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Association of Fluoroquinolone Resistance in Multi-drug Resistance Tuberculosis with Diabetes Mellitus: A Hospital-based Retrospective Study

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Abstract

INTRODUCTION:

Mycobacterium tuberculosis (MTB) is a highly adaptive organism as it effectively evades the immune system within the host. Fluoroquinolones (FQ) have broad-spectrum antibacterial activity, high oral bioavailability, good tolerability, easy dosing, and low to moderate cost. The main objective of this study is to evaluate the association of FQ resistance in MDR-TB patients with and without DM.

MATERIAL AND METHOD:

It is a hospital-based retrospective study that included data from 151 confirmed MDR-TB patients regardless of their DM status. Data were entered and compiled before being exported to Epi-Info software for analysis.

RESULTS AND DISCUSSIONS:

In this study, 106 (70.2 %) male and 45 (29.8 %) female patients were enrolled. Mean age of patients with MDR-TB and FQ resistance was 46.8 years. Out of 151 patients, 53 (35%) patients have FQ resistance. 135 (89.4%) do not have diabetes, while 16 (10.6%) patients have DM. Out of 135 patients without DM, 45 (33.33%) patients have FQ resistance. Out of 16 patients with DM, 8 (50%) patients exhibit FQ resistance.

CONCLUSION:

In our study, we found that gender plays an important role in the likelihood of developing FQ resistance. Further research is needed to identify possible underlying causes or contributing factors.

Key Words: Diabetes Mellitus; Fluoroquinolones; Mycobacterium tuberculosis; MDR-TB; Drug Resistance

Introduction

Mycobacterium tuberculosis (MTB) is a clever organism because it effectively evades the immune system within the host. There are only a few antimicrobial drugs available to treat the infection, and if the dosage or frequency of anti-TB drugs is inaccurate, drug resistance can develop. These result in an inability to control the disease, even though it has existed since

ancient times. MTB may infect any organ within the body, but Pulmonary Tuberculosis (PTB) is the most common infection. It mainly spreads via inhalation of infected droplets. MTB disease is treated with a combination of anti-TB drugs, whether it is drug-sensitive TB (DSTB) or drug-resistant TB (DRTB).Fluoroquinolones (FQ) are a group of drugs that mainly inhibit DNA synthesis. They have broad-spectrum antibacterial activity, high oral bioavailability, good tolerability, easy dosing, and low to moderate cost. These characteristics have made them the most commonly prescribed drugs worldwide for infections where organisms are susceptible or given empirically [1]. Its place in the treatment of TB is vital mainly because it is used as a second-line anti-TB drug when patients have intolerance to first-line anti-TB drugs. It is a constituent of the primary drug regimen for the treatment of DRTB and is used to treat latent TB infection (LTBI). Currently, a trial of a 24-week TB regimen is underway, which includes moxifloxacin as a core drug [2]. MTB develops resistance to FQ through mutations in the gene encoding a type II DNA topoisomerase, also known as the quinolone resistance determining region. Mutation in subunit A, known as gyrA, confers a high level of resistance, and the mutation is present in codons 88-94. Mutation in subunit B (gyrB) confers a low resistance level, with mutations in codons 500 and 538 [3].Diabetes Mellitus (DM) is a chronic metabolic disorder that affects the immune system and puts patients at high risk for various infections, including TB. Patients with DM-TB have a high risk of treatment failure, the development of drug-resistant tuberculosis, and the risk of death [4]. Patients with DM who are under 65 years old and have high HbA1c levels and a history of previous TB treatment were identified as independent risk factors for the development of multidrug-resistant TB (MDR-TB) [5]. The prevalence of MDR-TB among patients with DM ranges from 10% to 30%, and the cure rate of TB is reduced from 96% to 54% due to the combination of MDR-TB with DM [6]. MDR-TB in patients with DM is associated with adverse outcomes in the form of treatment failure and mortality [7].

There are only a few studies that investigate the prevalence of MDR-TB and DM, the association between DM and MDR-TB, and the outcomes of MDR-TB patients with DM. In light of the high treatment failure and mortality rates among patients with MDR-TB and DM, it is crucial to consider the possibility of additional resistance in MDR-TB patients. FQ-class drugs are being used widely in various countries to treat various infections. In regions where the prevalence of latent tuberculosis infection (LTBI) is high, there is a possibility of exposure to MTB through FQ use, increasing the risk of developing resistance even before formal treatment with anti-TB drugs. An extensive search was conducted using MESH terminology to search any research regarding association between MDR-TB and FQ resistance among patients with DM. To the best of the authors' knowledge, there are only few researches studying this association. The main objective of this study is to evaluate the association of fluoroquinolone resistance in MDR-TB among patients with and without DM.

Material and Methods

Study Design:

It is a hospital-based retrospective study that included data from 151 confirmed MDR-TB patients, regardless of their DM status.

Ethical Consideration

Approval for this study was obtained from the Institutional Ethical Committee for Human Research at the Medical College and SSG Hospital in Baroda, India, with approval number ECR/85/Int/Gj/2013/RR-16. The data collection process did not pose any potential risk or harm

to the participants, and there was no intervention or interference in the treatment. The names of the patients were not disclosed in the study. The confidentiality of all records was maintained.

Screening of Patients

Informed Consent: Informed consent was not required as we were obtaining secondary data.

Inclusion Criteria: Patients newly diagnosed with MDR-TB or a known case of MDR-TB confirmed with sputum cartridge-based nucleic acid amplification test (CBNAAT) and with available results from their sputum line probe assay (LPA) for second-line drugs or sputum culture with drug sensitivity test (DST).

Exclusion Criteria: All patients with MDR-TB are under 12 years of age. All patients with MDR-TB have a positive HIV status. All MDR-TB patients with LPA or DST for second-line drugs are not available.

Statistical Analysis

The data were checked for errors and corrected on the same day as the data collection. Data were entered and compiled into Microsoft Excel 2019 and then exported to Epi-Info software for analysis. Data were verified before conducting analysis. Descriptive and inferential statistics were used for analysis, and the results were displayed in tables and graphs.

Results

In this study, we retrospectively evaluated data from 151 patients. There were 106 male and 45 female patients included in this study. Out of the total number of patients, 53 (35%) have FQ resistance, while 98 (65%) do not have FQ resistance. The mean age of MDR-TB patients with FQ resistance was 46.8, while the mean age of those without FQ resistance was 49.34. Table 1 presents a comparative analysis of patients with and without fluoroquinolone (FQ) resistance, focusing on three main variables: mean age, gender, and diabetes status.

Table 1: Demographic and Diabetes Mellitus Status of MDR-TB Patients

	MDR-TB with FQ resistant (n=53)	MDR-TB without FQ resistance (n=98)	Total (n=151)	Chi-Square	*P* value
Mean Age	46.8 years	49.34 years	48.07 years	-	-
Male	31 (20.5 %)	75 (49.7 %)	106 (70.2 %)	5.351	0.02071
Female	22 (14.6 %)	23 (15.2 %)	45 (29.8 %)		
Patient with DM	8 (5.3%)	8 (5.3%)	16 (10.6%)	1.744	0.18659
Patient without DM	45 (29.8 %)	90 (59.6%)	135 (89.4%)		

Among the MDR-TB patients with FQ resistance, the status of DM was presented in Table 1. Out of a total of 53 patients with MDR-TB and FQ resistance, eight patients had DM, and 45 patients were non-diabetic. Out of 98 MDR-TB patients without FQ resistance, eight patients had DM, and 90 patients were non-diabetic. Table 2 presents a comparative analysis of patients with MDR-TB and FQ resistance, categorized based on their DM status. Patients with FQ resistance and DM are younger on average than those without DM. In this cohort, the number of male patients is higher than that of female patients. The number of diabetic patients is higher in males compared to females.

Table 2: Demographic and diabetes mellitus status of MDR-TB with fluoroquinolone resistance

	FQ resistant with DM (n=8)	FQ resistant without DM (n=45)	Total (n=53)	Chi-Square	*P* value
Mean Age	43.75 years	49.9 years	46.8 years	-	-
Male	5 (9.4%)	26 (49.1%)	31 (58.5%)	0.0623	0.8027
Female	3 (5.7%)	19 (35.8%)	22 (41.5%)		
Total	8 (15.1%)	45 (84.9%)	53 (100%)	-	-

Table 3 compares DM control status among MDR-TB patients with FQ resistance. The variables examined include mean age and gender distribution, with statistical significance evaluated using the chi-square test.

Table 3: Demographic and diabetes control status of MDR-TB patients with fluoroquinolone-resistant strains

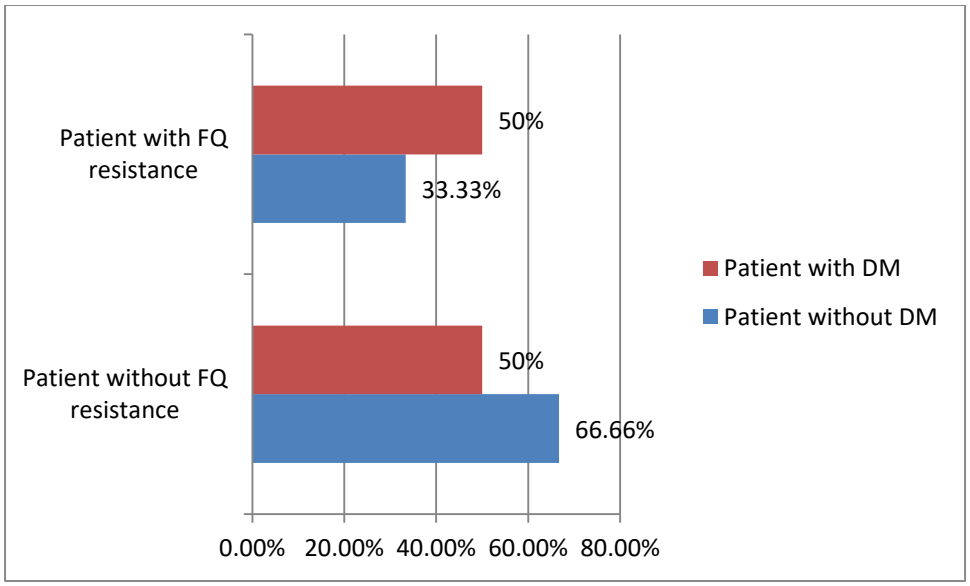
	Uncontrolled DM (n=13)	Controlled DM (n=3)	Total (n=16)	Chi-Square	*P* value
Mean Age	46.69 years	44.33 years	45.51 years	-	-
Male	9 (56.25%)	2 (12.5%)	11 (68.75%)	0.0075	0.93117
Female	4 (25%)	1 (6.25%)	5 (31.25%)		
Patient with FQ resistance (n=8)	7 (43.75%)	1 (6.25%)	8 (50%)	0.4102	0.8145
Patient without FQ resistance (n=8)	6 (37.5%)	2 (12.5%)	8 (50%)		

We analyzed the HbA1c level data of patients with DM and divided them into two groups based on their HbA1c levels. Uncontrolled groups have HbA1c levels >6.5, while controlled groups have HbA1c levels <6.5. The age of individuals with uncontrolled DM in this group is higher than that of the controlled DM group. Gender distribution correlates with the previously examined study group, as male patients outnumber female patients overall. We also found that there is no association between FQ resistance and MDR-TB patients, regardless of their DM control status.

Discussion

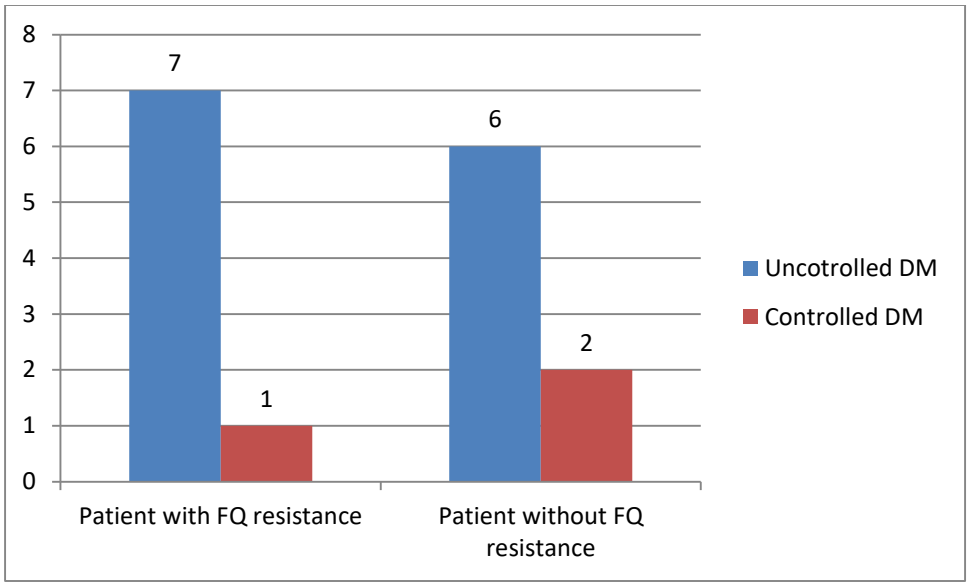
In our study, the mean age of MDR-TB patients with FQ resistance was lower than that of patients without FQ resistance. The proportion of male patients was higher than that of female patients. When we compare the number of patients with FQ resistance based on gender distribution, female patients exhibit a higher proportion of FQ resistance than male patients. Since the p-value (0.02071) is less than the significance level (0.05), we conclude that there is a significant difference in the distribution of males and females between the FQ-resistant and non-resistant groups. This suggests that gender may play a role in the likelihood of FQ resistance, warranting further investigation into underlying causes or contributing factors.As shown in Table 1, there is no significant association between diabetes status and FQ resistance, with a p-value of 0.18659. This suggests that having diabetes (DM) or not (No-DM) does not significantly affect the likelihood of FQ resistance in this sample.

Chart 1: Proportionate comparison of FQ resistance in patients with DM and without DM



Moreover, comparing the proportion of FQ resistance among patients with DM and those without DM, we found 50% in the DM population and 33.33% in the non-DM population. The National Anti-Tuberculosis Drug Resistance Survey (NDRS) from India reveals that among MDR-TB patients, additional resistance to any fluoroquinolones was 21.82% (17.33–26.87%) (8). This study indicates a higher prevalence of resistance in patients with and without diabetes mellitus. FQ drugs are an important component of TB treatment; the high level of resistance to these drugs is alarming. Due to the lower number of patients with diabetes mellitus (16) compared to those without diabetes mellitus (135) in this sample and the single-centre study design, the association level was found to be non-significant. If the same study is performed on a larger sample size or a Multi-centric study, there may be a possibility of association. We examine the status of DM and its control among patients with MDR-TB who are resistant to FQ. The distribution of both genders between the FQ resistance with and without DM groups is not statistically significant, indicating no significant association between gender and DM status in patients with FQ resistance. We also found that there is no significant association between gender and uncontrolled DM in patients with MDR-TB with FQ resistance and DM.

Chart 2: Proportionate comparison of the number of FQ resistance cases based on DM control status



Although we did not find any correlation between DM control status and FQ resistance in MDR-TB, our comparative analysis revealed that the number of FQ resistance cases in MDR-TB is higher in the uncontrolled DM group. The difference in such analysis may result from the smaller number of patients with DM in the study group compared to the larger number of non-DM patients.

There were several studies done on MDR-TB in DM, association of drug resistance in DM as well as risk factors for drug resistance in DM and outcome of MDR-TB in DM but, but, there are only few researches studying this association.

The association of DM with an increased risk of multidrug-resistant tuberculosis (MDR-TB) was found in a systematic review and meta-analysis. However, the pattern of FQ resistance was not studied according to the World Health Organization's definition of MDR-TB, which includes resistance to both isoniazid and rifampicin (9). This study suggests that DM significantly increases the odds of developing MDR-TB (9), but further analysis regarding additional resistance to other drugs used in the treatment of MDR-TB was not conducted. Similarly, another study was performed to identify genotypic drug resistance among DM patients. They found an association between diabetes and genotypic drug resistance in TB patients, increasing the risk of TB caused by strains with resistance mutations, particularly against rifampicin, but also against isoniazid, ethionamide, and fluoroquinolones (10).

Research was done in one of the largest city of India to determine the level of FQ drug resistance among TB patients. The study found high FQ resistance among both drug-sensitive and MDR-TB patients (11). This study included both drug-sensitive and MDR-TB patients regardless of their DM status. The discovery of high FQ resistance among the study population aligns with the findings of this research.

A study was conducted to investigate any differences in drug resistance among TB patients with or without DM. However, this study did not find any statistically significant difference in drug resistance patterns among MDR-TB patients with DM or without DM, except for arbitrary resistance to PTO and KM, mono-resistant SM and LFX, and pre-XDR-TB (12). This finding is consistent with the results of this study regarding FQ resistance. In this study, drug resistance patterns were not analyzed based on the status of DM control. In our study, we observed that uncontrolled DM patients had a proportionally higher FQ resistance compared to controlled DM patients, and a higher incidence of MDR-TB among uncontrolled DM patients

than controlled DM patients. Similarly, another study was conducted to investigate the drug resistance patterns of MDR-TB patients with DM, and they found that FQ resistance was 29.76% among DM patients and 29.53% among non-DM patients (13). In our study, we found that FQ resistance among the DM group was 50%, which is significantly higher than the 33.33% among non-DM patients. While that study aimed to study drug resistance to all drugs, our study primarily focused on FQ resistance among MDR-TB patients with DM. The study did not assess patients based on their DM control, but we did evaluate this and found that uncontrolled DM patients had higher FQ resistance than controlled DM patients.

Conclusion

Our study found that gender plays an important role in the likelihood of developing FQ resistance. Further research is needed to identify potential underlying causes or contributing factors. Females may have a higher probability of developing fluoroquinolone resistance in patients with MDR-TB. Understanding these associations can help develop targeted interventions and conduct further research. There is no significant association between diabetes status and FQ resistance, indicating that diabetes does not affect the likelihood of developing FQ resistance in this sample but, we see proportionally higher FQ resistance among DM patients than non-DM patients. However, further research and a larger sample size are needed to confirm this finding. Findings in this study indicate that gender is significantly associated with FQ resistance, while diabetes status is not. Patients with DM are, on average, younger than those without DM. The data indicates no significant association between gender and DM status in patients with FQ resistance, as shown by the non-significant p-value. We found no association between DM control status and MDR-TB with FQ resistance. It may be due to limitations such as a small sample size, a low number of DM patients with DM compared to non-DM patients, local prevalence of DM, and MDR-TB. To accurately study such associations, a large sample size with an adequate proportion of diabetic patients and a multicenter study may be helpful.

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