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ORIGINAL ARTICLE

Clinical, laboratory, and radiographic aspects of patients with pulmonary tuberculosis and dysglycemia and tuberculosis treatment outcomes

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ABSTRACT

Objective: To analyze the association of dysglycemia with clinical, laboratory, and radiographic characteristics of patients with pulmonary tuberculosis (PTB), as well as with their tuberculosis treatment outcomes. **Methods:** This was a longitudinal study involving 140 patients diagnosed with PTB (positive cultures for *Mycobacterium tuberculosis* or positive Xpert MTB/RIF results from sputum samples). Patients were evaluated at diagnosis (M_0), after completing the second month of treatment (M_2), and at the end of treatment (M_{END}). At M_0, the patients were classified into three groups: normoglycemia+PTB (NGTB); pre-diabetes mellitus+PTB (PDMTB), and diabetes mellitus+PTB (DMTB), in accordance with glycated hemoglobin levels (< 5.7%, 5.7%-6.4%, and ≥ 6.5%, respectively). Treatment outcomes were classified as favorable (cure or treatment completion) and unfavorable (death, loss to follow-up, or treatment failure). **Results:** In our sample, 76 patients (61.4%) had dysglycemia, 20 of whom (14.3%) had DM at M_0. The patients with dysglycemia, in comparison with those in the NGTB group, more frequently presented with positive sputum smear microscopy (94.2% vs. 75.9%; p = 0.003); cavities (80.2% vs. 63.0%; p = 0.03); bilateral lesions (67.4% vs. 46.0%; p = 0.02); and higher median of affected thirds of the lungs (3.0 vs. 2.0; p = 0.03) on chest radiography. No significant differences regarding outcomes were found among the groups, but tuberculosis lethality was higher in the DMTB group than in the PDMTB and NGTB groups (20% vs. 2.2%). **Conclusions:** PTB patients with dysglycemia had laboratory and radiographic manifestations indicative of more advanced disease, and the risk of death was higher in the DMTB group. These findings reinforce the recommendation for early screening for DM in patients with newly diagnosed tuberculosis in order to reduce the risk of death during treatment.

Keywords: Tuberculosis/diagnosis; Tuberculosis/diagnostic imaging; Tuberculosis/therapy; Diabetes mellitus; Treatment outcome.

INTRODUCTION

In recent years, the association between diabetes mellitus (DM) and tuberculosis (DMTB) has been recognized as an important public health problem. DM increases the risk of developing active tuberculosis by 2-3 times, and patients with DMTB more often have unfavorable tuberculosis treatment outcomes when compared with tuberculosis patients without DM.[1-3] The innate and adaptive immune responses to *Mycobacterium tuberculosis* are altered in patients with DM, increasing the risk of either primary infection or reactivation of tuberculosis infection.[4] The hyperinflammatory host response associated with tuberculosis can cause hyperglycemia, hinder the clinical management of patients with DM, and induce the development of DM in patients with pre-DM.[5]

The progress made toward tuberculosis elimination has been recently affected by the COVID-19 pandemic, which resulted in reduced access to tuberculosis

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services, leading to an 18% drop in the number of newly diagnosed tuberculosis cases and increased numbers of tuberculosis-related deaths. These figures may be further hampered by the rapid increase in DM in recent years, particularly in low- and middle-income countries.[6] Prospective studies evaluating the role of dysglycemia (DM and pre-DM) in the clinical presentation of tuberculosis and response to tuberculosis treatment under routine conditions carried out in countries with a high tuberculosis burden are still scarce in the literature.[7,8] Data on DMTB provided by the Brazilian Ministry of Health[9] and based on reported tuberculosis cases to the *Sistema de Informação de Agravos de Notificação* (Brazilian Case Registry Database) showed that, between 2019 and 2021, 10% of the patients with tuberculosis reported to be diabetic.

In the present study, we aimed to describe the clinical, laboratory, and radiographic characteristics of pulmonary tuberculosis (PTB) patients with and without dysglycemia, as well as to analyze the association of these characteristics with tuberculosis treatment outcomes.

METHODS

Between September of 2016 and November of 2020, we carried out a longitudinal study involving patients with PTB treated at the Municipal Health Care Center in the city of Duque de Caxias, Brazil.

A consecutive, convenience sample of individuals seeking the center with cough for at least two weeks was screened for tuberculosis with the use of a clinical score[10] based on respiratory signs and symptoms suggestive of the disease. Patients with a score ≥ 5 had a medium/high probability of having PTB and were invited to participate in the study.[10] Patients who were ≥ 18 years of age and agreed to be interviewed, to undergo anthropometric measurements and chest radiography (CXR), and to have clinical samples collected were included in the study. Participants with a positive culture for *M. tuberculosis* and/or a positive Xpert MTB/RIF assay (GeneXpert; Cepheid, Sunnyvale, CA, USA) result from sputum samples were defined as having PTB. According to the glycated hemoglobin (HbA1c) profile, tuberculosis patients were categorized into three groups: normoglycemic group (NGTB; HbA1c < 5.7%); pre-diabetic group (PDMTB; 5.7% ≤ HbA1c ≤ 6.4%); and diabetic group (DMTB; HbA1c ≥ 6.5%).[11-13] All HbA1c assays were performed in a certified laboratory (*Laboratório de Análises Clínicas da Unigranrio*) in the city of Duque de Caxias.

After giving written informed consent, the patients were evaluated at the moment of receiving the diagnosis of tuberculosis or during the first week of tuberculosis treatment initiation (M_0), after completing the second month of treatment (M_2), and at the end of the treatment (M_{END}). During the visits, patients underwent anthropometric measurements (weight and height), sputum tests (sputum smear microscopy, Xpert MTB/RIF, culture for *M. tuberculosis*, first-line drug susceptibility testing [BACTEC MGIT 960 SIRE; Becton Dickinson, Sparks, MD, USA]), blood tests (fasting glycemia and HbA1c), and CXR. Participants also completed a questionnaire, administered by a trained nurse, with questions about sociodemographic characteristics, as well as signs and symptoms suggestive of PTB. Tobacco, alcohol, and illicit drug use was evaluated by a specific questionnaire.[14] A pulmonologist, blinded to the patients' glycemic profile, evaluated CXR by using a standardized form regarding the presence of lung cavities (number and size) and extension of lung involvement (unilateral or bilateral lesions and number of affected thirds of the lungs). Information on tuberculosis treatment outcomes was obtained from clinical records, and these outcomes were classified as favorable (cure or treatment completion) or unfavorable (death, loss to follow-up, or treatment failure).

Absolute and relative frequencies of categorical variables were calculated; for continuous variables, medians and interquartile ranges were described. Associations of categorical variables with dysglycemia and treatment outcome were assessed by the chi-square test (or Fischer's exact test, when indicated), and ORs and respective 95% CIs were described. To compare continuous variables, the Wilcoxon-Mann-Whitney test was used. The significance level was set at 5%, and p values were two-tailed. Multivariate analyses of the association of clinical, laboratory, and radiographic characteristics with HbA1c levels and tuberculosis treatment outcomes were performed using logistic regression. Box plots of the distribution of HbA1c levels at M_0, M_2 and M_{END}, as well as among patients who died or not, were built. For statistical analyses, the IBM SPSS Statistics software package, version 23.0 (IBM Corporation, Armonk, NY, USA) and the R program 2019 (The R Foundation for Statistical Computing, Vienna, Austria) were used.

This study was approved by the Research Ethics Committee of the University Hospital Clementino Fraga Filho on 07/02/2015 (CAAE no. 45637715.5.0000.5257).

RESULTS

During the study period, 318 eligible patients with respiratory symptoms and medium/high clinical score results for PTB were identified. Of those 318 patients, 8 patients (3.8%) were excluded: 3 individuals were unable to collect or deliver a sputum sample and were referred to further investigation; blood samples were not collected from another 3; and it was not possible to process the samples sent to the laboratory from 2 participants. Of the 310 participants initially included in the study, 140 (45.2%) had a diagnosis of PTB.

Most PTB patients were male (n = 93; 66.4%); the medians of age and BMI were, respectively, 36 years and 19.7 kg/m^2. Non-White participants were more represented (n = 116; 82.9%), and 75 patients

(53.6%) attended school for less than 8 years. Tobacco, alcohol, and illicit drug use was identified, respectively, in 42.9%, 49.3%, and 24.3% of the patients (Table 1). Previous tuberculosis treatment and HIV infection were observed in 12.9% and 7.2%, respectively (Table S1).

The prevalence of dysglycemia among the patients at M_0 was 61.4% (pre-DM, in 47.1% and DM, in 14.3%). Among the 20 patients with DM, 13 (65.0%) had a previous diagnosis of type 2 DM. Blood glucose was measured in all patients; however, information on fasting was recorded only in 112 patients (80.0%). The test was performed after fasting in 73.2% (82/112), and in 11.0% (9/82) of these cases the values were ≥ 126 mg/dL. Of those 9 patients, 4 (44.4%) had a previous diagnosis of type 2 DM.

Age and BMI medians were significantly higher in the DMTB group. Higher use of tobacco, alcohol, and illicit drugs was observed in the PDMTB group (Table 1).

Regarding symptoms suggestive of PTB, previous tuberculosis treatment, and HIV infection, no statistical differences were observed between normoglycemic and dysglycemic patients with tuberculosis. Cough and sputum were reported by all patients, as both variables were included in the definition of individuals with respiratory symptoms, an eligibility criterion adopted in the study (Table S1).

CXR findings and microbiological and molecular test results at diagnosis of PTB and during follow-up

At diagnosis of PTB, patients in the PDMTB group more frequently presented with cavitary disease on CXR (84.8%) when compared with those in the NGTB (63.0%) and DMTB (65.0%) groups. There were no statistical differences in the mean number of cavities and in the number of cavities larger than 2 cm among the three groups of patients. However, bilateral lesions were more frequently observed in the DMTB group than in the NGTB group (70% vs. 46%; p = 0.03). The mean number of thirds of the lungs affected was statistically higher in the DMTB and PDMTB groups than in the NGTB group. In patients with dysglycemia, in comparison with those in the NGTB group, cavities (80.2% vs. 63.0%) and bilateral lesions on CXR (67.4% vs. 46.0%) were more common, and there was also a higher number of affected thirds of the lungs (median, 3 vs. 2). During the follow-up period (M_2 and M_{END}), no statistical differences were observed in CXR findings among the three groups of patients (Table 2).

Positivity on sputum smear microscopy was significantly higher in the PDMTB and DMTB groups (93.0%) than in the NGTB group (75.9%; p = 0.005); however, positive Xpert MTB/RIF and *M. tuberculosis* culture results in sputum were similar among the groups (Table 3). Resistant *M. tuberculosis* strains were more common in the NGTB (20.9%) and PDMTB (19.0%) groups than in the DMTB group (10.0%). The most common drug resistance patterns were monoresistance to streptomycin (45.8%, 11/24) and to isoniazid (25.0%, 6/24). During follow-up, no significant differences were observed regarding microbiological test results in the three groups of patients (Table 3).

Univariate and multivariate analyses of clinical, radiographic, and microbiological characteristics associated with dysglycemia

Univariate and multivariate logistic regression analyses of clinical, radiographic, and microbiological

Table 1. Sociodemographic data of patients with pulmonary tuberculosis (N = 140), in accordance with glycated hemoglobin levels at the time of diagnosis.[a]

Variable		NGTB group (n = 54)	PDMTB group (n = 66)	p[b]	DMTB group (n = 20)	p[c]	p[d]
Sex	Female	16 (29.6)	23 (34.8)	0.56	8 (40.0)	0.41	0.46
	Male	38 (70.4)	43 (65.2)		12 (60.0)		
Age	years	33.5 [24.0-46.0]	35.5 [26.7-48.5]	0.29	44.0 [37.2-57.0]	0.01	0.08
Skin color	White	12 (22.2)	9 (13.6)	0.23	3 (15.0)	0.74	0.25
	Non-White	42 (77.8)	57 (86.4)		17 (85.0)		
Schooling	< 8 years	25 (46.3)	40 (60.6)	0.14	10 (50.0)	0.79	0.22
	≥ 8 years	29 (53.7)	26 (39.4)		10 (50.0)		
BMI	kg/cm^2	19.6 [17.2-21.1]	19.2 [18.2-21.5]	0.38	23.1 [20.0-26.6]	< 0.005	0.05
BMI	≥ 18.5 kg/cm^2	33 (61.1)	44 (66.7)	0.56	18 (90.0)	0.02	0.19
	< 18.5 kg/cm^2	21 (38.9)	22 (33.3)		2 (10.0)		
Tobacco	No	33 (61.1)	31 (47.7)	0.19	15 (75.0)	0.41	0.48
	Yes	21 (38.9)	34 (52.3)		5 (25.0)		
Alcohol	No	27 (50.0)	30 (46.2)[e]	0.71	13 (65.0)	0.30	1.00
	Yes	27 (50.0)	35 (53.8)[e]		7 (35.0)		
Illicit drugs	No	41 (75.9)	47 (72.3)[e]	0.68	17 (85.5)	0.53	1.00
	Yes	13 (24.1)	18 (27.7)[e]		3 (15.0)		

NGTB: normoglycemia (NG; glycated hemoglobin [HbA1c < 5.7%]) + tuberculosis (TB); PDMTB: pre-diabetes mellitus (PDM; HbA1c = 5.7-6.4%) + TB; and DMTB: (DM; HbA1c ≥ 6.5%) + TB. [a]Values expressed as n (%) or median [IQR]. [b]NGTB vs. PDMTB. [c]NGTB vs. DMTB. [d]NGTB vs. PDMTB+DMTB. [e]n = 65.

Table 2. Chest radiography findings in patients with pulmonary tuberculosis (N = 140) at diagnosis, after completing the second month of treatment, and at the end of tuberculosis treatment, in accordance with the levels of glycated hemoglobin.[a]

Finding M_0		NGTB group (n = 54)	PDMTB group (n = 66)	p[b]	DMTB group (n = 20)	p[c]	p[d]
Presence of cavity	Yes	34 (63.0)	56 (84.8)	0.01	13 (65.0)	1.00	0.03
	No	20 (37.0)	10 (15.2)		7 (35.0)		
Number of cavities		3.0 [1.0-4.0]	3.0 [2.0-4.0]	0.64	3.0 [1.0-6.0]	0.97	0.68
Cavity > 2 cm	Yes	33 (97.1)	52 (92.9)	0.64	13 (100)	1.00	1.00
	No	1 (2.9)	4 (7.1)		0 (0.0)		
Lesion[e]	Unilateral	27 (54.0)	22 (33.3)	0.03	6 (30.0)	0.11	0.02
	Bilateral	23 (46.0)	44 (66.7)		14 (70.0)		
Number of affected thirds		2.0 [2.0-3.2]	3.0 [2.0-4.0]	0.06	3.0 [2.2-4.5]	0.06	0.03
M_2		NGTB group (n = 27)	PDMTB group (n = 26)	p[b]	DMTB group (n = 11)	p[c]	p[d]
Presence of cavity	Yes	13 (48.1)	14 (53.8)	0.78	7 (63.6)	0.48	0.61
	No	14 (51.9)	12 (46.2)		4 (36.4)		
Number of cavities		2.0 [1.0-3.0]	2.0 [1.0-3.0]	0.79	2.0 [1.0-4.0]	0.91	0.87
Cavity > 2 cm	Yes	8 (61.5)	10 (71.0)	0.69	6 (85.7)	0.35	0.45
	No	5 (38.5)	4 (28.6)		1 (14.3)		
Lesion[f]	Unilateral	15 (57.7)	9 (34.6)	0.16	9 (90.0)	0.11	0.61
	Bilateral	11 (42.3)	17 (65.4)		1 (10.0)		
Number of affected thirds		2.0 [1.0-2.2]	2.0 [2.0-3.0]	0.09	2.0 [1.7-2.0]	0.71	0.13
M_{END}		NGTB group (n = 29)	PDMTB group (n = 35)	p[b]	DMTB group (n = 12)	p[c]	p[d]
Presence of cavity	Yes	5 (17.2)	7 (20.0)	1.00	1 (8.3)	0.65	1.00
	No	24 (82.8)	28 (80.0)		11 (91.7)		
Number of cavities		1.0 [1.0-2.5]	1.0 [1.0-2.0]	0.75	1.0 [1.0-1.0]	1.00	0.83
Cavity > 2 cm	Yes	4 (80.0)	5 (71.4)	1.00	1 (100)	1.00	1.00
	No	1 (20.0)	2 (28.6)		0 (0.0)		
Lesion[g]	Unilateral	13 (65.0)	10 (37.0)	0.08	10 (100)	0.06	0.57
	Bilateral	7 (35.0)	17 (63.0)		0 (0.0)		
Number of affected thirds		1.5 [1.5-2.0]	2.0 [1.0-2.0]	0.17	1.0 [1.0-2.0]	0.39	0.48

NGTB: normoglycemia (NG; glycated hemoglobin [HbA1c < 5.7%]) + tuberculosis (TB); PDMTB: pre-diabetes mellitus (PDM; HbA1c = 5.7-6.4%) + TB; DMTB: (DM; HbA1c ≥ 6.5%) + TB; M_0: at diagnosis; M_2: after completing two months of treatment; and M_{END}: at the end of treatment. [a]Values expressed as n (%) or median [IQR]. [b]NGTB vs. PDMTB. [c]NGTB vs. DMTB. [d]NGTB vs. PDMTB + DMTB. [e]n = 136. [f]n = 62. [g]n = 57.

characteristics at M_0 associated with dysglycemia are presented in Table 4. Higher BMI, presence of cavities on CXR, and positive sputum smear microscopy were independently associated with dysglycemia among the patients with PTB.

Variation in HbA1c levels during tuberculosis treatment

The distributions of HbA1c levels (in %) assessed at M_0, M_2 and M_{END} are shown in Figure 1. A significant reduction in HbA1c above normal levels (≥ 5.7%) was observed at M_2, particularly in the PDMTB group (from 47% at M_0 to 14% at M_2), that is, among the 66 patients in the PDMTB group at M_0, dysglycemia was not confirmed at M_2 in 46 (70%). The median HbA1c levels in the PDMTB and DMTB groups, respectively, significantly decreased from M_0—5.9% [5.8-6.1%] and 9.7% [6.8-11.8%]—to M_2—5.4% [5.1-5.6%] and 8.1% [5.9-12.5%]—to M_{END}—5.4% [5.2-5.7%] and 8.4% [6.3-10.3%]. We found a significant reduction in dysglycemic levels at M_2 compared with those at M_0 (61% vs. 25%; p = 0.001), which stabilized between M_2 and M_{END} (25% vs. 28%; p = 1.0). However, among 8 of the patients in the PDMTB group at M_2, 5 (62.5%) already had HbA1c levels ≥ 5.7% at M_0.

Tuberculosis treatment outcomes

All patients used the standard regimen for tuberculosis treatment (including patients with isoniazid resistance, who had their treatment extended to nine months), and the mean duration of tuberculosis treatment (in months) in the NGTB, PDMTB, and DMTB groups, respectively, were 6.8, 6.2, and 7.1 months (p = 0.13). Information on tuberculosis treatment outcomes was available for all patients except 1 (referred to another clinic). Among the 139 patients evaluated, 29 were lost to follow-up, 2 had treatment failure, 102 had favorable treatment outcomes (7 cured and 95 completed treatment), and 6 died. There were no significant associations of sociodemographic, clinical, and laboratory variables with the treatment outcomes. Patients in the PDMTB

Table 3. Microbiological data of patients with pulmonary tuberculosis (N = 140) at diagnosis, after completing the second month of treatment, and at the end of tuberculosis treatment, in accordance with the levels of glycated hemoglobin.[a]

Variable		NGTB group	PDMTB group	p[b]	DMTB group	p[c]	p[d]
M_0		(n = 54)	(n = 66)		(n = 20)		
Xpert MTB/RIF in sputum[e]	Nondetectable	3 (5.7)	2 (3.0)	0.65	0 (0.0)	0.55	0.36
	Detectable	50 (94.3)	64 (97.0)		20 (100)		
Smear microscopy	Negative	13 (24.1)	5 (7.6)	0.01	1 (5.0)	0.09	0.005
	Positive	41 (75.9)	61 (92.4)		19 (95.0)		
Positive smear microscopy	< 3+	20 (48.8)	32 (52.5)	0.84	10 (52.6)	1.00	0.70
	3+	21 (51.2)	29 (47.5)		9 (47.0)		
MTB culture	Negative	3 (5.6)	1 (1.1)	0.32	0 (0.0)	0.55	0.29
	Positive	51 (94.4)	65 (98.5)		20 (100)		
Drug susceptibility testing[f]	Sensitive	38 (79.2)	51 (81.0)	1.00	18 (90.0)	0.41	0.81
	Resistant	10 (20.9)	12 (19.0)		2 (10.0)		
Drug resistance[f]	Rifampin	0 (0.0)	0 (0.0)	0.12	0 (0.0)	0.66	0.15
	Isoniazid	4 (8.3)	1 (1.6)		1 (5.0)		
	Ethambutol	1 (2.1)	0 (0.0)		0 (0.0)		
	Pyrazinamide	1 (2.1)	0 (0.0)		0 (0.0)		
	Streptomycin	2 (4.2)	8 (12.7)		1 (5.0)		
	Isoniazid + Streptomycin	2 (4.2)	3 (5.7)		0 (0.0)		
M_2		NGTB group	PDMTB group	p[b]	DMTB group	p[c]	p[d]
		(n = 25)	(n = 32)		(n = 9)		
Smear microscopy	Negative	19 (76.0)	26 (81.3)	0.74	7 (78.0)	1.00	0.76
	Positive	6 (24.0)	6 (18.8)		2 (22.0)		
Positive smear microscopy	< 3+	5 (83.3)	6 (100)	1.00	2 (100)	1.00	0.42
	3+	1 (16.7)	0 (0.0)		0 (0.0)		
MTB culture[g]	Negative	13 (72.0)	13 (87.0)	0.41	5 (83.0)	1.00	0.43
	Positive	5 (28.0)	2 (13.0)		1 (17.0)		
M_{END}		NGTB group	PDMTB group	p[b]	DMTB group	p[c]	p[d]
		(n = 13)	(n = 23)		(n = 3)		
Smear microscopy	Negative	12 (92.0)	22 (96.0)	1.00	3 (100)	1.00	1.00
	Positive	1 (8.0)	1 (4.0)		0 (0.0)		
Positive smear microscopy	< 3+	0 (0.0)	1 (100)	1.00	0 (0.0)	N/A	1.00
	3+	1 (100)	0 (0.0)		0 (0.0)	N/A	
MTB culture[h]	Negative	5 (83.0)	11 (100)	0.35	0 (0.0)		0.35
	Positive	1 (16.0)	0 (0.0)		0 (0.0)		

NGTB: normoglycemia (NG; glycated hemoglobin [HbA1c < 5.7%]) + tuberculosis (TB); PDMTB: pre-diabetes mellitus (PDM; HbA1c = 5.7-6.4%) + TB; DMTB: (DM; HbA1c ≥ 6.5%) + TB; MTB: *Mycobacterium tuberculosis*; M_0: at diagnosis; M_2: after completing two months of treatment; and M_{END}: at the end of treatment. [a]Values expressed as n (%). [b]NGTB vs. PDMTB. [c]NGTB vs. DMTB. [d]NGTB vs. PDMTB + DMTB. [e]n = 139. [f]n = 131. [g]n = 39. [h]n = 17.

Table 4. Univariate and multivariate analysis of clinical, radiographic, and microbiological characteristics at the time of diagnosis of tuberculosis associated with dysglycemia among patients with pulmonary tuberculosis.

Variable	Normoglycemia	Dysglycemia	Analysis	
	NGTB group	PDMTB + DMTB groups	Unadjusted	Adjusted
	(n = 54)	(n = 86)	OR (95% CI)	OR (95% CI)
Age, years	33.5 [24.4-45.0]	38.0 [27.0-50.8]	1.20 (0.95-1.52)	1.12 (0.86-1.46)*
Female sex	16 (29.6)	31 (36.0)	1.33 (0.64-2.82)	1.07 (0.48-1.46)
BMI, kg/m^2	19.6 [17.3-21.0]	19.9 [18.4-22.5]	1.11 (1.00-1.24)	2.36 (1.31-4.61)**
Positive smear microscopy	41 (75.9)	80 (93.0)	4.13 (1.50-12.07)	4.59 (1.38-17.75)
Cavity on chest radiography	34 (63.0)	69 (80.2)	2.37 (1.10-5.18)	2.81 (1.13-7.22)

[a]Values expressed as n (%) or median [IQR]. *OR considering an increment of 10 years. **OR considering an increment of 5 units of BMI.

and DMTB groups showed no significantly higher frequencies of unfavorable outcomes (death, treatment dropout, or treatment failure) when compared with those in the NGTB group (25.0% vs. 33.9%). At M_{END}, 12 patients in the PDMTB group had favorable outcomes (cure or treatment completion). Likewise, there was no significant difference between tuberculosis treatment outcomes (favorable or unfavorable) and HbA1c levels (p = 0.38). However, of the 6 patients who died, 4 were in the DMTB group. Tuberculosis lethality was 20% (4/20) among the patients in the DMTB group, whereas it was 2.2% in the PDMTB (1/46) and NGTB (1/45) groups. Despite the analysis limitation due to the small number of events, we observed a significant association between death and higher HbA1c levels (Figure 2).

DISCUSSION

In countries with a high tuberculosis burden such as Brazil, few prospective studies have analyzed the clinical, microbiological, and radiographic characteristics of PTB patients or the role of DM and pre-DM in PTB treatment outcomes.[8,10]

In our study, the frequency of DM among PTB patients (14.2%) was higher than that reported in another study in Brazil[8] and closer to those reported in other series (from 12.8% to 25%),[16-19] but lower than that reported in a study conducted in India,[15] in which the proportion of patients with tuberculosis and DM was 30%. In countries such as China[20] and Kenya,[21] the frequency of the DMTB association has been found to be lower (5.0% and 6.3%, respectively) than that found in our study. In other studies carried out in Brazil, the frequency of DM among tuberculosis patients was similar to our findings (13.6% and 14%).[22,23] The differences in the prevalence of DM observed in those studies, carried out in different geographical regions, may be associated with genetic predispositions to DM, dietary habits (including alcohol consumption), obesity, age distribution, and sedentary lifestyle, but they may also be due to diverse methods to evaluate dysglycemia.[15-23]

Although the screening for DM in patients with tuberculosis at the beginning of treatment is internationally recommended, the test to be used (fasting glucose, glucose tolerance test, or HbA1c) and the timing of repeat testing may vary according to local conditions.[24-26] In our study, the information on fasting glycemia was collected in only 58.6% of the patients. Therefore, we chose to use HbA1c as a screening test, considering levels ≥ 6.5% as the criterion for DM diagnosis.[11,13,27] The use of HbA1c as a screening test for DM has some advantages, such as not requiring the patient to fast and having greater pre-analytical stability. However, the test has limitations: it is more expensive and influenced by other conditions (age, ethnicity, and presence of anemia).[27] Moreover, HbA1c testing can detect up to a third less DM cases when compared with a blood glucose fasting level ≥ 126 mg/dL.[28]

Symptoms of tuberculosis in patients with DM appear to be more common and severe than do those described in patients with tuberculosis without DM.[22,29] However, we found no significant differences regarding the typology or duration of symptoms between the NGTB group and the dysglycemic groups in our cohort. Patients with DMTB had a higher mean age and BMI (suggestive of overweight), which is a common finding in patients with type 2 DM, as reported in other studies.[16,21,24]

CXR findings in patients with the DMTB are more frequently associated with the presence of multiple cavities and bilateral pulmonary involvement. Patients

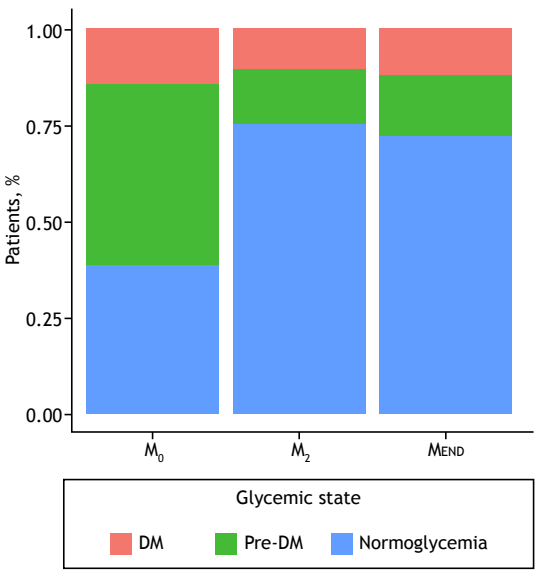

Figure 1. Proportion of patients diagnosed with pulmonary tuberculosis regarding glycemic state (determined by glycated hemoglobin levels) at three moments of evaluation: at the diagnosis of tuberculosis (M_0; n = 140); after completing the second month of treatment (M_2; n = 99); and at the end of tuberculosis treatment (M_{END}; n = 86). DM: diabetes mellitus.

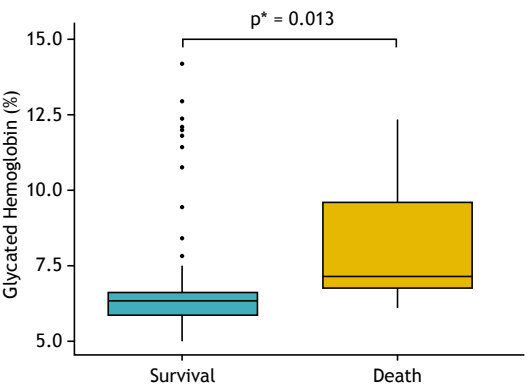

Figure 2. Box plots showing glycated hemoglobin levels at the diagnosis of pulmonary tuberculosis in patients with pulmonary tuberculosis whose outcome was survival or death. *Nonparametric Wilcoxon-Mann-Whiney test.

with DMTB also have a higher frequency of "atypical" findings on CXR, with lesions in the lower lobes, especially in patients with poor glycemic control.[30-32] In our sample, the presence of cavities, bilateral lesions, and involvement of a greater number of thirds of the lungs were more common among dysglycemic patients. As there are scarce data on the radiographic and inflammatory profiles of DMTB patients during tuberculosis treatment,[33] our findings corroborate the results described in one study[34] involving guinea pigs with chronic hyperglycemia and showing a lower innate immune response in the presence of alveolar macrophages infected by *M. tuberculosis*. The animals presented a delay in the specific T response and subsequent hyperinflammation, with high levels of Th1, Th2, and Th17 cytokines; neutrophilia; and high pulmonary bacillary load.[34] The fact that sputum smear microscopy is more frequently positive in dysglycemic patients might be a consequence of a reduced control in *M. tuberculosis* multiplication. In case series in India[17] and in China,[20] higher proportions of positive sputum smear microscopy were also reported among diabetic patients.

No differences regarding the use of alcohol, tobacco, or illicit drugs were found among the groups studied, corroborating what has been described in other studies.[19,20] However, studies carried out in Brazil[22,29] identified a higher frequency of tobacco use in patients with DMTB than in those with tuberculosis without DM. In a cohort of tuberculosis patients in South Korea, the risk of death was almost five-fold greater in the presence of DM and tobacco use.[35]

The differences in radiographic and microbiological findings observed between normoglycemic and dysglycemic patients at the diagnosis of tuberculosis were no longer present during follow-up. However, the analysis of radiographic and microbiological examinations during follow-up involved a smaller number of patients, and, therefore, our sample might have lacked power to identify such differences. In addition, the high proportion of deaths in the DMTB group (20%) might indicate a less effective response to antituberculosis therapy in patients with DMTB. The duration of tuberculosis treatment for patients with DMTB recommended by most guidelines,[24,36] including the Brazilian recommendations,[37] is the same for patients with tuberculosis without DM. However, patients with DMTB usually have a higher risk of toxicity to antituberculosis drugs (peripheral neuropathy due to isoniazid and ocular neuropathy due to ethambutol), drug interactions (in particular, rifampin), and low plasma concentrations of antituberculosis drugs.[38] All of these factors might contribute to unfavorable treatment outcomes in these patients.

In our study, pre-DM was identified in 47.1% of the patients with tuberculosis, which was higher than that described in other studies, with prevalences ranging from 7.4% to 37.5%.[8,16,17,19-21] However, we observed a significant reduction in HbA1c levels in the second month of treatment. Normalization of glycemic levels during tuberculosis treatment in initially dysglycemic patients has also been reported by other authors.[19,39,40] In the study by Calderon et al. carried out in Peru,[19] the prevalence of pre-DM patients decreased from 31% at the diagnosis of tuberculosis to 17% after completing the second month of treatment, maintaining the same proportion at the sixth month of treatment. These findings suggest that dysglycemia identified at the time of diagnosis is partially due to stress-induced hyperglycemia, a consequence of the inflammatory response to *M. tuberculosis*, which gradually decreases in consequence of infection control.[29,40]

Tuberculosis treatment outcomes were not significantly different between normoglycemic and dysglycemic patients. The reason for the lack of such differences might be due to the inclusion of a nonbiological variable, such as loss to follow-up, among the unfavorable outcomes. However, when analyzing the cases that progressed to death, there was higher lethality among the patients in the DMTB group, and an association between higher levels of HbA1c and death was observed. The association between DM and death during tuberculosis treatment was previously described in a systematic review and in a systematic review and meta-analysis,[2,3] in which the OR for death/treatment failure ranged from 1.69[2] to 1.88.[3]

Our study has limitations that are mainly related to the sample size, which might have limited the detection of significant associations, particularly during follow-up, when there was a further reduction in the number of participants. Furthermore, by including only patients with a medium/high probability of PTB using a clinical score for screening, we did not analyze patients with less exuberant symptoms, that is, in the early stages of the disease or with "atypical" presentations. Despite these limitations, the prospective nature of the study, with the collection of clinical, laboratory, and radiographic data at three different moments (M_0, M_2, and M_{END}) made it possible to assess the evolution of these parameters, such as the variation of HbA1c levels and their association with treatment outcomes.

In summary, we presented the results of a prospective cohort of patients with confirmed PTB, identifying high proportions of patients with associated DM and pre-DM, more advanced disease in patients with dysglycemia, and higher frequency of deaths among patients with the DMTB association. These findings reinforce the need for dysglycemia screening at the time of diagnosis of tuberculosis in order to identify patients with pre-DM and DM early, offering them treatment for both diseases. New prospective studies, involving a representative sample of patients with tuberculosis, are needed to understand the role of dysglycemic states in tuberculosis and in the risk of progression to DM.

AUTHOR CONTRIBUTIONS

ASRM and ACCC: conceptualization; data analysis; project administration; and drafting, editing, and

review of the manuscript. ALB: conceptualization; project administration; and drafting, editing, and review of the manuscript. ALK: conceptualization; funding acquisition; project administration; and drafting, editing, and review of the manuscript. CFSL: data collection; and editing and review of the manuscript. ECS: laboratory analysis; and editing and review of the manuscript. LIG: data collection; data analysis; and editing and review of the manuscript. GA: advanced statistical analysis; and editing and review of the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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