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Type 2 diabetes mellitus and its influence in the development of multidrug resistance tuberculosis in patients from southeastern Mexico

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ABSTRACT

Aims: To determine the factors associated with the presence of pulmonary tuberculosis in patients with type 2 diabetes mellitus and the effect in the development of drug and multi-drug resistance, in a population with tuberculosis from the southeast of Mexico.
Methods: This is a case–control study including 409 individuals, 146 with the binomial tuberculosis–type 2 diabetes mellitus and 263 individuals with tuberculosis. Demographic, epidemiological and outcome variables were collected. Risks were calculated.
Results: The factors associated with the presence of type 2 diabetes mellitus were age ≥35 years, (OR = 9.7; CI: 5.2–17.8), previous contact with a person infected with tuberculosis (OR = 1.7; CI: 1.1–3.1). Body mass index ≥25 kg/m^2 (OR = 2.2; CI: 1.1–4.3), and inherited family history of diabetes (OR = 5.4; CI: 3.2–9.2). It was also found that patients with tuberculosis–type 2 diabetes mellitus presented a 4.7-fold (CI: 1.4–11.3) and 3.5-fold (CI: 1.1–11.1) higher risk of developing drug- and multidrug resistance tuberculosis, respectively. By last, individuals with tuberculosis–type 2 diabetes had a 2.3-fold (CI: 1.5–4.1) greater chance of persisting as tuberculosis-positive by the second month of treatment, delaying the resolution of the tuberculosis infection.
Conclusions: Type 2 diabetes exerts a strong influence on the presentation and evolution of tuberculosis within the analyzed population and displays remarkable particularities, necessitating the development of dedicated tuberculosis–diabetes surveillance systems that consider the particular epidemiological characteristics of the population affected.

1. Introduction

According to the World Health Organization (WHO), in the world there are over 347 million people suffering from diabetes mellitus (DM), becoming a global epidemic. Projections indicate that by 2030 diabetes mellitus will become the seventh leading cause of death worldwide, and type 2 DM (T2DM) will be the responsible for 90% of cases. (Shaw, Sicree, & Zimmet, 2010; WHO, 2013b).

Although in the past, type 2 diabetes mellitus was recognized as a comorbidity of tuberculosis (Dooley & Chaisson, 2009; Wild, Roglic, Green, Sicree, & King, 2004), it was not until recent years that the increase in the prevalence of type 2 diabetes mellitus shown a significant impact in both tuberculosis and comorbidity, with rates ranging from 10% to 30%, mainly affecting developing countries. (Goldhaber-Fiebert, Jeon, Cohen, & Murray, 2011; Ponce de León et al., 2004; Shetty, Shemko, Vaz, & D'Souza, 2006; Singla et al., 2006; Wild et al., 2004). Furthermore, it has been demonstrated that this comorbidity also produces a significant increase in the generation of tuberculosis strains with single drug (DR) and multiple-drug (MDR) resistance (Dooley, Tanq, Golub, Dorman, & Cronin, 2009; Fisher-Hoch et al., 2008; Stevenson et al., 2007; Wada, 2000).

Several factors are involved in the development and outcome of both tuberculosis and type 2 diabetes mellitus comorbidity (TB-T2DM); the most commonly described are low or null education, male gender, low socioeconomic status, malnutrition, being overweight and presenting poor glucose control, however, percentages and levels vary depending on the populations involved (Amare, Gelaw, Anagaw, & Gelaw, 2013; Baldé et al., 2006; Ezung, Devi, & Singh, 2002; Jeon & Murray, 2008; Magee et al., 2013; Ponce de León et al., 2004; Reis-Santos et al., 2013; Restrepo et al., 2007; Shetty et al., 2006; Singla et al., 2006).

According to the Mexican Health Secretary, in 2013 the prevalence of T2DM was 414 per 100,000 habitants, and the incidence of pulmonary TB was 13.52 per 100,000 habitants, while the prevalence of TB-T2DM comorbidity was 21% (Epidemiological profile of

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tuberculosis in Mexico, 2012). This constitutes one of the highest comorbidities in an American country. Despite these figures, the characteristics associated with comorbidity in Mexican population are poorly understood, and studies have either been conducted in the context of a bi-national Mexico–United States population (Restrepo et al., 2007) or focused on very specific locations (García-García et al., 2001; Pérez-Navarro, Fuentes-Domínguez, Morales-Romero, & Zenteno-Cuevas, 2011; Ponce de León et al., 2004).

For these reasons, the aims of this study were to determine the factors and risks associated with the development of comorbidity and the outcome variables in a representative sample of patients with TB and TB-T2DM throughout the State of Veracruz, Mexico.

2. Methodology

2.1. Determination of population size, retrieval and analysis of epidemiological and clinical data

This is a case-control study; individuals included were from throughout the state of Veracruz, including the regions with highest incidence of TB in the state; they were diagnosed and treated by the Mycobacteriosis state program. The inclusion period was from January 2011 to October 2013. Patients with a diagnosis of pulmonary tuberculosis (TB) were considered controls and patients with a diagnosis of pulmonary tuberculosis and type 2 diabetes mellitus (TB-T2DM) as cases. The criterion for the diagnostic of T2DM followed the national regulations (NOM-015-SSA2-2010) and was conducted by the attending physician: Individuals who had fasted for at least 8 hours and showed a plasma glucose concentration $\geq$126 mg/dl were considered diabetic.

Determination of the population was based considering the comparison of the frequency of exposure to the variable drug resistant tuberculosis, according to reports from frequencies of exposure were 36% and 10% in the case and control groups respectively. Both the confidence level and test power were 95%. Calculations were performed using the Epidat 3.1 software, estimating a minimum sample size of 54 and 108 individuals in the case and control groups, respectively. Exclusion criteria were being infected with human immunodeficiency virus (HIV) and being less than 15 years old.

2.2. Retrieval of epidemiological and clinical data

Epidemiological and clinical variables were recovered by administering a questionnaire developed previously by our group (Pérez-Navarro et al., 2011). The variables considered were age, sex, socio-economic status, illiteracy, incidence of domestic overcrowding, belonging to an ethnic group, place of residence, alcohol and tobacco consumption, previous contact with a person infected with TB, active or sedentary lifestyle, body mass index (BMI), inherited family history of type 2 diabetes (IFH of T2DM), drug sensitivity test and glycemic value at the moment of TB diagnosis. Finally, we included information relating to the sputum smear taken at the time of diagnosis and subsequent monitoring, following the first three months of treatment.

2.3. Statistics and patient characteristics

Analysis of data was carried out using descriptive and analytical statistics. Estimation of mean differences was determined with a *t* test, while a *z* test was used to determine significant differences between groups, considering a value of $p < 0.05$ to be significant.

We estimated odds ratios (OR) and 95% confidence intervals (CI) by using chi square test with Yates's correction, where $p < 0.05$ was considered as significant. Finally, a multivariate analysis was performed, adjusting for the variable of age (<35 and $\geq$35 years). The statistical packages SPSS 15 and Epidat 3.0 were used for the calculations.

2.4. Ethical considerations

No physical interventions were developed in the patients, ethical considerations were strictly observed and all the collected information was treated as confidential, with prior written consent obtained from each patient. The committee of the Public Health Institute of the University of Veracruz oversaw the ethical issues derived from this study.

3. Results

3.1. Epidemiological characteristics of the population

Table 1 shows the general characteristics of the 409 individuals included in this study. The members of the case group “TB-T2DM” numbered 146 (36%), while the control group "TB" numbered 263 (64%). Comparison of mean age showed significant differences in the group TB-T2DM *vs.* TB (51.2 ± 11.2 *vs.* 38.7 ± 18.8; $p < 0.001$). However, two-cluster stratification of the variable age showed that age $\geq$35 years was a factor that increased the risk of developing comorbidity 9.7-fold. Previous TB contact and IFH of T2DM were identified as factors that increased close to 2- and 5-fold the risks of developing comorbidity (Table 1).

Significant differences were observed between both groups in terms of BMI. To be <18.5 kg/m2 was found as a protective factor against comorbidity. Stratification of BMI in two categories, $\geq$ and <25 kg/m^2, showed significant differences between the groups, and BMI $\geq$25 kg/m^2 provided a two-fold higher risk of comorbidity (Table 1).

3.2. Clinical characteristics and outcome of the population

Information relating to certain baseline clinical characteristics and outcome in both groups can be found in Tables 2 and 3. In addition, the occurrence of T2DM prior to TB diagnosis was found in 126 (86%) individuals with a mean for the progression of T2DM of 6.5 ± 5.6 years.

Oral hypoglycemic agents for the control of glucose were prescribed in 137 (93%) patients with type 2 diabetes; however, it was only possible to obtain the glucose values of 77 (53%) individuals, producing a mean value of 142 ± 86 mg/dl.

No associations were found in relation to diagnostic method, type of case, treatment and hospitalization; however Table 3 shows the first-line drug resistance profiles of 28 (7%) individuals who developed resistance.

Risk estimation showed that comorbidity was a factor that increased the development of DR-TB and MDR-TB 4.7-fold and 3-fold, respectively. Estimations for each one of the first line drugs showed that comorbidity increased 5.1-fold the risk of developing resistance to isoniazid, 3.5-fold to rifampicin and 9.7-fold to pyrazinamide.

3.3. Sputum smears evolution and influence of T2DM

The positive sputum smear evolutions of both groups are presented in Fig. 1. At the moment of initial diagnosis, the TB-T2DM group presented a higher bacillary load. It is remarkable that the occurrence of more than one bacillus per microscopy field in the groups showed differences during the initial diagnosis (65% *vs.* 55%), and in the first (40% *vs.* 23%), second (18% *vs.* 7%) and third (17% *vs.* 10%) month of treatment.

In addition, comorbidity was found to be a factor that increases the occurrence of more than one bacillus per field in the first (2.3 fold) and second (2.7 fold) month of treatment. Finally, we observed that patients with TB-T2DM had a 2.4-fold higher chance of persisting as TB-positive by the second month of treatment.