Poorly controlled Diabetes mellitus as a risk factor for resistant tuberculosis in the National Hospital Daniel Alcides Carrion, during the period 2010-2012

Cynthia Mendoza[1,2]

ABSTRACT

Objective: To determine the relation between poorly controlled type 2 diabetes mellitus (DM2) and anti-tuberculosis drug resistance. **Materials and Methods:** An observational, retrospective study was conducted, where a group of patients diagnosed with tuberculosis was studied, during the period 2010-2012. Patients diagnosed with DM2 were selected; their level of glycemic control (glycosylated hemoglobin) was surveilled, as well as their TB drug-susceptibility testing. **Results:** 1,083 medical records of patients diagnosed with pulmonary tuberculosis (new cases never treated before) were reviewed. 79 (7.3%) of them were simultaneously diagnosed with DM2, 79.7% (n=63) had poor glycemic control. Likewise, 45.6% (n=36) presented resistance to one or more anti-tuberculosis drugs. The statistical association (chi-square) between the variables poorly controlled DM2 and resistant tuberculosis, had a result of p=.870. **Conclusions:** There was no relation between the poor glycemic control in patients with DM2 and the development of tuberculosis resistant to anti-tuberculosis drugs.

Key words: Diabetes mellitus. Drug Resistance. Pulmonary tuberculosis.

1. Facultad de Medicina. Universidad Nacional Mayor de San Marcos. Lima, Perú.
2. Servicio de Neumología. Hospital Daniel Alcides Carrión. Callao, Perú.

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INTRODUCTION

Tuberculosis (TB) is a disease of high prevalence, morbidity and mortality in the world and in our country. In 1993, the World Health Organization (WHO) declared it as a global emergency, due to the appearance of drug-resistant strains[1,2]. TB is the second largest cause of death in the world, killing nearly two million people every year[3]. Malnutrition, overcrowding, poor hygiene conditions, HIV infection, immunosupressants, DM2, stress, silicosis, alcoholism, drug addiction and indigence, among other factors, increase susceptibility to this disease[4,5,6].

TB can be associated to other diseases; the most common ones in patients with pulmonary tuberculosis are HVI infection, DM2 and several types of neoplasia[7]. Regarding DM2, the increased prevalence observed over the last years[8,9], has had significant impact on TB dynamics, so that recent studies show that 10% to 30% of patients with TB also suffer from DM2, mainly in developing countries, and being it a generator of strains of drug-resistant TB[10,11].

Many studies have published the high prevalence of TB among patients with DM2, with higher prevalence of TB in diabetic people than in those ones who are not. Immune alterations in diabetic patients, mainly in the poor controlled ones, predispose to more susceptibility and a more severe type of TB.

The association between infections of multi-drug-resistant tuberculosis (TB-MDR) and DM2 has been reported in a series of publications in different populations[12], in cohorts[13,14,15], regarding immune response[16], study of clinical complications[17,18], and treatment resistance[19].

This study pretends to establish the existence of an association between glycemic control of DM2 and drug-resistant TB, searching for intervention strategies in this group of patients in order to maintain an appropriate metabolic control, allowing at the same time to reduce the occurrence and seriousness of infection by drug resistance TB.

MATERIALS AND METHODS

This study is observational and retrospective. Medical records of patients with TB (new cases) were reviewed, and from these ones we chose medical records of patients with DM2, surveiling their level of glycemic control (glycosylated hemoglobin) at the moment of diagnosing TB. Likewise, drug-susceptibility testings were received from the *Instituto Nacional de Salud* (National Healthcare Institute). All the patients admitted in the TB program of the *Hospital Daniel Alcides Carrión*, during the period 2010-2012, were included.

Table 1. Definitions.

Tuberculosis	
Mono-drug-resistant	Resistant to only one anti-tuberculosis drug.
Poli-drug-resistant	Resistant to two or more anti-tuberculosis drugs, but not to the primary nucleus.
Multi-drug-resistant	Resistant to isoniazid, rifampicin.
Extensively drug-resistant	Resistant to isoniazid, rifampicin, plus an aminoglycoside of second generation, plus a quinolone.
Totally drug-resistant	Resistant to all anti-tuberculosis drugs.
DM2	
Controlled	Level of HbA1c lower than or equal to 7 Glycemia <126 mg/dl in fasting
Non-controlled	Level of HbA1c higher than 7 Glycemia ≥126 mg/dl in fasting

The SPSS statistical package, version 15, was used for data input. For statistical analysis, the data was submitted to the measures of central tendency and chi-square.

RESULTS

1,083 medical records of patients diagnosed with pulmonary tuberculosis (new cases never treated before), between 2010 and 2012, were reviewed. 79 (7.3%) of them were simultaneously diagnosed with DM2.

Regarding population characteristics, 49.4% (n=40) were female patients. In Table 2 we can

observe the distribution of cases by age groups.

Table 2. Description of population with pulmonary TB and DM2 according to age.

Age Group	n	Percentage
<20 years	1	1.3 %
20-29	2	2.5 %
30-39	4	5.1 %
40-49	20	25.3 %
50-59	30	38.0 %
≥60 years old	22	27.8 %
Total	79	100 %

79.7% (n=63) of patients with DM2 and TB were poorly controlled (according to their glycemic control). From 79 cases, 45.6% (n=36) had anti-tuberculosis drug resistance: mono-resistance 22.2% (n=8), poly-resistance 19.4% (n=7) and MDR 58.3% (n=21).

In this study there is no association (p=0.870) between good or poor glycemic control and the existence of resistant or susceptible TB. This is due to diabetes mellitus by itself is a disease which alters cellular immune response of macrophages and lymphocytes, with alterations in the production of perforins, granzymes, and granulysins, and the production of cytokines such as IFN-γ, IL-6 and TNFα, which activate macrophage function. These alterations in patients with DM2 play an important role in the increase of susceptibility to *M. tuberculosis*, independently of glycemic control.

Table 3. Frequency distribution according to resistance to each anti-tuberculosis drug.

Medication	n
Isoniazid	32
Rifampicin	21
Streptomycin	17
Ethambutol	6
Ethionamide	4
Ciprofloxacin	4
Pyrazinamide	3
Cycloserine	1
Kanamycin	1
Capreomycin	1
Total	90

Table 4. Frequency distribution according to resistance pattern and glycemic control in patients with TB and DM2.

DM2 Control	Susceptibility			
	Resistant TB		Susceptible TB	
	n	%	n	%
Controlled DM2	7	43.75	9	56.25
Non-controlled DM2	29	46.04	34	53.96

Table 5. Frequency distribution according to resistance pattern and glycemic control in patients with TB and DM2.

Diabetes Control	Resistance Pattern						Total
	MDR		Mono-resistance		Poly-resistance		
	n	%	n	%	n	%	
Controlled DM2	4	57	2	29	1	14	7
Non-controlled DM2	17	58	6	21	6	21	29

DISCUSSION

According to the World Health Organization (WHO), TB is one of the most important infectious diseases for public health. Both drug resistance and the association with HIV are two important elements for TB resurgence. Among contagious diseases, TB is the second cause of death associated to a single infectious agent worldwide, killing about two million people every year, and tendencies in notifications of TB cases show TB global incidence rate is increasing (0.4% per year)[20]. However, the increasing prevalence of DM2 observed in the last few years has had significant effect on TB dynamics, so that recent studies show that 10% to 30% of patients with TB also suffer from DM2, mainly in developing countries, and being it a generator of strains of drug-resistant TB[19].

The WHO estimates that the global number of people with DM2 will have been doubled by 2030 as a consequence of people's ageing and urbanization, mainly in developing countries[10].

DM2 related to TB currently represents a synergic problem, driven by two simultaneous epidemics. Many studies have published the high prevalence of TB among diabetic patients, with higher prevalence of TB in diabetic people than in those ones who are not. Immune alterations in these patients, mainly in the poor controlled ones, predispose to more susceptibility and a more severe type of TB. The association between infections of TB-MDR and DM2 has been reported in a little series of hospitalized patients. More conclusive researches in different populations are needed[19].

There is increasing evidence that DM2 is an important risk factor for TB and could affect the type of the disease and treatment response. Several case-control studies have showed the possibilities of having TB in diabetic patients varies from 2.44 to 8.33 in comparison to non-diabetic patients, therefore the combination of TB and DM2 represents a threat for global health[20].

Cellular immune response plays an important role in protection against *M. tuberculosis*. The role of macrophages and CD4+ and CD8+ lymphocytes is exhaustively described in that protection: macrophages are responsible for phagocytosis and death for *M. tuberculosis* through mechanisms such as production of nitric oxide (ON) and lysosomal enzymes, while CD4+ y CD8+ lymphocytes exercise bactericidal activity by producing perforins, granzymes, and granulysins and producing cytokines such as IFN-γ, IL-6 and TNFα, which activate macrophage functions. On the other hand, evidences indicating that DM2 is a risk factor for the infection and development of TB can be explained, in part, because among the factors predisposing at this susceptibility, there are important immunological disorders. Thus, various defects have been documented mainly in mechanisms of the innate immune system in patients with DM2. One of them is the complement system, a fundamental component for immune response against different micro-organisms whose purpose is to strengthen inflammatory response, to facilitate phagocytosis and cell lysis.

We have observed that high glucose concentrations in patients with DM2 are correlated to alterations in phagocytosis and prevalence of respiratory infections, although immunological and biochemical mechanisms involved are unknown. Chen YH *et al* found high levels of glucose alter bactericidal activity associated to the production of ON. Although, in general, it has been reported the spontaneous production of TNFα , IL-6 and IL-8 in patients with DM2, it has also been observed changes due to DM2 in cytokine production affecting both innate and adaptive immunity.

Regarding the adaptive immune response in DM2, it is known that antibodies production is normal. Stalenhoef JE et al reported peripheral blood cells of patients with DM2 produced lesser quantities of IFN-γ toward non-specific stimulus in comparison to non-diabetic individuals, suggesting that the lack of IFN-γ production in patients with DM2 plays an important role in the increase of susceptibility to *M. tuberculosis*[21].

Radiological manifestations in patients with pulmonary TB associated to DM2 are different to those ones in non-diabetic patients. There are bigger lesions located everywhere in the former. Sosman MC *et al* and Pérez-Guzmán C *et al* reported that

radiological manifestations in TB-DM2 cases showed a larger number of cavities and lesions in the lower lobes than those ones described in patients without DM2[22]. On the other hand, regarding clinical manifestations in patients with TB-DM2, some reports suggest there is more severe symptomatology in these patients, e.g., in the study by Restrepo BI et al it was observed that patients with TB-DM2 had more severe symptoms such as cough, hemoptysis and fever, as well as greater number of cavitations in chest X-ray, regarding patients without DM2. However, there is controversy about this aspect, since in other study there was no difference in TB severity, as it was observed in the study made in Indonesia by Alisjahbana B et al, where it is reported that patients with TB-DM2 are more symptomatic, but bacteriological and radiological studies do not show greater severity of the disease regarding patients with TB without DM2[23]. As far as the effectiveness of the anti-tuberculosis treatment, there are studies with evidences of lesser efficiency in anti-tuberculosis treatment for patients with DM2. Other authors found that levels of rifampicin in serum are reduced in patients with DM2-TB, and in the same study pharmacokinetic in patients with TB, both with and without DM2, was researched. The results showed that the reduced plasma levels of rifampicin in patient with TB-DM2 were not due to the use of hypoglycemiant drugs such as glibenclamide, but they were correlated to greater body weight and hypoglycemia in patients with TB-DM2. This information suggests the need of the appropriate modification of drug dosage in obese patients and the adequate glycemic control[24].

In conclusion, and according to the results, DM2 by itself is a risk factor for drug-resistance TB, independently of the adequate glycemic control. Therefore, primary prevention of this disease is recommended, improving people's life styles with grater susceptibility to develop this metabolic pathology. A systematic screening of DM2 is suggested in all patients with TB.

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None.

CONFLICTS OF INTEREST

The authors report no conflict of interest regarding this manuscript.

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Correspondence:
Cynthia Mendoza
E-mail: cysomele@hotmail.com