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Tuberculosis and diabetes in Nigerian patients with and without HIV

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ABSTRACT

Background: Type 2 diabetes mellitus (DM) and HIV increase the risk of tuberculosis (TB). The frequency of DM among patients with TB with and without HIV is poorly documented in many low- and middle-income countries.

Methods: This was a cross-sectional hospital-based study performed in Abuja, Nigeria. Adults with presumptive TB were screened consecutively. Sputum culture was used for TB screening and blood was used for HIV screening, as well as fasting plasma glucose (FPG) and glycated haemoglobin (HbA1c) assessment for the diagnosis of DM. HbA1c was measured using the D-10 Haemoglobin Testing System and a point-of-care test (A1C Now+ system) for comparison. Patients were classified as having DM or pre-diabetes using the D-10 reference test.

Results: Four hundred and ten individuals had TB culture, FPG, and HbA1c results. Participants had a mean (± standard deviation) age of 37.8 ± 12.6 years and 217 (54.8%) were male. One hundred and thirteen (27.6%) patients were culture-positive, 62 (15.1%) had DM, and 46 (11.2%) had pre-diabetes. One hundred and eighty-four (53.3%) participants were HIV-positive and 95 (51.6%) were on antiretroviral therapy (ART). Patients with pre-diabetes and DM were more likely to have TB (odds ratio (OR) 1.94, 95% confidence interval (CI) 0.01–3.74, and OR 2.39, 95% CI 1.35–4.24, respectively). After adjustment for HIV, age, and sex, only DM was statistically associated with TB (adjusted OR (AOR) 3.10, 95% CI 1.62–5.94). HIV-negative patients with DM had a higher risk of TB (AOR 4.32, 95% CI 1.57–11.92) than HIV-positive patients with DM (AOR 3.31, 95% CI 1.29–8.54), but the difference was not statistically significant. A1C Now+ HbA1c measurements correlated poorly with the D-10 HbA1c reference test.

Conclusion: A high proportion of patients in Abuja have markers of DM and pre-diabetes at the time of TB diagnosis.

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Introduction

Tuberculosis (TB) remains an enormous burden and a challenge to public health in low- and middle-income countries (LMIC) (Uplekar et al., 2015). Nigeria, the most populous country in Africa, has one of the highest burdens of TB in the world, with a prevalence of 524 TB cases per 100 000 population (Anon., 2012). TB as a public health problem resurfaced with the emergence of HIV in the 1980s (Ronacher et al., 2015), currently affecting 3.34% of Nigerian adults. Nigeria has the second largest burden of HIV worldwide (Bashorun et al., 2014), and an estimated 27% of TB cases are co-infected with HIV, although this proportion is not evenly spread across the country (Umeh et al., 2007; Lawson et al., 2009; Iliyasu and Babashani, 2009).

Lifestyle changes have also led to an emerging epidemic of type 2 diabetes mellitus (DM), affecting an estimated 366 million people worldwide, with 80% living in LMIC (Aguiree et al., 2013). The intensive urbanization of Nigeria over recent decades has witnessed a large increase in DM from <1% of adults in the 1970s to 5% in 2013 (Aguiree et al., 2013).

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TB, HIV, and DM comorbidities often have synergistic and detrimental effects on health. DM is present in an estimated 15% of TB cases (Stevenson et al., 2007a), and TB rates are higher among those with the more severe DM phenotypes (Swai et al., 1990). Diabetic patients with TB have a higher mycobacterial burden than non-diabetics (Dave et al., 2013), require a longer time to culture conversion (Dooley et al., 2009), have a four times higher risk of treatment failure (Morsy et al., 2003), and have an over six times higher risk of death (Dooley et al., 2009).

HIV and DM increase the risk of TB, although the frequency of DM among patients with TB with and without HIV in LMIC is poorly documented and often counterintuitive. For example, Tanzanian patients with DM were found to have increased odds of TB among HIV-negative but not among HIV-positive patients (Faurholt-Jepsen et al., 2011), and DM was found to increase the risk of death among HIV-negative but not among HIV-positive patients with TB (Faurholt-Jepsen et al., 2013). Further studies are needed to examine these associations.

The diagnosis of DM in LMIC is often limited by the difficulty in measuring fasting plasma glucose (FPG), and the World Health Organization (WHO) recommends the use of glycated haemoglobin (HbA1c) as a more practical and reliable indicator of DM. HbA1c measures the percentage of glucose attached to haemoglobin (or glycosylated) and reflects the average blood sugar levels for the preceding 8–12 weeks. Measurements of HbA1c can be performed at any time of the day, and easy-to-use, portable kits have become available (Jiang et al., 2014). One of these, the A1C Now+ system provides a fast and easy method of obtaining HbA1c, providing immediate results for patient management. However, there have been very few field evaluations to assess whether its performance is similar to HbA1c measurements conducted using validated platforms at reference laboratories in LMIC.

The association between TB and DM and the relevance of HIV among patients attending district hospitals in Abuja, Nigeria is described here. As a sub-study, the agreement of a point-of-care test (A1C Now+) with the HbA1c reference test (D-10 Haemoglobin Testing System; Bio-Rad 2020) was also assessed.

Methods

This was a cross-sectional hospital-based study performed in Wuse and Nyanya district hospitals in Abuja Federal Capital Territory, Nigeria. Consecutive adults >18 years old with a cough of ≥2 weeks duration (presumptive TB), presenting spontaneously to the TB diagnostic and treatment clinics of the hospitals or referred from the general outpatient and HIV clinics for TB screening, were invited to participate. After obtaining written informed consent, patients were interviewed using a structured questionnaire to obtain demographic data and medical history. Individuals were invited to participate if they were adults and were not receiving anti-TB treatment, or had not received treatment in the preceding 2 months. Three sputum specimens were collected using routine procedures over a 2-day period. Venous blood samples were collected for diabetes testing at the study clinics the morning of the second day, after overnight fasting. Blood samples were distributed into bottles containing fluoride oxalate and ethylenediaminetetraacetic acid (EDTA), and transported in a cold chain to Zankli Tuberculosis Research Laboratory for testing within a maximum of 5–6 h of collection.

Sputum specimens were tested using light emission diode fluorescence microscopes (LED-FM), Gene Xpert, and culture on BACTEC MGIT 960. Patients were classified as having TB if the culture was positive. HIV counselling and testing were offered to all patients in the context of routine services and national guidelines. Patients were tested while in the clinic using two HIV rapid

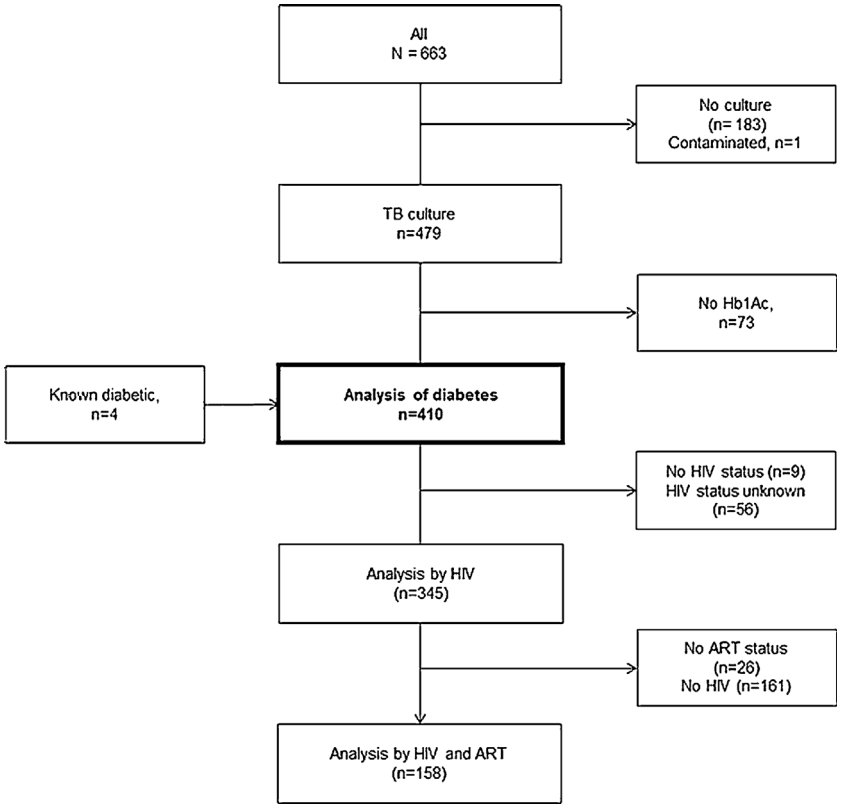

Figure 1. Study flow chart showing the inclusion and exclusion criteria.

diagnostic tests (RDTs) and, if positive, were asked if they were receiving antiretroviral therapy (ART). ART was offered to HIV patients following the national guidelines.

FPG was measured using a Hemolyzer and HbA1c was analysed using the D-10 Haemoglobin Testing System (Bio-Rad 2020) at the routine laboratory of Zankli Medical Centre; FPG tests were run in parallel with standard quality controls with every batch of the reagent kit. The A1C Now+ system was also used while patients were still in the clinic to assess the correlation of results with those of the D-10 Haemoglobin Testing System. The D-10 system measurements of HbA1c were considered the reference standard for the comparison of tests and was used to indicate the presence of DM in the risk factor analyses. Pre-diabetes was defined as HbA1c between 6.0% and 6.4% and DM as HbA1c >6.4% or self-reported DM at the time of the interview.

Statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). The associations of TB with HIV and DM were investigated using univariate and multivariate logistic regression analysis. A multivariate model was adjusted for all the variables significantly associated with TB in the univariate tests. The analyses of the association of TB and DM/pre-diabetes were repeated separately according to HIV status and adjusted. p-Values of <0.05 were considered statistically significant. The agreement of the Bio-Rad 2020 and the point-of-care test A1C Now+ system was assessed using the Spearman correlation test for continuous values of HbA1c and kappa statistics for categorical data.

Ethical approval was obtained from the Federal Capital Territory Research Ethics Committee. All participants were asked to provide written informed consent to participate.

Results

A total of 663 individuals were invited to participate. Of these, 479 had valid TB culture results and 410 had valid information to ascertain DM status (406 had HbA1c measurements and four had a known DM diagnosis) and were selected for analysis (Figure 1). The mean (± standard deviation) age of the participants was 37.8 ± 12.6 years and 227 (55.4%) were male.

One hundred and thirteen (27.6%) patients were culture-positive for TB and 297 (72.4%) were culture-negative. Sixty-two (15.1%) had DM, 46 (11.2%) had pre-diabetes, and 302 (73.7%) were euglycaemic. Six (9.7%) of the DM patients were aware and 52 (90.3%) were unaware of their DM (information was missing for four). Among the 410 participants, HIV status was known in 345 (84.1%) and unknown in 65 (15.9%) participants. The latter included patients who did not want to provide information from previous tests and those who refused testing.

One hundred and eighty-four (53.3%) were HIV-positive and 161 (46.7%) were HIV-negative. Among the HIV-positive patients, 95 (51.6%) were receiving ART at the time of data collection, as described in Table 1. One hundred and nineteen (29%) participants had high LDL concentrations (low density lipoprotein), 207 (50.5%) had low HDL concentrations (high density lipoprotein), and 27 (6.6%) had high triglycerides.

Factors associated with a positive Mycobacterium culture in the univariate analysis were the presence of pre-diabetes or DM, not having HIV, being male, and being aged between 18 and 28 years (Table 2). Patients with and without TB had similar lipid profiles, except for HDL, which was more likely to be low among patients with TB (67% and 49%, respectively; odds ratio (OR) 2.1, 95% confidence interval (CI) 1.3–3.4). Patients with pre-diabetes or DM were more likely to be culture-positive than non-diabetics (OR 1.94, 95% CI 0.01–3.74, and OR 2.39, 95% CI 1.35–4.24, respectively). HIV-positive patients were less likely to have positive culture than HIV-negative patients (OR 0.44, 95% CI 0.27–0.70), and receiving ART did not affect the likelihood of a positive culture. After adjustment for HIV status, age, and sex, only the association between TB and DM remained statistically significant (adjusted OR 3.10, 95% CI 1.62–5.94). A higher proportion of HIV-positive patients than HIV-negative patients had DM (30 (18.6%) vs. 26 (14.1%)) or pre-diabetes (19 (11.8%) vs. 18 (9.8%)), but these differences were not statistically significant ($p > 0.05$). Similarly, there was no statistically significant association between the use of ART and DM ($p > 0.05$).

After adjusting for age and sex, the association between HIV and DM was not statistically significant. Whether HbA1c values differed between patients with and without confirmed TB and HIV status was analysed further. Patients with TB had higher Hb1Ac than patients without TB (5.8% and 5.4%, respectively; $p < 0.001$). The difference was similar for patients with and without HIV co-infection ($p = 0.26$), as shown in Table 3. The agreement between the A1C Now+ system and the reference test showed a moderate correlation ($r = 0.34$, $p < 0.01$), with a kappa value of 12.6%, corresponding to poor agreement. The test had a sensitivity of 50% (95% CI 25.5–74.5) and specificity of 74.5% (95% CI 65.2–82.1%) when using a cut-off of 6.5%.

Table 1
Characteristics of the study participants.

		Participants ($N = 410$)
Age, years, mean ± SD		37.8 ± 12.6
Male to female ratio (% male)		227:183 (55.4)
TB culture	Positive	113 (27.6)
	Negative	297 (72.4)
TB treatment[a]	None	352 (87.3)
	Previously treated	51 (12.7)
TB symptoms	Weight loss	281 (69.2)
	Weakness	268 (66.0)
	Fever	259 (63.8)
	Chest pain	242 (59.6)
	Night sweats	201 (49.5)
	Loss of appetite	200 (49.3)
HIV	Positive	184 (45.9)
	Negative	161 (40.1)
	Unknown	65 (15.9)
ART	On ART	95 (27.5)
	No ART	63 (18.3)
	Unknown	26 (7.5)
	No HIV	161 (46.7)
HbA1c (%)	>6.4	51 (12.6)
	6.0–6.4	48 (11.8)
	<6.0	307 (75.6)
Known diabetes[b]		17 (4.2)
HbA1c >6.4 or known diabetes[b]		62 (15.1)
FPG mg/dl	≥126	23 (5.6)
	100–125	32 (7.8)
	≤99	344 (83.9)
	Unknown	11 (2.7)
LDL mg/dl	≥100	119 (29.0)
	<100	263 (64.1)
	Unknown	28 (6.8)
HDL mg/dl[c]	Low	207 (50.5)
	Normal	175 (42.7)
		28 (6.8)
Total cholesterol mg/dl	≥200	48 (11.7)
	<200	334 (81.5.4)
	Unknown	28 (6.8)
Triglycerides mg/dl	≥200	27 (6.6)
	150–199	35 (8.5)
	<150	319 (77.8)

ART, antiretroviral therapy; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; HIV, human immunodeficiency virus; LDL, low density lipoprotein; SD, standard deviation; TB, tuberculosis.
[a] Information missing for seven patients.
[b] Diabetes: HbA1c >6.4 or self-reported diabetes. Pre-diabetes: HbA1c 6.0–6.4.
[c] HDL: high is ≥40 mg/dl for men and ≥50 mg/dl for women; normal is <40 mg/dl for men and <50 mg/dl for women.

Table 2
Factors associated with tuberculosis on univariate and multivariate analysis.

		Confirmed TB, *n* (%)		OR (95% CI)	AOR (95% CI)[a]	*p*-Value
		Yes	No			
Diabetes status	Diabetes[b]	26 (23.0)	36 (12.1)	2.39 (1.35–4.24)	3.10 (1.62–5.94)	0.001
	Pre-diabetes	17 (15.0)	29 (9.8)	1.94 (0.01–3.74)	1.81 (0.82–3.97)	0.14
	No diabetes	70 (61.9)	232 (78.1)	1	1	
HIV	Positive	37 (38.5)	147 (59.0)	0.44 (0.27–0.70)	0.55 (0.32–0.95)	0.03
	Negative	59 (61.5)	102 (41.0)	1	1	
ART	On ART	20 (57.1)	75 (61.0)	0.85 (0.40– 1.83)	NA	
	Not on ART	15 (42.9)	48 (39.0)	1		
Sex	Male	74 (65.5)	153 (51.5)	1.79 (1.14–2.80)	1.80 (1.05–3.10)	0.03
	Female	39 (34.5)	144 (48.4)	1	Ref.	
Age quartiles	1st	37 (33.9)	57 (19.6)	2.37 (1.28–4.41)	2.68 (1.27–5.63)	0.01
	2nd	32 (29.4)	80 (27.6)	1.46 (0.79–2.71)	1.79 (0.86–3.71)	0.12
	3rd	17 (15.6)	69 (23.8)	0.90 (0.45–1.82)	1.01 (0.46–2.22)	0.98
	4th	23 (21.1)	84 (29.0)		1	

AOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; NA, Not available; OR, odds ratio; TB, tuberculosis.
[a] Adjusted for HIV status, age and sex.
[b] Diabetes: HbA1c >6.4 or self-reported diabetes. Pre-diabetes: HbA1c 6.0–6.4.

Table 3
Median HbA1c concentrations of patients with and without TB by HIV status.

HIV	TB	Number	Mean (SD) HbA1c
Negative	Positive	57	6.12 (1.8)
	Negative	101	5.53 (1.07)
Positive	Positive	37	5.88 (0.85)
	Negative	146	5.48 (0.68)
Main effect and interaction (ANOVA)	*p*-Value		
HIV	0.26		
TB culture result	0.001		
HIV × TB culture result	0.47		

ANOVA, analysis of variance; HbA1c, glycated haemoglobin; SD, standard deviation; TB, tuberculosis.

Discussion

Patients in Abuja, Nigeria with TB often have markers of DM and pre-diabetes. Individuals with DM are known to have a higher risk of developing TB after infection and to experience higher mycobacterial loads, with those with insulin-dependent DM having a higher risk than non-insulin-dependent DM patients. DM also increases the time required for culture conversion, the risk of treatment failure, and the risk of death (Dooley et al., 2009; Dooley and Chaisson, 2009). It may thus well be that a significant proportion of patients diagnosed in this study had pre-existing DM.

On the other hand, it is also well established that infection leads to inflammation, which in turn can lead to hyperglycaemia and increased HbA1c. Long-term infection with TB is also prone to cause chronic inflammation, and it is possible that a proportion of the patients had a transient hyperglycaemic state, which is reversible with treatment (Basoglu et al., 1999). Longitudinal studies to follow these patients to the end of treatment are thus needed to ascertain the proportion of patients who continue to have DM once they have recovered from TB.

The risk of TB in individuals with DM varies geographically. The highest risk has been reported in Latin America: in Mexico, patients with DM have a six times higher risk of developing TB than euglycaemic patients (risk ratio (RR) 6.8) (Ponce-De-Leon et al., 2004). This is followed by the Pacific Islands (Kiribati, OR 4.7) (Viney et al., 2015), Asia (OR and RR 2.5–3.5) (Shetty et al., 2006; Kim et al., 1995; Alisjahbana et al., 2006), and European populations (UK OR 3.8, Russia OR 2.66) (Jick et al., 2006; Coker et al., 2006), with the lowest risk reported from North America and Australia (RR/OR 1.5) (Pablos-Méndez et al., 1997; Perez et al., 2006; Dyck et al., 2007), although American Hispanics with DM have a higher risk than white and black American populations (Pablos-Méndez et al., 1997; Perez et al., 2006). Studies from Africa are sparse. A study performed in Tanzania and a former Nigerian study reported that patients with DM had RRs of 2 and 2.2 compared to euglycaemic patients (Faurholt-Jepsen et al., 2011; Ogbera et al., 2014), while in Guinea-Bissau there was no increased association (Haraldsdottir et al., 2015).

The risk of TB in DM patients also varies within populations. Generally, young adult males are reported to have a higher risk than females and older individuals (Stevenson et al., 2007b; Nhamoyebonde and Leslie, 2014). In agreement with these reports, DM patients with TB were more likely to be young and male, and diabetic men had a higher risk of TB than diabetic women, in the present study.

Patients with HIV were less likely to have a positive TB culture than HIV-negative individuals. This is an apparently paradoxical finding, as HIV infection is known to dramatically increase the risk of TB (Pawlowski et al., 2012). Although HIV patients are less likely to be able to produce infiltration and are more likely to have miliary TB and to have less energy to cough, this finding is likely due to the study design. HIV-positive individuals with respiratory symptoms are more likely to be referred early for TB screening and this early and repeated screening would likely identify more patients with TB. As these patients would have received treatment, they would have been excluded from this study, resulting in a cohort effect and selection bias, as the patients enrolled would be less likely to have TB than patients without HIV attending the clinics for the first time. Although, patients with HIV who initiate ART have been shown to have a higher risk of developing DM (Isa et al., 2016), the lack of association of DM and TB with HIV may only become evident after a longer exposure to ART, and longer studies are needed.

The point-of-care A1c test had poor agreement with the reference test and its unreliability prevented its further use in the clinic. Patients with a timely diagnosis of DM could benefit from a more holistic approach to the treatment of their multiple conditions. However, tests with poor performance would misclassify patients and further evaluations are needed to identify tests with adequate performance. The measurement of HbA1c in HIV also needs further validation, as patients with untreated HIV have chronic inflammation and ART containing protease inhibitors, nucleoside reverse transcriptase inhibitors, and non-nucleoside reverse transcriptase inhibitors can cause reversible hyperglycaemia. Furthermore, some HbA1c methods are unreliable in the presence of haemoglobinopathies.

Finally, although a large proportion of patients were aware of their HIV status, almost 90% of diabetics were unaware of their hyperglycaemic status and were not receiving DM medications. This has significance for the patients, as good glycaemic control is likely to result in a better response to TB treatment. Furthermore, from a public health perspective, this highlights the need to test for the glycaemic status in all cases of TB.

DM is a significant and increasing risk for TB in LMIC, which could increase the complexity of patient clinical management and worsen the treatment outcome. Nigerian TB and general services need to be aware of the need to screen for DM for its early identification and management.

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Conflict of interest

The authors have no conflict of interest to declare.

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