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Impact of diabetes mellitus on tuberculosis drug resistance in new cases of tuberculosis

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ABSTRACT

The objectives of this study were to determine the impact of diabetes mellitus (DM) on antituberculosis drug resistance in new cases of tuberculosis (TB). A case-control study was conducted on all newly diagnosed pulmonary TB adult patients with DM as cases and without DM as controls who were hospitalised from May 2013 to October 2013 in Iran. A molecular resistance test for rapid detection of resistance to isoniazid and rifampicin was done. Multivariate analysis was performed to determine the impact of DM on any anti-TB drug resistance. In total, 62 TB cases with DM and 64 TB cases without DM were included. TB cases with DM were more likely to be older (59 years vs. 43 years; $P = 0.001$). Two TB-DM patients had multidrug-resistant TB (MDR-TB) (3.2%) compared with no cases of MDR-TB in the control group, and more TB-DM cases had isolates that were resistant to at least one drug (12.9% vs. 10.9%). DM [odds ratio (OR) = 4.82, 95% confidence interval (CI) 1–23.57], age <40 years (OR = 5.48, 95% CI 1.19–25.29) and history of TB contact (OR = 5.86, 95% CI 1.69–20.36) remained significantly associated with any drug resistance in the multivariate analysis. In conclusion, new TB patients with DM are at increased risk of anti-TB drug resistance. More studies are needed to confirm these results.

1. Introduction

Among the most serious of challenges for physicians in the global fight against tuberculosis (TB) has been the emergence of multidrug-resistant TB (MDR-TB), defined as resistance to at least isoniazid (INH) and rifampicin (RIF), and extensively drug-resistant TB (XDR-TB), defined as MDR plus additional resistance to at least one of the quinolones and one of the injectable drugs [1–3]. Furthermore, the association between diabetes mellitus (DM) and TB is being increasingly demonstrated in most countries [4]. The relationship between the two diseases is important as DM has been shown to have an effect on anti-TB drug resistance, increasing the risk of MDR-TB and treatment failure as well as recurrence of TB after completion of treatment with a resistant strain [5–7].

There is a global epidemic of DM with a rising prevalence from 370 million in 2012 to a projected population of over 550 million by 2030 [4]. The prevalence of DM is estimated to be 24% in the general population aged >40 years, and ca. 10 million DM patients are currently living in Iran [8]. On the other hand, the prevalence of TB as of 2010 was estimated as 23 per 100,000 population in Iran, and MDR-TB comprised 2–5% of new TB patients [9]. However, in our referral hospital, the prevalence of MDR-TB and XDR-TB was high [10,11].

The majority of data up to now are from retrospective studies, some of which have reported high rates and others low rates of resistance to anti-TB drugs among DM patients [5,12,13]. There is no proven explanation regarding the impact of DM on drug resistance in TB. Thus, to better elucidate the association between TB drug resistance and patients with DM, drug resistance was compared among new TB patients with and without DM admitted and treated at the National Research Institute of Tuberculosis and

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Lung Diseases (NRITLD), Masih Daneshvari Hospital in Tehran, Iran. The aim was to determine whether patients with DM are at an increased risk of anti-TB drug resistance.

2. Materials and methods

2.1. Design

A nested case-control study of newly diagnosed TB patients who were admitted to the NRITLD was conducted from May to October 2013. TB diagnosis was made on the basis of a positive smear for acid-fast bacilli (AFB) and PCR. All new TB patients were treated with a standard four-drug regimen (INH, RIF, pyrazinamide and ethambutol for 2 months followed by INH and RIF for 4 months) based on national and international guidelines and, if necessary, were changed to other drugs [14]. Baseline laboratory measurements were evaluated at the beginning of treatment. Human immunodeficiency virus (HIV) testing was performed for all patients. In addition, a molecular resistance test for INH and RIF was done for all new TB patients with a positive sputum smear.

Fasting blood glucose (FBG) and glycosylated haemoglobin (HbA1c) were measured in all patients. Newly ascertained DM was diagnosed according to the World Health Organization (WHO) criteria, i.e. a FBG $\geq$ 126 mg/dL or HbA1c $\geq$ 6.5% [15]. Also, DM was diagnosed if patients had a history of known DM or were receiving antidiabetic agents. For patients with DM, additional evaluation included checking blood glucose and consultation with a nutritionist if deemed necessary by the treating physician. DM patients were managed by proper antidiabetic agents.

2.2. Mycobacteria laboratory

The Hain GenoType®MTBDR*plus* line-probe assay (Hain Life-Science GmbH, Nehren, Germany) for INH and RIF was performed for all patients with smear-positive sputum for the rapid detection of resistance to these drugs. Quality control of the referral laboratory is regularly supervised by the Swedish Institute for Infectious Disease Control (Solna, Sweden) and the Research Institute of Tuberculosis of the Japan Anti-Tuberculosis Association (Tokyo, Japan).

2.3. Patient selection

All new adult pulmonary TB patients with and without DM who were hospitalised in NRITLD were enrolled in this study. DM was diagnosed according to the WHO criteria, namely a FBG $\geq$ 126 mg/dL or HbA1c $\geq$ 6.5% [15]. Also, DM was diagnosed if patients had a history of known DM or were receiving antidiabetic agents. TB patients who had DM or newly diagnosed DM were included as cases. For each case, random controls without a history of DM and FBG $<$ 126 mg/dL or HbA1c $<$ 6.5% were selected. For both cases and controls, all pulmonary TB patients had a positive sputum AFB smear, PCR for *Mycobacterium tuberculosis* and molecular resistance test results.

2.4. Data variables, data sources and data collection

Patient data were obtained from a patient TB register into a paper-based pro forma. Data variables included age, sex, smoking status, drug abuse history, new or known DM, duration of symptoms, history of TB contact, presence of a cavitary lesion on chest radiography, grade of sputum smear, FBG level, HbA1c level and final molecular resistance test results. A molecular resistance test was defined as: sensitive if sensitive to both INH and RIF; mono-drug-resistant if resistant to INH or RIF; and multidrug-resistant (MDR) if resistant to both INH and RIF.

Data were entered into SPSS v.11.5 (SPSS Inc., Chicago, IL). All records were checked for completeness, reliability and precision.

2.5. Data analysis and statistics

All demographic and clinical information for TB patients were analyzed using SPSS v.11.5. Categorical variables were compared using the χ^2 or Fisher's exact test, and non-normally distributed continuous variables were compared using the Mann–Whitney *U*-test. A multivariate logistic regression was performed to determine whether DM was independently associated with any drug resistance. Other predictors were included in the model if they were associated with both DM and any drug resistance in bivariate analysis at $P < 0.2$. All reported *P*-values are two-sided.

Thirty-three patients were excluded from the final analysis because there was no *M. tuberculosis* DNA in their sputum sample.

3. Results

Of the 159 pulmonary TB patients who were admitted to hospital, 33 patients had no result for the molecular resistance test; thus, 62 cases with DM and 64 controls without DM were included in the analyses. The median FBG was 134 mg/dL [interquartile range (IQR) 103–216 mg/dL] and 99 mg/dL (IQR 90–123 mg/dL) among patients with and without DM, respectively. The median HbA1c among DM patients was 8.3% (IQR 7–10.3%). Known DM comprised 17 cases (27.4%) and the rest were newly diagnosed. Based on endocrinologist prescription, 22 patients were placed on insulin therapy during TB treatment. Demographic and clinical characteristics were similar between patients with and without DM, except that patients with DM were older, less smoked and more were female (Table 1). All patients included in the study were negative for HIV. All patients had pulmonary TB with positive smears for AFB and a PCR that was positive for *M. tuberculosis* DNA.

Of 126 patients, 111 (88.0%) had isolates with susceptibility to both INH and RIF. Fifteen patients had isolates with resistance to at least one drug (INH, RIF or both), among which 8 (53.3%) were in the DM group. Two DM patients had MDR-TB, one of whom died 70 days after the initiation of treatment (Table 2). All characteristics of patients associated with any drug resistance are shown in Table 3. After adjusting for age, sex, history of TB contact and presence of a cavitary lesion, the variables age $<$40 years, history of TB contact and DM (adjusted odds ratio = 4.82; $P = 0.05$) remained independently associated with any drug resistance (Table 4). Individual TB treatment was changed appropriately for the 15 patients with resistant isolates based on the national guidelines.

4. Discussion

The present study shows that DM patients are more prone to drug resistance, even after adjusting for other factors. Sensitivity to INH and RIF for the whole group was good, at 88.1%; however it was 87.1% in DM-TB patients compared with 89.1% in the control group.

In this study, the prevalence of RIF resistance was the same in both groups. However, all primary MDR-TB cases were in patients with DM, which is in accordance with other studies [5,12,16]. A recent study in Mexico documented that the development of drug- and multidrug-resistant TB is increased in patients with DM [17]. Resistance to RIF may possibly be related to a lower plasma concentration of RIF among DM patients [18].

Several studies have reported no relationship between DM and MDR-TB with consideration of previous TB treatment although they have not investigated this association just in new TB cases [19–21]. One mentioned hypothesis may be related to the protection of mycobacteria against oxidative damage and