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Transient Hyperglycemia in Patients With Tuberculosis in Tanzania: Implications for Diabetes Screening Algorithms

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Background. Diabetes mellitus (DM) increases tuberculosis risk while tuberculosis, as an infectious disease, leads to hyperglycemia. We compared hyperglycemia screening strategies in controls and patients with tuberculosis in Dar es Salaam, Tanzania.

Methods. Consecutive adults with tuberculosis and sex- and age-matched volunteers were included in a case-control study between July 2012 and June 2014. All underwent DM screening tests (fasting capillary glucose [FCG] level, 2-hour CG [2-hCG] level, and glycated hemoglobin A1c [HbA1c] level) at enrollment, and cases were tested again after receipt of tuberculosis treatment. Association of tuberculosis and its outcome with hyperglycemia was assessed using logistic regression analysis adjusted for sex, age, body mass index, human immunodeficiency virus infection status, and socioeconomic status. Patients with tuberculosis and newly diagnosed DM were not treated for hyperglycemia.

Results. At enrollment, DM prevalence was significantly higher among patients with tuberculosis (n = 539; FCG level > 7 mmol/L, 4.5% of patients, 2-hCG level > 11 mmol/L, 6.8%; and HbA1c level > 6.5%, 9.3%), compared with controls (n = 496; 1.2%, 3.1%, and 2.2%, respectively). The association between hyperglycemia and tuberculosis disappeared after tuberculosis treatment (adjusted odds ratio [aOR] for the FCG level: 9.6 [95% confidence interval {CI}, 3.7–24.7] at enrollment vs 2.4 [95% CI, .7–8.7] at follow-up; aOR for the 2-hCG level: 6.6 [95% CI, 4.0–11.1] vs 1.6 [95% CI, .8–2.9]; and aOR for the HbA1c level, 4.2 [95% CI, 2.9–6.0] vs 1.4 [95% CI, .9–2.0]). Hyperglycemia, based on the FCG level, at enrollment was associated with tuberculosis treatment failure or death (aOR, 3.3; 95% CI, 1.2–9.3).

Conclusions. Transient hyperglycemia is frequent during tuberculosis, and DM needs confirmation after tuberculosis treatment. Performance of DM screening at tuberculosis diagnosis gives the opportunity to detect patients at risk of adverse outcome.

Keywords. tuberculosis; diabetes mellitus; stress-induced hyperglycemia; transient hyperglycemia; sub-Saharan Africa.

Interest in the comorbidity between tuberculosis and diabetes mellitus (DM) has reemerged due to the global increase of DM and its potential impact on tuberculosis control. DM doubles or triples the incidence of active tuberculosis and increases the risk of tuberculosis treatment failure and death [1–3]. A framework was developed to guide national programs in their response to DM and tuberculosis [4]. The prevalence of DM among patients with tuberculosis differs between countries (16%–45%). Sub-Saharan Africa has the highest rate of undiagnosed DM, is expecting the sharpest increase in DM by 2035, has a high tuberculosis burden, and has the highest rate of tuberculosis and human immunodeficiency virus (HIV) coinfection [5, 6]. Two studies in Tanzania and Uganda confirmed the cross-sectional tuberculosis-DM association in the presence of high HIV prevalence [7, 8]. Unexpectedly, HIV seamed to protect against DM. The impact of HIV infection on the tuberculosis-DM association needs further investigations, as HIV increases metabolic risk but can also lower body mass index [9].

When and how best diagnose DM in the presence of infections is challenging. As an infectious disease, tuberculosis increases insulin resistance and stress-induced hyperglycemia, which may lead to overdiagnosis of DM during the acute phase of tuberculosis [10]. Screening of DM is based on blood glucose criteria and, lately, on the use of glycated hemoglobin A1c (HbA_{1c}), with its advantage of not requiring fasting and exhibiting fewer day-to-day variations during periods of stress and illness, owing to its half-life of 120 days [11–13]. Few small studies have examined the longitudinal course of glycemia during tuberculosis treatment, but none were conducted on the African continent or compared the performance of different DM screening tests over time within the same study population [14–17]. We therefore examined the association of tuberculosis and its outcome with the presence and persistence of hyperglycemia in Tanzania, using 3 different DM screening tests.

Received 23 September 2015; accepted 19 November 2015; published online 25 November 2015.

Presented in part: 9th European Congress on Tropical Medicine and International Health, Basel, Switzerland, 6–10 September 2015; 46th Union World Conference on Lung Health, Cape Toen, South Africa, 2–6 December 2015.

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The Journal of Infectious Diseases® 2016;213:1163–72

DOI: 10.1093/infdis/jiv568

METHODS

Study Design and Setting

Patients with tuberculosis were recruited between June 2012 and December 2013 and followed up for a median time of 5 months (interquartile range [IQR], 4.7–6.1 months) after the start of antituberculosis treatment. Controls were recruited between December 2012 and September 2013 and did not have follow-up visits. The study was performed in Kinondoni, the most populated district of Dar es Salaam. Patients were recruited in Mwananyamala Regional Hospital and connected health facilities (Sinza Hospital, Magomeni Health Centre, and Tandale Dispensary).

Study Participants

Cases

Consecutive adult patients (age ≥18 years; all were living in Kinondoni District) presenting in the participating hospitals with new active tuberculosis diagnosed by the National TB and Leprosy Control Programme (NTLP) were screened for study inclusion. Tuberculosis diagnosis was based on sputum smear microscopy findings, chest radiograph findings, clinical evidence of tuberculosis, and decision by the clinician to treat with a full-course of antituberculosis therapy [18]. Patients with tuberculosis were classified as having pulmonary smear-positive, smear-negative, or extrapulmonary tuberculosis. Patients with tuberculosis were treated for 6 months, or longer, if necessary, with a standard regimen [18, 19]. Sputum microscopy was repeated at months 2–3 and 5 by the NTLP to evaluate the response to treatment in patients with pulmonary smear-positive tuberculosis [18, 19]. Tuberculosis treatment outcome was defined according to World Health Organization (WHO) guidelines as successful (cure, treatment completed) or adverse (failure, death, and loss to follow-up) [19].

Controls

We used frequency matching on sex and age (by 10-year age groups) to select controls among adults accompanying patients, other than the one included in the study, to the outpatient departments and living in Kinondoni District. Exclusion criteria were a biological relationship to a case, tuberculosis history, symptoms or signs of tuberculosis, other acute infection, or major trauma within the last 3 months.

Study Procedures

Data Collection

Information on demographic characteristics, health history (DM, high blood pressure [BP], tuberculosis, and HIV infection) and symptoms (type and duration), socioeconomic status (SES; indicators of education, occupation, and wealth, determined using factor analysis), smoking (ever daily smoking), and alcohol misuse (≥3 drinks per day or ≥6 drinks per occasion [20]) was obtained during an in-person interview. Clinical examination and screening for hyperglycemia were performed on the day of the interview. Body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared. BP was measured and defined according to the WHO [21]. Data were entered directly into an open data kit in a personal digital assistant with real-time error, range, and consistency checks [22].

Laboratory Testing and Chest Radiography

Findings of chest radiography, performed for every patient with tuberculosis, were evaluated by an experienced radiologist. Participants were screened for HIV infection according to the national algorithm, using first a rapid immune-chromatographic test (Alere Determine HIV-1/2) and, for confirmation, a second rapid test (Trinity Biotech Uni-gold Recombigen HIV-1/2). In case of HIV infection diagnosis, combination antiretroviral therapy (cART) was started by the NTLP according to national guidelines [18]. Complete blood count was performed (Sysmex XS-800i automated hematology analyzer). Anemia was defined as a hemoglobin level of <13 g/dL in men and <12 g/dL in women [23].

Hyperglycemia Screening and DM Diagnosis

Blood glucose testing was conducted between 8 AM and 11 AM after an overnight fast of ≥8 hours, by measuring the fasting capillary glucose (FCG) level (GlucoPlus, Diabcare), the 2-hour capillary glucose (2-hCG) level (evaluated using a standard 75-g oral glucose tolerance test), and the glycated hemoglobin A1c (HbA1c) level (tested in whole-blood specimens obtained by venipuncture, using Tina-quant HbA1c Gen. 2 Cobas Integra 400 [Roche Diagnostics], an immunoassay certified by the National Glycohemoglobin Standardization Program and insensitive to hemoglobinopathies) [24, 25]. Testing for DM was performed at enrollment in controls and patients with tuberculosis (45% were screened after start of tuberculosis treatment (median, 2 days; IQR, 1–4 days), and screening was repeated in patients with tuberculosis after a median of 5 months of antituberculosis treatment (67% were screened during receipt of tuberculosis treatment).

DM is generally a chronic and permanent condition. However, for the sake of clarity, we define DM as repeated measurements of ≥7.0 mmol/L for the FCG level, ≥11.1 mmol/L for the 2-hCG level, or ≥6.5% for the HbA_{1c} level and/or if the patient had a history of and treatment for DM according to the standard American Diabetes Association and WHO criteria [11–13]. Prediabetes (pre-DM) was defined according to WHO criteria: a FCG level of 6.1–6.9 mmol/L, a 2-hCG level of 7.8–11 mmol/L; and a HbA1c level of 5.8%–6.4% (39–47 mmol/mol) [12, 13]. Hyperglycemia is used hereafter to denote patients with pre-DM or DM. Every abnormal glycemic test result (ie, a FCG level ≥5.6 mmol/L, a 2-hCG level of ≥7.8 mmol/L) or HbA1c value (level, ≥5.7% [≥39 mmol/mol]) was confirmed by repeat testing 2–5 days later. 2-hCG testing was omitted if the FCG level was ≥11.1 mmol/L. Participants who

received a diagnosis of DM were referred to the local DM clinic, but none initiated DM treatment.

Data Analysis

Case-Control Study at Enrollment

Patients with tuberculosis and controls with complete glucose status data (FCG, 2-hCG, and HbA1c levels) at enrollment were included in the cross-sectional analysis (Figure 1). Characteristics of patients with tuberculosis were compared to those of controls (with stratification by HIV infection status), and differences were tested with Wilcoxon–Mann–Whitney and χ^2 tests. The independent association of pre-DM and DM with tuberculosis status was evaluated by logistic regression (with stratification by HIV infection status) for every DM screening test independently. Covariates included in the final models were age, sex, BMI, SES, and HIV infection status (nonstratified analysis only). Lifestyle variables were not included in the models as they had no influence on the reported association. Additional sensitivity analysis excluded patients previously known and treated for DM.

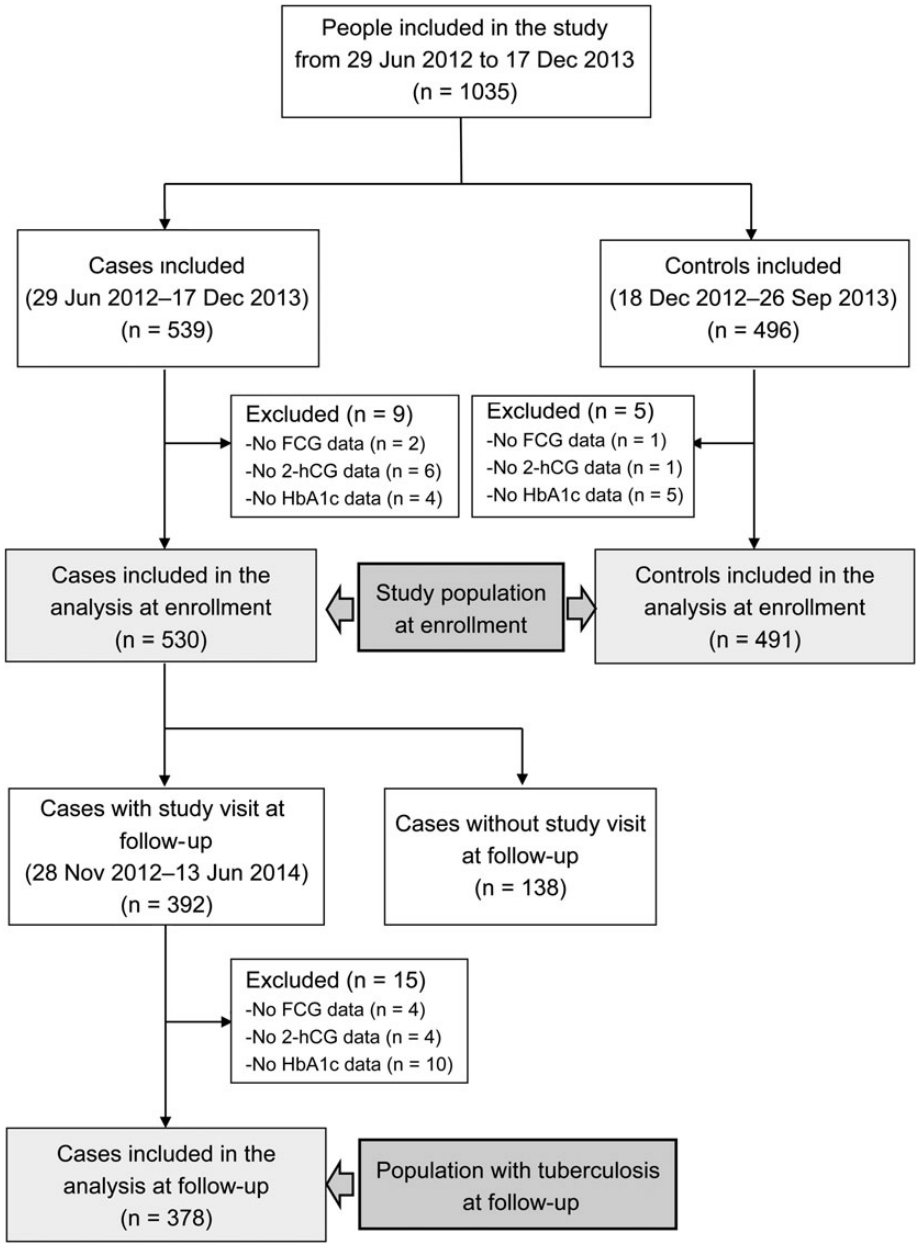

Figure 1. Flow chart of patients with tuberculosis (cases) and healthy controls. Abbreviations: 2-hCG, 2-hour capillary glucose; FCG, fasting glucose level; HbA1c, glycated hemoglobin; OR, odds ratio.

Longitudinal Course of Hyperglycemia in Patients With Tuberculosis

Longitudinal analysis of changes in blood glucose over follow-up of a median of 5 months of tuberculosis treatment was restricted to patients with complete DM screening data at enrollment and follow-up (Figure 1). Baseline characteristics of patients with and without follow-up were compared using Wilcoxon–Mann–Whitney and χ^2 tests. The longitudinal pattern of the association between tuberculosis and hyperglycemia was assessed for each DM screening test separately (1) with 2 cross-sectional comparisons (patients with tuberculosis at enrollment vs controls and patients with tuberculosis at follow-up vs controls, with stratification by HIV infection status) and (2) by using a binary generalized estimating equation model (with stratification by HIV infection status) to assess the change in the prevalence of hyperglycemia from the time of enrollment to follow-up among patients with tuberculosis. Potential confounding variables (age, sex, BMI, SES, and, in nonstratified analyses only, HIV infection status) were included in the final models. Lifestyle variables were not included in the models as they had no influence on the reported association.

Hyperglycemia at Enrollment and Tuberculosis Treatment Outcome

Baseline characteristics of patients with and without adverse tuberculosis outcome were compared using Wilcoxon–Mann–Whitney and χ^2 tests. The association between adverse tuberculosis outcome and hyperglycemia was assessed for each DM screening test separately with logistic regression adjusted for potential confounding variables (age, sex, BMI, SES, HIV infection status, duration of tuberculosis symptoms before diagnosis, and cavity on a radiograph). Lifestyle variables were not included in the models as they had no influence on the reported association.

Statistical analyses were performed using Stata software, version 12 (StataCorp, College Station, Texas).

Ethical Considerations

All participants consented in writing to interview and health examination. The Ifakara Health Institute Institutional Review Board and the Medical Research Coordinating Committee of the National Institute for Medical Research, Tanzania, gave ethical clearance.

RESULTS

Study Sample at Enrollment

A total of 539 patients with tuberculosis and 496 controls were enrolled in the study. Nine patients with tuberculosis and 5 controls were excluded because of missing FCG, 2-hCG, or HbA1c data at enrollment (Figure 1). Characteristics of the study sample are described in Table 1. Patients with tuberculosis were more often infected with HIV (32% vs 14%), underweight, and anemic. Only 10 patients with tuberculosis and 2 controls, all of whom were HIV negative, were already known and treated for DM at enrollment. DM prevalence at enrollment was significantly higher in patients with tuberculosis (4.5%, based on the FCG level; 6.8%, based on the 2-hCG level; and 9.3%, based on the HbA1c level), compared with controls (1.2%, 3.1%, and 2.2%, respectively; $P < .01$). This was also true for pre-DM, irrespective of HIV status. Mean FCG, 2-hCG, and HbA1c values were significantly higher in patients with tuberculosis (5.6 mmol/L, 7.8 mmol/L, and 6.1%, respectively), compared with controls (4.8 mmol/L, 6.7 mmol/L, and 5.6%, respectively).

Association Between Tuberculosis and DM at Enrollment

Irrespective of which DM test was used and whether diabetics previously diagnosed and treated were excluded, DM and pre-DM were independently associated with tuberculosis (Table 2). The OR for DM based on the HbA1c level was substantially lower in HIV-infected participants (interaction $P = .048$). The prevalence of DM among HIV-infected patients was not different according to the presence or absence of cART.

Study Sample at Follow-up

Of the 530 patients with tuberculosis, 392 (73%) presented for a follow-up visit; 15 patients with tuberculosis were excluded from the analysis because of missing FCG, 2-hCG, or HbA1c data at follow-up (Figure 1). Characteristics and glycemic status of patients with tuberculosis with and those without follow-up were comparable, except underweight and extrapulmonary tuberculosis being more common among subjects without follow-up (Supplementary Table 1).

Longitudinal Evolution of Glycemic Status and Its Association With Tuberculosis

The values of all 3 screening tests decreased over time (mean decrease [±SD], 0.3 mmol/L for FCG [±1.1], 1.0 mmol/L for 2-hCG (±2.1), and 0.3% for HbA1c [±0.5]).

After exclusion of patients with previously known DM, most patients with tuberculosis with glucose levels consistent with DM at enrollment were not diabetic at follow-up (75%, 64%, and 71%, using FCG, 2-hCG, and HbA1c criteria, respectively). Irrespective of HIV status, most patients with tuberculosis and a diagnosis of pre-DM at enrollment had a normal glycemic status at follow-up (100%, 90%, and 59%, using FCG, 2-hCG, and HbA1c data, respectively; Figure 2). There was a tendency for HbA1c-based DM and pre-DM to more likely persist as hyperglycemia at follow-up. More than 99% of patients with tuberculosis and without DM at enrollment, based on any of the 3 screening methods, did not have DM at follow-up.

Prevalence of newly diagnosed DM at follow-up was similar in patients with tuberculosis (0.8%, based on the FCG level; 1.4%, based on the 2-hCG level; and 2.2%, based on the HbAc1 level) and controls (0.8%, 2.7%, and 1.8%, respectively; $P > .1$). Based on epidemiological data, these patients probably had type 2 DM [26, 27]. Irrespective of HIV status and previous DM status, the adjusted ORs of the association between tuberculosis and hyperglycemia at enrollment consistently reverted

Table 1. Characteristics of Patients With Tuberculosis (Cases) and Healthy Controls at Enrollment, Overall and Stratified by Human Immunodeficiency Virus (HIV) Infection Status

	Overall			HIV Negative			HIV Infected		
Characteristic	Cases (n = 530)	Controls (n = 491)	*P* Value	Cases (n = 355)	Controls (n = 423)	*P* Value	Cases (n = 166)	Controls (n = 66)	*P* Value
Age, y	35.9 ± 12	36.7 ± 13	.75	35.0 ± 12	36.0 ± 14	.41	37.0 ± 9	41.0 ± 11	.06
Male sex	341 (64)	255 (52)	<.001	262 (74)	233 (55)	<.001	74 (45)	21 (32)	.08
History of smoking	149 (28)	99 (20)	.003	113 (32)	89 (21)	.001	34 (21)	10 (15)	.34
Alcohol misuse[a]	62 (12)	27 (6)	<.001	47 (13)	24 (6)	<.001	14 (8)	3 (5)	.31
Socioeconomic status[b]			<.001			<.001			<.001
Low	170 (32)	85 (18)	<.001	110 (31)	80 (19)	<.001	57 (35)	5 (8)	<.001
Medium	253 (48)	243 (50)	.3	165 (47)	196 (47)	1	83 (51)	46 (71)	.008
High	103 (20)	158 (33)	<.001	79 (22)	143 (34)	<.001	23 (14)	14 (22)	.17
Body mass index	19.6 ± 4	25.4 ± 5	<.001	19.3 ± 4	25.3 ± 6	<.001	20.2 ± 4	25.9 ± 5	<.001
High blood pressure[c]	44 (8)	74 (15)	.001	33 (9)	66 (16)	.008	10 (6)	8 (13)	.11
HIV infection	166 (32)	66 (14)	<.001	. . .	. . .		. . .	. . .	
Previously known HIV	86 (17)	10 (2)	<.001	. . .	. . .		86 (52)	10 (15)	<.001
HIV treated with cART	51 (9.6)	6 (1.2)	<.001	. . .	. . .		51 (30.7)	6 (9.1)	<.001
Anemia	425 (81)	172 (35)	<.001	271 (77)	142 (34)	<.001	149 (91)	30 (45)	<.001
Hemoglobin level, g/dL	10.8 ± 2.2	12.9 ± 1.7	<.001	11.3 ± 2.1	13.0 ± 1.7	<.001	9.6 ± 2.1	12.2 ± 1.8	<.001
Previously known DM	10 (1.9)	2 (0.4)	.03	10 (3)	2 (0.5)	.008	0 (0)	0 (0)	. . .
FCG level[d]			<.001			<.001			.02
Normal	459 (86.6)	479 (97.6)	<.001	316 (89.0)	414 (97.9)	<.001	135 (81.3)	63 (95.5)	.007
Prediabetes	47 (8.9)	6 (1.2)	<.001	24 (6.8)	5 (1.2)	<.001	23 (13.9)	1 (1.5)	.004
Diabetes	24 (4.5)	6 (1.2)	.002	15 (4.2)	4 (1.0)	.004	8 (4.8)	2 (3.0)	.73
Overall, mmol/L	5.6 ± 2.2	4.8 ± 0.8	<.001	5.7 ± 2.5	4.8 ± 0.7	<.001	5.6 ± 1.0	5.0 ± 1.4	<.001
2-hCG level[e]			<.001			<.001			<.001
Normal	365 (68.9)	446 (90.8)	<.001	257 (72.4)	387 (91.5)	<.001	101 (60.8)	57 (86.4)	<.001
Prediabetes	129 (24.3)	30 (6.1)	<.001	75 (21.1)	26 (6.2)	<.001	53 (31.9)	4 (6.1)	<.001
Diabetes	36 (6.8)	15 (3.1)	.006	23 (6.5)	10 (2.4)	.007	12 (7.2)	5 (7.6)	1
Overall, mmol/L	7.8 ± 2.1	6.7 ± 1.9	<.001	7.6 ± 2.0	6.7 ± 1.9	<.001	8.1 ± 2.3	7.0 ± 2.1	<.001
A1c level[f]			<.001			<.001			<.001
Normal	224 (42.3)	329 (67)	<.001	158 (44.5)	283 (66.9)	<.001	62 (37.4)	45 (68.2)	<.001
Prediabetes	257 (48.5)	151 (30.8)	<.001	164 (46.2)	135 (31.9)	<.001	88 (53.1)	15 (22.7)	<.001
Diabetes	49 (9.3)	11 (2.2)	<.001	33 (9.3)	5 (1.2)	<.001	16 (9.6)	6 (9.1)	1
Overall, %	6.1 ± 1.5	5.6 ± 0.6	<.001	6.1 ± 1.8	5.6 ± 0.5	<.001	5.9 ± 0.5	5.7 ± 1.0	<.001
Tuberculosis symptoms for >3 mo before diagnosis	97 (18)	. . .		69 (19)	. . .		25 (15)	. . .	
Tuberculosis category									
Smear positive	385 (73)	. . .		269 (76)	. . .		111 (67)	. . .	
Smear negative	111 (21)	. . .		64 (18)	. . .		44 (27)	. . .	
Extrapulmonary	34 (6)	. . .		22 (6)	. . .		11 (6.6)	. . .	
Cavity on radiograph	250 (50)	. . .		184 (55)	. . .		61 (38)	. . .	

Data are no. (%) of patients or mean value ± SD.

Abbreviations: cART, combination antiretroviral therapy; DM, diabetes mellitus.

[a] Defined as ≥3 drinks per day or ≥6 drinks per occasion.

[b] Assessed with indicators of scholarly education level, occupation, and wealth ownership, using factor analysis.

[c] Defined as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 or as self-reported use of antihypertensive medication.

[d] A fasting capillary glucose (FCG) level of <6.1 mmol/L was considered normal, 6.1–6.9 mmol/L was considered indicative of prediabetes, and ≥7 mmol/L was considered indicative of diabetes.

[e] A 2-hour capillary glucose (2-hCG) level of <7.8 mmol/L was considered normal, 7.8–11 mmol/L was considered indicative of prediabetes, and ≥11.1 mmol/L was considered indicative of diabetes.

[f] A glycated hemoglobin (HbA1c) level of <5.7% was considered normal, 5.8%–6.4% was considered indicative of prediabetes, and ≥6.5% was considered indicative of diabetes.

to the null value (OR, 1) during follow-up for all 3 DM screening tests (Figure 3). The changes in tuberculosis-hyperglycemia association between enrollment and follow-up were significant for all DM tests.

None of the patients with DM newly diagnosed at baseline were treated for DM. Hypoglycemic drugs were proposed only to 2 patients with a FCG level of >10 mmol/L, which is usual practice in Tanzania. One was lost to follow-up, and the

Table 2. Cross-sectional Association of Prediabetes and Diabetes With Tuberculosis Among Patients With Tuberculosis (Cases) and Healthy Controls at Enrollment, Overall and Stratified by Human Immunodeficiency Virus (HIV) Infection Status

	Overall				HIV Negative				HIV Infected			
Variable	Cases (n = 530)	Controls (n = 491)	OR (95% CI)	aOR[a] (95% CI)	Cases (n = 355)	Controls (n = 423)	OR (95% CI)	aOR[a] (95% CI)	Cases (n = 166)	Controls (n = 66)	OR (95% CI)	aOR[a] (95% CI)
FCG level[b]												
Normal	459 (86.6)	479 (97.6)	Reference	Reference	316 (89.0)	414 (97.9)	Reference	Reference	135 (81.3)	63 (95.5)	Reference	Reference
Prediabetes	47 (8.9)	6 (1.2)	8.2 (3.5–19.3)	8.8 (3.1–25.1)	24 (6.8)	5 (1.2)	6.3 (2.4–16.7)	7.2 (2.1–25.0)	23 (13.9)	1 (1.5)	10.7 (1.4–81.3)	15.5 (1.8–136)
Diabetes	24 (4.5)	6 (1.2)	4.2 (1.7–10.3)	10.6 (3.2–4.1)	15 (4.2)	4 (1.0)	4.9 (1.6–15.0)	8.8 (2.1–36.6)	8 (4.8)	2 (3.0)	1.9 (.4–9.1)	17.1 (1.6–179.4)
2-hCG level[c]												
Normal	365 (68.9)	446 (90.8)	Reference	Reference	257 (72.4)	387 (91.5)	Reference	Reference	101 (60.8)	57 (86.4)	Reference	Reference
Prediabetes	129 (24.3)	30 (6.1)	5.3 (3.5–8.0)	8.2 (4.6–14.6)	75 (21.1)	26 (6.2)	4.3 (2.7–7.0)	7.6 (3.9–14.8)	53 (31.9)	4 (6.1)	7.5 (2.6–21.7)	11.1 (3.1–39.9)
Diabetes	36 (6.8)	15 (3.1)	2.9 (1.6–5.4)	3.7 (1.6–8.3)	23 (6.5)	10 (2.4)	3.5 (1.6–7.4)	3.8 (1.4–10.5)	12 (7.2)	5 (7.6)	1.4 (.5–4.0)	3.8 (1.0–15.3)
HbA1c level[d]												
Normal	224 (42.3)	329 (67)	Reference	Reference	158 (44.5)	283 (66.9)	Reference	Reference	62 (37.4)	45 (68.2)	Reference	Reference
Prediabetes	257 (48.5)	151 (30.8)	2.5 (1.9–3.3)	3.6 (2.5–5.1)	164 (46.2)	135 (31.9)	2.2 (1.6–2.9)	3.1 (2.1–4.6)	88 (53.1)	15 (22.7)	4.3 (2.2–8.3)	7.9 (3.1–20.1)
Diabetes	49 (9.3)	11 (2.2)	6.5 (3.3–12.9)	10.7 (4.5–26)	33 (9.3)	5 (1.2)	11.8 (4.5–31)	19.3 (6.1–61)	16 (9.6)	6 (9.1)	1.9 (.7–5.3)	4.7 (1.1–20.8)

Data are no. (%) of patients. A *P* value of <.05 was considered statistically significant. The adjusted *P* value of the interaction between prediabetes and HIV infection status was as follows: for the FCG level, *P* = .66; for the 2-hCG level, *P* = .81; and for the HbA1c level, *P* = .16. The adjusted *P* value of the interaction between diabetes and HIV infection status was as follows: for the FCG level, *P* = .83; for the 2-hCG level, *P* = .73; and for the HbA1c level, *P* = .048. The adjusted *P* value of the interaction between HbA1c-based prediabetes and anemia was as follows: overall, *P* = .93; among HIV-negative subjects, *P* = .54; and among HIV-infected subjects, *P* = .94. The adjusted *P* value of the interaction between HbA1c-based diabetes and anemia was as follows: overall, *P* = .12; among HIV-negative subjects, *P* = .63; and among HIV-infected subjects, *P* = .17.

Abbreviations: 2-hCG, 2-hour capillary glucose; aOR, adjusted odds ratio; CI, confidence interval; FCG, fasting glucose level; HbA1c, glycated hemoglobin; OR, odds ratio.

[a] Adjusted for age, sex, socioeconomic status, body mass index, and HIV status (nonstratified models only).

[b] A FCG level of <6.1 mmol/L was considered normal, 6.1–6.9 mmol/L was considered indicative of prediabetes, and ≥7 mmol/L was considered indicative of diabetes.

[c] A 2-hCG level of <7.8 mmol/L was considered normal, 7.8–11 mmol/L was considered indicative of prediabetes, and ≥11.1 mmol/L was considered indicative of diabetes.

[d] A HbA1c level of <5.7% was considered normal, 5.8%–6.4% was considered indicative of prediabetes, and ≥6.5% was considered indicative of diabetes.

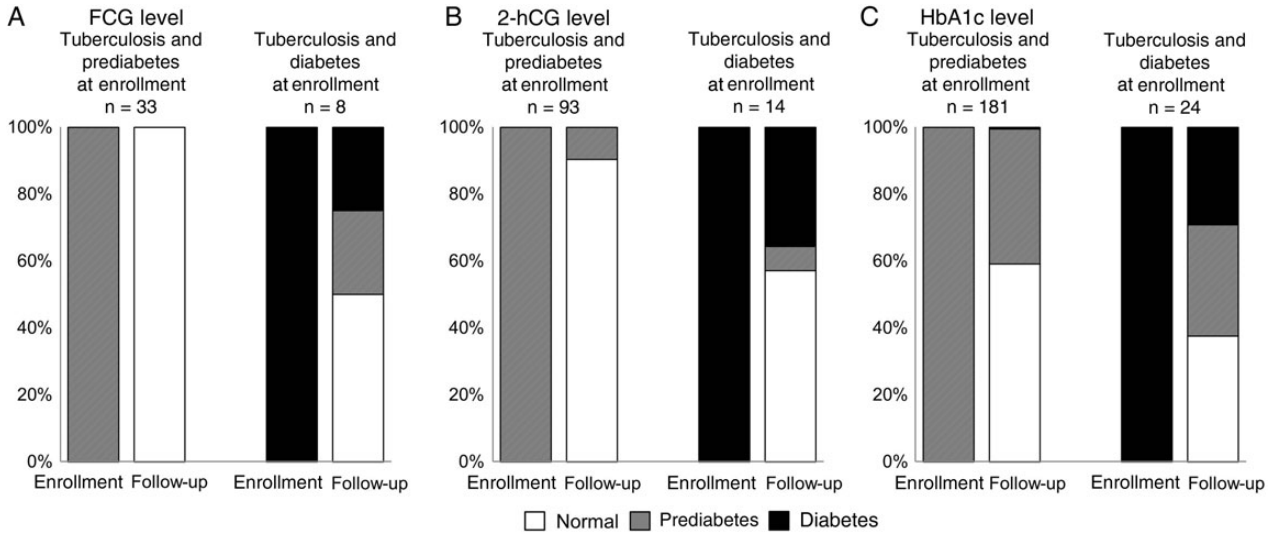

Figure 2. Longitudinal evolution of prediabetes and diabetes among patients with tuberculosis from enrollment to follow-up, using the fasting capillary glucose (FCG) level (*A*), 2-hour capillary glucose (2-hCG) level (*B*), and glycated hemoglobin (HbA1c) level (*C*), over 5 months of follow-up. The result of each screening test is compared to itself between enrollment and follow-up. Diabetics known and treated for the disease at baseline are excluded.

other did not start hypoglycemic treatment and still had a high glycemia level at follow-up.

Hyperglycemia at Enrollment and Tuberculosis Treatment Outcome

Information on tuberculosis treatment outcome was available for patients with and those without follow-up through the NTLP (Supplementary Figure 1). FCG and 2-hCG values in the range of DM or pre-DM at enrollment were significantly associated with adverse tuberculosis outcome (ie, loss to follow-up, treatment failure, or death; Table 3). Hyperglycemia detected by FCG at enrollment was the only test significantly associated with an increased risk of failure or death (adjusted OR, 3.32; 95% CI, 1.20–9.14).

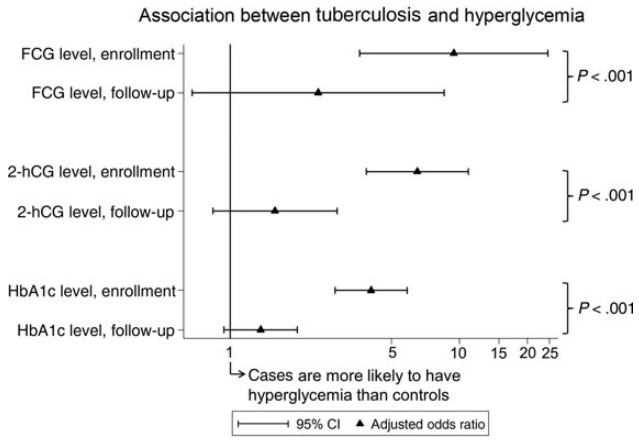

Figure 3. Longitudinal evolution of the association between tuberculosis and hyperglycemia among patients with tuberculosis (cases) and healthy controls, adjusted for age, sex, body mass index, and socioeconomic status. Diabetics known and treated for the disease at baseline are excluded. Abbreviations: 2-hCG, 2-hour capillary glucose; CI, confidence interval; FCG, fasting capillary glucose; HbA1c, glycated hemoglobin.

Diagnostic Discordance of DM Screening Tests at Enrollment

By use of any of the 3 screening tests, 68 patients with tuberculosis received a DM diagnosis at enrollment, and 19 received this diagnosis at follow-up. DM screening tests gave concordant results among 22% of patients with tuberculosis at enrollment and among 53% at follow-up.

DISCUSSION

In this sub-Saharan Africa urban setting, both DM and pre-DM at enrollment were more prevalent in patients with tuberculosis than in controls, irrespective of HIV status. But, in this environment with a low DM prevalence, new hyperglycemia at the level of DM or pre-DM seems to be the consequence rather than the cause of tuberculosis, and DM diagnosis must be confirmed after tuberculosis treatment. Testing for the presence of transient hyperglycemia by measuring the FCG level detects patients with tuberculosis who have a higher risk of an adverse outcome of tuberculosis and allows management of hyperglycemia, but the impact of such an intervention on tuberculosis outcome needs to be confirmed.

The positive cross-sectional associations between tuberculosis and hyperglycemia, irrespective of the type of DM test, are in agreement with the literature [2]. Previous data from Africa suggest that the associations may be weaker in HIV-infected persons [7, 8]. In this study, this was only true for an HbA1c-based DM, which is difficult to interpret owing to a high prevalence of anemia, particularly among HIV-infected patients. The complex

Table 3. Association of Hyperglycemia With Any Adverse Tuberculosis Outcome and With Treatment Failure or Death Among 530 Patients With Tuberculosis

	Any Adverse Outcome[a]		Treatment Failure or Death	
Hyperglycemia Determinant	OR (95% CI)	aOR[b] (95% CI)	OR (95% CI)	aOR[b] (95% CI)
FCG level[c]	2.29 (1.10–4.76)	2.46 (1.08–5.57)	3.33 (1.38–8.06)	3.32 (1.20–9.14)
2-hCG level[d]	2.29 (1.24–4.24)	2.26 (1.12–4.54)	1.88 (.83–4.24)	2.08 (.84–5.18)
HbA1c level[e]	0.50 (.27–.94)	0.57 (.28–1.14)	0.46 (.20–1.04)	0.58 (.23–1.45)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

[a] Defined as loss to follow-up, treatment failure or death.

[b] Adjusted for age, sex, socioeconomic status, body mass index, human immunodeficiency virus infection status, duration of tuberculosis symptoms before diagnosis, cavity on radiograph.

[c] Defined as a fasting capillary glucose (FCG) level of ≥6.1 mmol/L.

[d] Defined as a 2-hour capillary glucose (2-hCG) level of ≥7.8 mmol/L.

[e] Defined as a glycated hemoglobin (HbA1c) level of ≥5.8% (40 mmol/mol).

interplay between HIV-related immunosuppression, the immunosuppressive effect of preexisting DM, and the hyperglycemia subsequent to *M. tuberculosis* infection cannot be disentangled cross-sectionally.

Among patients with tuberculosis with glucose levels consistent with DM at enrollment, 58%–80% (depending on the screening test) had newly diagnosed DM. This is similar to the finding of 77% in the study conducted in Mwanza but differ from findings of studies in India or China, where >50% are known for DM before the onset of clinical tuberculosis [28, 29]. Most patients with newly diagnosed DM had a moderately increased glycemia level.

Hyperglycemia was transient in the large majority of patients with tuberculosis with newly diagnosed pre-DM and DM at the time of tuberculosis diagnosis. This transient hyperglycemia is well known in patients with sepsis [10]. The normalization of glycemic status during tuberculosis treatment has already been described in small study samples (n = 20–50), using oral glucose tolerance tests [15, 16]. A larger study conducted in Iran also reported that, in one third of patients with a high HbA1c level at tuberculosis diagnosis, the HbAc level returned to normal after 3 months of tuberculosis treatment [17]. The cause of this transient hyperglycemic status is likely multifactorial and might reflect inflammation induced by tuberculosis, the hyperglycemic effect of tuberculosis treatment, and patient predisposition. Stress hyperglycemia results from a complex interplay between disturbed cytokine and hormone production, leading to excessive hepatic glucose production and insulin resistance [10]. This high frequency of transient hyperglycemia in untreated patients with tuberculosis raises the question of reverse causality between tuberculosis and DM and highlights the necessity to repeat DM screening later in the course of tuberculosis treatment. Furthermore, studies are needed to assess whether patients with tuberculosis with transient hyperglycemia are at increased risk of developing DM later [30].

Hyperglycemia testing and control at tuberculosis diagnosis may have clinical utility in improving tuberculosis treatment outcome. A recent review showed that DM at tuberculosis diagnosis increases the risk of failure and death during tuberculosis treatment, and a large study conducted in Mwanza, Tanzania, showed an increased risk of death among patients with tuberculosis and DM, particularly among HIV-negative patients [1, 31]. In our study, patients with fasting hyperglycemia at tuberculosis diagnosis had a higher risk of tuberculosis treatment failure or death, while patients with an elevated HbA1c level were not at higher risk, as previously described [1, 17]. Short-term glycemic control with insulin has been linked to better outcome in septic patients, but only when using nonintensive glycemic targets [10]. This evidence indirectly suggests that short-term management of glycemia might also improve tuberculosis outcome. A recent study pointed to metformin as a potentially useful adjunct antituberculosis therapy. In mice, it enhances *Mycobacterium tuberculosis*–specific host immunity and reduces inflammation. In patients with tuberculosis-DM, metformin, but not other DM drugs, improved tuberculosis outcome [32]. The effect of controlling transient hyperglycemia, particularly with metformin, during tuberculosis treatment was not yet studied in a randomized trial [33].

The concordance between the 3 DM tests used in this study is imperfect, as previously described [34, 35]. A number of factors may be involved. The diagnostic cutoffs of the DM tests may need to be adapted in different populations, as they were defined in non-African people. The HbA1c level appears to overestimate DM prevalence in iron-deficient populations [36]. The fact that HbA1c, despite its longer half-life, does not capture long-term DM better than other tests among patients with tuberculosis might be related to the long duration of the disease before tuberculosis diagnosis and to prevalent anemia in these patients [36, 37]. According to our study, FCG testing at the time of tuberculosis diagnosis is preferable to HbA1c testing, which, in contrast to FCG testing, failed to detect patients at

risk of an adverse tuberculosis outcome. Finally, glucose-based tests are less expensive than HbA1c tests, which is a main consideration in low- and middle-income countries.

Our study has several strengths. We evaluated 3 recommended DM tests side by side, and the HbA1c test was nonsensitive to prevalent hemoglobinopathies [38]. The study population was well defined, and the patients were categorized according to WHO recommendations. Its limitation was that tuberculosis diagnosis was based on NTLP guidelines and smear results, rather than culture or GenXpert. However, the study was conducted under the real case scenario of tuberculosis treatment in this population. We did not screen for the presence of multidrug-resistant *M. tuberculosis*, but the prevalence is still low (incidence, 1.1% in 2014) in Tanzania and has probably not affected the association between tuberculosis and DM [39]. Fasting and 2-hour glucose levels were assessed in capillary whole blood, using a point-of-care test, and not in venous blood. However, we used a plasma-calibrated glucometer, for which accuracy conformed to the International Standardization Organization guidelines [40]. Our study was underpowered to investigate the DM course according to HIV infection status. Patients with tuberculosis and controls were not matched by SES, and patients with tuberculosis had a lower SES. However, the SES variable was included in every multivariate analysis. Thirty percent of patients with tuberculosis had no glycemic follow-up, but they are unlikely to have biased the observed results to a relevant degree, because sensitivity analyses using inverse probability weighting and multiple imputation gave similar results to those presented here.

In conclusion, our study showed that mild hyperglycemia is very common in patients with tuberculosis but that, in most of them, the glucose status is normalized with tuberculosis treatment. For the setting of sub-Saharan Africa, the clinical implications of this study, which is the first to describe the longitudinal evolution of the 3 recommended DM tests during tuberculosis treatment, are 2-fold. First, a new diagnosis of DM in a patient with tuberculosis must be confirmed after tuberculosis treatment. Larger studies using point-of-care DM tests that are insensitive to infection-induced hyperglycemia need to assess the role of DM as a risk factor for active tuberculosis in settings with a low DM prevalence and high tuberculosis burden, such as Sub-Saharan Africa. Second, FCG testing at enrollment best captures patients with tuberculosis at risk of treatment failure and death. This may give the opportunity to manage hyperglycemia, but the effect of such interventions on tuberculosis outcome requires confirmation through randomized controlled trials including both HIV-infected and HIV-negative patients.

Supplementary Data

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Acknowledgments. We thank the patients, for their participation and making this study possible; all of the clinical officers, nurses, and recruiters of Ifakara Health Institute and Mwananyamala Hospital, for working hard on this study; the National TB and Leprosy Control Programme team of Mwananyamala Hospital, Sinza Hospital, Magomeni Health Care Center, and Tandale Dispensary, for their active participation in the study; the medical officers in charge of Mwananyamala Hospital, Sinza Hospital, Magomeni Health Care Center, and Tandale Dispensary, for their support throughout the study; Dr Izhak Kimaro, for reading the radiographs of all patients with tuberculosis; Dr Clothilde Rambaud, for her pertinent advice during the study; Aurelio Di Pasquale, software project coordinator at SwissTPH, for providing us technical support for tablet programming; Dr Jean-Pierre Zellweger and Prof Thierry Rochat, for their critical review of the manuscript; and Prof T. Calandra, head of the Infectious Diseases Service at Lausanne University Hospital, and Prof M. Tanner, head of the SwissTPH, for their support and positive input on this research.

N. B.-B. and N. P.-H. contributed to study conception, study design, study performance, study management, data analysis, data interpretation, and manuscript writing. K. R. contributed to study conception, study design, study performance, study management, data interpretation, and critical review of the manuscript. C. D. and S. G. contributed to study conception, study design, study performance, data interpretation, and critical review of the manuscript. C. S. and P. B. contributed to data analysis, data interpretation, and critical review of the manuscript. M. M., L. T. M., K. L. R., and A. V. E. contributed to the acquisition of the data, interpretation of the data, and critical review of the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. N. B.-B. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial support. This work was supported by the Swiss National Science Foundation (grants PBLAP3-139981 and PBLAP3-145866), MSD Merck Sharp & Dohme, SICPA Foundation, and Academic Society of Lausanne.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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