Diabetes and Other Risk Factors for Multi-drug Resistant Tuberculosis in a Mexican Population with Pulmonary Tuberculosis: Case Control Study

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Background and Aims. Multidrug resistant tuberculosis (MDR-TB) poses problems in treatment, costs and treatment outcomes. It is not known if classically described risk factors for MDR-TB in other countries are the same in Mexico and the frequency of the association between diabetes mellitus (DM) and MDR-TB in our country is not clear. We undertook this study to analyze risk factors associated with the development of MDR-TB, with emphasis on DM.

Methods. A case-control study in the state of San Luis Potosí (SLP), Mexico was carried out. All pulmonary MDR-TB patients diagnosed in the state of SLP between 1998 and 2013 (36 cases) evaluated at a state pharmacoresistant tuberculosis (TB) clinic and committee; 139 controls were randomly selected from all pulmonary non-multidrug-resistant tuberculosis (non-MDR-TB) cases identified between 2003 and 2008. Cases and controls were diagnosed and treated under programmatic conditions.

Results. Age, gender, malnutrition, being a health-care worker, HIV/AIDS status, and drug abuse were not significantly different between MDR-TB and non-MDR-TB patients. Significant differences between MDR-TB and non-MDR-TB patients were DM (47.2 vs. 28.1%; p = 0.028); previous anti-TB treatments (3 vs. 0, respectively; p < 0.001), and duration of first anti-TB treatment (8 vs. 6 months, respectively; p < 0.001).

Conclusions. MDR-TB and DM are associated in 47.2% of MDR TB cases (17/36) in this study. Other recognized factors were not found to be significantly different in MDR-TB compared to non-MDR-TB in this study. Cost-feasible strategies must be implemented in the treatment of DM-TB in order to prevent the selection of MDR-TB.

Key Words: MDR-TB, Diabetes, Latin America.

Introduction

Tuberculosis (TB) remains a global public health problem (1,2). Multidrug-resistant TB (MDR-TB) is defined as a Mycobacterium tuberculosis strain that shows resistance to two or more drugs, at least simultaneously to rifampin.
(R) and isoniazid (H). Pulmonary infections caused by these strains are much more difficult and expensive to treat, with cure rates between 48 and 54% compared to 96% success in drug-susceptible pulmonary tuberculosis (DS-TB) (1–4).

The World Health Organization (WHO) has estimated 630,000 cases of MDR-TB worldwide (range 460,000–790,000) (1). WHO estimates that 3.7% of new TB cases and 20% of re-treatment cases are MDR-TB (1). According to the National Program for Tuberculosis Control and Prevention in Mexico, there were 18,848 new cases of tuberculosis in 2010 and 629 MDR-TB cases between the years 2010 and 2012 (5,6).

Many risk factors for the development of MDR-TB have been described but a history of multiple drug treatments is the most frequent factor (2,7–11). In Mexico, factors that have been reported in association with this condition include administration of monotherapy, treatment dropouts, long-term evolution of the disease, and multiple previous treatments (12,13). Other risk factors frequently reported in many countries (2,7–11) such as drug use, imprisonment, psychological disorders, HIV infection, and being a health-care worker have rarely been described in Mexican MDR-TB patients (6,12,13). The lack of Directly Observed Therapy Strategy (DOTS) is another risk factor in these studies; in Mexico DOTS is applied to 85–90% of DS TB patients (5). Mexico recommends a standardized treatment for all first anti-TB treatment recommended by WHO (14,15).

Diabetes mellitus (DM) has been clearly associated as a risk factor for TB; however, the prevalence of DM among TB patients varies widely (1.9–30%) in different studies. DM has also been shown to increase the risk of treatment failure (16–24). In the U.S. the frequency of DM among TB patients is higher in the Hispanic population (Mexican-Americans) than in other populations (17). The association of DM and MDR-TB is less clear and different studies have shown conflicting results with some reporting a significant association (25,26), whereas others have failed to do so (27,28); nevertheless, as DM has been associated with the number of cavities observed on chest films, delayed sputum conversion, and treatment failure (16,20,22), it is inferred to be a risk factor for MDR-TB. DM is present in 50% MDR-TB patients in Mexico (observational unpublished national data of MDR-TB patients between years 2010 and 2012; http://www.who.int/tb/mexico_pdf), the highest frequency for this association described in the world. Because of the elevated frequency of DM in Mexico compared to other countries (9.2% prevalence in the general population and 9.4–26.3% in persons between ages 40 and 69 years old (29), its impact on MDR-TB may be higher compared to other countries. Due to the elevated economic cost of treatment and high transmission risk of MDR-TB it is important to define the role of DM as a risk factor for this condition because this may lead to specific policies for the follow-up of DM-TB patients in Mexico. The objective of this study was to describe risk factors associated with pulmonary MDR-TB with emphasis in DM in a Mexican cohort of pulmonary non-MDR-TB and MDR-TB patients under programmatic conditions.

Materials and Methods

As of 1998, all patients with suspected MDR-TB in the state of San Luis Potosí (SLP) (total population 2,585,518 inhabitants according to the 2010 census) are referred to a multidisciplinary group for assessment, treatment, and follow-up (State Committee for MDR-TB). For this study, data from all cases ≥18 years of age with confirmed pulmonary MDR-TB evaluated from 1998–2013 by this committee was analyzed (n = 36). Patient assessment included a careful past treatment history obtained by a standardized protocol, sputum culture for mycobacteria, polymerase chain reaction (PCR) assay for Mycobacterium tuberculosis complex, and drug susceptibility test for first line antituberculosis drugs. HIV and general laboratory tests are performed in all MDR-TB cases as part of the initial evaluation. Drug susceptibility testing was done by the proportion method. All strains were tested at the Laboratorio Estatal de Salud Pública, a regional certified laboratory, for susceptibility to four first-line drugs as a policy of the Mexican Ministry of Health: the medium used was modified Middle-Brook 7H9–7H10-BACTEC™ MGIT™ 960 (30,31) and tests performed were for isoniazid (0.2 μg/mL), rifampin (2.0 μg/mL), streptomycin (4.0 μg/mL) and ethambutol (5.0 μg/mL). Resistance was defined as the growth of >1% of the colonies in drug-containing media compared with the growth in a drug-free (control) medium. All patients classified as MDR-TB had a positive culture and positive PCR test for M. tuberculosis as well as resistance to at least isoniazid and rifampin. In addition, 60% of samples from MDR-TB cases were also processed at the Instituto de Diagnóstico y Referencia Epidemiológicos (InDRE), a supranational laboratory for quality control that used Middlebrook 7H10- BACTEC™ MGIT™ 960 (30,31).

As a comparison group, we included information from patients treated in SLP for pulmonary TB during a 6-year period under programmatic conditions. For this group, 139 patients were randomly selected from all patients reported to the TB program in SLP between years 2003 and 2008 with sputum samples in which acid-fast bacilli were identified by Ziehl-Neelsen staining, with clinical-radiographic data compatible with the diagnosis of pulmonary TB and in whom resistance to rifampin and MDR-TB were excluded (non-MDR-TB). In Mexico it is not a standard practice to perform culture and drug susceptibility tests to all recently diagnosed cases of TB. The control population was selected from patients treated from 2003–2008.
because during this time period all pulmonary TB cases from SLP had drug susceptibility testing performed prior to first treatment as part of a project to determine primary MDR-TB frequency. All control subjects had sputum samples collected and *M. tuberculosis* was confirmed by culture and PCR; all controls were treated and followed accordingly to WHO and Mexican guidelines (14,15). All clinical, laboratory, and treatment outcomes were obtained from patient files and the state TB database (former EPI-TB, since 2007 Plataforma Unica de Informacion), which has been used since 1995 in the National Program for Tuberculosis Control in Mexico. Definitions of outcomes including death were according to WHO (32), except default for which the definition of Norma Oficial Mexicana was used (15). Data from MDR-TB cases as well as the comparison group were collected in standard forms including demographic, socioeconomic, clinical, and TB treatment-related variables. For all patients, DM cases were confirmed by two fasting serum glucose determinations (>126 mg/dL/70 mmol/L) and/or at least two abnormal glycosylated hemoglobin measurements (>7%); these data were supported by confirmation of the diagnosis of DM by the patient during follow-up and/or regular oral intake of a sulfonylurea. In the MDR-TB group, patients with DM were treated and followed-up by endocrinology specialists. To determine death rates in both groups, the national death certificate database of the Ministry of Health was consulted. Results were updated until October 2013. Initially we aimed to include four controls per subject (1:4 case/control ratio). Taking into account the observation of a high DM prevalence in MDR-TB patients from a preliminary analysis (9.2%), this would provide (40%) and the reported prevalence of DM in the Mexican population (9.2%), this would provide >95% power to detect a significant difference between both study groups with 95% confidence (29,33,34). In a subsequent analysis, taking into account the actual DM prevalence in the final study population, we obtained a 58.6% power to detect differences with 95% confidence. Patients’ characteristics between pulmonary non-MDR-TB and pulmonary MDR-TB subjects were analyzed. Continuous variables were compared using Student *t* test or Mann-Whitney *U* test according to data distribution. Categorical variables were compared using the *χ*² or Fisher’s exact test as appropriate. Odds ratios and 95% confidence intervals were calculated. Multivariate analysis was performed using logistic regression analysis. Statistical analyses were carried out using SPSS for Windows, version 14.0 and OpenEpi (35). A *p* value <0.05 was considered as significant. This study consisted of the review of existing databases and did not include any intervention. The study was approved by the Research and Ethics Committee at Servicios de Salud del Estado de San Luis Potosí.

### Results

Between 1999 and 2012 there were 4,293 cases of pulmonary TB diagnosed in San Luis Potosí. Among these, 1053 had drug susceptibility testing carried out between 2003 and 2008. Altogether, there were 36 patients with MDR-TB identified during this period. A total of 175 patients were analyzed in this study: the 36 cases of pulmonary MDR-TB and 139 controls of pulmonary non-MDR-TB (non MDR-TB); the control group was randomly selected from the 1053 pulmonary tuberculosis cases who had drug susceptibility testing prior to initiation of therapy (3.8 controls per case). The frequency of resistance to anti-TB medications in the control group were the following: isoniazid, 5.75%; rifampin, 0%; ethambutol, 2.2%; streptomycin, 3.6%. The demographic characteristics and comorbidities registered in the study subjects are presented in Table 1. There were two prisoners in the case population (one former and one current at the time of MDR-TB evaluation and treatment); in addition, two MDR-TB patients had COPD. There was no patient with HIV.

### Table 1. Demographic characteristics and comorbidities in MDR-TB and non-MDR-TB patients

<table>
<thead>
<tr>
<th></th>
<th>MDR-TB (<em>n</em> = 36)</th>
<th>Non MDR-TB (<em>n</em> = 139)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (77.8%)</td>
<td>96 (69.1%)</td>
<td>1.57</td>
<td>0.66–3.72</td>
</tr>
<tr>
<td>Age (years, mean, IQR)</td>
<td>47.5 (35–60)</td>
<td>50 (35–63)</td>
<td>1.01</td>
<td>0.99–1.03</td>
</tr>
<tr>
<td>Low income</td>
<td>29 (80.6%)</td>
<td>57/73 (78.1)</td>
<td>1.16</td>
<td>0.43–3.14</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td>11 (30.6%)</td>
<td>52 (37.4%)</td>
<td>0.74</td>
<td>0.33–1.62</td>
</tr>
<tr>
<td>Chronic alcohol abuse</td>
<td>10 (27.8%)</td>
<td>29 (20.9%)</td>
<td>1.46</td>
<td>0.63–3.37</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (25%)</td>
<td>19 (13.7%)</td>
<td>2.1</td>
<td>0.86–5.16</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>17 (47.2%)</td>
<td>39 (28.1%)</td>
<td>2.29</td>
<td>1.08–4.86</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>9 (6.5%)</td>
<td>0.19</td>
<td>0.01–3.31</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

aData available for 73 patients.

Some patients had more than one comorbidity.
infection among MDR-TB cases. There were no statistically significant differences in the history of smoking, alcohol abuse, or malnutrition between MDR-TB and non-MDR-TB patients (Table 1). However, the frequency of DM was significantly higher in patients with MDR-TB (47.2%, 17/36) compared to the non-MDR-TB group (28.1%, 39/139; OR 2.29, 95% CI 1.08–4.86). Because the prevalence of DM varies with age, and because smoking history differed between subjects with MDR-TB and non-MDR-TB (albeit not statistically significant), we decided to carry out a multivariate analysis to assess if the association between diabetes and MDR-TB was independent of other underlying conditions. In addition to age, sex, smoking history and DM, we included the presence of malnutrition, chronic alcohol abuse, and other underlying illnesses in the regression model. Multivariate logistic regression analysis indicated that the association between DM and MDR-TB was independent of other variables (adjusted OR 2.51; 95% CI 1.11–5.67).

Because DM prevalence increases with age, we analyzed the frequency of this disorder in different age groups. We also compared the frequency of DM in the study patients with the prevalence of this disorder in the Mexican population. The frequency of DM in both the MDR-TB (47.2%) and non-MDR-TB (28.1%) patients was much higher than the prevalence reported in adults in Mexico (9.2%) (29). The period of time since diabetes diagnosis ranged between 3 and 10 years before the first diagnosis of pulmonary TB among MDR cases.

Most non-MDR-TB patients (84.9%, 118/139) had never been treated previously for TB; in contrast, only one patient with MDR-TB had not been treated previously for TB (range 0−5 treatments; OR 14.99, 95% CI 6.1–36.82 when both groups were compared). When we compared the data from the first treatment that MDR-TB cases had ever received with the treatment received by the control patients, we found that patients with drug-resistant infections received treatment for longer periods of time (median 8 months vs. 6 months, OR 1.65, 95% CI 1.31–2.08) (Table 2). Of note, MDR-TB patients showed low clinical/bacteriological cure rates during their first treatment; 2.8% (1/36) had documented bacteriological cure. In 75%, treatment failure was documented, whereas in 19.4% (7/36) treatment outcome data were not available from the records. In contrast, control subjects had combined clinical/bacteriological cure rates of 89% (125/139). Directly observed treatment strategy (DOTS) during first anti-TB treatment was significantly lower among MDR-TB patients (Table 2).

Death occurred in 15/36 patients (42%) of MDR-TB group by October 2013, all due to TB. Nine deaths occurred in the control group (6.4%), eight during the study period and one more by the year 2013. Three were directly due to tuberculosis and six were non-TB related (two AIDS, two complications of DM, two due to malnutrition and other additional non-pulmonary bacterial infections).

### Discussion

This study compares pulmonary MDR-TB cases and pulmonary TB patients without MDR under programmatic conditions in a Mexican population. The characteristics of TB patients in this study are consistent with national data in terms of age, gender and other demographic features, prevalence of underlying disorders (including malnutrition, alcohol and other drug abuse, HIV/AIDS status, diabetes, among others), and cure rates (83.2%) as shown in national TB registries and large Mexican cohorts (5,16).

As reported in other national studies (12,13), in this report the number of previous anti-TB treatments (3 vs. 1), and the duration (8 vs. 6 months) and rate of failure (75 vs.

### Table 2. Comparison of treatment characteristics between MDR-TB and non-MDR-TB groups

<table>
<thead>
<tr>
<th></th>
<th>MDR-TB (n = 36)</th>
<th>Non-MDR-TB (n = 139)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of previous treatments (median, IQR)</td>
<td>3 (2–3.75)</td>
<td>0 (0–0)</td>
<td>14.99</td>
<td>6.1–36.82</td>
</tr>
<tr>
<td>Duration of treatment (months, median, IQR)</td>
<td>8 (6–12)b</td>
<td>6 (6–6)</td>
<td>1.65</td>
<td>1.31–2.08</td>
</tr>
<tr>
<td>DOTS</td>
<td>15 (53%)c</td>
<td>120 (86%)</td>
<td>0.18</td>
<td>0.07–0.44</td>
</tr>
<tr>
<td>Bacteriological cure</td>
<td>1 (2.8%)</td>
<td>104 (74%)</td>
<td>0.009</td>
<td>0.001–0.073</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>0</td>
<td>21 (15%)</td>
<td>0.07</td>
<td>0.004–1.28</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1 (2.8%)</td>
<td>2 (1.4%)</td>
<td>1.96</td>
<td>0.17–22.21</td>
</tr>
<tr>
<td>Not recorded</td>
<td>7 (19.4%)</td>
<td>10 (7.1%)</td>
<td>3.11</td>
<td>1.09–8.87</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>27 (75%)</td>
<td>2 (1.4%)</td>
<td>205.5</td>
<td>42.04–1004.51</td>
</tr>
<tr>
<td>Death by October 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB-related death</td>
<td>15 (42%)</td>
<td>3 (2.1%)</td>
<td>32.38</td>
<td>8.63–121.46</td>
</tr>
<tr>
<td>Non-TB related death</td>
<td>0</td>
<td>6 (4.3%)</td>
<td>0.28</td>
<td>0.01–5.11</td>
</tr>
</tbody>
</table>

DOTS, directly observed treatment strategy.

bFor MDR-TB cases, data (except the number of previous treatments) corresponds to the first TB treatment that the patient ever received; for non MDR-TB subjects, data corresponds to the treatment prescribed during the study episode.

cData available for 35 patients.

dData available for 28 patients.
1.4%) to first anti-TB treatment were significantly higher among MDR-TB patients compared to non-MDR-TB cases, respectively. Application of DOTS during the first anti-TB treatment was significantly lower among MDR-TB patients compared to non-MDR-TB cases (53 vs. 86%), respectively.

It is notable that risk factors for MDR-TB frequently reported in other countries (drug abuse, health care workers, HIV) were not significantly different between cases and control groups in this study (2,7–11) and this is supported by national data described previously in this report. Other known risk factors for MDR-TB such as low income, malnutrition, and alcohol were not significantly different between non-MDR-TB and MDR-TB groups.

The important finding in this study is the association between pulmonary MDR-TB and DM, present in 47.2% (17/36) of cases and these results are consistent with national data. In a national pulmonary MDR-TB cohort of Servicios de Salud de México involving all cases that started treatment for MDR-TB between years 2010 and 2012 (total = 629 cases), 50% had the association of MDR-TB and DM (6). The trend in frequency of this association has remained with little variation during this period of time at state (San Luis Potosí) and national levels, 42–48% and 45–50% respectively. Regarding the association of non-MDR-TB and DM, data from this study are consistent with national data as well as being demonstrated in two large cohorts. In a national cohort of Servicios de Salud de México including 19,491 cases (5), this association was present in 21% of all TB cases. In a recent study published by Jimenez-Corona and Ponce-de-León et al., frequency of DM in a cohort of 1,262 tuberculosis patients in Mexico was 29.6%. These figures are similar to the 28.1% found in non-MDR-TB patients in our study. Although the association between DM and TB is widely known, this is the first study to show that Mexico could have the highest frequency of DM among MDR-TB patients, but a national study is necessary to confirm this. This could be explained by a higher prevalence of DM in Mexico compared to other countries (29). Previous analyses of a smaller case series lead us to suspect this high association in Mexico (33,34). The frequency of the association of DM and MDR-TB is diverse in different regions. In a study in a mixed American-Mexican population near the Texas-Mexico border, Fisher-Hoch et al. found DM as a risk factor for MDR-TB, with a DM prevalence of 27.8% among MDR-TB cases (26). This association is considerably lower in other countries like China and India (14.5% and 5–8 to 11%, respectively) (36,37).

The association of DM and MDR-TB in Mexico can impact on the economic burden of treatment and the risk of MDR-TB transmission. In addition, it could have an impact on the generation of XDR-TB. Therefore, additional studies are warranted in our country to explore the potential causes for MDR-TB development among DM-TB patients.

Possible explanations for the increased frequency of MDR-TB among DM-TB patients include the following:

a) switching to the maintenance phase of anti-TB treatment (isoniazid and rifampin) in smear positive patients at the second month (16,36,38); b) a higher mycobacterial burden in DM-TB patients. In the same study by Jimenez-Corona et al., DM was associated with a higher frequency of cavities in chest x-rays, 45% among diabetics vs. 35% in non-diabetic patients (p < 0.001) (16); c) lower treatment adherence in DM-TB patients compared to those without DM although this has not been shown in other studies (16,21,37); in this report, 47% of MDR-TB patients were not treated under DOTS; d) obesity and glycemic control during anti-TB treatment with consequent alterations in immunity (39,40); e) a higher primary resistance to isoniazid among DM-TB patients although this has not been demonstrated in our country (12,16); and f) altered pharmacokinetic of anti-TB drugs and pharmacological interactions between anti-TB medications and sulfonylureas, mainly with rifampin where altered pharmacokinetics have been demonstrated (41,42).

Simple measures should be reinforced in patients with DM and pulmonary TB such as strengthening education to primary care physicians in charge of treatment of TB patients, apply DOTS to all patients treated for TB, change to second phase treatment with two drugs only when sputum conversion has been achieved and demonstrated; diagnose MDR-TB at the end of the second or at most at the fourth month of first anti-TB treatment, if rapid test or culture/drug-susceptibility tests are used, respectively; and refer patients to the state TB clinic after MDR has been demonstrated or patient remains with smear positive after the second month and culture has been performed.

There are other interventions that could be evaluated in DM-TB patients such as the use of rapid molecular tests. GeneXpert®, a test for rifampin resistance detection, has demonstrated an earlier diagnosis of MDR-TB and is cost-effective according to WHO recommendations (3). This measure seems already needed in Mexico given the high frequency of persistent smear positive at the end of the second month of four drug anti-TB treatment (46% in DM-TB and 37% in non-DM-TB patients) (16). It would be desirable to detect not only MDR-TB when it is already established, but also primary isoniazid resistance in patients with DM and first pulmonary TB diagnosis in order to offer appropriate treatment to decrease the probability to select multi-drug resistant strains during a standardized first anti-TB treatment. This can be achieved with the use of tests like Genotype® MTBDRplus. Although more expensive, it has demonstrated to be cost effective as well (3,43).
There are some potential changes in the treatment of DM-TB patients that could be evaluated in further studies such as increase in the dose of rifampin, controlling DM with insulin instead of oral drugs if uncontrolled DM is detected after the first month, select and appropriate treatment for patients with DM and TB and primary resistance to isoniazid. These measures could be evaluated in future studies in DM-TB patients.

The limitations of the study are the reduced number of cases, which may not be representative of all Mexican MDR-TB patients. Also, controls and cases were not recruited during the same period of time. Although according to the National Survey on Health and Nutrition there has been an increase in the prevalence of DM between 2000 and 2012 (29), the frequency of DM among MDR-TB cases in our cohort has remained very similar throughout the study period. Of note, our results are supported by similar rates of DM in both non-MDR-TB and MDR-TB in national data gathered during a long period of time.

In conclusion, DM is associated with MDR-TB in our region. Our study population appears to be consistent with national data for Mexican MDR-TB patients. Due to the high frequency of DM in Mexican MDR-TB patients and the high prevalence of DM in this country, future studies in this population must be conducted and development of specific recommendations for the treatment and follow-up of diabetic patients with TB may reduce the number of MDR-TB cases.

Conflict of Interest

The authors report no conflict of interest.

References