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Elevated blood glucose and unfavourable tuberculosis treatment outcomes in a low-income setting: findings from a prospective cohort study in Eswatini

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ABSTRACT

Introduction The increasing burden of diabetes mellitus in low- and middle-income countries negatively impacts tuberculosis control. To understand this dual burden in Eswatini, we describe the prevalence and predictors of elevated baseline blood glucose and unfavourable tuberculosis treatment outcomes.

Methods We conducted a prospective cohort study at 11 health facilities in Eswatini and included adults ≥18 years commencing tuberculosis treatment. Blood glucose measurements were taken at baseline, months 2 and 5, and patients' sociodemographic and clinical data were extracted. We computed the prevalence of elevated blood glucose and used logistic regression to determine the predictors of elevated baseline blood glucose and unfavourable treatment outcomes.

Results Of 369 consecutively enrolled patients, the mean age was 38.4 (SD 12.9) years, and 202 (54.7%) were males. The prevalence of elevated baseline blood glucose was 8.0% (95% CI: 5.5, 11.3); 8.9% in males (95% CI: 5.6, 13.9); highest at ≥55 years (13.6%; 95% CI: 6.2, 27.3) and in patients with reactive HIV at 9.5% (95% CI: 6.5, 13.7). A family history of diabetes mellitus (adjusted OR (AOR) 2.80; 95% CI: 1.08, 7.32) and a reactive HIV status (AOR 4.62; 95% CI: 1.06, 20.11) significantly predicted elevated baseline blood glucose. Three-quarters (n=276, 75.4%) had a favourable tuberculosis treatment outcome; more males (n=59, 66%) had an unfavourable treatment outcome (p=0.020), the most common unfavourable outcome being death (n=34, 9.2%). Hypertension (AOR 4.84; 95% CI: 1.48, 15.7), unemployment (AOR 2.01; 95% CI: 1.08, 3.71) and high school education (AOR 0.32; 95% CI: 0.16, 0.64) were associated with unfavourable treatment outcome.

Conclusion Our study shows the need to optimise care for patients receiving treatment for tuberculosis by integrating screening for and treatment of diabetes and hypertension, prioritising males, those aged ≥55 years and those with a reactive HIV status to limit unfavourable outcomes and death.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Diabetes mellitus increases the risk of tuberculosis (TB) disease with unfavourable outcomes in those receiving treatment for tuberculosis, directly limiting tuberculosis control efforts.

WHAT THIS STUDY ADDS

⇒ This study shows a higher prevalence of elevated baseline blood glucose in patients commencing TB treatment than in the general population. A family history of diabetes mellitus and reactive HIV status predicted elevated baseline blood glucose. Death was the most common unfavourable outcome, and hypertension and unemployment were predictors of unfavourable treatment outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The higher prevalence of elevated baseline blood glucose in patients with TB indicates the need to implement the framework for collaborative action on TB and comorbidities, as the WHO advocates. This can fast-track the timely diagnosis and treatment of diabetes and other non-communicable diseases among patients with TB to limit unfavourable treatment outcomes. Additional studies are required to identify and address the causes of death among patients with TB apart from HIV.

INTRODUCTION

The increasing burden of diabetes mellitus (DM) in low- and middle-income countries (LMICs) poses a significant risk for major global tuberculosis (TB) control efforts.[1 2] This is even as the COVID-19 pandemic halted and reversed gains from past TB efforts and impacted several TB indicators.[3–5] With an effective global COVID-19 response, healthcare services

and other economic activities have recovered. Still, different infrastructure and health system challenges that limit effective DM and other non-communicable disease (NCD) responses in most LMICs persist. This has enabled a concurrent increase in DM and other NCDs in LMICs that mostly saw infectious diseases, particularly HIV and TB.[2] Moreover, the WHO recognises DM as a significant risk for TB disease and unfavourable treatment outcomes in people receiving treatment for TB and drug-resistant TB (DRTB).[1 6–9]

To address this risk, the WHO has provided a framework to guide country programmes on the bidirectional screening and integrated treatment for TB in NCD programmes (including DM)[10] and the integration and prevention of NCDs in infectious disease programmes.[11] These guiding documents further advocate for political commitment, policy and financing to sustain collaborative actions for TB and comorbidities. They also encourage the institution of appropriate monitoring, evaluation and research measures to enable a better understanding of the burden of DM and TB comorbidity among people living with HIV. This would guide the integration of patient-centred services across programmes and diseases regardless of the population affected.

The global prevalence of DM in people receiving treatment for TB is estimated to be 15–16%.[12 13] This prevalence varies by region: 6.7–8% in Africa, 17% in Asia, 5.9–7.5% in Europe, 19–23.6% in North America, 7.7–11% in South America and 23.2% in Oceania.[12 13] Notwithstanding these estimates, the burden varies within countries as the prevalence of 44%, 16.7% and 12% has been reported in India, Tanzania and Fiji, respectively.[13] Male sex, older age, urban area residents, smoking, drinking alcohol, HIV coinfection and a family history of DM are identified as risk factors for DM in people receiving TB treatment.[13 14]

In Eswatini, where the HIV prevalence in adults aged ≥15 years is 24.8%, with an ageing cohort of people living with HIV, the annual TB incidence is 348/100 000 population.[15 16] Access to DM services, including screening, diagnostic testing and drugs, is limited and varies by site, with some patients paying out-of-pocket for care.[17–19] Available data to guide NCD programming are limited. The International Diabetes Federation in 2021 estimated a 3.6% prevalence of DM in adults in Eswatini.[20] A hospital-based outpatient study indicated the age-adjusted prevalence of pre-diabetes and type 2 DM was 3.8% and 3.9%, respectively.[21] There are no documented data on the prevalence of DM in people receiving treatment for TB in Eswatini. This study, therefore, aims to describe the epidemiology of elevated blood glucose (DM and pre-DM) in a cohort of patients from Eswatini who received TB treatment (the majority of whom are living with HIV), the effect of blood glucose on TB treatment outcome and predictors of elevated blood glucose and unfavourable TB treatment outcomes in the cohort.

METHODS

Study design, context and study setting

This study used a prospective cohort design. The cohort comprised newly diagnosed patients enrolled on TB care from 1 June to 30 September 2022. A description of the context and approach to TB services provision in Eswatini and the study setting has been published previously (online supplemental research protocol).[22] In brief, the Ministry of Health's (MOH) National Tuberculosis Control Program coordinates TB services in Eswatini through community and health facility-based case-finding, referral and linkage to treatment services. Different funding agencies, non-governmental organisations and civil society organisations also provide additional support for the provision of TB services. The study was conducted at 11 health facilities providing TB services in Eswatini (12 sites were selected, but 1 did not participate). Health facilities with the highest number of patients two-quarters before the study commenced were selected from the four regions of Eswatini to maximise the number of participants that can be enrolled.

Study participants, sample size and sampling

The study participants, sample size and sampling approach have been described.[22] In summary, the study participants were new patients aged ≥18 years enrolled on TB care and followed until the end of treatment for patients receiving treatment for drug-sensitive TB and the end of 6 months for patients receiving treatment for DRTB. From the study protocol,[22] using an estimated DM prevalence of 3.6%, an effect size of 0.05, a 5% error rate and a power of 90%, a sample size of 380–430 (mean 405) participants was expected. However, 352 participants were eventually enrolled in the study as one health facility did not participate. A consecutive sampling approach was used to include all consenting patients newly enrolled in TB care.

Data management

Data sources and approach to data collection

The data used for this study were from routine patient care. Data from patients at baseline, during follow-up visits (second and fifth months) and at the end of treatment were extracted from patient treatment cards and registers for analysis (online supplemental file 1). In addition, some sociodemographic variables that are not routinely collected at baseline (education status—none/primary/secondary/tertiary; marital status—single/married/widowed; smoking—yes/no; alcohol—yes/no; family history of DM—yes/no) were also collected.

One of the challenges observed at the health facilities that hindered access to blood glucose testing was the variable availability of glucometers and glucose test strips.[23] To mitigate this, we provided glucose meters (similar to those issued by MOH) and test strips to all the sites participating in the study during patient enrolment and follow-up. Healthcare workers at the TB clinic were

already trained to use the glucometer, so there was no need for further training.

At the commencement of the study, the different study sites were oriented on the research and provided with a logbook to document blood glucose and blood pressure measurements for patients at baseline, second and fifth months. The Eswatini Ministry of Health requires all patients to have random blood glucose tests at baseline, months 2 and 5, and at the end of treatment for screening purposes.

Study variables

Included study variables are broadly classified into baseline sociodemographic variables—region, age (<25, 25–34, 35–44, 45–54, 55+ years), sex, weight, height, educational status, marital status, occupation, smoking, drinking alcohol and a family history of DM; baseline clinical variables—blood glucose measurement, systolic blood pressure (SBP) and diastolic blood pressure (DBP) (categorised into normal, elevated, high blood pressure (HBP) stage 1, HBP stage 2) and hypertensive crises)[24]; HIV status, comorbidities, date of TB diagnosis, type of TB, baseline GeneXpert, baseline culture, TB lipoarabinomannan (TB-Lam); and follow-up variables—blood glucose measurement, SBP, DBP, sputum microscopy, GeneXpert, TB treatment outcome and date of TB treatment outcome.

Blood glucose measurements were done at baseline, second and fifth months using a glucometer. They were reclassified as normal (random <11.1 mmol/L or fasting ≤5.5 mmol/L) or elevated (pre-DM: fasting >5.5 to 6.9 mmol/L or DM: random ≥11.1 mmol/L or fasting ≥7.0 mmol/L) to enable a comparison of the proportion of patients with normal/elevated blood glucose between visits.[25] Blood pressure was measured using an electronic sphygmomanometer provided by MOH.

Statistical analysis

We described patient characteristics using mean with SD or median with IQR for continuous descriptors and proportions for categorical descriptors. This was disaggregated by the presence or absence of elevated blood glucose and presented in a table (table 1 and online supplemental table 1). The baseline prevalence of elevated blood glucose was defined as the proportion of all participants with elevated blood glucose. This prevalence was presented overall and by region, sex, age category and HIV status. A subanalysis for the prevalence of elevated baseline blood glucose was conducted for 33 patients with a fasting blood glucose measurement using a cut-off of >5.5–6.9 mmol/L for pre-DM and ≥7.0 mmol/L for blood glucose measurement in the diabetes range. Unpaired t-test and Kruskal-Wallis test compared blood glucose measurements and DBP and SBP changes between baseline, second- and fifth-month visits.

We used a logistic regression model to assess the predictors of elevated baseline blood glucose and adjusted for age, sex, HIV status and weight/body mass index (BMI) (selected a priori) in the final multivariate model. Variable selection was based on the forward and backward elimination process at p=0.2, verified with the adaptive Least Absolute Shrinkage and Selection Operator variable selection approach. A repeat analysis using blood glucose measurements at months 2 and 5 was impossible as very few participants had elevated measurements. Nonetheless, we conducted a sensitivity analysis employing a nested multilevel logistic regression model incorporating random effects at two levels to assess the influence of regional factors on the risk of elevated baseline blood glucose. This analysis accounted for the clustering of individuals within specific regions.

TB treatment outcome was the secondary outcome of this study. This was described and classified into two: favourable TB treatment outcome (defined as patients with either cured or completed outcome assigned at the end of treatment) or unfavourable TB treatment outcome (defined as those who died, lost to follow-up, stopped treatment, transferred out, reinitiated treatment or treatment failure outcome at the end of treatment). Participants receiving treatment for DRTB were excluded from the reclassification since they were still on treatment at the end of the study. The differences in TB treatment outcome and any possible association between blood glucose and TB treatment outcome were assessed. The baseline predictors of unfavourable TB treatment outcome were evaluated using a logistic regression with the new binary TB treatment outcome variable—favourable or unfavourable TB treatment outcome. We used the forward and backward elimination method at p=0.2 to identify variables for inclusion in the multivariate logistic model. We retained age, sex, HIV status and alcohol use (selected a priori) in the final multivariate model, and predictors were deemed significant at p<0.05. We used Stata 17 (Stata Corp LP, College Station, Texas, USA) for statistical analysis and the Hosmer-Lemeshow goodness-of-fit test to assess the fitness of the multivariate logistic model.

RESULTS

Descriptive characteristics of participants

We enrolled 369 participants in the study, and the baseline blood glucose was available for 352 participants. For the second- and fifth-month visits, 235 and 262 participants had documented blood glucose, respectively (figure 1). At baseline, more males were included compared with females (male-female ratio 1.2), and the mean age was 38.4 years (SD 12.9), 42.2 years (SD 12.3) in patients with elevated blood glucose and 38.1 years (SD 13.1), in those with normal blood glucose (table 1). The mean BMI was 22.4 (SD 5.2), and the TB-HIV coinfection rate was 76% (98.6%, n=275 on antiretroviral therapy).

The median baseline blood glucose was 5.5 mmol/L (IQR 4.8, 6.7) and 5.5 mmol/L (IQR 4.9, 6.4) in females, and 5.6 mmol/L (IQR 4.8, 6.8) in males; non-reactive HIV status 5.5 mmol/L (IQR 4.8, 6.8) and 5.5 mmol/L

Table 1 Descriptive characteristics of participants in the study and their blood glucose status

Participants characteristics	Normal glucose (n=324)	Elevated glucose* (n=28)	Total (n=369)†
Sex			
Female	150 (46.3%)	11 (39.3%)	167 (45.3%)
Male	174 (53.7%)	17 (60.7%)	202 (54.7%)
Age (years)			
<25	51 (15.8%)	3 (10.7%)	54 (14.7%)
25–34	82 (25.5%)	2 (7.1%)	91 (24.8%)
35–44	98 (30.4%)	11 (39.3%)	115 (31.3%)
45–54	53 (16.5%)	6 (21.4%)	62 (16.9%)
55+	38 (11.8%)	6 (21.4%)	45 (12.3%)
Mean (SD)	38.09 (13.11)	42.21 (12.29)	38.36 (12.91)
Marital status			
Married	79 (25.5%)	11 (44.0%)	93 (26.6%)
Single/widowed	231 (74.5%)	14 (56.0%)	256 (73.4%)
Baseline blood glucose			
Median (Q1, Q3)	5.4 (4.8, 6.3)	9.5 (5.9, 13.0)	5.5 (4.8, 6.7)
Baseline BMI			
Mean (SD)	22.40 (5.22)	22.64 (4.88)	22.4 (5.2)
Systolic blood pressure (mm Hg)‡			
Normal	183 (57.2%)	11 (40.7%)	202 (56.7%)
Elevated	65 (20.3%)	7 (25.9%)	71 (19.9%)
High BP stage 1	44 (13.8%)	5 (18.5%)	51 (14.3%)
High BP stage 2	27 (8.4%)	4 (14.8%)	31 (8.7%)
Hypertensive crises	1 (0.3%)	0 (0.0%)	1 (0.3%)
Median (Q1, Q3)	117 (110, 128)	122.0 (106, 132)	117.0 (109, 128)
Diastolic blood pressure (mm Hg)§			
Normal	215 (67.2%)	14 (51.9%)	236 (66.3%)
High BP stage 1	75 (23.4%)	6 (22.2%)	82 (23.0%)
High BP stage 2	29 (9.1%)	7 (25.9%)	37 (10.4%)
Hypertensive crises	1 (0.3%)	0 (0.0%)	1 (0.3%)
Median (Q1, Q3)	74.5 (67.0, 81.5)	77.0 (69.0, 91.0)	74.0 (67.0, 82.0)
Baseline HIV status			
Unknown	2 (0.6%)	1 (3.6%)	3 (0.8%)
Non-reactive	84 (25.9%)	2 (7.1%)	87 (23.6%)
Reactive	238 (73.5%)	25 (89.3%)	279 (75.6%)
Duration of TB treatment (months)			
Median (Q1, Q3)	6.2 (5.7, 6.9)	6.2 (4.7, 6.7)	6.2 (5.6, 6.9)
Family history of DM			
Unknown	38 (11.7%)	6 (21.4%)	52 (14.1%)
No	240 (74.1%)	14 (50.0%)	263 (71.3%)
Yes	46 (14.2%)	8 (28.6%)	54 (14.6%)
Education			
None/unknown	51 (15.7%)	8 (28.6%)	67 (18.2%)
Primary	66 (20.4%)	7 (25.0%)	74 (20.1%)
High school	174 (53.7%)	11 (39.3%)	191 (51.8%)

Continued

Table 1 Continued

Participants characteristics	Normal glucose (n=324)	Elevated glucose* (n=28)	Total (n=369)†
Tertiary	33 (10.2%)	2 (7.1%)	37 (10.0%)
Occupation			
Employed	149 (46.0%)	10 (35.7%)	160 (43.4%)
Unemployed	175 (54.0%)	18 (64.3%)	209 (56.6%)
Alcohol (current)			
Unknown	14 (4.3%)	2 (7.4%)	19 (5.2%)
No	164 (50.6%)	12 (44.4%)	181 (49.2%)
Yes	146 (45.1%)	13 (48.1%)	168 (45.7%)
Smoking (current)			
Unknown	16 (4.9%)	3 (10.7%)	22 (6.0%)
No	267 (82.4%)	22 (78.6%)	301 (81.6%)
Yes	41 (12.7%)	3 (10.7%)	46 (12.5%)

*Elevated if random ≥11.1 mmol/L and fasting >5.5 mmol/L.
†Summing up normal and elevated blood glucose will not equal the total since some participants (n=17) did not have baseline blood glucose data.
‡Normal: <120; elevated 120–129; High BP stage 1: 130–139; High BP stage 2: 140–180; hypertensive crises: >180.
§Normal: <80; high BP stage 1: 80–89; high BP stage 2: 90–120; hypertensive crises: >120.
BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; TB, tuberculosis.

(IQR 4.8, 6.5) for those with a reactive HIV status. Almost all participants (n=357, 97%) were enrolled for the treatment of drug-sensitive TB, while 323 (87.5%), 29 (7.9%) and 16 (4.3%) were new TB, previously treated and relapse TB, respectively. For access to baseline diagnostic and confirmatory TB services, 331 (89.7%) accessed GeneXpert (positive=171, 52%), 117 (33.8%) accessed baseline culture (positive=74, 63%), 202 (54.7%) accessed resistance testing (positive=3, 1.5%) and 175 (47.4%) accessed TB-Lam (positive=159, 91%) (online supplemental table 1). Few participants reported comorbidities at baseline: DM 2.4% (n=9), hypertension 4.3% (n=16) and HIV, hypertension and DM 0.5% (n=2) (online supplemental table 1).

Baseline prevalence of elevated blood glucose

The overall prevalence of elevated blood glucose was 8.0%, n=28 (95% CI: 5.5, 11.3), DM 5.1% (95% CI: 3.2, 8.0) and pre-diabetes 2.8% (95% CI: 1.5, 5.2). The prevalence was 9.6% (95% CI: 5.2, 17.0), 4.5% (95% CI: 0.6, 26.3), 8.7% (95% CI: 5.2, 14.2) and 4.5% (95% CI: 1.5, 13.2) in the Hhohho, Lubombo, Manzini and Shiselweni regions, respectively. Prevalence was 6.8% (95% CI: 3.8, 11.9) in females and 8.9% (95% CI: 5.6, 13.9)

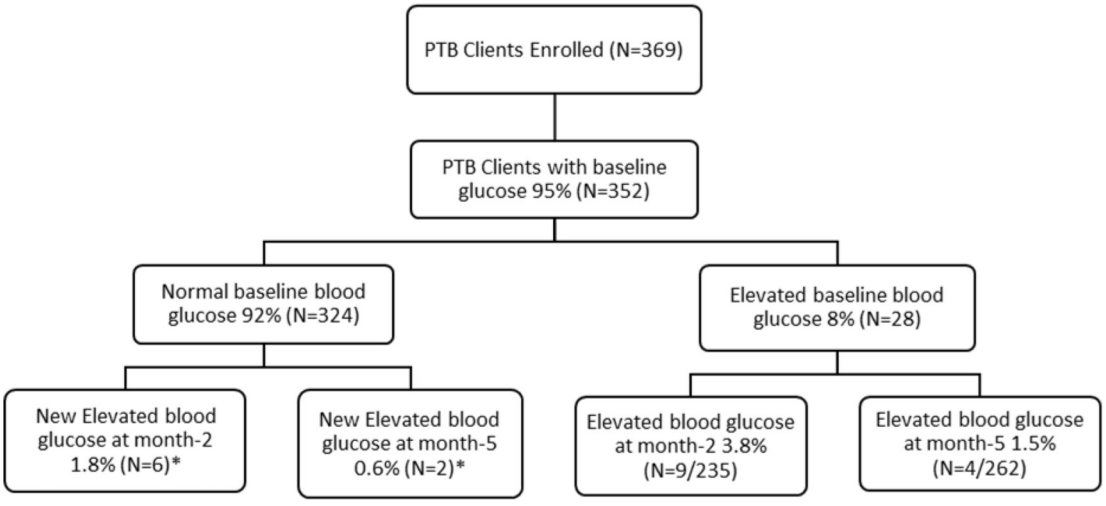

Figure 1 Flowchart describing patient enrolment and blood glucose status during follow-up. *This number is included in the total for elevated blood glucose during follow-up.

in males (p=0.475). The prevalence was 5.6% (95% CI: 1.8, 15.9), 2.4% (95% CI: 0.6, 9.1), 10.1% (95% CI: 5.7, 17.3), 10.2% (95% CI: 4.6, 20.9) and 13.6% (95% CI: 6.2, 27.3) in those aged <25 years, 25–34 years, 35–44 years, 45–54 years and ≥55 years. In patients with a non-reactive HIV status, the prevalence was 3.4% (95% CI: 1.1, 9.9) and 9.5% (95% CI: 6.5, 13.7) in those with a reactive HIV status (p=0.027).

Subanalysis of 33 patients with a fasting blood glucose

In a subanalysis of 33 patients from different health facilities with a baseline fasting blood glucose, prevalence values in the diabetic range were 12.1% (95% CI: 4.5, 29.0), while pre-diabetes was 30.3% (95% CI: 16.7, 48.5). More than half of these participants were males (56%, n=19), and only three reported a comorbidity at baseline (hypertension only).

Blood glucose and blood pressure changes during follow-up

235 (63.9%) and 262 participants (71.2%) had blood glucose measurements documented at the second- and fifth-month visits, respectively. Of 28 patients with elevated blood glucose at baseline, only 15 (54%) and 17 (61%) had a blood glucose measurement on the second- and fifth-month visits, respectively.

The median blood glucose was significantly different between visits (p=0.001). Compared with baseline median blood glucose, the median blood glucose at month 2 and month 5 reduced to 5.3 mmol/L (IQR 4.8, 6.2) (p=0.041) and 5.2 mmol/L (IQR 4.8, 5.9) (p<0.001). The number of patients with elevated blood glucose reduced from 28 (8.0%) at baseline to 9 (3.8%) at the second-month visit and 4 (1.5%) at the fifth-month visit. Among those with normal blood glucose at baseline (n=324), six (1.8%) had an elevated measurement during month 2 visit and two (0.6%) at month 5 (figure 1).

Overall, 43.3% and 33.8% of participants had elevated baseline SBP and DBP, respectively, and 38.6% had hypertension (table 1 and online supplemental table 1). The median baseline SBP was 117.0 mm Hg (IQR 109, 128) (with no significant change during follow-up). The median DBP at baseline increased from 74 mm Hg (IQR 67, 82) to 76 mm Hg (IQR 70, 84) at the second-month visit (p=0.024) and reduced slightly to 74 (IQR 67, 82) at the fifth-month visit (p=0.959). The difference in DBP between the second- and fifth-month visits was 2.0 mm Hg (p=0.026).

Predictors of elevated baseline blood glucose

In the univariate analysis, a positive family history of DM (OR 2.98; 95% CI: 1.18, 7.51; p=0.021) significantly predicted elevated baseline blood glucose (table 2). The baseline weight and age of participants were not significant predictors, while a reactive baseline HIV status (OR 3.01; 95% CI: 0.92, 11.5; p=0.077) and DBP (OR 1.03; 95% CI: 0.99, 1.07; p=0.085) were marginally statistically significant. A positive family history of DM (adjusted OR (AOR) 2.80; 95% CI: 1.08, 7.32; p=0.035) and a reactive HIV status (AOR 4.62; 95% CI: 1.06, 20.11; p=0.042) significantly predicted an elevated baseline blood glucose in the multivariate analysis. The multilevel logistic model was not different from the final multivariate logistic model (online supplemental file 2), and the intracluster effect was negligible (ICC=3.64e-16), indicating that within-region variation provided minimal explanation for elevated blood glucose among individuals.

Table 2 Predictors of elevated baseline blood glucose

	Univariate			Multivariate		
Variable	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Age (years)	1.02	0.99, 1.05	0.111			
Sex						
Female	1					
Male	1.33	0.61, 2.93	0.476			
Diastolic blood pressure	1.03	0.99, 1.07	0.085	1.02	0.99, 1.05	0.132
Baseline weight (kg)	0.98	0.96, 1.01	0.283			
Baseline HIV status						
Non-reactive	1					
Reactive	3.01	0.87, 10.23	0.077	4.62	1.06, 20.1	0.042
Family history of diabetes mellitus						
No	1					
Unknown	2.70	0.98, 7.47	0.055	2.81	0.99, 7.99	0.053
Yes	2.98	1.18, 7.51	0.021	2.80	1.08, 7.32	0.035

Hosmer-Lemeshow goodness-of-fit test: p=0.6438.

Tuberculosis treatment outcomes

Intermediate treatment outcomes

Of 216 (59%) participants with data for month 2 follow-up sputum, 214 (99%) had a negative sputum result, while 229 out of 232 (98.7%) had a negative sputum at the end of treatment.

Final treatment outcomes

All but one patient had a TB treatment outcome assigned: completed (n=150, 40.7%), cured (n=126, 34.2%), died (n=34, 9.2%), loss to follow-up (LTFU) (n=19, 5.2%), transferred out (n=13, 3.5%), active (n=6, 1.6%), reinitiated (n=6, 1.6%), DRTB on treatment (n=3, 0.8%) and stopped treatment (n=2, 0.5%) (online supplemental file 3). The median treatment duration for all patients was 6.2 months (SD 5.6, 6.8).

Overall, 276 patients (75.4%) had a favourable TB treatment outcome, with slightly more males than females (51% vs 49%). More males (n=59, 66%) had an unfavourable TB treatment outcome (n=90, 24.6%) compared with females (p=0.020), and the majority of those with an unfavourable outcome (n=82, 91%) were aged ≥25 years. Proportionately, 19%, 21%, 20%, 27% and 44% aged <25 years, 25–34 years, 35–44 years, 45–54 years and ≥55 years had an unfavourable outcome, respectively, and those with an unfavourable outcome were significantly older than those with a favourable outcome (p=0.003). 34 patients (9.2%) died, and more than half were males (n=20, 59%). More males were lost to follow-up (n=16, 84%), were reinitiated for any reason (n=5, 83%) and were transferred out (n=9, 69%) compared with females. For the patients who died, 14 (41.2%) died <1 month after commencing treatment, 6 (17.6%) died within 1–2 months, 10 (29.4%) died within 2–3 months and 4 (11.8%) died >3 months after commencing treatment.

Blood glucose and tuberculosis treatment outcomes

The median difference in blood glucose between patients with a favourable outcome and those with an unfavourable outcome was 0.1 mmol/L (p=0.7028) at baseline, 0.2 mmol/L (p=0.407) at the second-month visit and 0.2 mmol/L (p=0.266) at the fifth-month visit. After controlling for age, sex and baseline HIV status, elevated blood glucose did not predict an unfavourable outcome (OR 1.44; 95% CI: 0.61, 3.40; p=0.404).

More than two-thirds (n=19, 67.8%) of the patients with elevated baseline blood glucose had a favourable TB treatment outcome. Five (17.9%) died, two (7.1%) were lost to follow-up and one each stopped treatment and was transferred out.

Predictors of unfavourable tuberculosis treatment outcomes

Table 3 summarises the predictors of unfavourable TB treatment outcomes.

In the multivariate analysis, hypertension (AOR 4.84; p=0.009) and unemployment (AOR 2.01; 95% p=0.027) were significant positive predictors of unfavourable TB outcomes, while high school education (AOR 0.32; 95% CI: 0.16, 0.64; p=0.001) was a significant negative predictor of unfavourable TB outcome. The odds of an unfavourable TB outcome increased with alcohol use (AOR 1.68; 95% CI: 0.97, 2.89), but this was only marginally significant (p=0.062).

DISCUSSION

The prevalence of elevated blood glucose for patients commencing TB treatment at baseline was 8% (95% CI: 5.5, 11.3). It was highest in the Hhohho region, higher in males than females, increased with age and highest in those with a reactive HIV status at 9.5% compared with the non-reactive group. The proportion of patients with an elevated blood glucose measurement reduced at the second-month visit and even further at the fifth-month visit. At multivariate analysis, a family history of DM and a reactive HIV status were significant predictors of an elevated baseline blood glucose. Three-quarters of the participants (75.4%) had a favourable treatment outcome. Elevated baseline blood glucose was not associated with unfavourable treatment outcomes; instead, hypertension and unemployment predicted unfavourable treatment outcomes, while high school education was protective.

Our reported prevalence of 8.0% elevated blood glucose at diagnosis is similar to a pooled prevalence of 9% (95% CI: 6.0%, 12.0%) of DM for patients in Sub-Saharan Africa from a 2019 systematic review and meta-analysis.[26] This review similarly reported a higher prevalence in HIV-infected patients at 8.9%, with a DM prevalence of 15%, 11% and 10% in Nigeria, Tanzania and Ethiopia, respectively, indicating variations across countries.[26] Other studies from Tanzania, Uganda and Ethiopia have reported a prevalence of 9.2%, 8.5% and 5.1%, respectively. Our study prevalence is less than 17.7% reported from a global meta-analysis on the common comorbid conditions with TB[27] and in Asian countries of Nepal,[28] India,[29 30] Iran,[31] Vietnam[32] and Pakistan.[33] This higher prevalence in Asian countries is expected as they are known to have a higher prevalence of DM and TB than the rest of the world. In contrast, a much lower prevalence of 1.9% and 4.5% has been reported in Benin[34] and Brazil,[35] respectively. Our reported DM prevalence of 12% from a subanalysis of 33 patients should be interpreted cautiously as this could have been due to selection bias.

Consistent with our findings, a study from Tanzania[14] found that positive HIV status and a family history of DM were significant predictors of DM in patients receiving treatment for TB. Studies from India, Vietnam and Iran also corroborate this finding.[32 36 37] Another Tanzanian study, while confirming the effect of a positive family history for DM, contrasted our result on positive HIV status.[38] Given unverified claims on the impact of dolutegravir (an integrase strand inhibitor which is part of a three-drug regimen for the treatment of HIV) on blood glucose metabolism, this contrasting finding requires

Table 3 Predictors of unfavourable tuberculosis treatment outcome

	Univariate			Multivariate		
Variable	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Region						
Hhohho	1					
Lubombo	1.27	0.46, 3.45	0.643			
Manzini	0.72	0.41, 1.26	0.254			
Shiselweni	0.72	0.35, 1.46	0.360			
Age	1.03	1.01, 1.05	0.003	1.02	0.99, 1.04	0.102
Baseline HIV status						
Non-reactive	1			1		
Reactive	0.73	0.43, 1.24	0.245	0.80	0.43, 1.51	0.495
Sex						
Female	1			1		
Male	1.80	1.09, 2.95	0.020	1.37	0.78, 2.41	0.279
Alcohol use						
No	1			1		
Yes	2.02	1.25, 3.28	0.004	1.68	0.97, 2.89	0.062
Comorbidities						
None	1			1		
Diabetes	0.73	0.15, 3.45	0.693	0.90	0.18, 4.52	0.902
Hypertension	4.23	1.52, 11.73	0.006	4.84	1.48, 15.7	0.009
Elevated blood glucose						
No	1					
Yes	1.53	0.66, 3.52	0.32			
Education						
None	1			1		
Primary	0.47	0.24, 0.94	0.034	0.67	0.31, 1.43	0.300
High school	0.20	0.11, 0.37	<0.001	0.32	0.16, 0.64	0.001
Tertiary	0.26	0.10, 0.66	0.005	0.49	0.16, 1.43	0.192
Occupation						
Employed	1					
Unemployed	2.45	1.46, 4.12	0.001	2.01	1.08, 3.71	0.027

Hosmer-Lemeshow goodness-of-fit test: p=0.6861.

further scrutiny.[39–41] Older age (>45 years), female and male sex, BMI, poor glycaemic control, elevated DBP and residing in urban areas are some of the other predictors reported by other authors.[28 29 32 33 35 37 42 43] In our cohort, patients with elevated blood glucose were older and had slightly higher DBP. Moreover, more males had elevated blood glucose than females, but these were not significant predictors in our study. The reduced prevalence of elevated blood glucose at follow-up should be interpreted cautiously as some patients did not receive a blood glucose measurement. The reduced prevalence at follow-up may also be due to initial stress hyperglycaemia[44] or the treatment of patients with elevated blood glucose with metformin as mandated by MOH. The high prevalence of elevated SBP and DBP in our study indicates a need for integrated screening for and management of NCDs as elevated blood pressure may contribute to unfavourable outcomes.

Our treatment success rate (75.4%) is less than the 81% reported by the Eswatini National Tuberculosis Control Program for drug-sensitive TB.[16] About 9% and 5% of our patients who commenced treatment died and were lost to follow-up, respectively. These findings are similar to a nationally reported death rate of 10.0% and LTFU of 2.9%, indicating a need for further improvement in TB services to reduce both indicators to <5%. The unfavourable treatment outcome in our cohort, primarily due to death and LTFU, is a challenge for TB programmes across Sub-Saharan Africa. A recent systematic review indicated the contribution of death and LTFU

to unfavourable treatment outcomes was 48% (CI: 40%, 57%) and 47% (95% CI: 39%, 55%), respectively.[45]

In our study, elevated baseline blood glucose did not impact TB treatment outcomes. While this is consistent with a study conducted in Mali,[46] it is contrary to reports by other studies.[8 47 48] It could be because we are reporting less sensitive random blood glucose with a small number of patients with the outcome over 5 months. Hypertension as a predictor of unfavourable TB treatment outcomes may be associated with age as patients with hypertension are characteristically older. In our cohort, patients with unfavourable outcomes were significantly older than those with favourable outcomes. While unemployment is linked with a lower quality of life, inability to afford basic needs and access to healthcare, high school education (and education overall) is protective as it is directly correlated with a higher quality of life and access to healthcare.[49 50] Contrary to reports from other studies,[45 49–52] age, HIV status, male sex and alcohol use were not significant predictors of unfavourable TB treatment outcomes. This finding does not negate their relevance in planning and implementing early TB case finding and treatment activities as sample size, facility sampling procedure and patient enrolment may have impacted our results.

This is the first study to report on the prevalence of elevated blood glucose among patients with TB in Eswatini, a country with a high HIV prevalence. We sampled health facilities from the four regions of Eswatini, so our findings are representative; hence, this study will serve as a baseline for future studies. The study was pragmatic, using glucometers for blood glucose measurements per MOH guidelines and standard MOH treatment registers that healthcare workers complete as our data source. We collected additional vital sociodemographic information that was lacking to improve our study. This approach enabled us to obtain a true reflection of services and patient outcomes that would have otherwise been lost in a controlled study.

The first limitation is the missing data for follow-up blood glucose measurements. We provided health facilities with glucometers and glucose test strips to ensure completeness and consistency in measuring blood glucose. Despite this, some patients still missed blood glucose measurements during visits for different reasons, including changes in patient flow at health facilities, incomplete documentation and limited orientation for new staff on patient follow-up procedures. This indicates that besides the availability of testing supplies, other health system factors can hinder patients from accessing a blood glucose test or further vital investigations. Second, one health facility did not respond to a request to participate in the study, which also impacted our final sample size. Third, we could not fully assess patient conversions at 2 and 5 months due to the limited availability of sputum tests and the absence of culture during follow-up. Fourth, we had a few patients with our outcome of interest. Patient loss to follow-up could have been responsible for this, but those lost to follow-up were few. Similarly, we regarded transferred-out clients as having unfavourable outcomes as we did not know their outcome when completing treatment. This may have contributed to the overestimation of unfavourable outcomes. Finally, we used random blood glucose measurements per MOH guidelines. Noting that some patients do not receive the random blood glucose test to screen for elevated blood glucose as recommended by the MOH for different reasons, an HbA1c test at baseline and the end of treatment would provide more reliable estimates of blood glucose in the preceding 3 months. The fasting blood glucose test, an alternative, is similar to the random test but may provide similar results as most patients would have already had breakfast before getting to the clinic. Requesting patients to attend the clinic fasting during appointments would inconvenience the patients. It may negatively impact clinic visits since no meals are provided, and some patients walk to and from the clinic.

CONCLUSION

This study reveals a high prevalence of elevated baseline blood glucose in patients commencing TB treatment compared with the general population, higher in males, older age groups and HIV-positive patients. A concurrent high prevalence of elevated SBP and DBP did not change throughout treatment, possibly indicating a similarly high prevalence of elevated blood pressure in the general population. A family history of DM and reactive HIV status were predictors of elevated blood glucose. Given the high prevalence of HIV, this indicates a need for periodic screening of people living with HIV, males and people in the older age group. About a quarter of our patients had unfavourable TB treatment outcomes, with death being the most common unfavourable outcome. Hypertension and unemployment were positive predictors of unfavourable outcomes, while high school education was protective, underscoring the relevance of education in TB control. Systematically implementing and institutionalising the framework for collaborative action on TB and comorbidities and integrating NCDs in infectious disease programmes (TB, HIV and sexually transmitted infections) as recommended by WHO[10 11] can help accelerate the timely diagnosis and treatment of NCDs to limit unfavourable treatment outcomes for patients with TB.

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