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ASSOCIATION OF MULTI DRUG RESISTANT TUBERCULOSIS AND DIABETES MELLITUS PATIENTS IN A TERTIARY CARE HOSPITAL IN HARYANA

Pulmonary Medicine

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KEYWORDS

INTRODUCTION:

"Tuberculosis" once referred to as white plague[1] has existed for millennia and still remains a global menace. It affects the health of millions of people each year and in 2015 was one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease[2]. After more than 30 years of declines in reported tuberculosis cases and deaths, the mid-1980s and early 1990s saw a reversal of that trend in the United States. Between 1985 and 1992, reported cases of tuberculosis increased by 20 percent, from 22,201 in 1985 to 26,673 in 1992 (CDC 2000b).[3] The case rate per 100,000 population increased by more than 12 percent, from 9.3 in 1985 to 10.5 in 1992. The number of deaths rose from 1,752 in 1985 to 1,970 in 1989. Especially alarming was the increase in the number of more lethal multidrug-resistant strains of *mycobacterium tuberculosis,* the organism that causes the disease. In the early 1980s, about 0.5 percent of new tuberculosis cases were resistant to the two major drug treatments (Isoniazid and Rifampin).

Due to the complexity of chemotherapy regimens and the toxicity of alternative drugs, the treatment of patients infected with MDR TB strains is very challenging. Also, its treatment imposes huge financial burden on public health systems. However, compared to the cure rate of 96% in drug-susceptible TB, the cure rate of MDR TB reaches only 54%, making it known as a fatal disease[4,5]

However, the global epidemiological and demographic transitions also pose significant challenge to TB control programs by changing the relative importance of different risk factors for TB[6-7]. DM among MDR TB patients is a serious cause for concern, with a range of 10–23% of MDR TB patients having DM[8-11]. 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. The high prevalence of diabetes mellitus (DM) among multidrug resistant tuberculosis (MDR TB) patients is a serious concern.

In this study we attempt to find out the association of multi drug resistant tuberculosis and diabetes mellitus patients visiting the hospital in accordance with PMDT guidelines[12-14] we are including sputum negative retreatment cases, and even the drug sensitivity is being done by relatively new molecular (line probe assay).

MATERIALS AND METHOD:

The study was conducted in the department of Respiratory Medicine, MMIMS&R for period of two years (Oct 2014 - Sep 2016). 100 patients of PTB who were admitted in the Respiratory Medicine ward or reported to OPD and fulfilled the criteria of sputum positive pulmonary TB or Sputum negative retreatment cases were considered for the study.

INCLUSION CRITERIA (BASED ON PMDT GUIDELINES)

Criteria A –

1. All failures of new TB cases
2. Smear positive previously treated cases who remain smear positive at 4th month onwards
3. All pulmonary TB cases who are contacts of known MDR TB case

Criteria B – in addition to Criteria A:

1. All smear Positive previously treated pulmonary TB cases at diagnosis
2. Any smear Positive follow up result in new or previously treated cases

Criteria C – in addition to Criteria B

1. All smear Negative previously treated pulmonary TB cases at diagnosis.

Exclusion criteria

1. Presence of immunodeficiency conditions such as
a. HIV / AIDS.
b. Organ transplantation.
c. Malignancy
2. Extra-pulmonary TB and/or patients requiring surgical intervention.
3. Patients unwilling to take part in study.

STUDY SEQUENCE

Hundred patients who were smear positive or sputum negative retreatment cases were selected for the study. A written consent was obtained from each of these patients or their close relatives. These 100 patients were asked to submit their two sputum samples at least one morning and one spot sample. Up to 5 ml of sputum samples were collected in 50 ml falcon tubes marked A and B. The tubes were sealed with parafilm and labeled mentioning name of patient, sample A and sample B and date of collection on the specified rectangular space provided on the side of falcon tube using permanent marker pen. Annexure I was filled up mentioning the detail of patients. The duly labeled samples were individually packed in zip lock poly bags and placed in thermocol boxes after ice-gel packs below and above falcon tube packs following international guidelines for transportation of infectious substances. Annexure I was kept in separate poly bag inside the box. Then these samples are handed over to designated courier agency hired by District TB Officer, Ambala immediately so as to reach IRL Haryana Govt. Public Health Laboratory, Karnal within 72 hours of collection. These samples are received in the designated laboratory. Date of receipt was mentioned on the box and soon afterwards the samples are processed for evaluation of drug susceptibility pattern by MTB RIF/INH Line Probe Assay method. The tuberculosis patients admitted as inpatients or visited O.P.D. were subjected to thorough history taking, regarding clinical features and previous treatment. Patients who satisfied the inclusion criteria were included in the study with their consent. They were examined in detail and the study Performa was filled .Similar exercise was carried out with the outpatients, who were examined on their first visit and were regularly followed up. All the patients underwent HIV testing, chest x-ray imaging and sputum microscopy.

Classification of Sputum

Zn staining grading(RNTCP)	Reporting/ grading
>10 AFB per field after examination of 20 fields	Positive 3+
1-10 AFB per field after examination of 50 fields	Positive 2+

10-99 AFB per 100 fields	Positive 1+
1-9 AFB / 100 fields	Positive scanty
No AFB per 100 fields	negative

Sputum Samples Collection guidelines
Collection container: 50 ml sterile falcon tube
Storage Requirements: Room temperature 15-20 degrees Celcius refrigeration temperature.

Transport Conditions: Thermocol boxes with cold chain system maintaining temperature 15-20 degrees Celcius . If delay in transport of more than 1 hour expected, then samples were to be refrigerated.

Criteria for Rejection:
1. Salivary samples
2. Sample quantity less than 2 ml
3. New Pulmonary TB cases
4. Samples containing frank blood.

Instructions for patients:
1. Two sputum samples were to be collected in falcon tubes provided, both morning samples or at least one morning sample and one spot sample.
2. The patients were advised to rinse mouth and gargle with warm or fresh water prior to sputum collection.
3. No food particles should be there in the samples.
4. Approximately 5 ml of sample is needed for processing.
5. Collect fresh mucoid material (free of salivary secretions) produced by deep coughing with the patient being supervised as needed and deliver promptly to the laboratory.

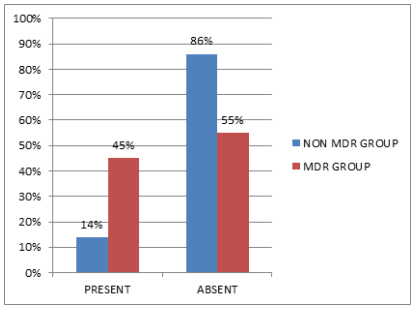
Statistical method:
Chi-square test was used to find the significance of frequency distribution of Diabetes Mellitus between MDR and non MDR groups. Student t test was used to find the significance of mean values of Diabetes Mellitus between both the groups. Microsoft Excel and Word were used to prepare the tables and graphs.

RESULTS
100 subjects with category II pulmonary TB patients were included in the study. Patients were divided into two groups of MDR (n-20) and Non MDR (n-80) as indicated by the drug susceptibility results.

Diabetes mellitus prevelance in the groups (Chi Square test)

	MDR		Non MDR		x^2	P - Value
Diabetes Mellitus	n	%	n	%		
Present	9	45%	11	14%	9.7656	.001778
Absent	11	55%	69	86%		
Total	20	100%	80	100%		

We observed statistically significant association between diabetes mellitus and MDR group (p=.0017). In MDR group 45 %(n=9) had diabetes mellitus where as in Non MDR group 14 % (n=11) had diabetes mellitus.

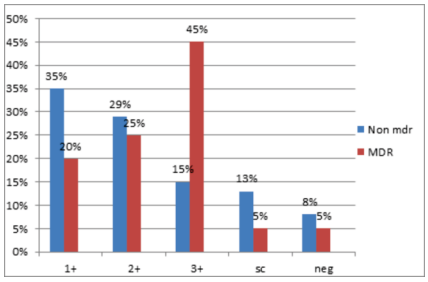


Diabetes Mellitus among MDR and non MDR groups

Bacillary Load in groups
In MDR group 45% patient were 3+ (n=9) as compared to 15 %(n=13) in Non MDR group. Bacillary load was 2+ in 25 % (n=5) in MDR group and 29 %(n=23) in Non MDR group. Bacillary load was 1+ in 20% in MDR group (n=4) and 35 % in Non MDR group (n=28). (n=1) that is 5 % was number of patient in MDR group with scanty bacillary load and n=6 that is 8% in Non MDR group. N=1 that is 5 % patient in MDR group had sputum negative where as n=6 that is 8% were sputum negative in Non MDR group.

Bacillary Load	MDR		Non MDR	
	n	%	n	%
1+	4	20%	28	35%
2+	5	25%	23	29%
3+	9	45%	13	15%
SC*	1	5%	10	13%
Neg**	1	5%	6	8%
Total	20	100%	80	100%

*SC-Scanty
**Neg-Negative



Bacillary load among MDR and non MDR groups
Signifying a stability of association, we found a significant and positive association between DM and MDR-TB. More nationwide studies on this topic would put more light, as our study has limitations.

DISCUSSION
This study was undertaken to determine the association of Diabetes Mellitus and MDR TB along with prevalence of MDR TB in patients visiting tertiary care hospital in Haryana. The patients were analyzed on basis of their bacillary load, clinical signs and symptoms and drug susceptibility.

Prevalence of MDR TB was found to be **20%** which was comparable to studies done by Sharma et al [15] at Delhi and another study done by Jain et al [16] at Lucknow which showed prevalence around 20.4 % and 19.8% in retreatment cases respectively. Table 1 shows MDR TB prevalence in different parts of country, in studies undertaken at different point of time.

Table 1: Prevalence of MDR TB in different parts of India

Location	Period Of Study	Prevalence of MDR TB %
Gujarat	1983-1986	30.2%
Delhi	1990-1991	33%
Haryana	1991-1995	49%
Delhi	1996 -1998	14%
Bangaluru	1999-2000	12.8%
Tamil Nadu	1999-2003	11.8%
Ahmadabad	2000-2001	37%
Gujarat	2002-2007	17.2%
Delhi	2006	47.1%

According to WHO report 2013 the incidence of MDR TB in new cases is 2.2% and in retreatment cases its 15% but there are some other studies like one done by Paramsivan et al[17] which was retrospective study of 2816 these patients were repeatedly treated and prevalence found was 53 % so we can deduce safely from data above from all parts of India that MDR prevalence varies from place to place and study to study, hence a large nationwide study is the need of the hour.

Many studies reported that subjects with diabetes were at three-fold higher risk of developing TB. In addition, studies that screened for DM among TB patients reported a wide range of DM prevalence among TB patients, ranging from 1.9% to as high as 35% [18,19]. A secondary data analysis on Indian population revealed that with an estimated 21 million adults with DM and 900,000 incident pulmonary tuberculosis (PTB) cases in 2000, 14.8% of the existing TB burden could be attributed to diabetes [20]. A recent nationwide study conducted in 2011 reported the prevalence rates of diabetes and pre-diabetes to be 10.4% and 8.3%, respectively, among the general population of Tamil Nadu, South India[21]

Therefore, it is necessary to consider the increasing prevalence of

diabetes since diabetes is associated with an increased risk of TB treatment failure and death during tuberculosis treatment, as well as an increased risk of relapse. A study from Jaipur, Rajasthan, which followed up TB cases taking Category I and II treatment for 2 years, reported diabetes as one of the associated factors for relapse of TB cases.[22] Similar findings were also reported in a study conducted amongst Chinese population.[23]

The growing prevalence of TB-DM comorbidity worldwide has provided a new challenge to clinical management and health systems control strategy. Fisher Hoch et al[24] showed association of MDR TB and Diabetes Mellitus, according to their study 36.7% patients of MDR TB in Texas had Diabetes Mellitus. **In our study 45% patients in MDR group had Diabetes Mellitus which is statistically significant with p value =0.001.**

In another study by Gomez etal[25] titled "diabetes and other risk factors of multi drug resistant tuberculosis in Mexican population with pulmonary tuberculosis a case control study". They showed that there were 47.2 % patient with MDR TB which was statically significant p value = 0.028.

If diabetes is associated with tuberculosis, question if the severity of diabetes is related to the magnitude of risk. Two studies have compared the incidence of active tuberculosis between insulin-dependent diabetes mellitus (IDDM) and NIDDM. In a cohort of 1529 diabetic individuals in Chile, who were followed prospectively from 1959 to 1982, the 10-year actuarial probability of developing tuberculosis was 24% in IDDM and 4·8% in NIDDM.[26] In a prospective study of diabetic patients followed for 1–7 years in Tanzania, 9·0% of patients with IDDM and 2·7% of patients with NIDDM developed pulmonary tuberculosis.[27] These two studies provide evidence that insulin dependence, as a marker for severity of disease, predicts increased tuberculosis risk. In a recent study of 4690 elderly diabetic patients in Hong Kong, those with haemoglobin A1c greater than 7% had a three times increased hazard of active tuberculosis compared with those with haemoglobin A1c less than 7% (hazard ratio 3·11; 95% CI 1·63–5·92).[28] These data suggest that poor glycaemic control is a risk factor for tuberculosis.

Although there is no reason, to expect an association with diabetes mellitus and drug resistance, two studies have shown that diabetic patients are more likely to develop multidrug-resistant tuberculosis than those without diabetes.[29,30] However, four studies in disparate settings showed no significant increased risk.[31-34] The scientific mechanism by which diabetes mellitus would lead to preferential acquisition of multidrug-resistant tuberculosis is unclear.

Bacillary load of all patient was evaluated in accordance with latest RNTCP guidelines and PMDT guidelines even sputum negative retreatment cases were included as per 2012 PMDT guidelines [35], the bacillary load was classified as negative, scanty, 1+, 2+, 3+, 5 % patients in MDR group were sputum negative, 5 % were in scanty group, 20% in 1+ group, 25% in 2+ group and 45% in 3+ group. In Non MDR group 35% were in 1+ group, 29% in 2+ group, 15% in 3+ group, 13% in scanty group and 8% in negative group. The most important finding was that there was a sputum negative retreatment case having MDR TB, now PMDT guidelines instruct us to send samples of all sputum negative retreatment cases. Since the recommendations by guidelines the trends of prevalence may show change and more studies including PMDT guidelines and sputum negative retreatment cases is need of hour.

Screening for DM in TB patients could improve DM case detection and early treatment and indirectly lead to better TB-specific treatment outcomes[36]. Many research questions regarding association between diabetes and TB remain unanswered because of lack of well-designed studies[37].

CONCLUSION:

As concluded by our study the MDR prevalence is 20% which is comparable to other hospital based studies, nationwide studies as well and the data obtained by WHO. In our study we found statistically significant association between DM and MDR TB, though it is a small scale hospital based study, with referral bias and exclusion criteria, more extensive studies on topic may put more light on subject. Although there are lot of studies at nationwide level proving affiliation between tuberculosis and smoking, tuberculosis and alcohol abuse and tuberculosis and Diabetes Mellitus, but nationwide studies are yet to reach conclusion with regard to MDR TB`s association with Diabetes mellitus and this being a hospital based study larger studies are need of hour. Another point of serious concern is MDR TB in sputum negative individuals we found a single case of patient having sputum negative state and being MDR TB in DST, since PMDT now has made sputum negative retreatment cases eligible for DST, more studies including smear negative retreatment cases must be included into the fold now.

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