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Associated Risk Factors for Latent Tuberculosis Infection in Subjects with Diabetes

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Background and Aims. Type 2 diabetes mellitus (DM2) confers a higher risk for active tuberculosis (TB). However, information on associated risk factors for latent tuberculosis infection (LTBI) inpatients with DM2 is limited. We conducted a cross-sectional study to elucidate the prevalence of LTBI and its associated factors on Mexican adults with DM2 receiving medical care at the Mexican Social Security Institute (IMSS).

Methods. Six hundred patients with DM2 without a prior history of TB from outpatient diabetes clinics were enrolled in the study. The tuberculin-skin-test (TST) was performed. The presence of LTBI was defined by a TST value of ≥5 mm. A standardized interview and physical examination were conducted to obtain clinical, demographic, and LTBI risk factor information; all subjects were laboratory tested to determine the presence of exclusion criteria. Microscopic examination of sputum samples and chest x-rays was performed to identify potential active TB. Subjects with any finding suggesting active TB or malignancy were excluded. A logistic regression model was used to identify variables associated with LTBI.

Results. LTBI prevalence among patients with DM2 was 51.3%. Risk factors for LTBI were living with a relative with TB, having been in prison, having hemoglobin values >14 g/dL, and glycosylated hemoglobin (HbA1c) values of >7%. Blood pressure, economic income, or anthropometric measurements were not associated risk factors.

Conclusions. Over one half of patients with DM harbor LTBI. Exposure to certain environmental conditions and poorly controlled DM2 (HbA1c >7.0%) were risk factors for having LTBI in persons with DM2.

Key Words: Latent tuberculosis, Diabetes mellitus type 2, Risk factors.

Introduction

According to the World Health Organization (WHO), 347 million persons worldwide are currently suffering from diabetes mellitus (DM), mainly type 2 diabetes mellitus (DM2) (1), one third of the world's population has latent tuberculosis infection (LTBI) and 8.6 million individuals developed tuberculosis (TB) in 2012 (2). In the same year, The Ministry of Health in México reported a TB prevalence of 16.8 cases/100,000 inhabitants, without official data regarding LTBI prevalence. In Mexico, the bacillus Calmette-Guérin (BCG) vaccine is applied at birth with a coverage of >95% (3). The association between DM and TB has been suggested for some time (4,5); however, comorbidities of these diseases were not reported until

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80 years ago and are now firmly established (6,7). The association between these diseases is of greater importance for populations with low socioeconomic status and high prevalence rates of both conditions (6) but, as the result of globalization and high migration rates, detecting patients with DM and who are at risk for active TB is a global public health challenge (8). As in other countries, in Mexico there is an increase in the frequency of TB among patients with DM2, and a higher frequency of DM2 among individuals with TB, regardless of whether human immunodeficiency virus (HIV) infections have been reported (6,9–11). Given the worldwide distribution of these pathologies, the comorbidity of DM2-TB is expected to occur more frequently in regions with low income and/or poor healthcare services (6). Other risk factors for the comorbidity of active TB in patients with DM include low body weight (12), poor glycemic control (13–16) and nutritional deficiencies (17,18).

It is well known that DM affects the immune system, impairing chemotaxis, phago- and monocyte activity, and also increasing T-cell activity. All these alterations are present during acute hyperglycemia (14,19). In addition, in patients with DM2, a decrease in circulating levels of Interferon gamma (IF-γ), interleukin 2 (IL-2), tumor necrosis factor α (TNF-α), and IL-17F (all of these implicated in the immune control of TB) have been reported (20). Although the association between DM2 and active TB is well established (9,11,21), the factors involved in the association between DM2 and LTBI are scarcely known and there are discrepancies (22–24) or no association at all (25–27). Over one quarter of patients with DM2 harbor LTBI (11,22–24). Given that reactivation of LTBI is influenced by the immune system, subjects with DM and LTBI may carry a greater risk for TB reactivation.

The tuberculin skin test (TST) is the most used diagnostic test for LTBI, and it measures the cellular immune response against *Mycobacterium tuberculosis* (*Mtb*) antigens. Considering that patients with DM2 present deficiencies with regard to the immunity (28,29), it is possible that the current cut-off value for TST considered to detect LTBI in patients with DM2 is higher than it should be; therefore, it exhibits lower sensitivity with respect to persons without DM2.

To gain insight into the association of LTBI and DM2, we conducted a cross-sectional study aimed at determining the risk factors associated with LTBI in Mexican adults with DM2 and the prevalence (using a TST ≥5-mm cut-off point) of LTBI in patients affiliated with the Mexican Social Security Institute (IMSS) in Durango and Zacatecas, states located in northern Mexico.

Materials and Methods

Study Design and Characteristics

With the approval of the Institutional Research Scientific and Ethics Committee (IMSS, 33-0119) and, after obtaining signed informed consent from the participants, we conducted a cross-sectional study. Subjects with a medical history of DM receiving hypoglycemic drugs and/or insulin treatment at IMSS primary healthcare services of Durango City, Durango, Guadalupe and Zacatecas, Zacatecas (cities located in the central region of Northern Mexico) were randomly selected and recruited between October 2006 and June 2007. We collected information on the entire population with a diagnoses of DM recorded at the primary Medical Care Units previously mentioned. A total of 11,587 (6,450 from Zacatecas, and 5,137 from Durango) electronic files were reviewed; a nominal list of eligible subjects was obtained, and a random selection of patients with DM was performed according to a computer-generated random numbers list. Clinical and laboratory tests were carried out to exclude patients with active TB. Patients who refused to participate were replaced, utilizing the same nominal list and random procedure. Health workers in the field visited the homes of the selected subjects, and adult men and non-pregnant women were invited to participate in the study. A standardized interview and physical examination were conducted to obtain clinical, demographic, and LTBI risk factor information; all subjects were laboratory tested in order to determine the presence of exclusion criteria. Use of immunosuppressant's or previous LTBI treatment was considered a reason for exclusion. Also, microscopic examination of sputum samples and chest x-rays was performed to identify potential active TB infection only in subjects with signs or symptoms suggestive of active TB. Chest x-ray and sputum samples were reviewed by two experts in the field. Subjects with any finding suggesting of active TB or malignancy were excluded from the study.

TST Application and Interpretation

TST, i.e., Mantoux test, was performed on the volar side of the forearm employing a 5-UT dose of purified protein derivative PPD-S (Tubersol, Aventis Pasteur). TST were administered and measured by trained health promoters, and any induration was measured (in mm) after 72 h using the ballpoint pen technique method (30). Indurations of ≥5 mm were considered positive. Subjects with a positive TST but with no evidence of active TB were considered as having LTBI.

Definitions and Risk Factor Assessment

Individuals were allocated into two groups: TST-positive or TST-negative. Risk factors analyzed by questionnaire included the following: unemployment or annual income <$500 U.S. dollars (USD); living with a relative with TB; living in overcrowded conditions; a history of being in prison; a history of working in healthcare institutions and/or mines; cigarette smoking; use of illegal drugs, and alcohol consumption. Previous contact with a patient with TB, age, a clinical history of DM, and kidney failure were