

Glycemic Control and Rate of Sputum Conversion in Diabetic Patients with Pulmonary Tuberculosis

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Received date: Dec 21, 2015; Accepted date: Feb 10, 2016; Published date: Feb 17, 2016

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Abstract

Introduction

The negative impact of DM and glycemic control on tuberculosis outcomes has been the subject of controversy. Twenty percent of tuberculosis (TB) cases in México are also diabetic; adequate control of glycaemia in Mexican patients due to several socioeconomic factors is rarely accomplished. Our objective was to determine the impact of glycemic control on sputum conversion and to compare the time for sputum smear and culture conversion amongst TB patients with or without diabetes.

Setting

Referral center for drug-resistant TB and TB complications. Retrospective analysis of cases treated during a five-year period.

Results

88 patients were referred for treatment; 30 patients (34.1%) had DM as a comorbidity. Twenty-seven (30.6%) had TB due to a multidrug resistant (MDR) strain; of the 30 TB-DM patients, 13 had MDR-TB (43.3%).

During follow-up, 27.6% of TB patients had converted their culture by day 60 vs. 26.6% of the TB + DM patients ($p = 0.58$). Culture conversion for TB + DM patients with $HbA1c \geq 6.5\%$ took 74.7 ± 32.2 days vs. 90.0 ± 25.3 days in patients with TB + DM and an $HbA1c < 6.5\%$ ($p = 0.26$).

Conclusion

Time for smear and culture conversion was not significantly different in patients with TB and patients with TB + DM, including cases with inadequate glycemic control and those with MDR-TB.

Keywords: Tuberculosis; Diabetes; Bacteriological conversion; Glycaemia

Introduction

DM Mellitus (DM) is a known risk factor for the development of active tuberculosis (TB), and an estimated 15% of patients with TB in countries with a high TB burden have DM [1].

The negative impact of DM and glycemic control on tuberculosis outcomes has been the subject of controversy. The bacteriological conversion has been reported to be slower in patients with DM in comparison to that of non-diabetic patients in some reports [2-4], and uncontrolled DM ($HbA1c \geq 7$) has been reported as a significant risk factor for positive sputum culture after two months [5]. Other reports, however, do not show DM to be an independent risk factor associated

with increased time to sputum conversion [6] or any relation between DM and sputum conversion rate at the end of the 2nd month [7,8].

The prevalence of DM in México has increased alarmingly in the past two decades and it currently causes 14% of all deaths in the country. DM is one of the main comorbidities associated to TB in Mexico; 20% of TB cases in México are also diabetic [9]. Adequate control of glycaemia in Mexican patients is very rare; in a national survey, only 6.6% of those diagnosed with DM had $HbA1c < 7\%$ [3,10].

Our objective was to determine the impact of glycemic control on sputum conversion and to compare the time for sputum smear and culture conversion amongst TB patients with or without diabetes.

Material and Methods

The Tuberculosis Clinic at the Tijuana General Hospital, Mexico is a regional referral center for patients with drug-resistant TB and TB in special situations (adverse reactions to drugs, pregnancy, etc.) located in Tijuana, Mexico. Tijuana is the city with the highest TB rate (50 per 100,000 h) in Mexico.

A review of the clinical charts for the period June 2009-December 2014 was carried out to extract demographic, clinical and microbiologic data for patients treated during that period. All cases had baseline culture and drug susceptibility tests (DST) for first-line drugs (MGIT 960°, Beckton Dickinson, New Jersey) as well as monthly Lowenstein-Jensen solid cultures during clinical follow-up. Second line DST was carried out (MGIT and pyrosequence) for rifampin-resistant and MDR-TB cases. Monthly central glycaemia and glycosylated hemoglobin (HbA1c) every 3 months were obtained for patients with TB+DM. Patients with DM were treated with metformin and dietary restriction. All our patients are under strict DOT by a health promoter.

The study protocol was reviewed and authorized by the Ethics Committee of the institution. Data was analyzed for descriptive and inferential statistics. Differences in categorical variables were analyzed utilizing the χ^2 test. The independent samples t-test was used for the analysis of culture conversion time. The analysis was performed with the commercial statistical package SPSS version 21 (IBM Corporation, Armonk, New York).

Results

During this period 71 (80.7%) patients with drug-resistant TB (DR-TB) and 17 patients (19.3%) with adverse reactions to antituberculosis drugs (ARTD) were referred for treatment; 30 patients (34.1%) had DM as a comorbidity and 58 (65.9%) did not. Seventy-nine (89.7%) were discharged as cured and 1 patient (1.1%) failed (non-diabetic). Seven patients (7.9%) were lost to follow-up and one patient (1.1%) was transferred to another state; these 8 patients had converted their culture before they were lost to follow-up.

Of the DR-TB cases, 23 (32.4%) harbored a mono-resistant strain (8 were also diabetic), 21 (29.5%) had a poly-resistant strain (7 were diabetic) and 27 (38.0%) had a multidrug-resistant (MDR) strain; 13 of this later group were also diabetic. Of the 30 TB-DM patients, 13 had MDR-TB (43.3%).

Twenty of the 54 males in the sample were diabetic (37.0%) vs. 8 of 34 females (23.5%, $p = 0.07$). Table 1 compares demographic and clinical data of TB patients with and without DM. Patients with TB + DM were significantly older than TB patients without DM.

Variable	TB+DM	TB	p
Age (years)	50.6 ± 12.4	33.2 ± 12.8	< 0.0001
Body Mass Index (BMI)	23.3 ± 5.3	20.17 ± 3.4	0.026
Baseline central glycaemia	173.0 ± 73.5	92.9 ± 9.7	< 0.0001
Central glycaemia at time of conversion	168.5 ± 89.5	92.1 ± 13.2	< 0.0001
Smoking (pack years)	2.93 ± 7.5	2.70 ± 7.7	0.89
Treatment regimens for TB in the past	1.81 ± 3.7	1.70 ± 8.9	0.62

History of TB (years)	1.87 ± 3.7	2.24 ± 4.4	0.69
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Table 1: Demographic and clinical baseline variables.

Table 2 utilizing the of days needed for smear and culture conversion; 27.6% of TB patients had converted their culture by day 60 vs. 26.6% of the TB + DM patients ($p = 0.58$). Patients with TB + DM that had an average HbA1c $\geq 6.5\%$ converted their sputum smears in 68.9 ± 52.3 days vs. 110.7 ± 47.2 days in patients with TB + DM and a HbA1c $< 6.5\%$ ($p=0.11$). Culture conversion for TB + DM patients with HbA1c $\geq 6.5\%$ took 74.7 ± 32.2 days vs. 90.0 ± 25.3 days in patients with TB + DM and HbA1c $< 6.5\%$ ($p = 0.26$). There were no significant differences amongst the groups in the extent of pulmonary lesions as measured by the number of affected quadrants (1.53 ± 0.7 for TB + DM vs. 1.53 ± 0.7 for TB; $p = 0.82$), the number of lung cavities (1.27 ± 0.9 vs. 1.33 ± 1.3 ; $p = 0.26$) and the presence or absence of mediastinal retraction (16.1% vs. 27.6%; $p = 0.17$) as shown in the chest radiograph.

Variable	TB + DM	TB	p
Affected quadrants in the chest	1.73 ± 0.87	1.53 ± 0.75	0.82
Number of lung cavities	1.27 ± 0.98	1.33 ± 1.36	0.26
Mediastinal retraction	16.1%	27.6%	0.17
Smears: time to conversion (days)	77.8 ± 48.1	71.6 ± 51.5	0.59
Culture: time to conversion (days)	80.3 ± 28.1	88.6 ± 42.7	0.33

Table 2: Disease severity and time to bacteriologic conversion.

There were no significant differences between patients with TB + DM and patients with TB in time to conversion when patients with a mono-resistant strain are classified according to resistance to a specific drug. Patients with MDR-TB and DM converted their culture in 93.5 ± 57.5 days vs. $75.9 \pm$ days for patients with MDR-TB without DM ($p = 0.07$). Patients with MDR-TB + DM and adequate glycemic control (HbA1c $< 6.5\%$) converted their culture in 90.5 ± 32.7 days vs. 65 ± 44.1 days for patients with MDR-TB + DM and inadequate glycemic control ($p = 0.36$).

Discussion

DM is a well-known predisposing factor for the development of active TB and is a highly prevalent co-morbidity in patients with DR-TB, with rates up to 20% in patients with MDR-TB [1].

The vast majority of patients with TB + DM in Mexico are poor and are not able to follow the dietary recommendations that complement their pharmacologic treatment, resulting in inadequate control of their metabolic disease. Various socioeconomic conditions in Mexico may have favored changes in diet, including slow economic growth, rising social inequality, declining agriculture production, decreased wages in relation to the increasing prices of healthy food and the low cost of processed foods and sugary refreshments [11]. Glycemic control in our patients was, in general, poor, but it was not correlated to delayed culture conversion, regardless of the presence or not of drug resistance.

The effect of glycemic control on sputum conversion in patients with TB + DM as mentioned has been a polemic issue. For example Chang et al. reported a delayed clearance of mycobacteria in patients with TB + DM when compared with TB patients without DM (2.5 ± 3.0 months vs. 1.6 ± 1.4 months, $p < 0.01$) [2].

In contradiction, several reports have not found differences in culture conversion time in TB patients with and without diabetes. Magee et al. found no difference in culture conversion between patients in Georgia with MDR-TB + DM and patients with MDR-TB (adjusted hazard ratio [aHR] 0.95, 95% CI 0.71–1.28 [12]. Similar results have been reported in studies conducted in Morocco [13], the United States [14], India [15], Fiji [16] and in a multinational study that included MDR-TB patients from Peru, Estonia, Russia and the Philippines [17].

Although it seems that deficient glycemic control does not correlate negatively with time for culture conversion, diabetes clearly has a negative impact on TB treatment outcomes, with higher failure, relapse, and mortality rates [18].

Conclusion

In our clinical experience, even patients with less than adequate glycemic control will convert their cultures when an effective drug regimen is strictly supervised. Although we try to achieve optimal metabolic control in all patients with TB + DM, the socioeconomic barriers already described will hinder this effort. The social drivers of disease in Mexico must be addressed; biomedical interventions by themselves will not be able to control the epidemic.

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