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Diabetes mellitus is associated with cavities, smear grade, and multidrug-resistant tuberculosis in Georgia

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SUMMARY

SETTING: National tuberculosis (TB) treatment facility in the country of Georgia.

OBJECTIVE: To determine the prevalence of diabetes mellitus (DM) and pre-DM among patients with TB using glycosylated-hemoglobin (HbA1c), and to estimate the association between DM and clinical characteristics and response to anti-tuberculosis treatment.

DESIGN: A cohort study was conducted from 2011 to 2014 at the National Centre for TB and Lung Disease in Tbilisi. Patients aged ⩾35 years with pulmonary TB were included. HbA1c was used to define DM (⩾6.5%), pre-DM (⩾5.7–6.4%), and no DM (<5.7%). Interviews and medical chart abstraction were performed. Regression analyses estimated associations between DM and 1) baseline TB characteristics and 2) anti-tuberculosis treatment outcomes.

RESULTS: A total of 318 newly diagnosed patients with TB were enrolled. The prevalence of DM and pre-DM was 11.6% and 16.4%, respectively. In multivariable analyses, patients with TB-DM had more cavitation (adjusted OR [aOR] 2.26), higher smear grade (aOR 2.37), and more multidrug-resistant TB (MDR-TB) (aOR 2.27) than patients without DM. The risk of poor anti-tuberculosis treatment outcomes was similar among patients with and those without DM (28.1% vs. 23.6%).

CONCLUSION: DM and pre-DM were common among adults with newly diagnosed pulmonary TB in Tbilisi, Georgia, and DM was associated with more clinical symptoms, and MDR-TB, at presentation.

KEY WORDS: hyperglycemia; hemoglobin A1c; treatment failure; epidemiology

DIABETES MELLITUS (DM) increases the risk of active tuberculosis (TB) by approximately three times.[1,2] Impaired immune responses that predispose persons with DM to active TB[3–5] may also confer a greater likelihood of severe TB disease and poor response to anti-tuberculosis treatment, thus threatening recent gains in global TB control.[6] Global increases in DM prevalence and persistently high TB incidence increase the importance of clarifying how DM affects TB disease presentation and response to anti-tuberculosis treatment.[7,8]

Studies have inconsistent findings regarding how DM affects anti-tuberculosis treatment. Some observational studies have reported that DM patients with TB require more time to convert sputum cultures from positive to negative,[9–11] are at increased risk of TB treatment failure,[12] and have higher rates of death during anti-tuberculosis treatment.[13–15] Other studies have not observed significant differences between these groups.[16,17] An important limitation of most studies to date is the reliance on self-reported DM status. Few studies have investigated the prevalence of pre-DM among patients with TB.[18] Moreover, most studies examining the relation between DM and TB were retrospective and did not adjust for important known confounders.[2,12]

The aims of the present study were 1) to estimate the prevalence of DM and pre-DM using a glycosolated hemoglobin A1c (HbA1c) test among new adult patients with TB in Tbilisi, Georgia; 2) to estimate the association between DM and clinical characteristics at the time of diagnosis, including multidrug-resistant TB (MDR-TB); and 3) to estimate the association between DM status and response to anti-tuberculosis treatment.

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METHODS

Setting and participants

Between October 2011 and May 2014, a prospective cohort study was conducted at the National Center for TB and Lung Disease (NCTLD) in Tbilisi, the largest anti-tuberculosis treatment and referral facility in Georgia. Eligible participants included newly diagnosed patients aged ⩾35 years with confirmed pulmonary TB (sputum acid-fast bacilli [AFB] smear-positive and/or culture-positive for *Mycobacterium tuberculosis*), or who met NCTLD's clinical definition, i.e., symptoms with chest X-ray (CXR) findings, and with no history of previous anti-tuberculosis treatment. Physicians and study staff recruited eligible participants from NCTLD in-patient and ambulatory out-patient clinics. Participants were treated with standard World Health Organization (WHO) recommended anti-tuberculosis treatment regimens,[19] and were monitored for study outcomes after 2 months of anti-tuberculosis treatment and at the end of treatment.

Definitions and study measures

HbA1c was measured using a rapid, point-of-care HbA1c device (Afinion; Axis Shield, Dundee, Scotland, UK). Capillary blood samples were collected from participants' fingers at study enrollment: the samples were analyzed for HbA1c within 30 s of collection. HbA1c levels were included in the patient's medical record and reported to the physicians. Treatment for DM was at the discretion of the physicians. For the primary measure of DM status, we categorized HbA1c according to the American Diabetes Association's recommended scale: DM ⩾6.5%, pre-DM 5.7–6.4%, and no DM <5.7%.[20] Participants with HbA1c <6.5%, with a previous DM diagnosis by a physician or health care worker and documented use of DM medication were also defined as DM. In secondary analyses, we categorized DM by history of DM diagnosis, use of DM medication, or uncontrolled DM (HbA1c ⩾8.0%).

Clinical TB characteristics (CXR findings, body mass index [BMI], and human immunodeficiency virus [HIV] status) were abstracted from patient medical records at the time of TB diagnosis. Laboratory results were obtained from the Georgia National TB Reference Laboratory, which undergoes annual WHO external quality assessment.[21] Ziehl-Neelsen staining was used for sputum smear AFB, Löwenstein-Jensen and BACTEC™ MGIT™ (BD, Sparks, MD, USA) for *M. tuberculosis* culture, and the absolute concentration method for drug susceptibility testing (DST), as previously described.[21] Sputum AFB smears were graded following Centers for Disease Control and Prevention (CDC) guidelines:[22] those with 3+ or 4+ were defined as high AFB smear grade. MDR-TB was defined as resistance to at least isoniazid and rifampicin. Serologic testing for HIV was performed for all participants.

At enrollment, patients were interviewed in Georgian (Kartuli) or Russian to determine sociodemographics, smoking and alcohol use, TB symptom history, and previous DM diagnosis. Patients were asked about tobacco use: those indicating they smoked were considered current smokers, patients who were not current smokers but indicated previous regular tobacco use were considered past smokers, and those without current or past tobacco use were considered never smokers. Alcohol use was defined as heavy (⩾5 drinks per day), intermediate (⩽4 drinks/day), frequent (⩾3 days/week), and infrequent (⩽2 days/week).

Sputum testing for AFB smear and culture was repeated after 2 months of anti-tuberculosis treatment when participants visited the NCTLD DOTS clinic or at the hospital for admitted patients. At the end of the study follow-up period (May 2014), treatment outcomes were assessed using the NCTLD treatment database. Treatment result was categorized, according WHO guidelines, as cured, completed, lost to follow-up, failed, died, or transferred.[19] Favorable outcome was defined as participants who were cured or completed after 6 months of treatment, and poor outcome included participants who defaulted, failed, or died.

Data analyses

Analyses were performed using SAS version 9.3 (Statistical Analysis System Institute, Cary, NC, USA). Categorical baseline characteristics were compared by DM status using Fisher's exact or χ^2 tests; the Kruskal-Wallis test was used for continuous variables. Logistic models were used to estimate the association between DM status and baseline patient characteristics (self-reported symptoms, CXR, sputum microscopy, and DST results). Log-binomial or log-Poisson regressions were used to estimate the association between DM status and longitudinal outcomes (poor/favorable treatment outcome, 2-month AFB status, 2-month culture status). Covariates included in multivariable models were chosen based on previous literature, bivariate associations in the data, and directed-acyclic graph theory.[23]

Ethical approval

The study protocol and materials were reviewed and approved by the Institutional Review Boards of the NCTLD, Tbilisi, Georgia, and Emory University, Atlanta, GA, USA.

RESULTS

Of 586 eligible TB patients who sought treatment at NCTLD during the study period, 324 were invited to participate and 318 were enrolled (2 were ineligible, 4 refused). Enrolled participants were demographically

Table 1 Distribution of hemoglobin A1c blood glucose levels and baseline characteristics of culture-positive adult pulmonary TB patients in Tbilisi, Georgia, 2011–2012

Baseline patient characteristics	Total ($n = 318$) *n* (%)	No DM HbA1c ⩽5.6% ($n = 229$, 72.0%) *n* (%)	Pre-DM HbA1c 5.7–6.4% ($n = 52$, 16.4%) *n* (%)	DM* HbA1c ⩾6.5% ($n = 37$, 11.6%) *n* (%)	*P* value†
Demographics					
Age, years, median [IQR]	49.0 [42–58]	49.0 [41–57]	52.5 [44–61]	50.0 [42–59]	0.99
Sex, female	79 (24.8)	60 (26.2)	7 (13.5)	12 (32.4)	0.26
Monthly income,‡ USD, median [IQR]	132 [47–412]	147 [47–412]	117 [41–294]	177 [88–412]	0.46
Internally displaced person	27 (8.5)	21 (9.2)	4 (7.8)	2 (5.4)	0.47
Ever imprisoned	42 (13.5)	33 (14.8)	7 (14.0)	2 (5.4)	0.12
Smoking status					0.05
Never smoker	75 (23.7)	54 (23.7)	9 (17.3)	12 (32.4)	
Past smoker	80 (25.2)	54 (23.7)	13 (25.0)	13 (35.1)	
Current smoker	162 (51.1)	120 (52.6)	30 (57.7)	12 (32.4)	
High alcohol use§	51 (16.1)	39 (17.1)	10 (19.2)	2 (5.6)	0.06
Self-reported symptoms					
Cough	234 (77.5)	162 (73.6)	40 (85.1)	32 (91.4)	0.04¶
Hemoptysis	68 (22.6)	46 (21.0)	9 (19.1)	13 (37.1)	0.03¶
Chest pain	107 (35.7)	71 (32.4)	22 (47.8)	14 (40.0)	0.57
Fever#	124 (63.3)	95 (60.7)	17 (60.7)	12 (66.7)	0.75
Weight loss#	127 (65.8)	90 (61.2)	22 (78.6)	15 (83.3)	0.1
Night sweats#	124 (64.9)	91 (62.8)	21 (75.0)	12 (66.7)	0.46
Weakness#	149 (77.2)	110 (74.8)	25 (89.3)	14 (77.8)	0.95
Symptom to diagnosis time, days, median [IQR]	35 [20–108]	35 [19–108]	40 [19–141]	35 [17–102]	0.96
Clinical information					
BMI, kg/m^2					
<18.5	54 (17.5)	44 (19.6)	8 (16.0)	2 (5.7)	0.02
18.5–24.9	207 (67.0)	148 (66.1)	36 (72.0)	23 (65.7)	
⩾25	48 (15.5)	32 (14.3)	6 (12.0)	10 (28.6)	
HIV-positive	12 (3.8)	11 (4.8)	0	1 (2.7)	0.93
Baseline AFB smear-positive	218 (68.8)	150 (65.5)	36 (70.6)	32 (86.5)	0.01¶
Baseline sputum culture					0.06
Negative	50 (16.2)	40 (17.5)	9 (17.3)	1 (2.7)	
Positive	255 (82.5)	181 (79.0)	39 (75.0)	35 (94.6)	
Contaminated/missing	13 (4.1)	8 (3.5)	4 (7.7)	1 (2.7)	
Treatment regimen					0.01¶**
First-line treatment	266 (83.7)	194 (84.7)	46 (88.5)	26 (70.3)	
MDR-TB	49 (15.4)	32 (14.0)	6 (11.5)	11 (29.7)	
XDR-TB	3 (0.9)	3 (1.3)	0	0	
Drug susceptibility					0.04¶
Sensitive pan-susceptible	214 (67.3)	153 (66.8)	36 (69.2)	25 (67.6)	
MDR- or XDR-TB	52 (16.4)	35 (15.3)	6 (11.5)	11 (29.7)	
Clinical case	52 (16.4)	41 (17.9)	10 (19.2)	1 (2.7)	
Any lung cavity	69 (22.5)	45 (20.4)	11 (22.4)	13 (36.1)	0.04¶
Infiltrate, upper	298 (95.8)	218 (96.9)	49 (98.0)	31 (86.1)	0.01¶
Infiltrate, lower	133 (42.9)	100 (44.4)	19 (38.8)	14 (38.9)	0.67

* DM defined by HbA1c ⩾6.5%, and 5 patients with HbA1c <6.5% who self-reported physician-diagnosed DM and current use of DM medications.
† Two-sided *P* value, χ^2 tests or Fisher's exact test for categorical variables and Kruskal-Wallis tests for continuous variables, comparing DM with pre-DM and no DM combined.
‡ Household monthly income in USD; exchange rate used 1 USD ≈ 1.7 Georgian lari.
§ High alcohol use defined as ⩾5 drinks per day and ⩾3 days/week.
¶ Statistically significant.
# Fever ($n = 122$), weight loss ($n = 125$), night sweats ($n = 127$), and weakness ($n = 125$); >30% were missing data.
** MDR-TB status was dichotomous (yes/no).
DM = diabetes mellitus; HbA1c = hemoglobin A1c; IQR = interquartile range; USD = US dollar; BMI = body mass index; HIV = human immunodeficiency virus; AFB = acid-fast bacilli; MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant TB.

similar to all patients with TB from Georgia (data not shown). Among the 318 enrolled participants, 291 (91.5%) had final anti-tuberculosis treatment outcome information available. Of the remaining participants, 26 were still on treatment (20 with MDR-TB), and the outcome for one was missing.

The median age of the study participants was 49 years (interquartile range [IQR] 42–58); 75.2% were male (Table 1). Most participants had received a high school education (55.2%). Median income was equivalent to US$132 per month. Current smoking was reported by more than half the study subjects (51.1%), and 45.5% indicated heavy alcohol use. Median BMI was 21.3 kg/m^2 (IQR 19.4–23.6); most participants were HIV-negative ($n = 298$ 93.7%), and MDR-TB prevalence was 15.4% ($n = 49$).

DM prevalence was 11.6% (95% confidence interval [CI] 8.4–15.5); 31 (9.7%) participants had

Table 2 Multivariable analyses for self-reported TB symptoms at the time of TB presentation among new adult TB patients with DM in Tbilisi, Georgia, 2011–2012

	Cough*		Hemoptysis*	
DM status	OR (95%CI)	aOR (95%CI)†	OR (95%CI)	aOR (95%CI)†
DM	3.86 (1.13–12.93)‡	3.43 (1.00–11.79)‡	2.22 (1.04–4.75)‡	2.21 (1.02–4.78)‡
Pre-DM	2.05 (0.87–4.82)	1.91 (0.80–4.56)	0.89 (0.40–1.97)	0.85 (0.38–1.90)
No DM	1.00	1.00	1.00	1.00
DM, no medication	3.22 (0.40–25.60)	2.97 (0.37–23.88)	3.20 (0.94–10.87)	3.23 (0.94–11.10)
DM medication	3.54 (0.81–15.44)	3.22 (0.72–14.49)	1.92 (0.78–4.71)	1.89 (0.75–4.78)
Pre-DM/no DM	1	1	1	1
HbA1c ⩾8.0%	2.10 (0.47–9.48)	2.03 (0.44–9.42)	0.47 (0.11–2.14)	0.49 (0.11–2.24)
HbA1c <8.0%	1.00	1.00	1.00	1.00
HbA1c, per 1% increase	1.55 (1.03–2.34)‡	1.48 (0.99–2.21)	1.02 (0.81–1.29)	1.02 (0.81–1.29)

* Self-reported by patients at baseline, cough ($n = 302$) and hemoptysis ($n = 301$).
† In addition to DM status, adjusted models included age, sex, HIV status, smoking status.
‡ Statistically significant.
TB = tuberculosis; DM = diabetes mellitus; OR = odds ratio; CI = confidence interval; aOR = multivariable adjusted odds ratio; HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus.

baseline HbA1c >6.5% and six (1.9%) had been diagnosed with DM and had HbA1c <6.5%. Among the 37 patients with DM, 24.3% had not previously been diagnosed with DM ($n = 9$) and 32.4% were not receiving DM medications ($n = 12$). Median time with DM among those with a previous DM diagnosis was 2.5 years (IQR 0.0–8.0). Median HbA1c among patients with TB and DM was 7.9%; it was non-significantly higher among patients with previous DM diagnoses (8.0% vs. 7.6%, $P = 0.63$), and lower among those currently receiving DM medications (7.9% vs. 8.2%, $P = 0.26$). There were 52 (16.4%, 95%CI 12.6–20.8) patients with TB and pre-DM. The total proportion of participants with any hyperglycemia (DM and pre-DM combined) was 28.0% (95%CI 23.3–33.1).

Diabetes status and clinical presentation of tuberculosis

Among the enrolled patients, 80.4% were sputum culture-positive for *M. tuberculosis*, 68.6% were sputum AFB smear-positive, 270 (85.2%) were either culture- or AFB-positive, and 47 (14.5%) were clinical cases. Compared to TB patients without DM, participants with TB and DM were more likely to have hemoptysis, positive baseline AFB smear, positive baseline culture, MDR-TB, and cavitary disease, but were less likely to have upper lung infiltration ($P < 0.05$ for all comparisons).

In multivariable analyses (adjusted for age, sex, HIV status, and smoking status), TB patients with DM were more likely to have cough (adjusted odds ratio [aOR] 3.43, 95%CI 1.00–11.79) and hemoptysis (aOR 2.21, 95%CI 1.02–4.78) than those without DM (Table 2). Patients with TB and DM were also more likely to have any cavitary disease (aOR 2.26, 95%CI 1.04–4.90), higher AFB smear grade (aOR 2.37, 95%CI 1.14–4.94), and MDR-TB (aOR 2.27, 95%CI 1.02–5.08) than those without DM (Table 3). The aOR of having any lung cavity among patients

Table 3 Multivariable analyses of chest radiograph, sputum microscopy, and drug susceptibility at the time of TB presentation among new adult TB patients with DM in Tbilisi, Georgia, 2011–2012

	Cavity*		High AFB grade†		MDR-TB‡	
DM status§	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)
DM	2.21 (1.04–4.70)¶	2.26 (1.04–4.90)¶	2.30 (1.12–4.71)¶	2.37 (1.14–4.94)¶	2.35 (1.06–5.18)¶	2.27 (1.02–5.08)¶
Pre-DM	1.13 (0.54–2.39)	1.18 (0.55–2.54)	1.70 (0.89–3.25)	1.55 (0.80–3.01)	0.72 (0.29–1.82)	0.80 (0.31–2.04)
No DM	1.00	1.00	1.00	1.00	1.00	1.00
Previous DM	1.53 (0.64–3.65)	1.50 (0.61–3.68)	1.76 (0.79–3.93)	1.95 (0.85–4.49)	3.25 (1.40–7.54)¶	3.09 (1.31–7.32)¶
New DM	6.37 (1.48–27.44)¶	6.81 (1.56–29.84)¶	3.40 (0.89–13.00)	3.00 (0.77–11.64)	0.73 (0.09–6.01)	0.72 (0.09–5.99)
Pre-DM/no DM	1.00	1.00	1.00	1.00	1.00	1.00
DM, no medication	3.19 (0.94–10.81)	3.63 (1.05–12.60)¶	2.72 (0.85–8.69)	2.46 (0.76–7.98)	0.53 (0.07–4.23)	0.54 (0.07–4.30)
DM medication	1.80 (0.74–4.38)	1.71 (0.68–4.31)	1.81 (0.78–4.21)	2.05 (0.85–4.95)	3.90 (1.64–9.28)¶	3.71 (1.51–9.07)¶
Pre-DM/no DM	1.00	1.00	1.00	1.00	1.00	1.00
HbA1c ⩾8.0%	1.47 (0.50–4.31)	1.62 (0.54–4.91)	2.63 (1.01–6.87)¶	3.06 (1.13–8.28)¶	3.61 (1.33–9.80)¶	3.31 (1.19–9.16)¶
HbA1c <8.0%	1.00	1.00	1.00	1.00	1.00	1.00
HbA1c, per 1% increase	1.12 (0.91–1.38)	1.14 (0.92–1.41)	1.25 (1.03–1.53)	1.26 (1.03–1.54)	1.18 (0.95–1.47)	1.18 (0.95–1.46)

* Any cavitary disease, $n = 306$.
† Baseline sputum AFB smear 4+ or 3+ vs. 2+, 1+, or negative, $n = 316$.
‡ Any resistance pattern that includes resistance to both rifampin and isoniazid, $n = 318$.
§ In addition to DM status, adjusted models included age, sex, HIV status, smoking status.
¶ Statistically significant.
TB = tuberculosis; DM = diabetes mellitus; AFB = acid-fast bacilli; MDR-TB = multidrug-resistant TB; OR = odds ratio; CI = confidence interval; aOR = multivariable adjusted odds ratio; HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus.

Table 4 Patient characteristics associated with 2-month AFB sputum smear-positive results among adult pulmonary TB patients in Tbilisi, Georgia, 2011–2012

Baseline patient characteristics	Poor TB outcome* 70/291 (24.1) Positive *n* /total *N* (%)	RR (95%CI)	aRR (95%CI)†
DM status			
No DM	50/212 (23.6)	1	1
Pre-DM	11/47 (23.4)	0.99 (0.56–1.76)	0.95 (0.45–1.99)
DM	9/32 (28.1)	1.19 (0.65–2.18)	1.29 (0.55–3.06)
Age, years			
35–44	25/98 (25.5)	1	1
45–54	28/94 (29.8)	1.17 (0.74–1.85)	1.01 (0.56–1.81)
55–64	14/64 (21.9)	0.86 (0.48–1.52)	0.68 (0.34–1.39)
⩾65	3/35 (8.6)	0.37 (0.11–1.04)	0.62 (0.18–2.19)
Sex			
Female	7/70 (10.0)	1	1
Male	63/221 (28.5)	2.85 (1.37–5.93)‡	1.82 (0.68–4.91)
Income, household, USD/month§			
⩽59	21/85 (24.7)	1	
60–176	19/85 (22.4)	0.90 (0.53–1.56)	
⩾177	29/117 (24.8)	1.00 (0.62–1.63)	
Internally displaced person			
No	63/264 (23.9)	1	
Yes	6/26 (23.1)	0.97 (0.46–2.01)	
Ever imprisoned			
No	55/244 (22.5)	1	
Yes	13/39 (33.3)	1.48 (0.90–2.44)	
Smoking status			
Never smoker	7/67 (10.5)	1	1
Past smoker	6/71 (8.5)	0.81 (0.29–2.28)	0.49 (0.14–1.73)
Current smoker	57/153 (37.3)	3.57 (1.72–7.40)‡	1.94 (0.67–5.60)
Alcohol use¶			
Never	10/82 (12.2)	1	1
Frequent/infrequent intermediate	21/75 (28.0)	2.30 (1.16–4.55)‡	1.26 (0.49–3.25)
Infrequent heavy	23/84 (27.4)	2.25 (1.14–4.42)‡	0.99 (0.38–2.60)
Frequent heavy	16/48 (33.3)	2.73 (1.35–5.53)‡	1.34 (0.48–3.73)
Cough			
No	21/63 (33.3)	1	1
Yes	46/213 (21.6)	0.65 (0.14–1.00)‡	0.76 (0.44–1.33)
Hemoptysis			
No	54/213 (25.4)	1	
Yes	13/62 (21.0)	0.83 (0.48–1.41)	
BMI, kg/m^2			
<18.5	7/51 (13.7)	1	1
18.5–24.9	46/191 (30.0)	1.75 (0.84–3.65)	1.28 (0.55–2.96)
⩾25	15/40 (37.5)	2.73 (1.23–6.06)‡	2.13 (0.80–5.69)
HIV status			
Negative	66/274 (24.1)	1	
Positive	3/10 (30.0)	1.25 (0.47–3.28)	
Unknown	1/7 (14.3)	0.59 (0.10–3.69)	
AFB smear			
Negative	26/97 (26.8)	1	
1 or 2+	28/112 (25.0)	0.93 (0.59–1.48)	
3 or 4+	16/81 (19.8)	0.74 (0.43–1.28)	
Drug susceptibility			
Drug-susceptible	50/259 (19.3)	1	1
XDR-/MDR-TB	20/32 (62.5)	3.24 (2.25–4.67)‡	2.96 (1.71–5.13)‡
Cavitary disease			
None	56/223 (25.1)	1	
Any	11/58 (19.0)	0.76 (0.42–1.35)	

* Defined as default, failure, or death according to 2013 WHO criteria. Patients still on treatment ($n = 27$) at the end of follow-up were excluded from the analysis.
† Age was also included in the multivariable model as a continuous variable.
‡ Statistically significant.
§ 1 USD ≈ 1.7 Georgian lari.
¶ Heavy ⩾5 drinks/day, intermediate ⩽4 drinks/day, frequent ⩾3 days/week, infrequent ⩽2 days/week.
AFB = acid-fast bacilli; TB = tuberculosis; RR = risk ratio; CI = confidence interval; aRR = adjusted RR; DM = diabetes mellitus; USD = US dollar; BMI = body mass index; HIV = human immunodeficiency virus; XDR-TB = extensively drug-resistant TB; MDR-TB = multidrug-resistant TB.

with DM but who were not currently taking DM medications was 3.63 times (95%CI 1.05–12.60) the odds among patients without DM or with pre-DM. In an adjusted model, each percentage increase in HbA1c increased the odds of having higher AFB smear grade (3+ or 4+) by 1.26 times (95%CI 1.03–1.54). Compared to patients without DM or with pre-DM, MDR-TB was significantly more prevalent among patients with a previous DM diagnosis (aOR 3.09, 95%CI 1.31–7.32), and among those currently using DM medications (aOR 3.71, 95%CI 1.51–9.07). The aOR of prevalent MDR-TB among patients with HbA1c $\geqslant$8.0% was 3.31 times (95%CI 1.19–9.16) the odds among patients HbA1c $<$8.0%.

Diabetes status and response to anti-tuberculosis treatment

Of 291 TB patients who had complete treatment follow-up, 70 (24.1%) had poor TB outcomes (Table 4), including 46 who were lost to follow-up, 17 who failed, and 7 who died. In primary outcome analyses, compared to those without DM, DM patients did not have a significantly greater risk of poor TB outcomes in unadjusted (28.1% vs. 23.6%) or adjusted models (adjusted risk ratio [aRR] 1.29, 95%CI 0.55–3.06). In the multivariable analysis for poor TB outcome, only baseline MDR-TB (aRR 2.96, 95%CI 1.71–5.13) was significantly associated with an increased risk of poor outcome.

We performed additional analyses of response to anti-tuberculosis treatment among patients without MDR-TB. After 2 months of anti-tuberculosis treatment, 170 of 176 baseline AFB smear-positive patients without MDR-TB underwent follow-up AFB examinations and 164/208 baseline culture-positive patients underwent follow-up culture. Of those who were initially positive, 31.8% remained AFB smear-positive and 34.1% remained culture-positive after 2 months of treatment. Compared to patients without DM, there was a non-significant trend toward an increased risk of remaining AFB smear-positive after 2 months among DM patients (aRR 1.82, 95%CI 0.68–4.81), but this trend was not observed for sputum culture. Of 259 patients without MDR-TB who had complete final information on treatment, 19.3% had a poor outcome. In a multivariable model, the risk of poor TB outcomes among patients with DM was 1.39 times (95%CI 0.44–4.39) the risk of patients without DM.

DISCUSSION

At the time of TB diagnosis and treatment initiation, we found that a high proportion of new adult patients with pulmonary TB also had DM (11.6%). Among those identified with DM, a quarter had not been previously diagnosed with DM and nearly a third were not receiving treatment for DM. We also identified a high proportion of pre-DM patients (16.4%); overall, 28.0% of the TB patients in our study had either DM or pre-DM. Patients with TB and DM had significantly more severe clinical disease at the time of TB diagnosis than those without DM, including more hemoptysis, higher AFB smear grade, and cavitary lung disease, and were more likely to have MDR-TB.

The present study prospectively screened new adult TB patients for DM and pre-DM by directly measuring HbA1c, a key strength of our study. Compared to most previous studies of DM and TB that relied on self-reported DM and could not examine pre-DM, we used a valid average measure of hyperglycemia. Another advantage of our study was the rigorous analysis of responses to anti-tuberculosis treatment, including three outcome measures. Our analyses were appropriately designed to estimate the association between DM and longitudinal TB outcomes with proper modeling procedures (log binomial and Poisson).

Most previous studies that have examined baseline smear results among patients with TB-DM reported a greater proportion AFB-positive[11,15,24–27] and higher smear grades[26,28] among DM patients. Consistent with our results, a study of TB among patients in Texas, USA, reported that DM patients were more likely to be baseline AFB smear-positive (aOR 1.8, 95%CI 1.3–2.4).[25] Also similar to our results, previous studies comparing TB symptoms at the time of presentation have reported more cough,[24,25] hemoptysis,[15,24,25] and lung cavitation[15,25–27] among DM patients.

We found that patients with TB and DM were significantly more likely to have MDR-TB at the time of diagnosis than those without DM (aOR 2.27). To our knowledge, this is the first study to find DM associated with MDR-TB in patients without a previous history of anti-tuberculosis treatment. A study from Texas, USA, found more MDR-TB among those with TB-DM; however, that study included retreatment TB cases, in whom MDR-TB is much more common.[29] Despite excluding patients with previous TB, our observed association (aOR 2.27) between DM and MDR-TB was similar to the Texas study results (aOR 2.14). Additional studies from settings with high MDR-TB burdens are needed to confirm the association between DM and primary MDR-TB.

Our study has several limitations. Patients were enrolled at a limited number of sites, and 54% of those eligible were enrolled. However, we compared demographic characteristics with national TB data and found that patients enrolled in our study were similar to TB patients from the entire country of Georgia. Second, HbA1c screening was not performed at a standard time for all patients, and anti-

tuberculosis regimens or anemia from iron deficiency may influence blood-glucose levels for some individuals.[30] We analyzed HbA1c results by time between treatment initiation and study enrollment, and found that TB regimens did not substantially affect our results. Third, we measured HbA1c once. Because TB disease may cause prolonged inflammation,[8] hyperglycemia at the time of anti-tuberculosis treatment initiation may be transient for some participants. This has the potential to introduce misclassification of DM or pre-DM status. Patients with new DM according to HbA1c should ideally be confirmed using repeat testing with fasting plasma glucose or oral glucose tolerance tests, although this may not be feasible in low- and middle-income countries. If DM status was misclassified, our prevalence estimates for DM may have been overestimated. However, the relationship between HbA1c, TB severity, and TB outcomes is of clinical importance regardless of DM classification; bias from misclassification of DM status is thus of minimal concern, as reported measures of association between HbA1c and study outcomes were unaffected. Fourth, we did not have complete data on treatment adherence or duration of intensive phase treatment. However, DOTS was the standard of care during the study. If clinicians extended intensive phase treatment due to suspected risk for TB-DM, our results would likely underestimate the effect of DM on poor outcomes.

CONCLUSIONS

We found a high prevalence of DM and pre-DM in adult TB patients in Tbilisi. TB-DM patients had more severe clinical disease at time of treatment initiation than patients without DM. We also found DM was associated with MDR-TB among patients without a previous history of TB. Our findings suggest that clinical guidelines should recommend DM screening in patients with TB and MDR-TB. Data from our study also highlight the importance of expanding public health programs that link TB and DM diagnostic and treatment services. Additional studies are needed to better understand the risk of poor anti-tuberculosis treatment outcomes in patients with TB and DM.

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RESUME

CONTEXTE : Centre national de traitement de la tuberculose (TB) en Géorgie.
OBJECTIF : Déterminer la prévalence du diabète (DM) et du pré-DM chez les patients tuberculeux utilisant l'hémoglobine glycosylée (HbA1c) et estimer l'association entre DM et caractéristiques cliniques et réponse au traitement de la TB.
SCHÉMA : Une étude de cohorte a été réalisée (2011–2014) au Centre National de la TB et des Maladies pulmonaires de Tbilissi. Les patients âgés de ⩾35 ans atteints de TB pulmonaire ont été inclus. L'HbA1c a permis de définir le DM (⩾6,5%), le pré-DM (⩾5,7%–6,4%), et l'absence de DM (<5,7%). Les entretiens et l'extraction des données des dossiers médicaux ont été réalisés. Les analyses de régression ont estimé les associations entre DM et 1) les caractéristiques de départ de la TB et 2) les résultats du traitement de la TB.
RÉSULTATS : Un total de 318 patients ayant eu un diagnostic récent de TB a été enrôlé. La prévalence du DM a été de 11,6% et celle du pré-DM de 16,4%. En analyse multivariée, les patients ayant à la fois TB et DM avaient davantage de cavitation (ORa 2,26), un score de frottis plus élevé (ORa 2,37) et davantage de TB multirésistante (TB-MDR) (ORa 2,27) par comparaison aux patients exempts de DM. Le risque de résultats médiocres du traitement de la TB était par contre similaire chez les patients avec et sans DM (28,1% contre 23,6%).
CONCLUSIONS : Le DM et le pré-DM ont été fréquents chez les adultes ayant un diagnostic récent de TB pulmonaire à Tbilissi, Géorgie, et le DM a été associé avec davantage de signes cliniques dès le début, notamment la TB-MDR.

RESUMEN

MARCO DE REFERENCIA: Un centro nacional de tratamiento de la tuberculosis (TB) en Georgia.
OBJETIVO: Determinar la prevalencia de diabetes sacarina (DM) y pre-DM en los pacientes con diagnóstico de TB, mediante la prueba de la hemoglobina glucosilada (HbA1c) y se examinó la relación entre la DM, las características clínicas de la TB y su respuesta al tratamiento.
MÉTODOS: Se llevó a cabo un estudio de cohortes (del 2011 al 2014) en el Centro Nacional de la Tuberculosis y las Enfermedades Respiratorias de Tbilisi. Participaron en el estudio pacientes de edad de ⩾35 años con diagnóstico de TB pulmonar; mediante la prueba HbA1c se definió el diagnóstico de DM (⩾6,5%), de pre-DM (⩾5,7% a 6,4%) y de ausencia de DM (<5,7%). Se practicaron entrevistas y se extrajeron datos de las historias clínicas. Mediante un análisis de regresión se estudió la relación entre la DM, las características iniciales de la TB y los desenlaces del tratamiento antituberculoso.
RESULTADOS: Participaron en el estudio 318 pacientes con diagnóstico reciente de TB. La prevalencia de DM fue 11,6% y la prevalencia de pre-DM fue 16,4%. El análisis multifactorial puso en evidencia que los pacientes con diagnóstico de TB y DM presentaban más lesiones cavernosas (ORa 2,26), una calificación más alta de la baciloscopia (ORa 2,37) y mayor frecuencia de TB multidrogorresistente (TB-MDR; ORa 2,27), en comparación con los pacientes sin DM. El riesgo de obtener un desenlace terapéutico desfavorable fue igual en los pacientes con o sin DM (28,1% contra 23,6%).
CONCLUSIÓN: La DM y la pre-DM son enfermedades intercurrentes frecuentes en los pacientes adultos con diagnóstico nuevo de TB pulmonar en Tbilisi, en Georgia. La diabetes se asoció con la presencia de más síntomas y una mayor frecuencia de TB-MDR en el momento del diagnóstico.