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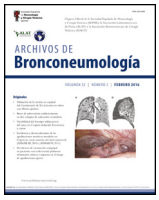

Original Article

Diabetes is Associated With Severe Adverse Events in Multidrug-Resistant Tuberculosis☆

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ABSTRACT

Introduction: Diabetes mellitus (DM), a very common disease in Mexico, is a well-known risk factor for tuberculosis (TB). However, it is not known by which extent DM predisposes to adverse events (AE) to anti-TB drugs and/or to worse outcomes in patients with multidrug-resistant (MDR-TB) and extensively drug-resistant TB (XDR-TB). The main objective of this study was to describe the outcomes of TB treatment, the impact of DM and the prevalence of AE in a cohort of patients with MDR-/XDR pulmonary TB treated at the national TB referral centre in Mexico City.

Results: Ninety patients were enrolled between 2010 and 2015: 73 with MDR-TB (81.1%), 11 with pre-XDR-TB (12.2%) and 6 (6.7%) with XDR-TB, including 49 (54.4%) with DM, and 3 with Human Immunodeficiency Virus (HIV) co-infection (3.3%). In 98% of patients, diagnosis was made by culture and drug susceptibility testing, while in a single case the diagnosis was made by a molecular test. The presence of DM was associated with an increased risk of serious drug-related AEs, such as nephrotoxicity (Odds Ratio [OR]=6.5; 95% Confidence Interval [95% CI]: 1.9–21.8) and hypothyroidism (OR=8.8; 95% CI: 1.8–54.2), but not for a worse outcome.

Conclusions: Our data suggest that DM does not impact second-line TB treatment outcomes, but patients with DM have a higher risk of developing serious AEs to drug-resistant TB treatment, such as nephrotoxicity and hypothyroidism.

La diabetes se asocia con reacciones adversas graves en la tuberculosis multirresistente

Palabras clave:
Tuberculosis
Tuberculosis multirresistente
Diabetes mellitus
Reacciones adversas
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RESUMEN

Introducción: La diabetes mellitus (DM), una enfermedad muy frecuente en México, es un factor de riesgo bien conocido para el desarrollo de tuberculosis (TB). Sin embargo, se desconoce en qué medida la DM predispone al desarrollo de reacciones adversas (RA) a los fármacos anti-tuberculosis y/o si predispone a un peor resultado en pacientes con pacientes con TB multirresistente (TB-MR) y TB extremadamente resistente (TB-XR). El objetivo principal de este estudio fue describir los resultados del tratamiento anti-tuberculosis, el impacto de la DM y la prevalencia de RA en una cohorte de pacientes con TB pulmonar MR/XR tratados en el centro de referencia nacional para TB, en la Ciudad de México.

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Resultados: Entre 2010 y 2015 se incluyeron 90 pacientes —73 con TB-MR (81,1%), 11 con TB pre-XR (12,2%) y 6 (6,7%) con TB-XR—, 49 (54,4%) de los cuales tenían DM y 3 con co-infección por el virus de la inmunodeficiencia humana (VIH) (3,3%). El diagnóstico se realizó mediante cultivo y pruebas de fármacosensibilidad (PFS) en el 98% de los pacientes y mediante prueba molecular en un caso. La presencia de DM se asoció con un mayor riesgo de RA graves, tales como nefrotoxicidad (odds ratio [OR] = 6,5; intervalo de confianza del 95% [IC 95%]: 1,9–21,8) e hipotiroidismo (OR = 8,8; IC 95%: 1,8–54,2), aunque no con peor resultado del tratamiento.
Conclusiones: Nuestros datos sugieren que la DM no tiene un impacto sobre los resultados del tratamiento anti-tuberculosis de segunda línea, pero los pacientes con DM tienen mayor riesgo de presentar RA graves secundarias al tratamiento, tales como nefrotoxicidad e hipotiroidismo.

Introduction

The Region of the Americas accounts for <10% of the global total of tuberculosis (TB) cases, the lowest burden of TB in the world[1]; however, it is among the regions with the highest prevalence of diabetes mellitus (DM): 11.4% according to the International Diabetes Federation.[2] DM is a known risk factor for the development of TB (it increases the risk between 2 and 4 fold) depending on the population.[3]

During the last decade, a decreasing trend in TB cases has been reported in Mexico; however, there is also a persistent increase in cases of multidrug-resistant tuberculosis (MDR-TB; *Mycobacterium tuberculosis* strain resistant to, at least, isoniazid and rifampicin)[4] and extensively drug-resistant TB(XDR-TB) (an MDR strain with additional resistance to a fluoroquinolone and to, at least, one second-line injectable drug).[5]

Mexico, in particular, is facing an overall increasing rate of DM, from 5.8% in 2000 to 9.2% in 2012.[6] To date, it is not clear by which extent DM predisposes to worse outcomes in MDR-TB patients and/or to adverse events (AE) of anti-TB drugs.

The main objective of this study, therefore, was to describe the outcomes of TB treatment, the impact of DM and the prevalence of AE in a cohort of patients with MDR/XDR pulmonary TB treated at the national TB referral centre in Mexico City.

Methods

The study was performed under a cooperative project, which involved the Mexican National Tuberculosis Programme, the *Instituto Nacional de Enfermedades Respiratorias* (INER) in Mexico City, the International Union Against Tuberculosis and Lung Disease, the *Asociación Latinoamericana de Tórax*, and the European Respiratory Society (ERS/ALAT SinTB project). The INER, as the national reference centre for TB, receives mostly uninsured patients from several Mexican states, the majority from Mexico City and neighbouring states.

This is a retrospective study based on a review of the clinical charts of drug resistant pulmonary TB patients monitored at the INER's tuberculosis clinic; therefore no special approval by the institutional ethics committee was required. The study was not interventional, and confidentiality was ensured.

In Mexico, culture and drug susceptibility tests (DST) are only performed in patients suspected of having drug-resistant TB, e.g. patients with a history of previous treatment. Mycobacterial culture and DST are carried out at national reference laboratories, including the INER Clinical Microbiology Laboratory (which belongs to the network of World Health Organization (WHO) reference Laboratories).

All pulmonary samples were decontaminated by the modified Petroff method and were grown on Löwenstein-Jensen medium and in BACTEC-960 Mycobacterial Growth Indicator Tubes (MGIT). Identification was made using molecular methods and DST was performed using the following doses: isoniazid (0.1 μg/ml and 0.4 μg/ml); rifampicin (1.0 μg/ml); ethambutol (5.0 μg/ml); streptomycin (1.0 μg/ml), and pyrazinamide (100.0 μg/ml). After 2013, all samples resistant to, at least, rifampicin (RR-TB) were also tested for the following second-line drugs: amikacin (1.0 μg/ml); kanamycin (2.5 μg/ml); ofloxacin (2.0 μg/ml), and ethionamide (5.0 μg/ml), which was previously performed only if requested and if the resource was available.

Once the diagnosis of RR-TB or MDR-TB was established, a pulmonary physician evaluated all patients, focussing particularly on anti-TB drug history and the presence of other co-morbidities such as DM, Human Immunodeficiency Virus (HIV) infection, and chronic kidney failure. All patients underwent blood tests as part of the routine pre-treatment assessment or during the first week of therapy. DM was defined as fasting blood glucose >126 mg/dL in patients with no known history of DM; in patients with a previous history of DM, evolution and treatment type were also assessed. In addition, blood biometry, blood chemistry, glycated haemoglobin (HbAC1), thyroid-stimulating hormone (TSH) at baseline and final visits were performed.

The placement of an indwelling central venous line for intravenous (IV) drug administration was offered to all patients on admission to hospital (standard double lumen central venous line, 7 Fr, Arrow International or a peripherally inserted central double lumen catheter,5 Fr Groshong, BARD Access Systems, Inc.). After discharge (2 weeks on average), treatment was administered in a primary care centre (PCC) under strict directly observed therapy (DOT).[7,8] Follow-up was performed monthly during the intensive phase of treatment, and thereafter every 2 months until treatment completion (20–24 months). At each visit, blood tests were requested to assess AE and a sputum sample for culture was obtained to monitor treatment. DST was repeated only if the patients did not convert culture after 6 months of treatment.

All treatment regimens were individualized and based on WHO and Mexican guidelines,[9–12] the patient's anti-TB drug history, and the *M. tuberculosis* culture and DST results. Each regimen included at least 4 active drugs. Drug was considered to be active on the basis of DST results coupled with evidence that the patient had not taken the drug for 30 days or more. The regimens always included at least 1 fluoroquinolone (ofloxacin, levofloxacin, or moxifloxacin), 1 second-line injectable drug (amikacin, kanamycin, capreomycin), and 1 of the former WHO group 4[13–15] (prothionamide, cycloserine, para-aminosalicylic acid [PAS]) or group 5[16] (linezolid, amoxicillin/clavulanate, and high-dose isoniazid) drugs, if necessary. The prescription of each drug was based on the patient's body weight and the presence of co-morbidities such as DM, chronic kidney failure, and a history of central nervous system or psychiatric disorders. All drugs were provided by the National Tuberculosis Programme (NTP) and were administered from Monday to Saturday at the PCC. All patients were prescribed pyridoxine (at