The impact of Diabetes Mellitus on epidemiological, clinical, radiological features of tuberculosis. Seven years experience in a Mexican teaching hospital

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Abstract

Background: studies from Asia revealed a three-fold increase in the risk of active tuberculosis (TB) for patients with diabetes mellitus (DM). Given the increasing incidence of metabolic syndrome and DM in developing countries with a high incidence of TB, there may be a convergence of the two diseases resulting in increased morbidity and mortality with a high impact for global health. The aim of this study was to evaluate the contribution of type 2 DM to TB rates in Mexican population. A comparison with TB/HIV coinfection was also done.

Materials and Methods: we performed a retrospective study in the Civil Hospital “Fray Antonio Alcalde”, Guadalajara, Mexico. All TB patients hospitalized between 2005-2011 were studied. Demographic data, clinical and radiological findings and sputum microscopy were assessed in TB patients with and without DM and in a TB/HIV coinfected group. The data underwent statistical analysis. We used Pearson’s x² test to compare the characteristics of the three groups, a P value of <0.05 was considered statistically significant. For continuous variables the non-parametric analysis of Mann-Whitney U test was used.

Results: a total of 1225 patients with TB were analysed and DM type 2 was diagnosed in 16.8% of TB patients, whereas HIV infection was observed in 9.1%. Smoking/alcohol/drugs use and a history of prison were more common in TB/HIV patients (p≤0.001), while no significant differences were found between TB/DM and non-DM patients. TB/DM patients showed more symptoms like expectoration and haemoptysis, (p<0.05); cavitations were more often found in TB/DM (p<0.05). Also fibronodular forms were more common in TB/DM (p<0.05). By contrast in the TB/HIV group, the constitutional symptoms and miliar lesions were prevalent. Regarding sputum microscopy no differences were detected at the time of diagnosis, while at 2 months of follow-up TB/DM and TB/HIV patients were still positive (17.1% and 17.2% versus 12.7% of only TB). At the end of treatment TB/HIV showed the higher % of positive sputum.

Discussion: although HIV is considered to be the most important risk factor for TB development, we cannot ignore DM, which showed a significantly higher prevalence in active TB patients compared to HIV+ people. A global strategy to improve prevention, early detection and treatment of concomitant DM and TB should be implemented.

KEY WORDS: tuberculosis, diabetes, HIV.

Introduction

TB is now the second cause of death due to infectious diseases worldwide especially in low- and middle-income countries, where populations are more susceptible to developing tuberculosis for inadequate environmental, hygienic and social conditions. WHO target is to reduce the global incidence of TB disease to less than 1 case per million people per year (definition for TB elimination) by 2050, but we are still far from the goal with 8.6 million of people who developed TB and 1.3 million who died for TB in 2012 (1). There is no doubt that TB epidemiology is strictly linked to risk factors, such as the strong migratory flows from highly endemic developing countries to high-income countries with low TB endemicity, the high incidence of TB-HIV co-infection and the spread of resistant forms of TB, such as MDR (Multi-Drug-resistant) and XDR-TB (Extensively Drug Resistant). In recent years, particular attention has been given to a re-emerging risk factor, such as diabetes. The profound social changes in lifestyle that affected low- and middle-income countries during the second half of the twentieth century, have resulted in a transformation of the main health problems. The interaction between the two epidemics in fact, plays an even
more important role in developing countries and can be considered as an expression of globalization. In many countries malnutrition has been replaced by overweight and obesity. In this new epidemiological scenario, in which developing countries have a high incidence of metabolic diseases (diabetes, dyslipidaemia) and communicable diseases linked to poverty (HIV, diabetes) promises of a new situation in which the strong links between diabetes (DM), tuberculosis (TB) and HIV (2, 3) emerge.

The aim of the study was to evaluate tuberculosis in a group of Mexican patients, and the impact of diabetes and HIV infection in order to point out possible differences in epidemiological, clinical feature and outcome.

Materials and methods

Study subjects

A retrospective study of 1225 TB subjects of Mexican nationality, admitted at the Civil Hospital “Fray Antonio Alcalde” (Guadalajara, Mexico) between 2005 and 2011 was performed. Data were collected in a database and subsequently analysed. The diagnosis of tuberculosis was formulated according to standard WHO definitions: microbiological diagnostic tests (BAAR or culture positive for tuberculosis bacillus) or clinical-radiological, when microbiological tests were negative or not available (symptoms compatible with a diagnosis of TB and radiological evidence diagnostic). The guidelines of the American Diabetes Association were used for the diagnosis of diabetes mellitus: HbA1c >6.5 (with dosage aligned NGSP certified and standardized to the DCCT assay), fasting plasma glucose ≥ 126 mg/dl (or 7 mmol/l), blood glucose ≥ 200 mg/dl (or 11.1 mmol/l) after 2 hours taking orally 75 g of glucose (glucose tolerance test) and random blood glucose ≥200 mg/dl (or 11.1 mmol/l) and the presence of symptoms of hyperglycaemia (such as polyuria and polydipsia). All patients underwent a rapid test for HIV.

The following groups were identified and compared: Group TB DM, consisted of patients with active tuberculosis and diabetes mellitus type 2 (the majority of patients in the group was treated with oral hypoglycaemic agents), Group TB HIV, patients with active tuberculosis and HIV infection (patients with a diagnosis of concomitant diabetes mellitus have been excluded from the TB/DM population). The diagnosis of HIV was made by means of the rapid test, in use at the Mexican hospital. Group TB, patients with active TB without diabetes mellitus and without HIV. We excluded subjects for whom other diagnoses were made like pneumonia or other bacterial infection, cancer, immunological disease, < 18 years of age, pregnant or lactating women, terminally ill from TB (judged unlikely to survive > 48 hours), other severe diseases (chronic renal failure, chronic liver disease, malignancies), or on long term steroid (inhaled corticosteroids or peroral corticosteroids) or on cytotoxic treatment, or on immunosuppressive medications.

Methodology: data collection and statistical analysis

Patient data included socio-demographic characteristics and social risk factors (age, sex, smoking history and alcohol use, drug and prison), clinical features (symptoms), radiological features and direct sputum smear for acid fast bacilli at the time of diagnosis and during the 6-month follow-up. Ethical approval was obtained by local institutional review board as the study was a retrospective analysis and all data were collected in anonymous format. Data was collected in the database using the software Microsoft Excel XP and underwent statistical analysis with SPSS 17.0 (SPSS, Chicago, III, USA). We used Pearson’s x² test to compare the characteristics of the three groups, a P value of <0.05 was considered statistically significant. For continuous variables the non-parametric analysis of Mann-Whitney U test was used.

Results

Of the 1225 patients with active tuberculosis, diabetes mellitus was detected in 17.5% (215/1225) patients and 16.8% (206/1225) was affected by diabetes mellitus type 2 (TBDM), 9.1% (112/1225) was infected with HIV (TBHIV), while 72.8% (892/1225) was not affected by either diabetes mellitus or HIV infection (TB). We excluded from TB/DM population 9 patients with diabetes mellitus type 1 and 6 patients with both diseases (Fig. 1). The majority of patients in the TB/DM group had not a good glycaemic control. The median age of patients with TBDM was 54 (range 23-87) years compared to 47 (15-99) of only TB patients and 36 (20-67) of HIV patients. The male gender was dominant in all three groups. Patients with a history of smoking, alcohol, drugs and prison were more common in TB/HIV group of patients compared to the other two groups (p<0.001) (Tab. 1).

With respect to the clinical presentation, TB/DM patients showed more symptoms like expectoration (50.5% vs 40% of only TB and 36.6% of TB/HIV with p<0.05) and haemoptysis (15.5% vs 10.5% of only TB and 5.3% of TB/HIV pts, p<0.05). On the other hand in the TB/HIV group, constitutional symptoms like fever, loss of weight, cachexia and lymphadenopathy were found more frequently in the HIV/TB group (Fig. 2).

Regarding the radiological characteristics, the presence of bilateral lesions was observed with greater frequency in HIV compared to TB/DM patients and TB patients (66% vs 56% and 63.6% respectively, p=0.05). In TB/DM group the prevalent radiological finding was the cavern (26.2% n=54 versus 18.6% n=166 for TB and 12.5% n=14 for TB/HIV with p<0.05). Also fibronodular forms were more common in TB/DM patients (p=0.05). By contrast, in the TB/HIV group, miliary lesions were prevalent (multiple nodular infiltrates, approximately 3 mm wide distribution and generalized) with 19.6% versus 5.8% of diabetics and 8.1% of TB patients (p=0.05) (Tab. 2). The positive sputum microscopy showed no significant differences among the three groups either at the time of diagnosis or during treatment. However, at 2 months of follow-up TB/DM2 and TB/HIV patients were more positive (17.1% and 17.2% versus 12.7% of TB). At the end
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Figure 1 - Study population: study population included patients with active tuberculosis (TB) actively screened for diabetes (TB/DM) and HIV infection (TB/HIV). DM type 1 and HIV infected patients with concomitant DM were excluded from TB/DM population.

Table 1 - Socio-demographic characteristics in patients with TB, TB/DM and TB/HIV.

<table>
<thead>
<tr>
<th></th>
<th>TB (n=892)</th>
<th>TB/DM (n=206)</th>
<th>P TB vs TB/DM</th>
<th>TB/HIV (n=112)</th>
<th>P TB vs TB/HIV</th>
<th>P TB/DM vs. TB/HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≥50)</td>
<td>56% (500)</td>
<td>61.6% (127)</td>
<td>0.143</td>
<td>8.9% (10)</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex male</td>
<td>67% (598)</td>
<td>64.6% (133)</td>
<td>0.496</td>
<td>85.9% (97)</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex female</td>
<td>32.8% (293)</td>
<td>35.4% (73)</td>
<td>0.477</td>
<td>13.4% (15)</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Smokers</td>
<td>47.3% (422)</td>
<td>46.1% (95)</td>
<td>0.757</td>
<td>70.5% (79)</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Alcoholics</td>
<td>38.6% (344)</td>
<td>38.3% (79)</td>
<td>0.954</td>
<td>55.3% (62)</td>
<td>0.002</td>
<td>0.003</td>
</tr>
<tr>
<td>Prison</td>
<td>13.7% (122)</td>
<td>12.1% (25)</td>
<td>0.558</td>
<td>25% (28)</td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>drug abusers</td>
<td>22.5% (201)</td>
<td>11.2% (23)</td>
<td>0.003</td>
<td>52.7% (59)</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Figure 2 - Clinical features in patients with TB, TB/DM and TB/HIV: with respect to the clinical presentation, TB/DM patients showed more symptoms like expectoration and haemoptysis. On the other hand in the TB/HIV group, constitutional symptoms like fever, loss weight, cachexia and lymphadenopathy were found more frequently. * indicates a p<0.05.
of the 19th century the diabetic patient appeared doomed to die of pulmonary tuberculosis if he succeeded in escaping. The association between DM and TB has been recognized again in 1990 and it is currently supported by a growing literature. Data shows that the risk of developing tuberculosis in patients with DM is 1.3 to 8.2 times greater compared to non-diabetic patients and several studies report a fraction of TB cases linked to diabetes instead of between from 15 to 25%. Although the risk of tuberculosis associated with DM is lower than the risk of tuberculosis associated with AIDS (14, 15), considering the larger number of patients with DM, it is likely that diabetes could have the same impact on public health in determining TB diffusion. Tuberculosis and diabetes not only are becoming co-existing diseases but they interact strongly interact with each other. In fact, diabetes suppresses the immune response, which facilitates the transition from latent tuberculosis infection to active tuberculosis: this can be attributed to the important immunological changes induced by hyperglycaemia such as abnormalities of chemotaxis, phagocytosis, bactericidal function of PBMC (Peripheral blood mononuclear cell) and alteration of cytokine production due to low-grade chronic inflammatory response (16-20).

On the other hand, it is plausible that TB leads to a transient or permanent impairment of glucose metabolism, which eventually will turn into diabetes. It has been suggested that tuberculosis could lead to chronic hyperglycaemia mediated by the persistent lack of insulin (21), but considering that severe tuberculosis can induce a non-diabetic acute stress hyperglycaemia, often misinterpreted as diabetes (this is obviously a problem for screening for DM in patients with TB) but may be overcome by the use of glycoside haemoglobin (22).
Our study aimed at evaluating the contribution of type 2 DM to TB rates in Mexican population and to describe the epidemiological interactions and the effects on clinical presentation and response to treatment. We also compared TB-DM with the other important co-morbidities, TB-HIV. The results of data analysis showed that almost 17% of cases of tuberculosis hospitalized at a large hospital in Mexico were also suffering from diabetes mellitus type 2, while only 9% were coinfected with HIV.
DM patients had an average age greater than that of the other two groups, indicating a converging risk of DM and TB in elderly people.
As expected, lifestyles related to social exclusion as smoking, alcohol and drugs use, prison staying were more prevalent in patients with TB/HIV.
With regard to the clinical presentation and radiological features, patients with diabetes had a higher frequency of expectoration and haemoptysis than other groups.
Finally, with regard to sputum microscopy, no significant differences were found among the three groups at the time of diagnosis, while at two months of follow-up greater positivity was observed in patients with TB/DM and TB/HIV suggesting a negative impact of the two comorbidities, diabetes and HIV infection, on the outcome and especially on TB infectivity, even if our study was not well designed to stress this issue and longitudinal studies are needed.

Table 2 - Radiological features in patients with TB, TB/DM and TB/HIV.

<table>
<thead>
<tr>
<th>Feature</th>
<th>TB (n=892)</th>
<th>TB/DM (n=206)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral lesions</td>
<td>56% (504)</td>
<td>63.6% (131)</td>
<td>0.063</td>
</tr>
<tr>
<td>Cavity</td>
<td>18.6% (166)</td>
<td>26.2% (54)</td>
<td>0.014</td>
</tr>
<tr>
<td>Miliary</td>
<td>8.1% (72)</td>
<td>5.8% (12)</td>
<td>0.274</td>
</tr>
<tr>
<td>Fibronodular infiltrations</td>
<td>7.2% (64)</td>
<td>12.6% (26)</td>
<td>0.010</td>
</tr>
<tr>
<td>Micronodular infiltrations</td>
<td>33.8% (302)</td>
<td>37.8% (78)</td>
<td>0.001</td>
</tr>
<tr>
<td>Macronodular infiltrations</td>
<td>11.3% (101)</td>
<td>14.5% (30)</td>
<td>0.196</td>
</tr>
</tbody>
</table>

Discussion

Recent reviews and meta-analyses show that diabetes mellitus type 2 triples the risk of developing active tuberculosis than people without DM (4, 5). The association between tuberculosis and diabetes has been well known in the past. In fact, before the discovery of insulin (21), a diagnosis of diabetes represented a death sentence within about 5 years, and the usual cause of death was tuberculosis, while only 9% were coinfected with HIV.
In conclusion, the study confirms that diabetes is frequent among TB patients, in particular in our cohort it was a more frequent comorbidity than HIV infection. DM seems to be able to influence the clinical presentation of tuberculosis in terms of a higher frequency of sputum production and haemoptysis, as well as the radiological presentation, in terms of greater presence of bilateral lesions and caverns. Therefore, considering the rising rates of obesity and DM, especially in low- and middle-income countries, where highest incidence of TB is found, we can expect that the number of individuals with TB and DM will continue to grow significantly in the coming decades. It would be necessary to adopt and implement a possible bidirectional and a low-cost screening strategy for the two diseases, in order to perform early diagnosis and then treat cases of DM in patients with TB and cases of active or latent TB in patients with DM. The percentage of cases of active TB that could be prevented with this type of approach, according to the results of our and previously mentioned studies, would then be about 20%.

Therefore, it is essential to take as an example what happened in the 80's/90's, regarding the management of TB-HIV co-infection, when a slow and uncoordinated global response has allowed the increase of HIV-associated TB mortality (23). As for HIV, in fact, possible screening tests, such as the measurement of glycosuria, random blood glucose, fasting blood glucose, oral glucose tolerance test and HbA1c, would lead to early detection of DM at a primary healthcare level (24-27). On the other hand, screening for DM in patients with tuberculosis could lead to early detection of DM cases and to an early connection between TB and DM, as indicated by the WHO in a context of cooperation with the International Union Against Tuberculosis and Lung Diseases in order to improve the joint management of the two diseases (28) in terms of treatment and outcome.

References


