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Original Article

Occurrence of adverse drug reactions in multidrug drug resistant tuberculosis patients with diabetes mellitus

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Abstract
Introduction: *Previous data has suggested a significantly higher risk of adverse outcomes among patients with drug resistant tuberculosis (TB) and diabetes mellitus (DM). The present study was conducted to assess the adverse reactions to anti-tubercular treatment among diabetic and non-diabetic tuberculosis patients.*
Methodology: *The present study was conducted to describe the side effects of anti-tubercular therapy in patients of TB with and without diabetes mellitus. Equal number of diabetic and non-diabetic (n=75 each) multi-drug resistant (MDR) TB patients who received at least 3 months of anti-TB treatment at our centre were included in the study. All patients in the diabetic group were diagnosed using Genexpert and Mycobacteria growth indicator tube. Adverse drug reactions were determined based on the clinical presentation.*
Results: *Most common presenting complaint in both the patient groups was cough was almost universal in both the patient groups. Most common side effect reported by the diabetic tuberculosis patients was nausea (in 45%) which had a median onset time of 6 days after starting tuberculosis treatment. Other common adverse effects reported among diabetics was gastritis (43%), vomiting (32%) and peripheral neuropathy (29%). Most common adverse effect reported by patients without diabetes was gastritis which started at a median time of 14 days. Non-diabetics also reported adverse effects like vomiting (49%), dizziness (28%), nausea (28%), peripheral neuropathy (28%) and joint pain (24%).*
Conclusions: *Screening of DM in TB patients and TB in DM is suggested as high incidence of adverse effects can affect the treatment compliance.*
Keywords: *MDR tuberculosis, diabetes mellitus, adverse drug reaction.*

Introduction

For numerous years there have been reports and studies about the interaction between diabetes mellitus (DM) and tuberculosis (TB). TB, relatively rare in western countries where DM is prevalent and DM believed to be a minor problem

in low income countries where TB is endemic. Global interests in these two diseases has changed. Two systematic reviews highlighted the important risk that DM poses for the development of active TB, with cohort studies indicating a relative risk of 3.1 (95% CI 2.3 to 4.3) and case- control studies indicating odds ratios of 1.2 to 7.8.[1,2] The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) jointly proposed the 'collaborative framework for care and control of tuberculosis and diabetes', which comprehensively explored the relationships between TB and DM. They concluded that DM was recognized as one of the risk factors for TB. Various studies conducted in different countries have suggested that there is a significantly higher risk of adverse outcomes among patients with DR-TB and DM,[3] although some authors have refuted such associations between the two.[4] The present study was conducted to assess the adverse reactions to anti-tubercular treatment among diabetic and non-diabetic tuberculosis patients.

Methodology

Study design and sample selection

The present study was conducted to describe the side effects of anti-tubercular therapy in patients of TB with and without diabetes mellitus. New and retreatment tuberculosis patients aged 18 years and above who received at least 3 months of anti-TB treatment under directly observed treatment short course (DOTS) at the Department of Pulmonary Medicine, Dr. DY Patil Medical College, Navi Mumbai from January 2018 till December 2018 were included in the study. Patients those of category I (new cases of sputum smear positive, sputum smear negative, extra pulmonary tuberculosis, and other cases) or category II (retreatment cases of recurrent TB, treatment after failure, treatment after loss to follow-up, and other previously treated patients) were eligible for this study. We went through the hospital records of the included patients to know their MDR status. MDR TB was defined as the resistance to at least isoniazid and rifampicin. In addition, hospital or treatment records of MDR patients were checked to know if they had an established diagnosis of DM. Patients below the age of 18 years, refusing informed consent and suffering from any other disease other than TB or DM were also excluded from the study. The study was conducted after obtaining approval of the institutional ethics committee and the treatment of the patients was not affected in any way by being included or excluded from the study. The facilities for the study including laboratory investigations were available in the institute and the study was not funded by any external agency.

Data Collection and Data Analysis

Presumptive diagnosis of multi-drug resistant tuberculosis was made using the GeneXpert®. Physicians assessed the patients and their laboratory and radiological data to arrive at the diagnosis. Using a pre-deisgned semi-structured questionnaire, patients' socio-demographic profile, symptoms at their presentation, past medical history were noted from their treatment card. Clinical information pertaining to TB diagnosis and categorization was noted from the treatment records of the patients. Clinical history taking and examination of the patient revealed the side effects experienced by the patients. In routine, patients enrolled with DOTS at our centre are closely monitored for side effects. However, for the purpose of this study, patients were specifically asked for different side effects. Adverse drug reaction was defined as a noxious response which is unintended and occurs at doses which are routinely used in human patients.[5] All adverse drug reactions were determined based on the clinical presentation and were ascertained after examination by a senior physician. Patient data were analysed descriptively as percentages and was tabulated for comparison and discussion.

Results

The present study included75 diabetics and non-diabetics each diagnosed with MDR tuberculosis during the study period. 36 to 45 was the most

common age group among diabetics and 46 to 55 years among non-diabetics. Males were more common in both the patient groups (Table 1). Most common presenting complaint in both the patient groups was cough was almost universal in both the patient groups. Other common symptoms were breathlessness, fever and weight loss. There were 64% and 65% category I tuberculosis patients in diabetic and non-diabetic patient groups respectively and rest received category II treatment. History of substance abuse was given by patients in diabetic as well non-diabetic groups. History of tobacco chewing was given by 19% among the diabetics and 21% in the non-diabetic group. All patients in the diabetic group were diagnosed using Genexpert and Mycobacteria growth indicator tube. Most common side effect reported by the diabetic tuberculosis patients was nausea (in 45%) which had a median onset time of 6 days after starting tuberculosis treatment. Other common adverse effects reported among diabetics was gastritis (43%), vomiting (32%) and peripheral neuropathy (29%). Most common adverse effect reported by patients without diabetes was gastritis which started at a median time of 14 days (Table 2). Non-diabetics also reported adverse effects like vomiting (49%), dizziness (28%), nausea (28%), peripheral neuropathy (28%) and joint pain (24%).

Table 1 Baseline characteristics of the patients included in the study

	Patients with DM		**Patients without DM**	
Age structure	N	%	N	%
25 to 35	12	16%	12	16%
36 to 45	27	36%	21	28%
46 to 55	23	31%	28	37%
56 to 65	13	17%	14	19%
Gender distribution				
Males	41	55%	46	61%
Females	34	45%	29	39%
Symptoms				
Cough	54	72%	61	81%
Breathlessness	32	43%	39	52%
Fever	52	69%	51	68%
Weight loss	26	35%	21	28%
Hemoptysis	27	36%	20	27%
Chest pain	25	33%	28	37%
Loss appetite	17	23%	11	15%
Hoarseness of voice	8	11%	9	12%
Lymphadenopathy	7	9%	4	5%
Treatment category				
Category I	48	64%	49	65%
Category II	27	36%	26	35%
History of substance abuse				
Alcohol	12	16%	14	19%
Smoking	10	13%	11	15%
Tobacco chewing	14	19%	16	21%
Smoking and tobacco chewing	6	8%	8	11%
Alcohol, smoking and tobacco chewing	12	16%	8	11%
Diagnosis of tuberculosis				
Genexpert	75	100%	70	93%
Liquid probe assay	25	33%	14	19%
Mycobacteria Growth Indicator Tube	75	100%	15	20%

Table 2 Distribution of patients according to side effects experienced by the patients

	Patients with DM			Patients without DM		
	Incidence		Onset time in days (median, IQR)	Incidence		Onset time in days (median, IQR)
	N	%		N	%	
Gastritis	32	43%	13 (9-17)	47	63%	14 (10-18)
Vomiting	24	32%	14 (8-19)	37	49%	15 (10-19)
Joint pain	12	16%	18 (13-22)	18	24%	16 (11-20)
Headache	6	8%	8 (5-11)	6	8%	9 (6-14)
Dizziness	16	21%	18 (14-23)	21	28%	19 (15-26)
Nausea	34	45%	6 (4-11)	21	28%	5 (3-9)
Peripheral neuropathy	22	29%	17 (14-24)	21	28%	16 (12-23)
Hearing loss	9	12%	20 (15-24)	7	9%	21 (13-26)
Weakness	8	11%	16 (13-21)	14	19%	15 (10-19)

Discussion

DM is a metabolic disease with a strong pathogenetic background of chronic inflammation. Current understanding tells us that hyperglycaemia and advanced glycation end-products, result from poor control of the metabolic derangement inherent to the disease, and are conducive to inappropriate oxidative stress and mitochondrial dysfunction. These mechanisms underlie the accelerated development of diabetic complications, especially those pertaining to the cardiovascular and neurological systems.[6] Ahadpur et al demonstrated that oxidative stress and mitochondrial dysfunction are responsible for isoniazid-induced neurotoxicity and hepatotoxicity in the rat model.[7] Similarly, these mechanisms have also been implicated in the pathogenesis of toxicities induced by pyrazinamide, aminoglycosides and fluoroquinolones in different experimental laboratory based models.

Regarding the treatment of multidrug-resistant tuberculosis, linezolid use has been shown to incur peripheral neuropathy, even at a low daily dose, which was observed among 29% of diabetics and 28% of non-diabetics. Though not investigated in the present study, biomarkers to assess mitochondrial function, in form of translational competence, the serum trough concentration of linezolid were demonstrated to correlate positively with mitochondrial dysfunction in patients with extensively drug-resistant tuberculosis by Song et al.[8] The recent introduction of bed aquiline, delamanid, or a later-generation fluoroquinolone has been shown to be associated with risk of cardiotoxicity, as oxidative stress and mitochondrial dysfunction are also the underlying mechanisms for cardiotoxicity induced by a variety of drugs.[9] Assessment of pharmacokinetics can help in the clinical management of adverse drug reactions in patients taking other medications or with co-morbidities. Manipulation of the dosing schedule, like for instance from daily to three-times-weekly administration of linezolid to reduce the serum trough concentration of the drug has been shown to reduce its neurotoxicity.[10] Therapeutic monitoring of serum drug concentrations in selected patients, particularly elderly diabetics with comorbidities, to optimise drug exposure, to manage drug-drug interactions, and to ameliorate drug toxicity[11] would favourably address the efficacy versus toxicity of antituberculosis drugs.

Siddiqui et al conducted a prospective study on patients receiving anti-tubercular treatment in urban slum region of South Delhi, India, to evaluate the effect of DM on treatment outcome, and ADR due to anti-TB treatment. [12] They found that a total of 224 patients presented with at least one ADR, of which 66.9% had no DM and 92.0% had DM. The median duration between onset of anti-TB treatment and first-time adverse reaction occurrence was 14 (±14.63) and 14 (±14.06) days in DM and no-DM group, respectively. Gholami

et al revealed 54.3% ADR incidences, associated with TB medications, in Iranian patients.[13] Presence of DM is significantly associated (OR: 3.578 95% CI: 1.114–11.494, p = 0.032) with anti-TB ADR, which may be attributed to the concomitant antidiabetic medications.

There are a few limitations of this study. First, we did not collect information regarding the concomitant pharmacotherapy among diabetic patients to assess associations with adverse effects. Secondly, serum trough levels of rifampicin and isoniazide would have enabled us to perform find associations of serum drug levels with specific adverse effects. Lastly, relationships between severity of diabetes and various adverse effects could not be elicited in the present study and could be investigated in future studies.

Conclusion

The findings of the present study stress the importance of bi-directional screening programmes for TB and DM. Glycaemic control in MDR TB patients should be monitored to assess the severity of DM and its impact on the management and outcomes of TB patients. Further studies are needed to study the effect of DM on clinical outcomes of anti-tubercular treatment.

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Conflict of interest: None

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