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Short Communication

Clinical and epidemiological aspects of cases of tuberculosis associated with diabetes in Salvador, Bahia, Brazil

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Abstract

Introduction: This study compares the clinical and epidemiological features of patients with TB, with and without DM. **Methods**: New cases of active pulmonary TB that occurred in Salvador, Bahia, Brazil between 2008 and 2010 were included. DM was diagnosed by based on diagnostic criteria established by the American Diabetes Association. **Result**s: Of the 323 cases of TB, 44 (13.6%) were diabetic . Patients with TB and DM were older (44.7%), with a high level of education (34.%); had s**low** wound healing (23.4%) and fatigue (61.7%). **Conclusions**: Clinical symptoms differed between patients with TB, with and without DM.

Keywords: Tuberculosis. Diabetes. Symptoms.

In Brazil, the growing prevalence of chronic diseases, such as diabetes mellitus (DM), affects individuals of working age, increases the burden on social security systems, and perpetuates a vicious cycle of poverty and social exclusion. There are an estimated 6,317,621 diagnosed cases of DM in Brazil, corresponding to 5.2% of the population[1]. The greatest economic impact is on healthcare, with increasing costs of treatment of the disease and its complications.

There is evidence that DM increases the risk of lower respiratory tract infections and the incidence of tuberculosis (TB) among patients with diabetes mellitus has been reported to be 2-3 times higher than that of the general population[2,3]. This increased risk is the result of a reduction in phagocytic activity and in the production of T-cells and interferon-gamma, due to high levels of hemoglobin A1c in diabetic patients[2,4].

Brazil is among the 22 countries with the highest number of cases of TB. In 2014, the incidence rate of all forms of TB was 33.5/100,000 inhabitants[5] and this was higher among immunocompromised individuals, such as those co-infected with the human immunodeficiency virus (HIV) and patients with DM[6]. These co-morbidities favor the permanence of high incidence rates of TB and hamper TB control[2,3,6]. Studies comparing the clinical characteristics of patients with these two comorbidities are scarce. The aim of the present study was to describe and compare the clinical and epidemiological features of patients with TB, with and without diabetes.

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This cross-sectional study included diabetic and non-diabetic patients with TB, with no previous history of TB treatment or of multidrug resistance. All patients were undergoing treatment provided by healthcare services in Salvador, Bahia, Brazil, between August 2008 and December 2010.

New cases of active pulmonary TB were defined as individuals over 14 years of age living in Salvador and presenting with respiratory symptoms, who were investigated for TB at any of a number of health care units. Individuals had no previous history of TB, and all agreed to participate. Cases were defined as individuals diagnosed with pulmonary TB by the attending chest physician. All potential cases underwent a smear microscopy and culture for *Mycobacterium tuberculosis*, and individuals without a positive result or who did not live in Salvador were excluded.

DM was diagnosed based on the measurement of blood glucose levels using a glucose meter and lancing device, irrespective of the time of the last meal. A blood sample was obtained by pricking the lateral surface of a fingertip with the lancet, after cleaning the area. The blood sample was then applied to a reagent test strip, previously inserted into an Accu-Chek Advantage II meter.

According to the diagnostic criteria set by the American Diabetes Association[7], DM is defined as fasting glucose levels ≥ 126mg/dl or the presence of classic symptoms of hyperglycemia or hyperglycemic crisis, with glucose levels of 200mg/dl. Fasting is defined as no caloric intake for at least 8 hours. The clinical criteria for diagnosis were polydipsia; polyphagia; and weight loss, pain and wounds that were difficult to heal. Patients with a previous diagnosis of diabetes and those who reported use of medication for DM were considered diabetic, regardless of the results of tests for glycemia.

Patients with active pulmonary TB and blood glucose levels above normal were informed of their results and referred to healthcare professionals at the Tuberculosis Control Program for the necessary therapeutic adjustments.

A standardized questionnaire was administered by trained nursing technicians, under nurse supervisions. This instrument was designed to collect data on the patient's clinical and sociodemographic status, lifestyle, the presence or absence of symptoms of DM, the presence or absence of a Bacillus Calmette Guerin (BCG) immunization scar, and the number of scars. Furthermore, records were reviewed in an attempt to collect data of any previous history of diabetes.

A descriptive analysis of patient clinical and sociodemographic characteristics was performed. The STATA software program, version 12.0, was used for the analysis. The chi-square test and Student's t-test were used to compare the results, which were expressed as means and standard deviations of the mean, to estimate the p-value of continuous variables that do not have a normal distribution, with a log-transformation for base 10.

The Internal Review Board of the Institute of Public Health, Federal University of Bahia, approved the study under reference (Process number 2007/012). All participants signed an informed consent form, according to the requirements of the standardized guidelines established by the Brazilian Ministry of Health's Resolutions 196/96 and 304/2000. The committee determined that the study met ethical, legal, and regulatory norms and standards for research involving human subjects in Brazil, as well as international norms and standards.

Of the 323 cases of tuberculosis included in the study, 47 (14.6%) patients were classified as diabetic. Comparing the sociodemographic variables between diabetic and non-diabetic patients with TB, the former group were older (44.7% of the patients were ≥ 50 years of age), had a higher educational level (34% high school or above), and a lower family income (48.9% with < R$600 Brazilian reals per month). These differences were statistically significant. Conversely, no differences were found between the two groups in the number of male subjects, single subjects, or homeowners (**Table 1**).

TABLE 1

Socio-demographic characteristics of tuberculosis with and without diabetes. Salvador, August 2008 to December 2010.

	Cases of tuberculosis				
	diabetes		no diabetes		p-value
	n	%	n	%	
Variables					
Sex					
female	24	51.1	102	36.9	0.07
male	23	48.9	174	63.1	
Age (years)					
14-29	3	6.4	90	32.6	0.01
30-39	9	19.5	72	26.1	
40-49	14	29.8	61	22.1	
≥50	21	44.7	53	19.2	
Marital status					
single	20	42.5	146	52.9	0.07
married	18	40.4	111	39.9	
other*	6	17.1	22	7.2	
House					
own	39	82.9	225	81.5	0.91
rented	5	10.6	35	12.7	
others**	3	6.4	16	5.8	
Education					
elementary school	14	29.8	116	42.0	0.01
middle school	17	36.2	119	43.1	
high school or more	16	34.0	41	14.9	
Family income (R$)* **					
40-300	1	2.2	16	5.8	0.05
301-600	21	46.7	77	27.9	
601-1,000	13	28.9	78	28.3	
≥1,001	6	13.3	40	14.5	
no information	4	8.9	66	23.5	

*Separated/divorced widower and others. **Assigned + in + occupation sublet + other. ***Minimum salary: R$415,00 in 2008; R$465,00 in 2009 and R$510,00 in 2010.

There were no differences between the two groups in the following factors: previous history of tuberculosis, TB contact, previous treatment for tuberculosis, presence of fever or cough with sputum, hemoptysis, night sweats, weight loss, fever, coughing, or any other symptom, or the presence of a BCG immunization scar (**Table 2**). There was a positive and statistically significant association with slow wound healing in the group of diabetic patients [11 (23.4%) vs 12 (4.4%),

TABLE 2

Comparison of clinical cases of tuberculosis with and without diabetes. Salvador, August 2008 to December 2010.

	Cases of tuberculosis				
	diabetes		no diabetes		p-value
	n	%	n	%	
Variables					
Previous tuberculosis					
yes	3	6.4	19	6.9	0.99
no	44	93.6	257	93.1	
Tuberculosis contact					
yes	13	27.6	76	27.5	0.97
no	34	72.4	200	72.5	
TB treatment history					
yes	3	6.4	17	6.2	0.95
no	44	93.6	259	93.8	
Fever					
yes	34	72.4	193	69.9	0.74
no	13	27.6	83	30.1	
Adenomegaly					
yes	1	2.1	20	7.3	0.19
no	46	97.9	255	92.7	
Coughing					
yes	46	97.9	268	97.1	0.77
no	1	2.1	8	2.9	
Expectoration					
yes	37	78.7	217	78.6	0.98
no	10	21.3	59	21.4	
Hemoptysis					
yes	16	34.0	73	26.6	0.29
no	31	66.0	202	73.4	
Night sweats					
yes	24	51.1	158	57.4	0.41
no	23	48.9	117	42.6	
Weight loss					
yes	40	85.1	229	83.0	0.71
no	7	14.9	47	17.0	
Other symptoms					
chest pain	14	29.8	93	33.7	0.04
dyspnea\fatigue\asthenia	3	6.4	11	4.0	
body ache\leg pain\feet pain	8	17.0	20	7.3	
headache	3	6.4	7	2.5	
other	4	8.5	11	4.0	
no information	15	31.9	134	48.5	
Slow wound healing					
yes	11	23.4	12	4.4	0.01
no	36	76.6	263	95.6	
Fatigue or leg pain					
yes	29	61.7	118	42.9	0.02
no	18	38.3	159	57.1	
Bacille calmette guérin vaccine scar					
yes	39	83.0	233	84.4	0.80
no	8	17.0	43	15.6	

p-value = 0.01)]; fatigue or leg pain [29 (61.7%) vs 118 (42.9%), p-value = 0.02)], and other symptoms (dyspnea\fatigue\asthenia [3 (6.4%) vs 11 (4%)]; body ache\leg pain\foot pain [8 (17%) vs 20 (7.3%)]; headache [3 (6.4%) vs 7 (2.5%) p-value = 0.04] (**Table 2**).

Furthermore, the log mean of duration of fever was significantly higher in the group with diabetes (25.3 ± 27.1 days) compared to the non-diabetic group (16.6 ± 22.7 days p-value = 0.01) (**Table 3**). The mean time of cough duration (p-value= 0.13) and the mean time until the onset of TB symptoms (p-value=0.15) were comparable in both groups (**Table 3**).

These results show that patients with TB with DM are older, have a higher level of schooling, and a lower income compared to non-diabetic patients with TB. The findings regarding age are consistent with previous findings that patients with TB with DM tend to belong to an older age group[3,8].

With the aging population, the prevalence of DM tends to increase and add to the burden already caused by TB, characterizing confluent epidemics, occurring in developing countries, such as Brazil. The association among TB, DM, and older age affects the presentation of TB, and is characterized by more severe clinical signs[3,9,10].

This study demonstrated that the combination of DM and TB occurred more frequently among patients from lower income families. It appears that an individual's social circumstances increase susceptibility to DM in the same way that tuberculosis is associated with the poorest living conditions[9,10]. The association between poor social status, TB[11] and DM[2,12] reflects the increased vulnerability of this group in which two chronic diseases with specific follow-up requirements are superimposed.

TB requires regular monitoring by healthcare services for six months, while DM requires continuous care over a lifetime, with regular daily medication, adequate diet, physical activity, and blood glucose control, as well as other requirements[7]. It is important to address this aspect when planning health strategies for this group of patients.

To the best of our knowledge, there are no studies specifically reporting the duration of fever in patients with TB with DM. Most studies have focused on the probability of fever or frequency of fever at diagnosis. This symptom was described as three times higher among patients with TB and DM (OR 2.9, CI 95% 1.5-5.7)[9,13]. The present finding of a longer duration of fever is compatible with clinical changes related to DM. Diabetic patients with TB have a higher bacterial load, which takes longer to become negative in follow-up smears after the commencement of treatment because lung infiltrates and cavities are more common in these patients, and which may also explain the longer duration of fever in this group[14,15]. Fever is a reaction that depends on endogenous pyrogens. In the case of comorbidity between TB and DM, the toxins produced and released by the bacilli may account for the differences. A higher (44.6%) frequency of fever has been reported among patients with DM compared to those without DM (26.6%) (OR 2.2, CI 95%:1.2 - 4.0)[10].

Regarding other clinical manifestations, some symptoms, such as fatigue and weight loss, are common to both diseases; therefore, it is difficult to determine the precise onset of symptoms of TB in individuals who are also diabetic. Furthermore, DM potentially contributes to increased immune pathology and poor control in TB infection, and alters the natural history of this infection. DM may also exacerbate the clinical manifestations of TB; Previous reports indicate that diabetic patients with TB are more likely to complain of physical symptoms, such as dyspnea, fatigue, asthenia, body pain, and headache[3,9,13].

Over time, DM causes functional and structural changes in the circulation, explaining the differences in healing time between diabetic and non-diabetic patients with TB. The primary determinant of these complications is sustained hyperglycemia, which causes biochemical and structural abnormalities in the blood vessels and peripheral nerves. Endothelial damage appears to be the factor triggering the pathogenesis of microvascular complications related to these abnormalities, representing possible symptoms of complications of DM[3,10]. Higher proportion of TB severity were observed among patients with TB and DM from Brazil, after adjustment for confounding factors[9].

These results are relevant because the differences identified between the two groups of TB patients support the need for an assessment of patients with both conditions (TB and DM). Therefore, the association between TB and DM should be prioritized when diagnosing and treating TB. More information is required on the clinical presentation of these comorbidities in Brazil. Taking in account the clinical impact of this comorbidity it is important that clinical cases are identified early and that diagnosis and treatment are not delayed.

TABLE 3

Comparison of clinical cases of tuberculosis with and without diabetes. Salvador, August 2008 to December 2010.

Characteristics	Obs*	Diabetes (n=47)	Obs*	No diabetes (n=279)	p value**
		Mean (standard deviation)		Mean (standard deviation)	
Duration of fever-days***	34	25.3 (27.1)	193	16.6 (22.7)	0.01
Duration of coughing-days***	45	73.5 (75.2)	269	67.1 (101.7)	0.13
Onset of symptoms-days***	39	67.1 (45.7)	225	62.3(51.5)	0.15

*Number of observations; **t-test with $\log_{10;}$ ***Continuous variables measured in days.

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Conflict of interest

The authors declare that have no conflicts of interest.

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REFERENCES

1. Schmidt MI, Duncan BB, Hoffmann JF, de Moura L, Malta DC, de Carvalho RMSV. Prevalência de diabetes e hipertensão no Brasil baseada em inquérito de morbidade auto-referida Brasil 2006. Rev Saúde Pública. 2009;43(supl 2):74-82.
2. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med. 2008;5(7):e181. https://doi.org/10.1371/journal.pmed.0050181.
3. Restrepo BI, Schlesinger LS. Impact of diabetes on the natural history of tuberculosis. Diabetes Res Clin Pract. 2014; 106(2):191-9.
4. Kumar NP, Sridhar R, Banurekha VV, Jawahar MS, Fay MP, Nutman TB, et al. Type 2 diabetes mellitus coincident with pulmonary tuberculosis is associated with heightened systemic type 1, type 17, and other proinflammatory cytokines. Ann Am Thorac Soc. 2013;10(5):441-9.
5. Ministério da Saúde. Secretaria de Vigilância em Saúde. Boletim Epidemiológico. Especial tuberculose. Brasília: Ministério da Saúde; 2015; volume 46 nº 9. p. 1-19. Disponível em: http://portalarquivos.saude.gov.br/images/pdf/2015/marco/27/2015-007---BE-Tuberculose---para-substitui----o-no-site.pdf.
6. Ronacher K, Joosten SA, van Crevel R, Dockrell HM, Walzl G, Ottenhoff THM. Acquired immunodeficiencies and tuberculosis: focus on HIV/AIDS and diabetes mellitus. Immunol Rev. 2015;264(1):121-37.
7. American Diabetes Association. Standards of medical care in diabetes 2013. Diabetes Care. 2013;36(suppl 1):S11-66.
8. Baghaei P, Marjani M, Javanmard P, Tabarsi P, Masjedi MR. Diabetes mellitus and tuberculosis facts and controversies. J Diabetes Metab Disord. 2013;12(1):12-58.
9. Gil-Santana L, Almeida-Junior JL, Oliveira CAM, Hickson LS, Daltro C, Castro S, et al. Diabetes is associated with worse clinical presentation in tuberculosis patients from Brazil: a retrospective cohort study. PLoS One. 2016;11(1):1-13.
10. Wang C, Yang C, Chen H, Chuang S, Chong I, Hwang J, et al. Impact of type 2 diabetes on manifestations and treatment outcome of pulmonary tuberculosis. Epidemiol Infect. 2009;137(2):203-10.
11. Boccia D, Hargreaves J, De Stavola BL, Fielding K, Schaap A, Godfrey-Faussett P, et al. The association between household socioeconomic position and prevalent tuberculosis in Zambia: a case-control study. PloS One. 2011;6(6):1-11.
12. Espelt A, Borrell C, Palència L, Goday A, Spadea T, Gnavi R, et al. Socioeconomic inequalities in the incidence and prevalence of type 2 diabetes mellitus in Europe. Gac Sanit. 2013;27(6):494-501.
13. Faurholt-Jepsen D, Range N, PrayGod G, Kidola J, Faurholt-Jepsen M, Aabye MG, et al. The role of diabetes on the clinical manifestations of pulmonary tuberculosis. Trop Med Int Health. 2012;17(7):877-83.
14. Magee MJ, Kempker RR, Kipiani M, Gandhi NR, Darchia L, Tukvadze N, et al. Diabetes mellitus is associated with cavities, smear grade, and multidrug-resistant tuberculosis in Georgia. Int J Tuberc Lung Dis. 2015;19(6):685-92.
15. Jiyani M, Vadgama PK, Pandey AS, Modh DA. Clinical profile and outcome of tuberculosis in patients with diabetes. Int J Res Med. 2015;4(2):36-40.