased incidence of TB in diabetics.[20] It is shown that 1.2 % of newly diagnosed diabetics present with the manifestation of TBI. The association of diabetes mellitus and drug resistant TB is noted in some studies. In one study 16 % of the diabetic subjects had resistant TB.[21,22] The risk factors for MDR TB are recorded as inadequate past anti-TB treatment and exposure to patients with MDR TB.[21] It has been shown that the relative risk of MDR TB is about 4.9 % if there is previous history of anti-TB treatment." A study done by Subhash et al. in CMC Vellore, reported that drug resistant TB was significantly associated with a past history of TB and with prolonged symptoms related to TB and pulmonary involvement (88 %).[23]

In this study, we showed that resistance to rifampicin was 54 % higher in patients with TB and DM compared with patients with TB who did not have DM. Despite of high burden of TB & amp; DM & the worse consequence of tuberculosis diabetes mellitus cases (referring to tuberculosis subjects suffering from diabetes), & TB cases that are drug-resistant, exploring co-relation between primary drug-resistant tuberculosis & diabetes for tuberculosis elimination is of great importance. We evaluated the clinical characteristics, drug-resistance profile, & risk factors of resistance among tuberculosis-diabetes mellitus subjects in Bangalore South Karnataka part of India.

A meta-analysis on eighty-four studies from thirty-one countries showed that the diabetes mellitus ratio among tuberculosis subjects in different countries having low & middle income ranged from 1.80 % to 45 %, with the majority ranging from ten to thirty percent.[24] It has been accepted widely that diabetes mellitus was a significant factor of risk of tuberculosis infection due to weakened immune system,[25-27] for e.g., diabetes mellitus subjects had a tendency to be associated with abnormally regulated cytokine responses to *Mycobacterium tuberculosis*.[28] We observed, majority of the patients diagnosed with tuberculosis-diabetes mellitus were in the range group of age 21- 40 years (39 %) followed by 41 to 60 years (35 %), and 21 % of study subjects fallen in less than 20 years of age. The female preponderance (57 %) was observed among the study subjects as compared to males (43 %). Our studies were consistent with former findings that age[29] was major risk factor for DM among TB cases.

In our study the incidence of rifampicin resistance was 45.16 % in diabetes and 5.79 % in non-diabetes which was statistically significant (χ^2-1.1; p-0.01) between rifampicin resistance and diabetic patients status with active TB in South Karnataka, India. This result supports previous research showing a higher multidrug-resistant tuberculosis risk in tuberculosis & amp; diabetes patients relative to those with no diabetes.[30] Additionally, other findings correlation between type 2 diabetes & multidrug-resistant tuberculosis[31] as well as delayed time to sputum smear conversion were confirmed.[32] Another study among subjects suffering from tuberculosis showed nearly fifty percent decreases in rifampicin & isoniazid plasma concentrations among diabetic subjects in comparison to subjects with no diabetes.[33] However, in contrast, other findings revealed no co-relation between tuberculosis drug resistance & diabetes, or changes in outcomes of treatment on basis of tuberculosis drug resistance & diabetes status.[34]

In our study, we found increased incidence of rifampicin resistance in diabetes particularly on insulin compared to oral anti-diabetic drugs it was statistically not significant (χ^2-0.009; P - 0.92) between anti-diabetic drugs viz. oral hypoglycaemic agents (OHA) & insulin and rifampicin resistance. Oral hypoglycaemic agents are contraindicated in severe TB but may be used with caution once the disease has settled.

Rifampicin is a potent hepatic enzyme-inducer. It accelerates several oral hypoglycaemic agents' metabolism, mainly biguanides & sulphonylureas & reduces their plasma levels. Hence, it might induce hyperglycaemia in diabetes subjects who makes use of these drugs. In non-diabetics, it enhances the glucose absorption in the intestine & might

simulate the diabetic symptoms.[35] Furthermore, rifampicin has been noted to interfere with glycaemic control due to its interactions with most oral antidiabetic drugs.[36]

Diabetes mellitus is associated strongly with microvascular damage viz. retinopathy, nephropathy and neuropathy.[37] Mitchison has indicated that rifampicin have unique sterilizing activity against slowly or intermittently metabolizing bacilli that remain after the initial phase of multidrug therapy & that low rifampicin concentrations results in inadequate mycobacterial suppression.[38] There was no significant association between the diabetic complication and rifampicin resistance.

CONCLUSIONS

Results of the present study showed correlation between diabetes & rifampicin resistance and probably suggest the necessity of integrated diabetes and tuberculosis surveillance programs in South Karnataka, India. Xpert MTB/RIF assay should be used as the initial diagnostic test for detection of tuberculosis as well as rifampicin resistance in diabetic patients by TB control programme. At the same time, all suspected TB-DM patients should also undergo TB culture for confirmation.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
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