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Adverse Drug Reactions in Multidrug and Extensively Drug Resistant Tuberculosis Patients with Diabetes Mellitus.

Sarang Patil[1], Priyanka Bhoir[2]

[1]Junior Resident, Department of Pulmonary Medicine, Dr D. Y. Patil Hospital, Navi Mumbai.
[2]Junior Resident, Department of General Medicine, Dr D. Y. Patil Hospital, Navi Mumbai.

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ABSTRACT

Background: Prevalence of DM among TB patients range between 5% and 50%, while the prevalence of TB among DM patients has been reported approximately two to ten times higher than that of the general population. The purpose of this study is to describe the side effects of anti-tubercular drugs in patients with MDR/XDR tuberculosis with and without DM. **Methods:** This cross-sectional 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=100 each) MDR and XDR TB patients who received at least 3 months of anti-TB treatment under directly observed treatment short course (DOTS) at our centre were included. Adverse drug reactions were determined based on the clinical presentation and were ascertained after examination by a senior physician. **Results:** Presenting complaint of cough was almost universal in both the patient groups. Most common side effect reported by the diabetic tuberculosis patients was gastritis (55%), followed by vomiting (45%). Less common side effects in this patient group was peripheral neuropathy, depression, dizziness, joint pain and hearing loss. Gastritis was also the most commonly reported side effect in non-diabetic tuberculosis patients (85%), followed by the complaint of vomiting in 65%. Other common side effects reported in this patient group were peripheral neuropathy, depression, hypothyroidism and dizziness. **Conclusion:** Bidirectional screening of DM in TB patients and TB in DM patients needs to be encouraged. Further studies are needed to study the long term effect of DM on TB management and their final clinical outcomes.

Keywords: Tuberculosis, diabetes mellitus, adverse drug reaction, outcome.

INTRODUCTION

Low and middle income countries have seen a huge increase in the prevalence of Diabetes mellitus (DM) patients, along with a gradual control of tuberculosis (TB) cases.[1] Currently, approximately 95% of global TB cases, with India accounting for 23% of these cases and 70% of DM patients live in low and middle income countries.+[2] Diabetic patients suffer pulmonary TB being one of its top ten complications. With rising proportions of patients with each of these two diseases, and many of them coexisting in the same patient, TB and DM comorbidity warrants our attention. Multiple studies conducted in different parts of the world have determined the worldwide prevalence of DM to range between 1.9% and 44.0% among TB patients.[3] In Asian countries, the prevalence of DM among TB patients range between 5% and 50%, while the prevalence of TB among DM patients has been reported approximately two to ten times higher than that of the general population.[4] In addition, DM delays bacteriological conversion, resulting in lower cure rate, higher relapse and overall mortality among TB patients. This is evidenced from a high prevalence of DM among multi-drug resistant (MDR) and extensively-drug resistant (XDR) TB patients has become a serious cause for concern, with approximately 10 to 23% of MDR TB patients having a history of DM. Anti-tubercular therapy has also been shown to result in more drug toxicities and adverse reactions in diabetic patients, which require a more careful management.[5] The purpose of this study is to describe the side effects of anti-tubercular drugs in patients with MDR/XDR tuberculosis with and without DM.

Name & Address of Corresponding Author
Dr Priyanka Bhoir
Junior Resident,
Department of General Medicine
Dr D. Y. Patil Hospital,
Navi Mumbai.

MATERIALS AND METHODS

Study design and sample selection

This cross-sectional study was conducted to describe the side effects of anti-tubercular therapy in patients

of TB with and without diabetes mellitus. New and retreatment TB patients aged 15 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 June 2017 till December 2017 were eligible for inclusion 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. Their treatment records were checked to know their MDR/XDR status. MDR TB is defined as the resistance to at least isoniazid and rifampicin, and XDR TB is defined as MDR plus resistance to at least one of the quinolones and the injectable drugs. In addition, hospital or treatment records of MDR/XDR patients were checked to know if they had an established diagnosis of DM. Patients below the age of 15 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 according to the principles of the Declaration of Helsinki 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 agency.

Data Collection and Data Analysis

Using a pretested semi-structured questionnaire, patients' socio-demographic profile, symptoms at their presentation, past medical history were noted. 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.[6] 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

During the study period, we included 100 diabetics and non-diabetics each who were diagnosed with MDR/XDR tuberculosis. Diabetics were most common from the age group 36 to 45 years and non-diabetics from 25 to 35 years. Males were more common in both the patient groups [Table 1]. Presenting complaint of cough was almost universal in both the patient groups. Other common symptoms were breathlessness, fever and weight loss. There were 80% and 85% category I tuberculosis patients in diabetic and non-diabetic patient groups respectively. History of substance abuse was given by patients in diabetic as well non-diabetic groups. History of tobacco chewing was given by 45% 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 gastritis (55%), followed by vomiting (45%). Less common side effects in this patient group was peripheral neuropathy, depression, dizziness, joint pain and hearing loss [Table 2]. Gastritis was also the most commonly reported side effect in non-diabetic tuberculosis patients (85%), followed by the complaint of vomiting in 65%. Other common side effects reported in this patient group were peripheral neuropathy, depression, hypothyroidism and dizziness.

Table 1: Baseline characteristics of the patients included in the study

Variable	Diabetes mellitus patients (n=100)	Non-diabetes mellitus patients (n=100)
Age structure		
25 to 35	5 (5%)	55 (55%)
36 to 45	45 (45%)	30 (30%)
46 to 55	25 (25%)	15 (15%)
56 to 65	25 (25%)	0 (0)
Gender distribution		
Males	80 (80%)	60 (60%)
Females	20 (20%)	40 (40%)
Symptoms		
Cough	95 (95%)	100 (100%)
Breathlessness	60 (60%)	50 (50%)
Fever	45 (45%)	50 (50%)
Weight loss	55 (55%)	55 (55%)
Hemoptysis	20 (20%)	35 (35%)
Chest pain	10 (10%)	15 (15%)
Loss appetite	0 (0)	0 (0)
Hoarseness of voice	5 (5%)	15 (15%)
Lymphadenopathy	5 (5%)	0 (0)
Categorization of patients		
Category I	80 (80%)	85 (85%)
Category II	20 (20%)	15 (15%)
History of substance abuse		
Alcohol	10 (10%)	20 (20%)
Smoking	10 (10%)	15 (15%)
Tobacco chewing	15 (15%)	45 (45%)
Smoking and tobacco chewing	5 (5%)	15 (15%)
Alcohol, smoking and tobacco chewing	15 (15%)	25 (25%)
Diagnosis of tuberculosis		
Genexpert	100 (100%)	90 (90%)
Liquid probe assay	30 (30%)	10 (10%)
Mycobacteria Growth Indicator Tube	100 (100%)	10 (10%)

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

Side effects	Diabetes mellitus patients (n=100)	Non-diabetes mellitus patients (n=100)
Gastritis	55 (55%)	85 (85%)
Vomiting	45 (45%)	65 (65%)
Joint pain	15 (15%)	10 (10%)
Headache	5 (5%)	5 (5%)
Dizziness	20 (20%)	20 (20%)
Nausea	10 (10%)	5 (5%)
Peripheral neuropathy	25 (25%)	40 (40%)
Depression	4 (20%)	25 (25%)
Hypothyroidism	5 (5%)	20 (20%)
Hearing loss	10 (10%)	0 (0)
Weakness	15 (15%)	0 (0)

DISCUSSION

Diabetes mellitus is a metabolic disease and poor glycemic control results in hyperglycemia and advanced glycation end products, which are known to be associated with oxidative stress and mitochondrial dysfunction. These have been shown to be the underlying mechanism in isoniazid induced neurotoxicity and hepatotoxicity in animal model.[7] Similar mechanisms have been described in toxicities induced by pyrazinamide and aminoglycosides as well. In MDR TB patients, linezolid, even when used in low dose, has been shown to result in peripheral neuropathy. By using biomarkers in patients with XDR TB, serum linezolid concentration have correlated positively with mitochondrial dysfunction.[8] Newer anti-tubercular drugs like bedaquiline and delamanid, though oxidative stress and mitochondrial dysfunction, have been associated with cardiotoxicities.[9]

The present study described the side effects which were experienced by MDR and XDR TB patients taking DOTS at our centre, with and without DM. Studies have reported that DM itself increases the chance of developing MDR or XDR TB. A higher frequency of MDR TB patients were noted among diabetics as compared to non-diabetics.[10] Furthermore, DM has shown to be significantly associated with any drug resistance in TB patients.[2] Very few studies have explored the association between DM and adverse effects of anti-TB treatment. Though not statistically significant, DM was found to be 2.5 and 3.9 times increased risk of developing adverse drug reactions in the intensive and continuation phase respectively.[11] Similarly, other studies have also reported higher incidence of side effects in adverse reactions in diabetics as compared to non-diabetics.[12] After adjusting for age and gender, insignificant associations were found between having DM and the risk of developing side effects from anti-TB drugs.[13] Higher side effects among diabetics could also be due to concurrent use of multiple medications. Studies are required to understand the mechanisms involved in interactions between anti-TB and anti-diabetic drugs. Furthermore, DM over a period of time can result in complications like peripheral neuropathy and nephropathy.

Previously, authors have shown that clinical management of adverse drug reactions of anti-TB drugs can be done by assessing and understanding the pharmacokinetics of the drugs. Though a few single centre studies have been done in India which have analysed adverse drug reactions during anti-tubercular therapy, but the incidence of side effects have not been published. DM has been significantly associated with anti-TB adverse reactions (odds ratio = 3.56, p value <0.05) and might have been due to concomitant anti-diabetic therapy.[5] Furthermore, lower plasma concentration of rifampicin has been reported in patients with DM patients, though the exact mechanism is not clearly understood.[14] By altering dosing schedules and by reducing serum trough levels, some of the toxicities can be avoided.[15] Therefore at the start of DOTS, screening for diabetes and other chronic diseases is necessary so as to identify patients early in the course of the disease. In addition, therapeutic monitoring of serum drug levels at regular intervals in TB patients with multiple comorbidities can help to control drug toxicities and can address the development of resistance as well.[16]

CONCLUSION

With the convergence of TB and DM epidemics in low middle income countries like India and increasing prevalence of TB-DM comorbidity, bidirectional screening of DM in TB patients and TB in DM patients needs to be encouraged. Further studies are needed to study the long term effect of DM on TB management and their final clinical outcomes.

REFERENCES

1. Harries AD, Kumar AM, Satyanarayana S, Lin Y, Zachariah R, Lönnroth K, et al. Diabetes mellitus and tuberculosis: programmatic management issues. Int J Tuberc Lung Dis 2015;19:879–86
2. Baghaei P, Marjani M, Javanmard P, Tabarsi P, Masjedi MR. Diabetes mellitus and tuberculosis facts and controversies. J Diabetes Metab Disord 2013;12(58)
3. Balakrishnan S, Vijayan S, Nair S, Subramoniapillai J, Mrithyunjayan S, Wilson N, et al. High diabetes prevalence among tuberculosis cases in Kerala, India. PLoS One 2012;7:e46502
4. Zheng C, Hu M, Gao F. Diabetes and pulmonary tuberculosis: a global overview with special focus on the situation in Asian countries with high TB-DM burden. Glob Health Action 2017;10
5. Siddiqui AN, Khayyam KU, Sharma M. Effect of diabetes mellitus on tuberculosis treatment outcome and adverse reactions in patients receiving directly observed treatment

strategy in India: a prospective study. Biomed Res Int 2016; 2016: 7273935.
6. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. The lancet. 2000;356(9237):1255-9.
7. Ahadpour M, Eskandari MR, Mashayekhi V, et al. Mitochondrial oxidative stress and dysfunction induced by isoniazid: study on isolated rat liver and brain mitochondria. Drug Chem Toxicol 2016;39: 224–232.
8. Song T, Lee M, Jeon HS, et al. Linezolid trough concentrations correlate with mitochondrial toxicity-related adverse events in the treatment of chronic extensively drug-resistant tuberculosis. EBioMedicine 2015;2:1627–1633.
9. Varga ZV, Ferdinandy P, Liaudet L, et al. Drug-induced mitochondrial dysfunction and cardiotoxicity. Am J Physiol Heart Circ Physiol 2015; 309: H1453–H1467.
10. Baghaei P, Tabarsi P, Abrishami Z, Mirsaeidi M, Faghani YA, Mansouri SD, et al. Comparison of pulmonary TB patients with and without diabetes mellitus type II. Tanaffos 2010;9:13–20.
11. Duangrithi D, Thanachartwet V, Desakorn V, Jitruckthai P, Phojanamongkolkij K, Rienthong S, Chuchottaworn C, Pitisuttithum P. Impact of diabetes mellitus on clinical parameters and treatment outcomes of newly diagnosed pulmonary tuberculosis patients in Thailand. Int. J. Clin. Pract. 2013; 67: 1199–209.
12. e Castro AT, Mendes M, Freitas S, Roxo PC. Incidence and risk factors of major toxicity associated to first-line antituberculosis drugs for latent and active tuberculosis during a period of 10 years. Revista Portuguesa de Pneumologia (English Edition). 2015;21(3):144-50.
13. Chung-Delgado K, Revilla-Montag A, Guillen-Bravo S, Velez- Segovia E, Soria-Montoya A, Nuñez-Garbin A, Silva-Caso W, Bernabe-Ortiz A. Factors associated with anti-tuberculosis medica- tion adverse effects: a case-control study in Lima, Peru. PLoS One 2011; 6: e27610.
14. Gwilt PR, Nahhas RR, Tracewell WG. The effects of diabetes mellitus on pharmacokinetics and pharmacodynamics in humans. Clinical pharmacokinetics. 1991 Jun 1;20(6):477-90.
15. Chang KC, Yew WW, Cheung SW, et al. Can intermittent dosing optimize prolonged linezolid treatment of difficult multidrug-resistant tuberculosis. Antimicrob Agents Chemother 2013; 57: 3445–3449.
16. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. Drugs 2014; 74: 839–854.

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