CHARACTERISTICS OF THE DIAGNOSIS AND TREATMENT OF PULMONARY TUBERCULOSIS IN PATIENTS WITH AND WITHOUT DIABETES MELLITUS TYPE 2

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ABSTRACT

Objectives. To determine whether there are demographic, clinical and radiological differences among patients with pulmonary tuberculosis (TB) and patients with TB and type 2 diabetes mellitus (DM2 + TB). ***Materials and methods.*** Observational retrospective cohort study. We compared the clinical characteristics of patients according to sex, age, time to sputum conversion to negative, presence of cavitation and the cure rate, duration of treatment and the proportion of change of treatment regimen, in patients with and without DM2 served by the Tuberculosis Control Program from 2010 to 2012 in the Rebagliati Healthcare Network of Lima, Peru. ***Results.*** 31 patients with TB+DM2 and 144 patients with TB were included. Differences ($p<0.05$) in the diagnostic method, the average of symptoms and the resistance pattern of TB among patients with and without DM2 were found. The presence of cavitation was more frequent in patients with TB + DM2. Having TB + DM2 delayed the time to sputum smear conversion to negative (RRa 4.16, 95% CI: 1.1-1.6) in the adjusted Cox regression analysis. ***Conclusions.*** There are differences in demographic, clinical and radiological characteristics in TB patients with and without DM2.The time to sputum conversion to negative is greater in patients with DM2.

Key words: Tuberculosis; Diabetes Mellitus, Type 2; Longitudinal studies; Comorbidity (source: MeSH NLM).

INTRODUCTION

Tuberculosis (TB) is a global public health problem. There are three subtypes: 1) pulmonary TB is characterized by chronic cough, sputum, weight loss, loss of appetite, fever, night sweats, and hemoptysis; 2) the extrapulmonary TB can compromise other organs and have different clinical presentation; and 3) TB coinfection with other agents [(1)]. From the point of view of sensitivity to anti-TB medications, TB is classified as pansusceptible, multidrug-resistant, and extensively resistant [(2)].

In 2012, there were an estimated 8.6 million new TB cases worldwide, and 1.3 million patients died of the disease; 450 thousand died of multidrug-resistant TB (MDR TB), and 320 thousand died of HIV coinfection. Peru is one of the endemic countries for both TB and the MDR type. The incidence accumulated in 2012 was 93 cases for every 100,000 people, and the region of Lima

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ranks fifth among all regions: the incidence of 148 for every 100,000 people [4].

There is an increase in the comorbidity of TB with other diseases such as HIV, malnutrition, and type 2 diabetes mellitus (TB+DM2) [5]. A systematic review showed that in cohort studies, diabetes increases the risk of active TB by more than threefold as compared to patients without diabetes, and in studies with cases and controls the odds ratios ranged from 1.16 to 7.83 [6]. According to reports on the proportion of TB+DM2 cases, in the United States, the proportion is 11.4% [7], 13.1% in Japan [8], 29.6% in Mexico [9], and 6.3% in Peru [10]. Although the prevalence of diabetes is low in Peru, its increase in the coming years may lead to increased comorbidity (TB+DM2) [11.12].

Diabetes is an important risk factor of TB [6,13] due to the immunosuppression it causes. Some studies suggest that diabetes changes the clinical and bacteriological presentation as well as the response to treatment, increasing the risk of resistance to medication and the risk of death [10,14-19].

TB+DM2 prolongs the positive bacilloscopy (BK) time and causes a delay in the negativization of micro-bacterial cultures [9,20,21]; this situation implies longer time of transmission to the community. Some investigators estimate that radiographic pulmonary cavitary lesions among diabetic patients are more severe [14]. Likewise, the rate of failure of anti-TB treatment is higher for diabetic patients than for nondiabetic ones [9,22], and the duration of TB treatment is longer in patients with diabetes [17].

There are few studies on the characteristics of TB patients with and without diabetes. It is estimated that by 2030, 80% of diabetic patients will live in Latin America; therefore, it is important to elucidate the clinical and epidemiological characteristics of the combination TB+DM2 in order to provide adequate treatment and to control the spread [23].

The purpose of this study was to determine whether there are differences in gender, age, and sputum negativization time, the presence of cavitation, and other clinical characteristics as well as the cure rate, duration of treatment, and proportion of change in the treatment regimen between pulmonary-TB patients with and without type 2 diabetes mellitus.

MATERIALS AND METHODS

STUDY DESIGN

This was a historical cohort study of adult patients with pulmonary-TB diagnosis confirmed clinically, with a culture or sputum positive for BK [24]. Patients who received the diagnosis of TB via BK and/or culture + DM2 were defined as exposed, and patients who received the diagnosis only via BK and/or TB culture were defined as unexposed. They were identified at the same time. The participants were new cases, and the sources of information were medical histories.

THE STUDY POPULATION AND SAMPLE SIZE

The study population consisted of the patients treated between January 2010 and December 2012 by the medical centers: Pablo Bermúdez, Chincha, Carlos Alcántara Hospital, Angamos Hospital, and Uldarico Roca Hospital within the framework of the Tuberculosis Program of the Rebagliati Assistance Network (Lima, Peru).

The sample size for the cohort study was calculated in the EpiInfo 7.0 software by means of the StatCalc application considering the power of 80%, confidence interval of 95%, and a proportion of one (exposed group) to four (unexposed group). The proportion of exposure to the factor of interest (resistance to TB treatment) among the exposed (TB+DM2) that we analyzed was 26.1%, and the proportion of the factor (resistance to TB treatment) among the unexposed (TB) was 5.6% [17]. The calculated sample size was 26 subjects for the exposed group, whereas for the unexposed group, it was 102 subjects. The total sample to be selected from both groups was 128 participants according to the Fleiss method. Nevertheless, in order to have greater consistency, we added 5 exposed subjects and 42 unexposed ones, thus obtaining the final sample of 175 participants.

DEFINITION OF VARIABLES

The TB treatment regimens of the Ministry of Health are the following: H (isoniazid), R (rifampicin), Z (pyrazinamide), E (ethambutol), and S (streptomycin). The EsSalud TB Control Program is governed by the technical regulations of the Ministry of Health [24], meaning that patients with drug-susceptible TB are treated and managed at their reference polyclinic with the strategy known as direct treatment monitoring program, whereas patients with multidrug-resistant TB are treated and managed at the reference hospital.

A case of pulmonary TB is defined as a person with a BK and/or positive BK culture, with compromised lung parenchyma as evidenced by X-ray imaging, and relevant signs and symptoms. A case of pansusceptible TB is defined as TB infection that shows sensitivity to all first-line medications in conventional drug sensitivity tests, and a case of MDR TB is a TB infection showing simultaneous resistance to isoniazid and rifampicin in conventional tests [24].

Likewise, sputum negativization is defined as conversion of the BK or positive culture of a patient prior to initiation of treatment into test-negative after 4 months of treatment. The presence of an adverse reaction to antituberculosis drugs (ARAD) is assumed when some adverse reaction occurs in response to the antituberculosis drugs recorded in the medical history.

Treatment failure is defined as the persistence of the BK or positive culture after 4 months of antituberculosis treatment. According to the TB program, all patients are monitored through monthly BKs or cultures until the patient becomes test-negative or up to 12 test-positive months. The time of antituberculosis treatment is defined as the duration of the antituberculosis therapy. The change of antituberculosis treatment is any change in the medications that is not stipulated in the initial regimen. Finally, the presence of cavitations was diagnosed during treatment.

SELECTION OF PARTICIPANTS AND COLLECTION OF INFORMATION

In order to identify the exposed (TB+DM2) patients, we listed the cases of primary TB that had completed treatment and met the definition of exposed, on the basis of the attendance control and medication administration card of the Tuberculosis Control Program (Spanish acronym PCT) between January 2010 and December 2012. Once a patient was identified, his/her medical history with the type 2 diabetes mellitus diagnosis was retrieved from the archives of any of the medical centers or hospitals of the Rebagliati Assistance Network of Lima. Finally, medical histories for the exposed cases that met the criteria were selected on the basis of convenience.

The selection of unexposed patients was as follows: a) We listed the tuberculosis cases that met the definition of unexposed on the basis of the list of patients treated at the PCT, with treatment completed between 2010 and 2012 in the Rebagliati Assistance Network of Lima. b) We used simple random sampling to select the patients. c) The selected medical histories were located and examined to confirm that they met the criteria. The data related to the variables age, gender, origin, diagnosis, symptoms, radiological findings, negativization time in months, duration in months, treatment results, the pattern of resistance, presence of adverse reactions, diabetes diagnosis, and duration of illness, were recorded on a form.

SELECTION CRITERIA

For the unexposed group, the inclusion criteria were as follows: patients with pulmonary TB confirmed by a BK-positive sputum and/or culture, who had completed treatment and did not meet any DM2 criteria according to the Latin American Diabetes Association (Spanish acronym ALAD) [25].

For the exposed (TB+DM2) group, the inclusion criteria were the following: patients with pulmonary TB confirmed by a BK-positive sputum and/or culture, who had completed treatment, and who also had a recorded diagnosis of DM2 in their medical history.

We excluded patients with a history of TB and/or some immunosuppressive condition such as HIV, cancer, or the use corticosteroids at immunosuppressive doses and TB cases identified by clinical criteria only. We also excluded patients who abandoned treatment or were transferred without further information, in order to evaluate only those patients who had completed the treatment provided.

STATISTICAL ANALYSIS

The data were entered into a 2010 Microsoft Excel database. Patients who abandoned treatment, cases diagnosed clinically only, or patients who were transferred were excluded from the analysis because we were interested in evaluating only the patients who completed the treatment provided. For analysis of categorical variables, we used the chi squared test, and differences with $p < 0.05$ were considered statistically significant. In order to identify risk factors, we used relative risk (RR) with a confidence interval of 95%. Finally, we estimated the hazard ratio (HR) of the adjusted variables from the bivariate analysis based on the Cox regression, and we utilized the Efron method to handle concomitant failures. To compare the occurrence of an event (negativization time), the log-rank test was employed. This database was analyzed in the Epi Info 7.0.9.34 software.

ETHICAL CONSIDERATIONS

The project was approved by the Ethics Committee of the School of Health Science of the Peruvian University of Applied Sciences (Spanish acronym UPC; approval No. PI028-12), and by the Office of Training, Research and Teaching of the Rebagliati Assistance Network of Lima. Given that the study was based on secondary sources and there was no contact with the patients, there were no consent forms. Nonetheless, patients' names were kept confidential at all times.

RESULTS

The study included 31 exposed patients and 144 unexposed ones. The average age in the exposed group was 51.8 ± 13.9 years, median 51 years (interquartile range [IQR] 24–78), and the average age in the unexposed group was 45.6 ± 18.8 years, median 45 years (IQR 12–90).

The differences in diagnostic and clinical characteristics between the exposed and unexposed groups are shown in Table 1. The evaluated symptoms were the following: cough, night sweats, expectoration, weight loss, general malaise, loss of appetite, chest pain, hemoptysis, and others. We found statistically significant differences ($p < 0.05$) between TB+DM2 patients and TB patients in the method of diagnosis, average symptoms, and the TB resistance pattern. Likewise, in terms of cavitation, there were significant differences between TB+DM2 patients and pulmonary-TB patients.

Regarding the results of the anti-TB treatment, we found differences between the patients with diabetes and those

Table 1. Features of patients with tuberculosis according to the presence of diabetes mellitus, Rebagliati Assistance Network, Lima 2010-2014

Variable	With diabetes n=31 (%)	Without diabetes n=144 (%)	*p** value
Gender			
Males	16 (51.6)	73 (50.7)	0.916
Women	15 (8.4)	71 (49.3)	
Age			
< 45 years	9 (29.0)	71 (49.3)	0.063
≥ 45 years	22 (71.0)	73 (50.7)	
District of origin			
Central Lima	23 (74.2)	111 (77.1)	0.911
Other districts of Lima and Callao	8 (25.8)	35 (22.9)	
Diagnosis			
BK (+)	23 (74.2)	135 (93.7)	0.002
Culture (+)	8 (25.8)	9(6.3)	
Number of symptoms Average (SD)	2.8 (1.1)	2.3 (1.4)	0.023**
Cavitations			
Yes	15(48.4)	7 (4.9)	<0.001
No	16 (51.6)	137 (95.1)	
Pattern of resistance			
Multidrug-resistant tuberculosis	4 (12.9)	3 (2.1)	0.022
Pansusceptible pulmonary tuberculosis	27 (87.1)	141 (97.9)	

SD: Standard deviation
* Comparisons were made by the chi squared test and Fisher's exact test.
** Mann-Whitney U test

Table 2. Results of antituberculosis treatment in patients with and without type 2 diabetes mellitus treated by the Rebagliati Assistance Network (Lima, 2010–2014)

Variables	With diabetes n=34 (%)	Without diabetes n=133 (%)	RR (IC 95%)	*p** value
Adverse reactions to the antituberculosis treatment				
Yes	4 (12.9)	8 (5.6)	1.2 (0.8-1.8)	0.291
No	27 (87.1)	136 (94.4)		
Changed treatment regimen				
Yes	13 (41.9)	1 (0.7)	12.4 (1.8-82.2)	<0.001
No	18 (58.1)	143 (99.3)		
Changed treatment regimen	6 (0)	6.4 (1.1)		<0.001**
Treatment result				
Failure	11 (35.5)	3 (2.1)	4.1 (1.4-11.1)	<0.001
Cured	20 (64.5)	141 (97.9)		
Negativization of sputum				
≤ 4 months	14 (45.2)	2 (1.4)	7.1 (1.9-26.1)	<0.001
> 3 months	17 (54.8)	142 (98.6)		

SD: Standard deviation.
* Fisher's exact test
** Mann-Whitney U test

Table 3. Association between diabetes and negativization of sputum in patients with pulmonary tuberculosis. Crude and adjusted Cox regression models.

Diabetes	Crude HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR** (95% CI)
No	Reference	Reference	Reference
Yes	4.00 (6.25–2.5)	4.76 (7.69–2.9)	4.16 (1.1–1.6)

Efron's method was used to handle concomitant failures.
* The model adjusted for gender, age, and district of origin.
** The model adjusted for gender, age, district of origin, presence of cavitation, TB resistance pattern, and change of treatment.
† Log-rank ($p < 0.001$)

without diabetes in the change of regimen, duration of treatment, treatment results, and sputum negativization (Table 2). The Cox regression model adjusted for gender, age, the district of origin, presence of cavitation, TB resistance pattern, and change of treatment was used to determine that the group of TB+DM2 patients showed delayed negativization of the sputum BK (RR 4.16; 95% CI: 1.1–1.6; Table 3). This means that for TB+DM2 patients, the risk of remaining test-positive was four times higher than for those with TB only.

Patients with TB+DM2 had longer sputum BK negativization time as compared to non-DM2 patients; DM2 patients became negative after the fourth month, whereas non-DM2 patients did so after the second month (Figure 1).

DISCUSSION

In this study, we found that exposed patients (TB+DM2) become negative after a longer period as compared to pulmonary-TB patients, have a higher risk of changing the treatment regimen, require longer treatment, and the risk of failure increases significantly. These findings have also been reported in other studies [9,20-21]. One of the most important effects of the prolonged negativization is the increased risk of transmission and elevated treatment costs because medications are required for a longer period. Furthermore, having TB+DM2 delays the negativization of BK sputum, as corroborated by the regression analysis after adjustment for some confounders such as age, gender, the district of origin, TB resistance pattern, and change of treatment. Similar results have been reported for Indonesian cohorts of patients [20].

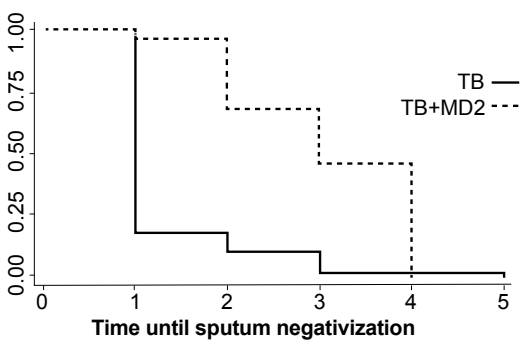

Figure 1. A Kaplan-Meier curve showing time in months until sputum negativization in patients with tuberculosis (TB) and tuberculosis with type 2 diabetes mellitus (TB+DM2)

In our study, we found that patients with TB+DM2 have fewer symptoms than do those with pulmonary TB only; this finding contradicts some studies where no significant differences were found in the symptoms of diabetic patients [26-28]. On the other hand, a study conducted on the Mexico-United States border showed that diabetic patients show a higher frequency of fever and hemoptysis [29]. A study in Indonesia revealed that patients with diabetes have more signs and symptoms as compared to nondiabetic ones; however, this result does not imply greater severity of the TB [20].

Age is considered a risk factor for the development of TB+DM2 [30,31]. Nevertheless, there are studies indicating that there is a stronger association with the development of TB+DM2 in younger patients, which is why it is still debated whether age is a risk factor of this condition [13,32] or if it is a confounding variable.

There is no pathognomonic pattern to support this notion. Nevertheless, a study in India indicates that patients with diabetes have a higher incidence of cavitations according to radiological analysis [33]. The negativity period for bronchial smears was found to be higher here among patients with TB+DM2 when compared to nondiabetic patients. The same result was reported by others who used this measure as an important variable due to its repercussions at the time of the therapeutic decision at the end of phase 1 of treatment (regimen 1) among patients treated for pansusceptible pulmonary TB. We did not find any studies that linked this variable to diabetic patients.

As for the results of the treatment, most cases categorized as treatment failure were found in the group of TB+DM2 patients. Previous research indicates that diabetic patients are at a higher risk of developing TB treatment failure due to the immunosuppression caused by diabetes [15]. Likewise, there was no significant evidence of ARAD and its association in the TB+DM2 patient group. Nonetheless, it is worth noting that these reactions were weaker in the exposed group. It is possible that there is a bias in the ARAD records because this is a retrospective study. It is also noteworthy that there is a smaller number of TB+DM2 subjects.

There were more treatment changes in the TB+DM2 group. This variable has not been considered in other studies. Nevertheless, it is an important factor when handling this type of patients because diabetes can change the BK negativization, which does not necessarily reflect a treatment failure. Likewise, the lack of a treatment strategy for this type of patients makes physicians try different approaches to pharmacological management.

Diabetes is one of the comorbidities most frequently associated with pulmonary TB infections [34]. Our study revealed differences in the clinical, radiological, and bacteriological manifestations that alter the course of the disease. This is why a specific treatment regimen is important for this condition. In Brazil, the Brazilian Pneumology Society recommends (in their latest tuberculosis management guide) considering a 9-month regimen for patients with TB+DM2 [35].

The unexposed group was selected on the basis of convenience; this situation prevents generalization of the results. Given that the study was based on secondary sources, the data described in the medical history depend on the radiological and clinical assessment, assuming that the description of the chest X-ray imaging is correct and that the anamnesis of the patients under study was recorded properly. This situation may have influenced our results. Utilization of sputum BK as diagnostic criterion is a questionable practice because of the low sensitivity in the detection of TB in patients with low bacillary loads [36]. We did not find reasons for the change of a treatment regimen; nor did we find the complete data on the body weight variation. Glycemic values during the antituberculosis treatment could not be collected because they are not considered in the PCT control sheet. Finally, the behavior of patients categorized as treatment failure was not recorded because it was not the focus of this study.

In order to better understand TB+DM2, it is important to conduct other studies with the prospective cohort design that take into account the changes that have been incorporated into the national TB standards [24].

In this study, TB+DM2 patients take two months longer than pulmonary TB patients to show negative results of BK, and the presence of cavitation is greater in TB+DM2 patients.

There are significant differences in the changes of treatment regimens, results, and duration of treatment between the exposed group (TB+DM2) and the unexposed group (pulmonary TB). Similarly, there are statistically significant differences between TB+DM2 patients and pulmonary TB patients in terms of age, the median number of symptoms, and the clinical type of TB.

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