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Diabetes Mellitus Among Pulmonary Tuberculosis Patients From 4 Tuberculosis-endemic Countries: The TANDEM Study

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Background. Diabetes mellitus (DM) increases active tuberculosis (TB) risk and worsens TB outcomes, jeopardizing TB control especially in TB-endemic countries with rising DM prevalence rates. We assessed DM status and clinical correlates in TB patients across settings in Indonesia, Peru, Romania, and South Africa.

Methods. Age-adjusted DM prevalence was estimated using laboratory glycated hemoglobin (HbA1c) or fasting plasma glucose in TB patients. Detailed and standardized sociodemographic, anthropometric, and clinical measurements were made. Characteristics of TB patients with or without DM were compared using multilevel mixed-effect regression models with robust standard errors.

Results. Of 2185 TB patients (median age 36.6 years, 61.2% male, 3.8% human immunodeficiency virus–infected), 12.5% (267/2128) had DM, one third of whom were newly diagnosed. Age-standardized DM prevalence ranged from 10.9% (South Africa) to 19.7% (Indonesia). Median HbA1c in TB–DM patients ranged from 7.4% (Romania) to 11.3% (Indonesia). Compared to those without DM, TB–DM patients were older and had a higher body mass index (BMI) (P value < .05). Compared to those with newly diagnosed DM, TB patients with diagnosed DM had higher BMI and HbA1c, less severe TB, and more frequent comorbidities, DM complications, and hypertension (P value < .05).

Conclusions. We show that DM prevalence and clinical characteristics of TB–DM vary across settings. Diabetes is primarily known but untreated, hyperglycemia is often severe, and many patients with TB–DM have significant cardiovascular disease risk and severe TB. This underlines the need to improve strategies for better clinical management of combined TB and DM.

Keywords. tuberculosis; diabetes; syndemic; prevalence; HbA1c.

Prevalence of type 2 diabetes mellitus (DM) has been increasing in low- and middle-income countries (LMICs) in areas that also have high tuberculosis (TB) incidence [1, 2]. DM increases the risk of active TB 3-fold and worsens disease outcomes [3]. There were about 10 million cases of TB and 1.3 million deaths due to TB globally in 2017 [4]. Currently, global TB incidence rates are modestly declining, and rising DM prevalence threatens global TB control [4]. Despite expanding evidence on the effect of DM on TB risk and outcome and increasing insights on mechanisms that underlie these effects [5], there are limited global data on those with combined TB and DM. The Global Tuberculosis Report (2018) [4] and related World Health Organization (WHO) documents do not report TB–DM numbers worldwide (in contrast to national-level data on TB–human immunodeficiency virus [HIV]), which makes assessment of the burden of this comorbidity challenging. Much of the available TB–DM data are based on retrospective studies, which could underestimate the scale of TB–DM comorbidity, particularly as a high proportion of DM is believed to be undiagnosed in LMICs [6]. Furthermore, most studies conducted on cohorts of TB patients

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have used routine or administrative data (eg, TB program registries) in which key risk factor and clinical data associated with DM (such as hypertension, anthropometric measures, cardiovascular health, DM duration, medication, or control) are not routinely recorded. This data gap constrains the capacity to provide a complete characterization of patients with TB–DM and hinders the ability to design appropriate TB–DM screening and management strategies.

As part of a European Union–funded consortium [7], TB patients from 4 epidemiologically distinct settings (Indonesia, Peru, Romania, and South Africa) were investigated for comorbid DM, facilitating standardized, prospective comparison of populations with differences in DM and TB prevalence, ethnicity, and health systems. We report the country-specific, age-adjusted prevalence and clinical characteristics of TB patients who presented with previously diagnosed DM, newly diagnosed DM, and intermediate hyperglycemia, along with an evaluation of possible risk factors, among newly diagnosed TB patients in each setting.

METHODS

Study Design and Study Population

This study was part of TANDEM [7], a consortium that explores the interaction between TB and DM. Details of the sites and definitions were described elsewhere [8].

Study Measurements and Definitions

We defined individuals as having pulmonary TB if they initiated treatment at a local TB program, based on bacteriological (sputum smear, sputum culture, or Xpert test), radiological, and/or clinical evidence. Further details are published elsewhere [9, 10] and are freely available in online appendices [8].

All participants underwent laboratory glycated hemoglobin (HbA1c) testing (using the high-performance liquid chromatography method), as recommended by WHO for DM screening [11], regardless of their previous DM status. Random plasma glucose (RPG) was measured; if RPG was >110 mg/dL but <200 mg/dL (the recognized cut-point for diagnosing DM if symptomatic), this was also followed with a fasting blood glucose (FPG) test. Patients were deemed to have DM if they had repeated test results (HbA1c, RPG, or FPG) above the diagnostic threshold (see Appendix).

"Previously diagnosed DM" was defined as any patient who self-reported a physician diagnosis of DM and was either taking standard anti-DM drugs at the time of recruitment or had a subsequent study HbA1c of ≥6.5%. "Newly diagnosed DM" was defined based on repeated laboratory testing (see Appendix), mostly HbA1c. Intermediate hyperglycemia (or "prediabetes"; raised blood glucose or HbA1c above normal but below the threshold for identifying DM) was defined as patients with a single measurement of either FPG in the pre-DM range (6.1–7.0 mmol/L) or HbA1c in the intermediate range (6.0%–6.4%) [12] (see Appendix). Evaluation of the performance of these laboratory tests for diagnosis of DM in TB patients in a TANDEM cohort has been published recently [9].

Underweight was defined as body mass index (BMI) <18 kg/m^2; normal weight BMI 18 kg/m^2–24.9 kg/m^2; overweight BMI 25 kg/m^2–29.9 kg/m^2; and obese BMI ≥30 kg/m^2. In Indonesia accepted BMI categories for South Asian populations were used; overweight was defined as BMI 23–27.49 kg/m^2 and obesity as ≥27.5 kg/m^2 [13]. Kidney disease was defined according to the National Kidney Foundation guidelines [14]. Principal component analysis was performed to build a socioeconomic status index in order to classify study populations from each country into quintiles based on asset ownership by patients that included nonsellable (eg, possession of a bank account, type of sanitation facility, household water source) and sellable (eg, stove, refrigerator, washing machine, television) assets [15].

A family history of DM was defined by self-report of having a parent, sibling, or child with DM. Smoking status was recorded from self-report of currently smoking (including those who had quit for less than 6 months), past smokers, or having never smoked. Hypertension was categorized as follows: prehypertension, systolic or diastolic 120/80–129/80 mm Hg; stage I, systolic or diastolic 130/80–139/89 mm Hg; and stage II, systolic or diastolic >140/90 mm Hg [16]. Ten-year risk of a fatal or major cardiovascular event (myocardial infarction or stroke, using WHO/International Society of Hypertension cardiovascular risk prediction charts) [17] and the Charlson comorbidity index (CMI) were calculated [18]. To assess TB severity, we used TB score, which is a simple clinical score used for clinical monitoring of TB, and hemoptysis [19].

Data Analyses

We used REDCap 6.9.1 [20] for data collection and management and Stata 15.0 (StataCorp, College Station, TX) for statistical analyses. Categorical variables were presented with their frequencies, and continuous variables were summarized using mean and standard deviation or, where appropriate, median and interquartile ranges (IQRs). Between-country comparisons were done using the nonparametric Kruskal-Wallis test; χ^2 tests were performed for categorical variables; and the *t* test or analysis of variance was used for continuous variables. The crude prevalence of DM was calculated for each country overall and stratified by age group. A directly standardized prevalence rate was also calculated using the world standard population as a reference [21]. Factors potentially associated with prevalent DM were assessed by calculating crude odds ratios. All factors significant at $P < .15$ in this univariate analysis were then included in a multivariate model. A multilevel mixed-effect regression model was used, with country entered as a random error term (representing a random intercept) and robust standard errors calculated using "country" as a cluster variable to account for the clustering of TB–DM patients within countries. In sensitivity analysis, alternative models were explored where country

was entered as a fixed effect and interaction terms included between age groups and country.

Ethics

The institutional review board (IRB) at the London School of Hygiene and Tropical Medicine as the TANDEM coordinating center (ethics reference 6449) and the local IRB at each site approved the study. All participants were provided with an information sheet that explained the study and provided written informed consent.

RESULTS

A total of 2185 pulmonary TB patients were enrolled (Indonesia, n = 748; Peru, n = 600; Romania, n = 506; and South Africa, n = 331). Most patients were male (61.2%); the median age was 36.6 years (IQR, 26.0–49.1); and 82 patients (3.8%) were HIV positive, the highest proportion from South Africa (9.7%; Table 1). Of the TB patients recruited, 78.8% had bacteriologically confirmed disease, positive on either culture (78.8%) or sputum smear (72.5%). One quarter of patients (24.6%) reported a previous TB episode. More than half reported having ever smoked, with the highest frequencies in South Africa (86.1%) and Indonesia (62.0%). The overall median BMI was 19.6 kg/m^2 in males and 20.6 kg/m^2 in females; 2.2% of patients were obese, the highest was in Peru at 3.7% (Table 1).

Of the 2185 patients, 57 were missing data on DM diagnostic tests. A total of 267 TB patients had confirmed DM after repeated testing; the crude prevalence was 12.5% (95% confidence interval [CI],11.1%–14.0%). Age standardized DM prevalence was highest in Indonesia at 19.7% (95% CI, 16.8%–22.5%), similar in Peru (12.3%; 95% CI, 9.2%–15.3%) and Romania (12.3%; 95% CI, 9.7%–15.0%), and lowest in South Africa at 10.9% (95% CI, 7.0%–14.9%). More than two-thirds of diabetes detected in this study had already been previously diagnosed; 12.8% of TB patients in Indonesia, 5.8% in Peru, 6.9% in Romania, and 5.1% in South Africa. There were substantial between-country differences in HbA1c values among TB–DM patients, with a median HbA1c of 11.3% among TB–DM patients in Indonesia, 10.6% in Peru, 7.4% in Romania, and 10.1% in South Africa.

Compared to TB patients without DM, TB–DM patients were more frequently smear (72.7% vs 80.2%, $P = .009$) and culture positive (81.4% vs 91.5%, $P < .001$; Table 3).

TB patients with DM were older (median age 51.0 vs 33.0 years, $P < .001$), had higher BMI (21.9 vs 19.6 kg/m^2, $P < .001$), had lower waist-to-hip ratios (male 0.86 vs 0.89, $P < .001$ and female 0.83 vs 0.87, $P < .001$), were of lower socioeconomic status (Wald test, $P < .001$), were more likely to have a family history of DM (adjusted odds ratio, 3.7 (1.8–7.3), $P < .001$), and were less likely to have been previously treated for TB (16.9% vs 25.7%, $P = .02$) when compared to those without DM (Tables 2 and 3). Hemoptysis was slightly more common in TB–DM patients (30.0% vs 26.6%, $P = .1$), and the TB score was higher among TB–DM patients in Indonesia. Individuals with TB–DM were also more likely to have more than 10% risk of a major cardiovascular disease event occurring within 10 years compared to those with TB (24.5% vs 5.5%; Table 3). In female patients, anemia was consistently less frequent among those with DM (42.1% vs 52.1% overall, $P = .001$), but there was little difference in anemia prevalence among men, except in Indonesia (56.1% TB only vs 29.5% TB–DM, $P < .001$).

TB patients with newly and previously diagnosed DM were of similar age (52.1 vs 51.0 years; Table 4). However, compared to TB patients with previously known DM, those with a new DM diagnosis had a worse TB score on diagnosis (77.4% had a score of 3 or above compared to 65.6% of known DM patients, $P \leq .001$), suggesting greater TB disease severity, lower BMI (20.0 vs 22.5, $P = .02$), and lower HbA1c (8.0% vs 10.9%, $P = .05$). They were also less likely to have a family history of DM (19.1% vs 43.2%, $P < .001$), a lower CMI score (2.4% vs 47.0% had a score ≥2, $P < .001$), and fewer DM complications including hypertension and macro- or microvascular disease (2.4% vs 43.2%, $P < .001$; Table 4).

Despite the poor DM control evidenced by high HbA1c results, a significant proportion of those with a previous DM diagnosis reported taking insulin (20.2%) or metformin (61.2%). The overall poor health of this group of patients was clear from the high proportion (20.0%) who reported at least 1 DM-attributable hospital admission in the preceding 5 years.

TB patients with intermediate hyperglycemia (or prediabetes) were slightly older compared to those with TB only (median age 39 vs 32 years), but otherwise appeared to be more like TB-only patients than TB–DM patients in terms of BMI and disease characteristics (Supplementary Table 1).

DISCUSSION

In this multicountry cohort, patients with newly diagnosed TB had a high prevalence of both newly diagnosed (3.8%) and previously known (8.4%) DM. Diabetes prevalence among TB patients varied among countries, as did the proportion of known vs newly diagnosed DM. DM was very uncommon in younger patients, with the risk of having DM increasing substantially for those aged ≥35 years; between 20% and 35% of TB patients aged >50 years had new or previously diagnosed DM. Most patients had been diagnosed with DM relatively recently, many within the past year. Among these individuals, TB may have been their first complication of DM, and among those newly diagnosed with DM, their incident TB disease revealed their underlying DM.

TB patients with known DM were characterized by poor glycemic control despite knowledge of their DM status (median HbA1c of 10.9%, with outlying values as high as 17%). Better glycemic control is known to reduce future risk of macro- and microvascular disease and would likely reduce the risk of many infections among DM patients [22]. Though direct evidence that enhanced

Table 1. Baseline Characteristics

Characteristic		Total (N = 2185)	Indonesia (n = 748)	Peru (n = 600)	Romania (n = 506)	South Africa (n = 331)
Median age (IQR), y		36.6 (25.5–49.1)	37.0 (27.0–49.0)	30.0 (22.0–43.0)	43.0 (30.0–54.0)	35.0 (28.0–48.0)
Aged ≥35 years, no. (%)		1171 (53.6)	416 (55.6)	246 (41.0)	341 (67.4)	168 (50.8)
Male, no. (%)		1337 (61.2)	426 (57.0)	348 (58. 0)	358 (70.8)	205 (61.9)
Median BMI (IQR), kg/m^2						
	All	19.9 (17.7–22.5)	18.2 (16.3–20.6)	22.1 (20.0–24.4)	20.3 (18.7–22.2)	18.5 (17.0–20.8)
	Male	19.6 (17.5–21.9)	17.8 (16.1–19.7)	21.7 (19.9–23.8)	20.3 (18.8–22.0)	18.2 (16.6–20.0)
	Female	20.6 (18.0–23.4)	19.2 (16.7–22.1)	22.7 (20.0–25.3)	20.3 (18.3–22.6)	19.5 (17.7–22.6)
Obesity (BMI ≥30 kg/m^2)[a] (%)		49 (2.2)	14 (1.9)	22 (3.7)	4 (0.8)	9 (2.7)
Human immunodeficiency virus status positive,[b] no. (%)		82 (3.8)	26 (3.5)	23 (3.8)	1 (0.2)	32 (9.7)
Sputum smear result, no. (%)						
	Positive	1583 (72.5)	629 (84.1)	387 (64.5)	345 (68.2)	222 (67.1)
	Missing	34 (1.6)	1 (0.1)	2 (0.3)	13 (2.6)	18 (5.4)
Sputum culture result, no. (%)						
	Positive	1721 (78.8)	610 (81.6)	491 (81.8)	390 (77.1)	230 (69.5)
	Missing	113 (5.2)	25 (3.3)	2 (0.3)	25 (4.9)	11(30.1)
Previous TB, no. (%)		538 (24.6)	185 (24.7)	123 (20.5)	97 (19.2)	133 (40.2)
Fever ≥38°C, no. (%)		123 (5.6)	38 (5.1)	34 (5.7)	32 (6.3)	19 (5.7)
Smoking, no. (%)						
	Current	903 (41.3)	132 (17.7)	66 (11)	233 (46.1)	273 (82.5)
	Past	355 (16.3)	331 (44.3)	178 (29.7)	33 (6.5)	12 (3.6)
	Never	927 (42.4)	285 (38.1)	356 (59.3)	240 (47.4)	46 (13.9)
Weight loss, no. (%)						
	(≥10 kg)	163 (7.5)	67 (9.0)	30 (5.0)	20 (4.0)	46 (13.9)
	(5–10 kg)	610 (27.9)	259 (34.6)	135 (22.5)	119 (23.5)	97 (29.3)
	(<5 kg)	917 (42.0)	292 (39.0)	248 (41.3)	216 (42.7)	161 (48.6)
Hemoptysis, no. (%)		532 (24.4)	228 (30.5)	195 (32.5)	48 (9.5)	61 (18.4)
TB score, no. (%)						
	0–2	691 (31.6)	109 (14.6)	274 (45.7)	251 (49.6)	57 (17.2)
	3–5	1184 (54.2)	408 (54.6)	311 (51.2)	235 (46.4)	230 (69.5)
	6+	310 (14.2)	231 (30.9)	15 (2.5)	20 (4.0)	44 (13.3)
Diabetes, no. (%)						
	No	1348 (61.7)	523 (69.2)	464 (77.3)	209 (41.3)	152 (45.9)
	Pre-DM	458 (21.0)	90 (12.0)	82 (13.7)	199 (39.3)	87 (26.3)
	New DM	84 (3.8)	32 (4.3)	12 (2.0)	31 (6.2)	3 (0.9)
	Known DM[c]	183 (8.4)	96 (12.8)	35 (5.8)	35 (6.9)	17 (5.1)
	Missing data	57 (2.6)	3 (0.4)	1 (0.2)	0 (0)	53 (16.0)
Education, no. (%)						
	≤ Primary	593 (27.2)	240 (32.1)	99 (16.5)	48 (9.6)	206 (62.2)
	≥ Secondary	1582 (72.5)	508 (67.9)	500 (83.3)	452 (89.7)	122 (36.9)
Socioeconomic status, no. (%)						
	Quintile 1	627 (28.7)	202 (27.0)	161 (26.8)	176 (34.8)	88 (26.6)
	Quintile 2	501 (22.9)	178 (23.8)	125 (20.8)	122 (24.1)	76 (23.0)
	Quintile 3	451 (20.6)	181 (24.2)	106 (17.7)	100 (19.8)	64 (19.3)
	Quintile 4	358 (16.4)	129 (17.3)	108 (18.0)	67 (13.2)	54 (16.3)
	Quintile 5	207 (9.5)	53 (7.1)	90 (15.0)	26 (5.1)	38 (11.5)
	Missing	41 (1.9)	5 (0.7)	10 (1.7)	15 (3.0)	11 (3.3)

Values rounded to 1 decimal point including percentages; percentage given of relevant whole sample with missing values only noted where >3%. Some values may differ from other TANDEM analyses due to minor differences in inclusion criteria or case definitions.

Abbreviations: BMI, body mass index; DM, diabetes mellitus; IQR, interquartile range; TB, tuberculosis.

[a]Obesity in Indonesian population defined as BMI >27.5 kg/m^2.

[b]Human immunodeficiency virus status data were available for only 730 patients in Indonesia, 506 in Peru, 364 in Romania, and 328 in South Africa.

[c]Both self-report of prior DM diagnosis and either use of DM medication or study glycated hemoglobin of ≥6.5%.

Table 2. Factors Associated With New or Previously Diagnosed Diabetes Mellitus Among Tuberculosis Patients Aged >35 Years

Factor		Crude OR (95% CI)	*P* Value	Adjusted OR (95% Confidence Interval)	*P* Value
Age, y					
	35–44	1	…	1	…
	45–54	3.2 (1.4–6.6)	.006	2.9 (1.5–5.9)	.004
	55–64	3.8 (2.8–5.3)	<.0001	3.6 (2.8–4.5)	<.001
	>65	3.5 (2.6–4.7)	<.0001	3.5 (2.3–5.3)	<.001
Sex					
	Female	1	…	1	…
	Male	0.7 (.5–.9)	.003	0.9 (.7–1.0)	.1
Smear test result					
	Negative	1	…	1	…
	Positive	0.8 (.4–1.4)	.4	0.9 (.4–1.7)	.7
	Missing	1.4 (.9–2.2)	.09	1.9 (1.2–3.0)	.007
Previous tuberculosis episode					
	No	1	…	1	…
	Yes	0.4 (.3–.6)	<.0001	0.5 (.3–.9)	.02
Body mass index					
	Underweight	0.5 (.4–.7)	<.001	0.4 (.3–.5)	<.001
	Normal	1	…	1	…
	Overweight	2.3 (1.4–3.8)	.001	2.0 (1.3–3.3)	.003
	Obese	5.9 (198–17.0)	.002	6.5 (1.7–24.7)	.006
Family history of diabetes mellitus					
	No	1	…	1	…
	Yes	3.6 (2.0–6.6)	<.0001	3.7 (1.8–7.3)	<.001
Socioeconomic status					
	1 (richest)	1	…	1	…
	2	1.1 (.8–1.3)	.5	1.0 (.7–1.4)	.9
	3	1.6 (1.3–2.1)	<.001	1.2 (1.1–1.3)	<.001
	4	1.3 (.8–2.1)	.4	0.8 (.6–1.0)	.08
	5 (poorest)	1.9 (1.0–3.7)	.005[a]	1.43 (.6–2.7)	.5[a]
Country (Indonesia as reference)[b]					
	Indonesia	1	…	…	…
	Peru	0.5 (.3–.8)	.002	…	…
	Romania	0.5 (.4–.8)	<.001	…	…
	South Africa	0.4 (.3–.5)	<.001	…	…

[a]Wald test for statistical significance across categories of socioeconomic status, $P < .001$.

[b]Country entered as a random effect into the adjusted model.

glycemic control reduces TB risk is lacking, the increased risk of TB among individuals with DM [6] and the association with poorer TB treatment outcomes [3] suggest that improved glycemic control should be among the suite of interventions to prevent TB, especially in areas with high TB prevalence. Cases of TB in poorly controlled DM may be viewed as missed opportunities for TB prevention; conversely, incident TB, when adequately treated, provides a "second chance" to reengage previously neglected patients back into DM care. Incident TB also offers an opportunity for new diagnosis and management of previously unrecognized DM, potentially reducing downstream DM-related morbidity.

Our findings are consistent with those from earlier studies that show age is an important risk factor for DM among TB patients [23–25]. Obesity was also strongly associated with diabetes [26], which is in line with some [27–29], but not all, studies [30]. While obesity is known to be a strong risk factor for diabetes in the general population, it has not always been identified as a risk factor among TB patients, likely due to the weight loss that often accompanies TB disease. In addition to obesity and increasing age, a family history of DM was also strongly associated with having DM in this population.

At 21%, the prevalence of intermediate hyperglycemia (prediabetes) identified in TB patients was higher than expected, although a rising prevalence of intermediate hyperglycemia has been reported in LMICs [31]. This figure would have been even higher based on point-of-care HbA1c results [10] or use of the lower American Diabetes Association cut-point. Caution is advised in interpreting the significance of intermediate hyperglycemia as transient hyperglycemia may occur in hypermetabolic inflammatory conditions and infections, including TB [32] (see Supplementary Figure 1 [9]). The definition of intermediate hyperglycemia itself is under scrutiny as DM only develops within

Table 3. Comparison of Tuberculosis Patients With and Without Diabetes

Characteristic	Total			Indonesia			Peru			Romania			South Africa		
	TB Only (n = 1918)	TB–DM (n = 267)	*P* Value	TB Only (n = 620)	TB–DM (n = 128)	*P* Value	TB Only (n = 553)	TB–DM (n = 47)	*P* Value	TB Only (n = 440)	TB–DM (n = 66)	*P* Value	TB Only (n = 305)	TB–DM (n = 26)	*P* Value
Median age (interquartile range), y	33.0 (27.0–47.0)	51.0 (45.0–59.0)	<.001	34.10 (25.3–45.0)	50.5 (45.1–57.8)	<.001	28.0 (22.0–39.5)	51.0 (47.0–58.0)	<.001	41.0 (27.0–52.0)	56.0 (45.0–65.0)	<.001	32.0 (27.0–47.0)	45.5 (40.5–52.0)	<.001
≥35 years, %	48.1	93.0	<.001	47.7	93.8	<.001	36.7	91.5	<.001	63.2	95.4	<.001	47.8	84.6	<.001
Male, %	62.0	55.4	<.001	58.9	47.7	.02	58.6	51.1	.3	69.8	77.3	.2	63.3	46.2	.08
Previous TB, %	25.7	16.9	.02	25.7	20.3	.3	21.0	14.9	.3	20.2	12.1	.09	42.3	15.4	.007
Smoking, %															
Current smoker	42.7	31.8	.002	46.5	33.6	.002	11.9	0	.001	47.5	36.4	.03	83.6	69.2	.001
Past smoker	16.2	16.5		17.3	19.5		30.2	23.4		6.4	7.6		3	11.5	
Never smoker	41.1	51.7		36.3	46.9		57.9	76.6		46.1	56.1		13.4	19.2	
Median body mass index, kg/m^2	19.6 (17.6–22.1)	21.9 (19.0–25.7)	<.001	17.9 (16.1–19.9)	21.1 (18.4–24.9)	<.001	21.9 (19.9–24.1)	24.7 (21.8–28.4)	<.001	20.2 (18.5–22.0)	21.4 (19.3–23.9)	.02	18.4 (16.9–20.3)	22.3 (18.6–27.0)	.004
Mean waist hip ratio, no. (standard deviation)															
Men	0.86 (0.067)	0.89 (0.077)	<.001	0.83 (0.068)	0.88 (0.063)	<.0001	0.89 (0.060)	0.95 (0.067)	<.0001	0.86 (0.063)	0.88 (0.088)	.07	0.86 (0.059)	0.89 (0.072)	.063
Women	0.83 (0.073)	0.87 (0.077)	<.001	0.81 (0.071)	0.86 (0.072)	<.0001	0.87 (0.062)	0.91 (0.078)	.007	0.79 (0.072)	0.829 (0.090)	.06	0.83 (0.58)	0.89 (0.056)	.001
Mean laboratory glycated hemoglobin, % (range)	5.6 (5.3–5.9)	10.4 (7.9–12.3)		5.5 (5.3–5.8)	11.3 (9.1–12.9)	<.001	5.5 (5.2–5.8)	10.6 (9.0–13.3)	<.001	5.8 (5.5–6.1)	7.4 (6.7–10.8)[a]		5.8 (5.5–6.1)	10.1 (7.8–11.9)	<.001
Antihypertensive medication use, %	3.2	16.9	<.001	4.0	13.3	<.001	0.5	8.5	<.001	4.1	22.7	<.001	5.0	34.6	<.001
Cardiovascular disease risk, % with 10-year risk estimated >10%	5.5	24.5	.06	7.0%	17.9	.1	2.8	22.2	.02	5.24	38	<.001	5.5	8.3	.2
Smear positive, %	72.7	80.2	.009	83.1	89.1	.09	64.2	68.1	.6	67.5	72.7	.4	67.2	65.4	1.0
Culture positive, %	81.4	91.5	<.001	79.5	91.4	.002	82.1	89.4	.2	76.1	83.3	.1	83.7	88.0	1.0
Smear grade, %															
Max at baseline	26.8	19.5	…	16.8	10.9	…	35.4	32.0	…	29.8	24.2	…	26.9	26.9	…
Negative	31.3	30.3	.0001	29.4	26.6	.2	31.7	29.8	.8	33.0	34.9	.8	32.1	38.5	.8
Scanty and 1 + 2+ and 3+	40.3	48.7		53.	62.5	…	32.6	38.3	…	34.6	37.9	…	35.1	26.9	…
Anemia,[b] %															
Men	46.9	43.2	.8	56.1	29.5	<.001	30.3	37.5	.5	42.4	53.0	.2	66.8	83.3	.2
Women	52.1	42.0	.001	61.9	49.2	.06	38.4	26.1%	.2	48.1	40.0	.6	62.5	35.7	.05
Hemoptysis, %	23.6	30.0	.1	28.9	38.3	.03	32.2	36.2	.8	8.9	13.6	.02	18.4	19.2	.6
TB score, %															
0–2	31.8	30.7	.03	13.8	18.0	<.001	45.3	48.9	.5	50.7	42.4	.3	16.1	30.8	.09
3–5	53.4	60.0		52.1	66.4		51.9	51.1		45.7	51.5		69.8	65.4	
6+	14.9	9.4		34.0	15.6		2.7	0.0		3.6	6.1		14.1	3.8	

Values are rounded to 1 decimal place including percentages; percentage given of relevant whole sample with missing values only shown where >3%.

Abbreviations: DM, diabetes mellitus; FPG, fasting blood glucose; TB, tuberculosis.

[a]In Romania, where TB patients are treated as in-patients, repeated FPG measurements were available; 9 of 66 DM patients were classified using FPG rather than repeated glycated hemoglobin.

[b]Anemia defined as hemoglobin <13 in men (n = 1337) and <12 in women (n = 846).

Table 4. Comparative Characteristics of Tuberculosis Patients With Newly and Previously Diagnosed Diabetes Mellitus

Characteristic		New DM (N = 84)	Known DM (N = 183)	*P* Value
Median age (IQR), y		52.0 (45.1–62.0)	51.0 (45.1–59.0)	.9
Male sex, no. (%)		52 (61.9)	96 (52.5)	.2
Hemoptysis, no. (%)		28 (35.4)	52 (32.1)	.2
Tuberculosis score				
	0–2	19 (22.3)	63 (34.4)	<.001
	3–5	51 (60.7)	109 (59.6)	…
	6+	14 (16.7)	11 (6.0)	…
Median body mass index (IQR), kg/m^2		20.0 (17.9–24.5)	22.5 (19.7–25.9)	.02
Median glycated hemoglobin, % (IQR)				
	Laboratory	8.0 (6.8–11.7)	10.9 (9.1–12.6)	.05
	Repeat	6.9 (6.5–12.4)	10.8 (8.9–12.4)	.2
Duration of DM diagnosis, no. (%)				
	<1 year	NA	53 (29.0)	…
	1–5 years	NA	77 (42.1)	…
	6–15 years	NA	42 (23.0)	…
	15+ years	NA	11 (6.0)	…
Treatment including insulin, no. (%)	…	NA	37 (20.2)	…
Treatment including metformin, no. (%)	…	NA	112 (61.2)	…
Any hospital admission in the last 5 years due to DM, no. (%)	…	NA	36 (20.0)	…
Family history of DM, no. (%)	…	16 (19.1)	79 (43.2)	<.001
Charlson comorbidity index score ≥2, no. (%)	…	2 (2.4)	86 (47.0)	<.001
Any diabetes complication, no. (%)	…	2 (2.4%)	79 (43.2%)	<.001
Hypertension, no. (%)				
	Prehypertension	13 (15.5)	15 (8.2)	<.001[a]
	Stage I	21 (25)	48 (26.2)	…
	Stage II	18 (21.4)	59 (32.2%	…
Antihypertensive medication, No. (%)		7 (8.3)	38 (20.8)	.006
Renal function,[b] no. (%)		2 (2.4)	10 (5.5)	.3

Values are rounded to 1 decimal point including percentages; percentage given of relevant whole sample with missing values only shown where >3%.

Abbreviations: DM, diabetes mellitus; IQR, interquartile range; NA, not applicable.

[a]Wald test for statistical significance across categories of hypertension, $P < .001$.

[b]Chronic kidney disease stage 3–5 (estimated glomerular filtration rate <60).

10 years in <50% of those identified with pre-DM based on a single FPG or HbA1c test [33], and uncertainty about the cut-point when using HbA1c. Our data suggest that TB patients with intermediate hyperglycemia were clinically more like patients without diabetes than those with diabetes. Overdiagnosis and overtreatment of intermediate hyperglycemia [34] may increase potentially unnecessary risks (eg, stress, drug adverse events) in vulnerable populations such as those with TB and does not appear warranted on the basis of our data.

Patients with previously diagnosed DM often had serious comorbidities and DM complications such as chronic kidney disease, which itself is an independent risk factor for TB [35], and microvascular and/or macrovascular complications. Patients with newly diagnosed DM had fewer DM complications but more severe TB, despite better glycemic control, suggesting that some of those newly diagnosed patients were experiencing "transient hyperglycemia" due to severe TB. In general, TB patients with diabetes appeared to have somewhat worse TB disease compared to those without DM.

For patients with TB–DM, an important consideration in the aftermath of successful TB treatment is glycemic control and management of cardiovascular risk associated with DM. Despite poor glycemic control, only 20% of TB patients with previously known DM used insulin, and only 61% used metformin. Also, hypertension was common but often untreated. These values are in line with significant gaps in management of DM in general that we found in these same settings [36].

The between-country heterogeneity for certain parameters (HbA1c and BMI distributions) highlights the inherent variability across different populations and epidemiological settings. Though this observation is a finding that stresses the importance of understanding the local in-country epidemiology, it adds complexity to analyses that pool data from such diverse sites. We used robust standard errors to adjust for clustering within sites and included country as a random effect in our regression modeling.

A potential limitation of this study is that laboratory tests were taken at the time of diagnosis and confirmatory tests up to

2 weeks later. Elevated measurements may therefore reflect stress hyperglycemia, overestimating DM prevalence [37], although available repeated HbA1c or FPG tests at the end of TB treatment remained abnormal in the large majority (data not shown).

This study has many strengths. All patients were screened for DM with HbA1c, a standardized and validated measure in accredited laboratories, and the recruitment processes were standardized (using case record forms, standard operating procedures, and standardized definitions of all major variables), which enhances the cross-site comparability. In contrast to many studies of DM prevalence among TB patients, a repeated laboratory-based measure was used for screening. Many earlier studies have been limited to a single test, often using point-of-care methods that are not universally considered appropriate for DM diagnosis [11]. The case definition used here is thus likely to be more robust. Recruitment criteria were specific but sufficiently flexible to ensure the representativeness of participants within sites and included microbiological assessment of TB status.

Our data enforce recently updated recommendations published by the International Union Against Tuberculosis and Lung Diseases and the World Diabetes Foundation regarding DM screening and management among TB patients [38]. These recommendations aimed to help front-line health workers at TB and DM clinics and highlight some of the challenges in management of comorbid disease [22]. However, stronger evidence (particularly in implementation of comorbidity care and treatment) is urgently needed. Further longitudinal studies that explore the role and importance of transient hyperglycemia in TB patients and its association with future DM are also essential, as are studies that examine the longer-term effects of DM screening and management on both TB and DM outcomes. Future studies should explore improved models of care, such as training of healthcare professionals to deliver integrated management of TB and DM in primary care in LMICs. Such integrated management could increase uptake of appropriate secondary preventive therapies for patients with TB–DM who are at high risk of cardiovascular disease and may also improve TB treatment outcomes [39], given the high prevalence of uncontrolled DM at baseline in our cohort. Attention should also be paid to health systems interventions to enhance and promote referral to local DM services after the end of TB treatment. Despite this evident need, there are no published randomized, controlled trials that have explored integrated management options, and there is a paucity of ongoing studies that address these key clinical issues [39, 40].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The TANDEM consortium member list is provided in Supplementary Table 2.

Disclaimer. The findings presented herein are solely the responsibility of the authors.

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APPENDIX CONFIRMATORY DIABETES MELLITUS TESTS

In this analysis, new diabetes was defined consistently in each country on the basis of repeated laboratory tests.

We classified individuals as being confirmed with diabetes if, in addition to their single elevated glycated hemoglobin (HbA1c), they also had at least 1 of the following:

- Baseline fasting plasma glucose test in the diagnostic range ≥7.0 mmol/L,
- At least 1 nonfasting (random) plasma glucose in the diagnostic range (≥11.1 mmol/L),
- A second (repeated) HbA1c test >6.5%.

In the case of a small number individuals where no second laboratory test was available (all had been missed), we classified new diabetes mellitus on the basis of a single baseline HbA1c result >7.0%.