Diabetes mellitus among pulmonary tuberculosis patients from four TB-endemic countries: the TANDEM study

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Summary:

Prevalence and characteristics of DM in TB patients vary considerably between countries, underlining the need for country and setting specific information. However, in all four countries, the majority of DM among TB patients was previously diagnosed but poorly controlled. Amongst individuals with TB-DM DM complications were highly prevalent as were comorbidities and CVD risk was raised.

Abstract:

Background. Diabetes mellitus (DM) increases the risk of active tuberculosis (TB) and worsens TB outcomes, putting TB control in jeopardy 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 haemoglobin (HbA1c) or fasting plasma glucose (FPG) in TB patients. Detailed and standardized socio-demographic, anthropometric and clinical measurements were made. Characteristics of TB patients with or without DM were compared using multi-level mixed effect regression models with robust standard errors.

Results. Of 2185 TB patients (median 36.6 years, 61.2% male, 3.8% HIV-infected), 12.5% (267/2128) had DM, 1/3 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 with higher Body Mass Index (BMI) (p-value<0.05). Compared to those with newly diagnosed DM, TB patients previously known to have DM had higher BMI and HbA1c, less severe TB, and more frequent comorbidities, DM complications and hypertension (p-value<0.05).

Conclusions: We show that DM prevalence and clinical characteristics of TB-DM vary considerably between countries. Diabetes is mostly known but untreated, hyperglycemia is often severe, and many patients with combined TB and DM have significant cardiovascular disease risk and severe TB, underlining the need to improve strategies for better clinical management of combined TB and DM.

Keywords: Tuberculosis, Diabetes, syndemic, Prevalence, HbA1c

Introduction

Prevalence of type 2 Diabetes Mellitus (DM) has been increasing in low and middle-income countries (LMICs), in areas that also have high 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]. Global TB incidence rates are currently 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 upon mechanisms underlying these effects[5], there are limited global data on those with combined TB and DM. Neither the Global Tuberculosis Report (2018) [4] or related World Health Organization (WHO) documents report TB-DM numbers worldwide (in contrast to the national level data on TB-HIV), which makes assessment of the burden of this co-morbidity challenging. Much of the available TB-DM data is 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 have been conducted on cohorts of TB patients using routine or administrative data (e.g. 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 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 an EU-funded consortium[7], TB patients from four epidemiologically distinct settings (Indonesia, Peru, Romania and South Africa) were investigated for co-morbid

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 presenting with previously diagnosed DM, newly diagnosed DM, and intermediate hyperglycaemia, along with an evaluation of possible risk factors, amongst newly diagnosed TB patients in each setting.

Material and methods

Study design and study population

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

Study measurements and definitions

We defined individuals with 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 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 and if >110 mg/dL but <200 mg/dL (the recognised 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 tests (HbA1c, RPG or FPG) above the diagnostic threshold, see Appendix 1.

'Previously diagnosed DM' was defined as any patient who self-reported a doctor 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 ~~principally~~ based on repeated laboratory testing (see Appendix 1), mostly HbA1c. Intermediate hyperglycaemia (or 'pre-diabetes'; raised blood glucose or HbA1c above normal, but below the threshold for identifying DM) was defined as patients with a single measurement of either FBG in the pre-DM range (6.1–7.0 mmol/l) or HbA1c in the intermediate range (6.0-6.4%) [12](See Appendix 1). Evaluation of the performance of these laboratory tests for diagnosis of DM in TB patients in a TANDEM cohort has recently been published[9].

Underweight was defined as BMI <18 kg/m^2; normal weight BMI of 18 kg/m^2 – 24.9 kg/m^2; overweight BMI 25kg/m^2-29.9kg/m^2; and obesity ≥30 kg/m^2. In Indonesia accepted BMI categories for South Asian populations were used; overweight was defined as BMI 23kg/m^2-27.49 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 socio-economic status index classifying study populations from each country in to quintiles based on asset ownership by patients that included non-sellable (possession of a bank account, type of sanitation facility, household water source) and sellable assets (e.g. stove, refrigerator, washing machine, television). [15].

Family history of DM was defined by self-report of having either 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 categorised as follows; pre-hypertension systolic or diastolic 120/80-129/80 mmHg, Stage I systolic or diastolic 130/80-139/89 mmHg, Stage II systolic or diastolic over 140/90 mmHg[16]. Ten year risk of a fatal or major cardiovascular event (myocardial infarction or stroke, using WHO/ISH Cardiovascular Risk Prediction Charts)[17] and the Charlson comorbidity index was calculated[18]. To assess TB severity, we used TB score, which is a simple clinical score used for clinical monitoring of TB, and haemoptysis[19].

Data analysis

We used REDCap 6.9.1 [20] for data collection and management and STATA 15.0 (StataCorp, Texas, USA) for statistical analysis. Categorical variables were presented with their frequencies and continuous variables summarized using mean and standard deviation (SD) or where appropriate median and interquartile ranges (IQR). Between country comparisons were done using the non-parametric Kruskal-Wallis and Chi-square tests were performed for categorical variables and for continuous variables, t-test or ANOVA. The crude prevalence of DM was calculated for each country overall and stratified by age group. A directly standardised 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 $P<0.15$ in this univariate analysis were then included in a multivariate model. A multi-level 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 analyses, alternative models were explored where country was entered as a fixed effect and interaction terms included between age groups and country.

Ethics

This study was approved by the Institutional Review Board (IRB) at the London School of Hygiene and Tropical Medicine as the TANDEM Coordinating Centre (Ethics Reference Number 6449), and approved by the local IRB at each site. All participants were provided with an information sheet explaining 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, either positive on 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 with 2.2% of patients obese, highest 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; a crude prevalence of 12.5% (95% CI 11.1% to 14.0%). Age standardised 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=0.009) and culture positive (81.4% vs 91.5%, p<0.001, table 3).

TB patients with DM were older (median age 51.0 vs. 33.0 years, p<0.001), had higher BMI (21.9 vs 19.6 kg/m2, p<0.001) and lower waist-hip ratios (Male 0.86 vs 0.89, p<0.001; Female 0.83 vs 0.87 <0.001), lower socioeconomic status (wald test p<0.001), were more likely to have a family history of DM (aOR 3.7 (1.8 - 7.3), p<0.001) and less likely to have been previously treated for TB (16.9% vs 25.7%, p=0.02) when compared to those without DM (tables 2 and 3). Haemoptysis was slightly more common in TB-DM patients (30.0% vs 26.6%, p =0.1), and 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 CVD event occurring within 10 years compared to those with TB (24.5% vs 5.5%, table 3). In female patients, anaemia was consistently less frequent among those with DM (42.1% vs 52.1% overall, p=0.001), but there was little difference in anaemia prevalence amongst men except in Indonesia (56.1% TB only vs 29.5% TB-DM, p<0.001).

TB patients with newly and previously diagnosed DM were of similar age (52.1 vs 51.0; 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 with 65.6% of known DM patients, p=<0.001) suggesting greater TB disease severity, lower BMI (20.0 vs 22.5, p=0.02) and lower HbA1c (8.0% vs 10.9%, p=0.05). They were also less likely to have a family history of DM (19.1% vs 43.2%, p<0.001), had lower Charlson co-morbidity index (CMI) scores (2.4% vs 47.0% had a score ≥2, p<0.001) and fewer DM complications including hypertension and macro or microvascular disease (2.4% vs 43.2%, p<0.001) (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%) reporting at least one DM-attributable hospital admission in the preceding 5 years.

TB patients with intermediate hyperglycaemia (or "pre-diabetes") were slightly older compared to those with TB only (median age of 39 vs 32), 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 multi-country cohort patients with newly diagnosed TB had a high prevalence of both newly diagnosed (3.8%) and previously known (8.4%) DM. Diabetes prevalence amongst TB patients varied between countries, as did the proportion of known versus newly diagnosed DM. DM was very uncommon in younger patients, with the risk of having DM increasing substantially for those 35 years and over, and between 20-35% of TB patients aged over 50 years old having new or previously diagnosed DM. Most patients had been diagnosed with DM relatively recently, many within the past year. Amongst these individuals TB may have been their first complication of DM, and amongst those newly diagnosed with DM their incident TB disease revealed their underlying DM.

TB patients with known DM were characterised by poor glycaemic control despite their knowledge of their DM status (median HbA1c 10.9% with outlying values as high as 17%). Better glycaemic 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 glycaemic control reduces TB risk is lacking, the increased risk of TB amongst individuals with DM [6] and the association with poorer TB treatment outcomes[3], suggest that improved glycaemic control should be amongst 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 re-engage previously neglected patients back into DM care. Incident TB also offers an opportunity for new diagnosis and management of previously unrecognised DM, potentially reducing downstream DM-related morbidity.

Our findings are consistent with 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], in line with some [27-29] but not all studies [30]. Whilst obesity is well 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. Besides obesity and increasing age, family history of DM was also strongly associated with having DM in this population.

At 21%, the prevalence of intermediate hyperglycaemia ("pre-diabetes") identified in TB patients was higher than expected, although a rising prevalence of intermediate hyperglycaemia has been reported in LMICs [31]. This figure would have even been 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 hyperglycaemia may occur in hypermetabolic inflammatory

conditions and infections, including TB[32] (see Supplementary Figure 1)[9]. The definition of intermediate hyperglycaemia itself is under scrutiny as DM only develops within 10 years in <50% of those identified with pre-DM based on a single FBG or HbA1c test [33], and uncertainty about the cut-point when using HbA1c. Our data suggest that TB patients with intermediate hyperglycaemia were clinically more like those without diabetes than people with diabetes. Over- diagnosis and over-treatment of intermediate hyperglycaemia [34] may increase potentially unnecessary risks (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 glycaemic control, suggesting that some of those newly diagnosed were experiencing "transient hyperglycaemia" 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 figures 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 which 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 modelling.

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 hyperglycaemia, overestimating DM prevalence [37] although available repeated HbA1c or FBG tests at the end of TB treatment remained abnormal in the large majority (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, 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 regarding DM screening and management among TB patients published by the UNION (International Union Against Tuberculosis and Lung Diseases) and World Diabetes Foundation[38]. These 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 & treatment) are urgently needed. Further longitudinal studies exploring the role and importance of transient hyperglycaemia in TB patients and its association with future DM are also essential, as are studies examining 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 health care professionals to deliver integrated management of TB-DM in primary care in LMIC. Such integrated management could increase uptake of appropriate secondary preventive therapies for patients with TB-DM 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 a paucity of on-going studies addressing these key clinical issues[39, 40].

Author contributions

HMD, RvC, PCH, BA, RR, JAC, MI, GW, and DM obtained funding for the project and designed the study. All authors contributed to data collection and quality assurance. FP and JAC developed the statistical analysis plan and performed analyses. CUG drafted the manuscript. All authors critiqued the paper for important intellectual content, contributed to manuscript revision and approved the final version.

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TANDEM Consortium Member List is in the Supplementary Table 2.

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Disclosure

The authors report no conflicts of interest in this work.

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Table 1. Baseline characteristics

Characteristics		*Total (N=2185)*	*Indonesia (N=748)*	*Peru (N=600)*	*Romania (N=506)*	*South Africa (N=331)*
Median Age (IQR)		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)
≥35 years old (%)		1171 (53.6%)	416 (55.6%)	246 (41.0%)	341 (67.4%)	168 (50.8%)
Gender (%)	Male	1337 (61.2%)	426 (57.0%)	348 (58. 0%)	358 (70.8%)	205 (61.9%)
Median BMI 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)
(IQR)	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) [1]		49 (2.2%)	14 (1.9%)	22 (3.7%)	4 (0.8%)	9 (2.7%)
HIV status[2] (%)	Positive	82 (3.8%)	26 (3.5%)	23 (3.8%)	1 (0.2%)	32 (9.7%)
Sputum smear result	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	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 (%)	Yes	538 (24.6%)	185 (24.7%)	123 (20.5%)	97 (19.2%)	133 (40.2%)
Fever, ≥38℃ (%)	Yes	123 (5.6%)	38 (5.1%)	34 (5.7%)	32 (6.3%)	19 (5.7%)

Characteristics		*Total (N=2185)*	*Indonesia (N=748)*	*Peru (N=600)*	*Romania (N=506)*	*South Africa (N=331)*
Smoking (%)	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 (%)	(>=10kg)	163 (7.5%)	67 (9.0%)	30 (5.0%)	20 (4.0%)	46 (13.9%)
	(5-10kg)	610 (27.9%)	259 (34.6%)	135 (22.5%)	119 (23.5%)	97 (29.3%)
	(< 5kg)	917 (42.0%)	292 (39.0%)	248 (41.3%)	216 (42.7%)	161 (48.6%)
Haemoptysis	Any	532 (24.4%)	228 (30.5%)	195 (32.5%)	48 (9.5%)	61 (18.4%)
TB Score	0 to 2	691 (31.6%)	109 (14.6%)	274 (45.7%)	251 (49.6%)	57 (17.2%)
	3 to 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	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[3]	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%)

Characteristics		*Total (N=2185)*	*Indonesia (N=748)*	*Peru (N=600)*	*Romania (N=506)*	*South Africa (N=331)*
Education	≤ 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%)
Socio-Economic Status	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%)

Figures rounded to 1DP including percentages, percentage given of relevant whole sample with missing values only noted where >3%. Some figures may differ from other TANDEM analyses due to minor differences in inclusion criteria or case definitions. IQR=interquartile range

[1] obesity in Indonesian population defined as BMI>27.5 kg/m^2

[2] HIV status data was only available for 730 patients in Indonesia, 506 in Peru, 364 in Romania and 328 in South Africa.

[3] both self-report of prior DM diagnosis and either (a) use of DM medication or (b) study HbA1c of ≥6.5%

Table 2 - Factors associated with DM (new or previously diagnosed) among TB patients over 35 years of age

Factors		*Crude OR (95% CI)*	*P-value*	*Adjusted OR (95% CI)*	*P-value*
Age	35-44 years	1		1	
	45-54 years	3.2 (1.4 - 6.6)	0.006	2.9 (1.5 –5.9)	0.004
	55-64 years	3.8 (2.8 – 5.3)	<.0001	3.6 (2.8 – 4.5)	<0.001
	>65 years	3.5 (2.6 – 4.7)	<.0001	3.5 (2.3 – 5.3)	<0.001
Gender	Female	1		1	
	Male	0.7 (0.5 - 0.9)	0.003	0.9 (0.7 - 1.0)	0.1
Smear test result	Negative	1		1	
	Positive	0.8 (0.4-1.4)	0.4	0.9 (0.4-1.7)	0.7
	Missing	1.4 (0.9-2.2)	0.09	1.9 (1.2-3.0)	0.007
Previous TB episode	No	1		1	
	Yes	0.4 (0.3 - 0.6)	<.0001	0.5 (0.3 – 0.9)	0.02
BMI	Underweight	0.5 (0.4 - 0.7)	<0.001	0.4 (0.3 - 0.5)	<0.001
	Normal	1		1	
	Overweight	2.3 (1.4 – 3.8)	0.001	2.0 (1.3 -3.3)	0.003
	Obese	5.9 (198 - 17.0)	0.002	6.5 (1.7 – 24.7)	0.006
Family history of DM	No	1		1	
	Yes	3.6 (2.0 - 6.6)	<.0001	3.7 (1.8 - 7.3)	<0.001
Socio Economic Status	1 (richest)	1		1	
	2	1.1 (0.8-1.3)	0.5	1.0 (0.7 – 1.4)	0.9

Factors		*Crude OR (95% CI)*	*P-value*	*Adjusted OR (95% CI)*	*P-value*
	3	1.6 (1.3 - 2.1)	<0.001	1.2 (1.1- 1.3)	<0.001
	4	1.3 (0.8 – 2.1)	0.4	0.8 (0.6- 1.0)	0.08
	5 (poorest)	1.9 (1.0 – 3.7)	0.005[1]	1.43 (0.6 – 2.7)	0.5[1]
Country (Indonesia as reference)	Indonesia	1		[2]	
	Peru	0.5 (0.3-0.8)	0.002		
	Romania	0.5 (0.4-0.8)	<0.001		
	South Africa	0.4 (0.3-0.5)	<0.001		

[1] Wald test for statistical significance across categories of SES, p<0.001
[2] Country entered as a random effect into the adjusted model

Table 3. Comparison of TB patients with and without diabetes (TB-DM and TB respectively)

		Total			***Indonesia***			***Peru***			***Romania***			***South Africa***		
		TB-only (N=1918)	*TB-DM (N=267)*	*p*	*TB-only (N=620)*	*TB-DM (N=128)*	*p*	*TB-only (N=553)*	*TB-DM (N=47)*	*p*	*TB-only (N=440)*	*TB-DM (N=66)*	*P*	*TB-only (N=305)*	*TB-DM (N=26)*	*p*
Median age (IQR)		33.0 (27.0-47.0)	51.0 (45.0-59.0)	<0.001	34.10 (25.3-45.0)	50.5 (45.1-57.8)	<0.001	28.0 (22.0-39.5)	51.0 (47.0-58.0)	<0.001	41.0 (27.0-52.0)	56.0 (45.0-65.0)	<0.001	32.0 (27.0-47.0)	45.5 (40.5-52.0)	<0.001
≥35 years old (%)		48.1%	93.0%	<0.001	47.7%	93.8%	<0.001	36.7%	91.5%	<0.001	63.2%	95.4%	<0.001	47.8%	84.6%	<0.001
Gender (% male)		62.0%	55.4%	<0.001	58.9%	47.7%	0.02	58.6%	51.1%	0.3	69.8%	77.3%	0.2	63.3%	46.2%	0.08
Previous TB (%)		25.7%	16.9%	0.02	25.7%	20.3%	0.3	21.0%	14.9%	0.3	20.2%	12.1%	0.09	42.3%	15.4%	0.007
Smoking* (%)	Current smoker	42.7%	31.8%	0.002	46.5%	33.6%	0.002	11.9%	0%	0.001	47.5%	36.4%	0.03	83.6%	69.2%	0.001
	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 BMI (kg/m^2)		19.6 (17.6-22.1)	21.9 (19.0-25.7)	<0.001	17.9 (16.1-19.9)	21.1 (18.4-24.9)	<0.001	21.9 (19.9-24.1)	24.7 (21.8-28.4)	<0.001	20.2 (18.5-22.0)	21.4 (19.3-23.9)	0.02	18.4 (16.9-20.3)	22.3 (18.6-27.0)	0.004
Mean WHR	Men (SD)	0.86 (0.067)	0.89 (0.077)	<0.001	0.83 (0.068)	0.88 (0.063)	<0.0001	0.89 (0.060)	0.95 (0.067)	<0.0001	0.86 (0.063)	0.88 (0.088)	0.07	0.86 (0.059)	0.89 (0.072)	0.063
	Women (SD)	0.83 (0.073)	0.87 (0.077)	<0.001	0.81 (0.071)	0.86 (0.072)	<0.0001	0.87 (0.062)	0.91 (0.078)	0.007	0.79 (0.072)	0.829 (0.090)	0.06	0.83 (0.58)	0.89 (0.056)	0.001
Mean Laboratory HbA1c(%)		5.6 (5.3-5.9)	10.4 (7.9–12.3)		5.5 (5.3–5.8)	11.3 (9.1–12.9)	<0.001	5.5 (5.2–5.8)	10.6 (9.0–13.3)	<0.001	5.8 (5.5–6.1)	7.4 (6.7-10.8)[1]		5.8 (5.5–6.1)	10.1 (7.8–11.9)	<0.001
Antihypertensive medication use (%)		3.2%	16.9%	<0.001	4.0%	13.3%	<0.001	0.5%	8.5%	<0.001	4.1%	22.7%	<0.001	5.0%	34.6%	<0.001

		Total			*Indonesia*			*Peru*			*Romania*			*South Africa*		
		TB-only (N=1918)	*TB-DM (N=267)*	*p*	*TB-only (N=620)*	*TB-DM (N=128)*	*p*	*TB-only (N=553)*	*TB-DM (N=47)*	*p*	*TB-only (N=440)*	*TB-DM (N=66)*	*P*	*TB-only (N=305)*	*TB-DM (N=26)*	*p*
CVD Risk (% with 10 year risk estimated over 10%)		5.5%	24.5%	0.06	7.0%%	17.9&	0.1	2.8%	22.2%	0.02	5.24%	38%	<0.001	5.5%	8.3$	0.2
Smear positive (%)		72.7%	80.2%	0.009	83.1%	89.1%	0.09	64.2%	68.1%	0.6	67.5%	72.7%	0.4	67.2%	65.4%	1.0
Culture positive (%)		81.4%	91.5%	<0.001	79.5%	91.4%	0.002	82.1%	89.4%	0.2	76.1%	83.3%	0.1	83.7%	88.0%	1.0
Smear grade (max at baseline, %)																
Negative		26.8%	19.5%	0.0001	16.8%	10.9%	0.2	35.4%	32.0%	0.8	29.8%	24.2%	0.8	26.9%	26.9%	0.8
Scanty and 1+		31.3%	30.3%		29.4%	26.6%		31.7%	29.8%		33.0%	34.9%		32.1%	38.5%	
2+ and 3+		40.3%	48.7%		53.7%	62.5%		32.6%	38.3%		34.6%	37.9%		35.1%	26.9%	
Anaemia amongst men (%)[2]		46.9%	43.2%	0.8	56.1%	29.5	<0.001	30.3%	37.5%	0.5	42.4%	53.0%	0.2	66.8%	83.3%	0.2
Anaemia amongst women (%)[2]		52.1%	42.0%	0.001	61.9%	49.2	0.06	38.4%	26.1%	0.2	48.1%	40.0%	0.6	62.5%	35.7%	0.05
Haemoptysis (%)		23.6%	30.0%	0.1	28.9%	38.3	0.03	32.2%	36.2%	0.8	8.9%	13.6%	0.02	18.4%	19.2%	0.6
TB Score	0 to 2	31.8%	30.7%	0.03	13.8%	18.0%	P<0.001	45.3%	48.9%	0.5	50.7%	42.4%	0.3	16.1%	30.8%	0.09
	3 to 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%	

Figures rounded to 1 decimal place including percentages, percentage given of relevant whole sample with missing values only shown where >3%

[1] In Romania, where TB patients are treated as in-patients, repeated FBG measurements were available. 9 of 66 DM patients were classified using FBG rather than repeated HbA1c

[2] Anaemia defined as Hb<13 in men (n=1337) and <12 in women (n=846)

Table 4 – Comparative characteristics of TB patients with newly and previously diagnosed DM

		New DM (N=84)	***Known DM (N=183)***	***P-values***
Median Age in years (IQR)		52.0 (45.1-62.0)	51.0 (45.1-59.0)	0.9
Gender (%)	Male	52 (61.9%)	96 (52.5%)	0.2
Haemoptysis		28 (35.4%)	52 (32.1%)	0.2
TB Score	0 to 2	19 (22.3%)	63 (34.4%)	<0.001
	3 to 5	51 (60.7%)	109 (59.6%)	
	6+	14 (16.7%)	11 (6.0%)	
Median BMI kg/m^2 (IQR)		20.0 (17.9-24.5)	22.5 (19.7-25.9)	0.02
Median HbA1c% (IQR)	Lab	8.0 (6.8-11.7)	10.9 (9.1-12.6)	0.05
	Repeat	6.9 (6.5-12.4)	10.8 (8.9-12.4)	0.2
Duration of DM diagnosis N (%)	< 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 N		NA	37 (20.2%)	

		New DM (N=84)	*Known DM (N=183)*	*P-values*
(%)				
Treatment including Metformin N (%)		NA	112 (61.2%)	
Any hospital admission in the last 5 years due to DM N (%)		NA	36 (20.0%)	
Family history of DM N (%)		16 (19.1%)	79 (43.2%)	<0.001
CMI score ≥ 2 (%)		2 (2.4%)	86 (47.0%)	<0.001
Any Diabetes Complication (%)		2 (2.4%)	79 (43.2%)	<0.001
Hypertension	Pre-hypertension N (%)	13 (15.5%)	15 (8.2%)	<0.001 [1]
	Stage I N (%)	21 (25%)	48 (26.2%)	
	Stage II N (%)	18 (21.4%)	59 (32.2%)	
Antihypertensive medication N (%)		7 (8.3%)	38 (20.8%)	0.006
Renal function N (%)	CKD Stage 3-5 (eGFR < 60)	2 (2.4%)	10 (5.5%)	0.3

Figures rounded to 1DP including percentages, percentage given of relevant whole sample with missing values only shown where >3%

IQR=interquartile range,

CMI=Charlson co-morbidity index.
NA: Not Applicable
[1] Wald test for statistical significance across categories of hypertension, p<0.001