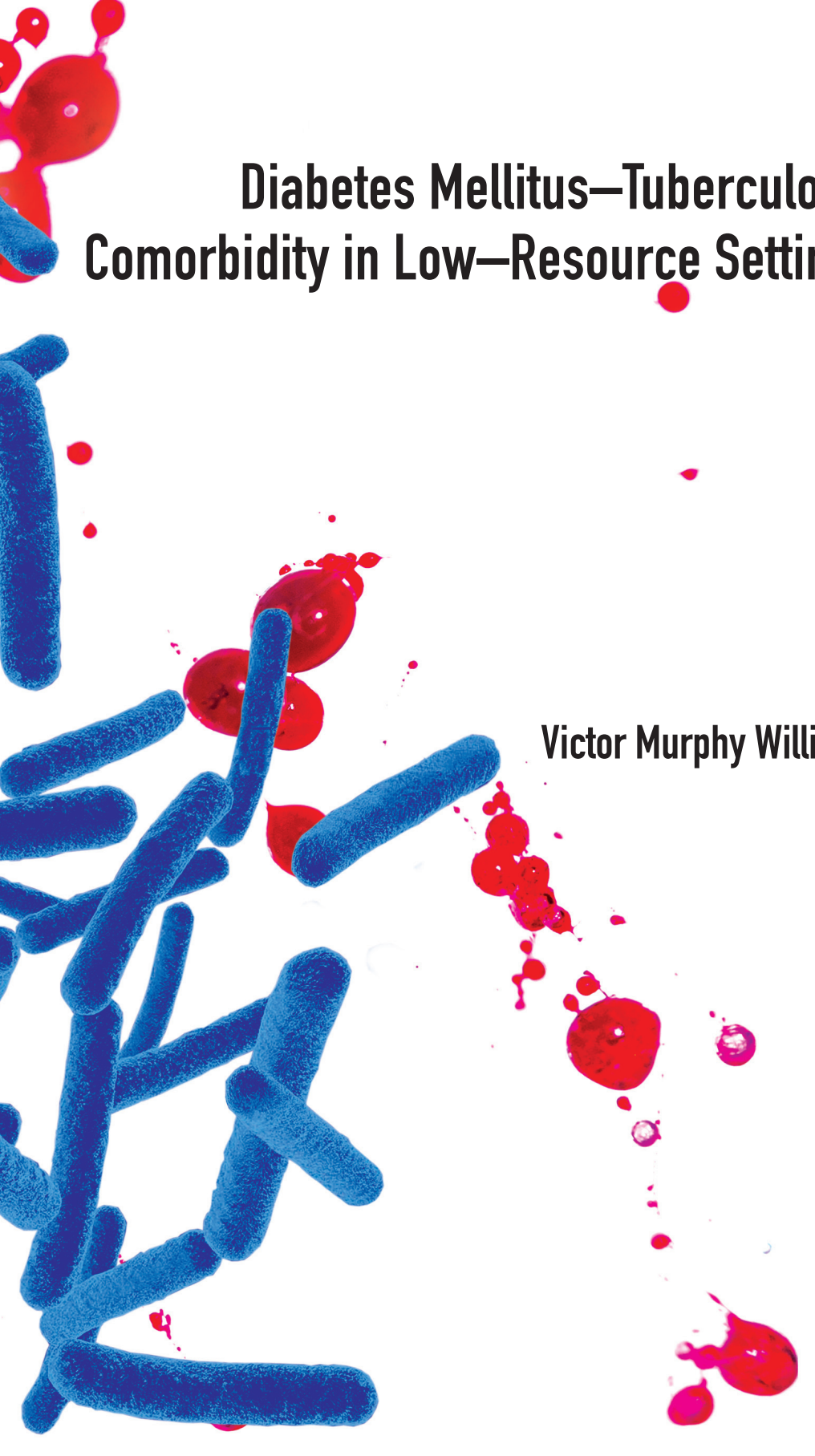
Diabetes Mellitus–Tuberculosis Comorbidity in Low–Resource Settings



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Diabetes Mellitus–Tuberculosis Comorbidity in Low–Resource Settings

De interactie tussen diabetes mellitus en tuberculose in een omgeving met een laag inkomen

(met een samenvatting in het Nederlands)

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Contents

Chapter 1

General Introduction

Global Tuberculosis Burden and Risk Factors

Despite investments in tuberculosis (TB) control, 10.6 million people were ill with TB in 2022, with 1.3 million TB-related deaths [1]. Country programs were on track to end TB in line with the United Nations Sustainable Development Goals (SDG) 2030 targets, but the measures aimed at contending the COVID-19 pandemic halted these gains [2,3]. Recent global TB reports indicate a surge in TB-related deaths in 2020 and 2021 back to the 2017 levels, with a gap in the number of people with TB disease accessing treatment and reduced spending on TB-related prevention and treatment activities [4]. Consequently, ending TB by 2030 is presently out of reach, except innovative approaches are developed to increase TB prevention services, TB active case finding, and treatment of new and relapse TB cases to match and supersede pre-COVID-19 pandemic levels.

Although TB is present in all countries, the incidence is highest in Southeast Asia, followed by Africa and the Western Pacific (Figure 1). Eight countries contribute to 68% of new global TB cases, while 30 contribute to 85% of all new global TB cases [4,5]. Seventeen of the thirty high-burden TB countries are from Sub-Saharan Africa. This high incidence has been attributed to the high HIV prevalence, undernourishment, alcohol use, smoking, diabetes, overcrowding, and poor housing infrastructure in Sub-Saharan Africa [1,6,7].

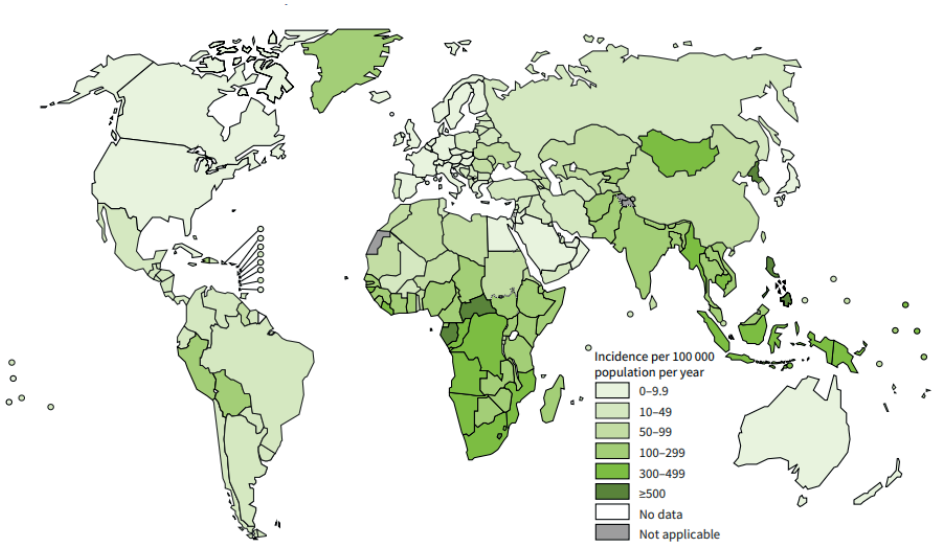

Figure 1: Estimated TB incidence rates per 100,000 population in 2022. Countries in the WHO African region had the highest TB incidence rates (WHO 2023 Global Tuberculosis Report - https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023)

The role of HIV in propagating the TB epidemic in Sub-Saharan Africa and other regions of the world is well documented. It constitutes the most important driver of TB disease and poor treatment outcomes in the last decade [8–10]. People living with HIV have increased susceptibility to TB relapse and new infections, delayed sputum conversion and poor treatment outcomes [9]. The rollout of antiretroviral therapy (ART) in most Sub-Saharan African countries and improvement in TB infection prevention and treatment services has contributed to a noted decline in new TB infections [11,12].

Increasing Diabetes Mellitus Burden in Low- and Middle-Income Countries

Non-communicable diseases (NCDs) surpassed infectious diseases as the most common cause of death globally. An estimated 41 million people die from NCDs (74% of all deaths) annually, with 77% of all NCD-related deaths occurring in low- and middle-income countries (LMICs) [13] (Figure 2). Similarly, about 86% of 17 million people who die prematurely annually (before age 70) are from LMICs [13]. Most of these NCD-related deaths are from cardiovascular diseases (44%), cancers (23%), chronic respiratory diseases (10%) and diabetes (5%) [13]. Physical inactivity, unhealthy diet, smoking, alcohol, overweight and obesity, elevated blood pressure and uncontrolled blood glucose are known risks of NCDs [13–15]. War and political instability, insecurity, lack of infrastructure for physical activities, natural disasters, and air pollution are external factors contributing to increased NCD prevalence and death in LMICs, particularly in Sub-Saharan Africa [16–18].

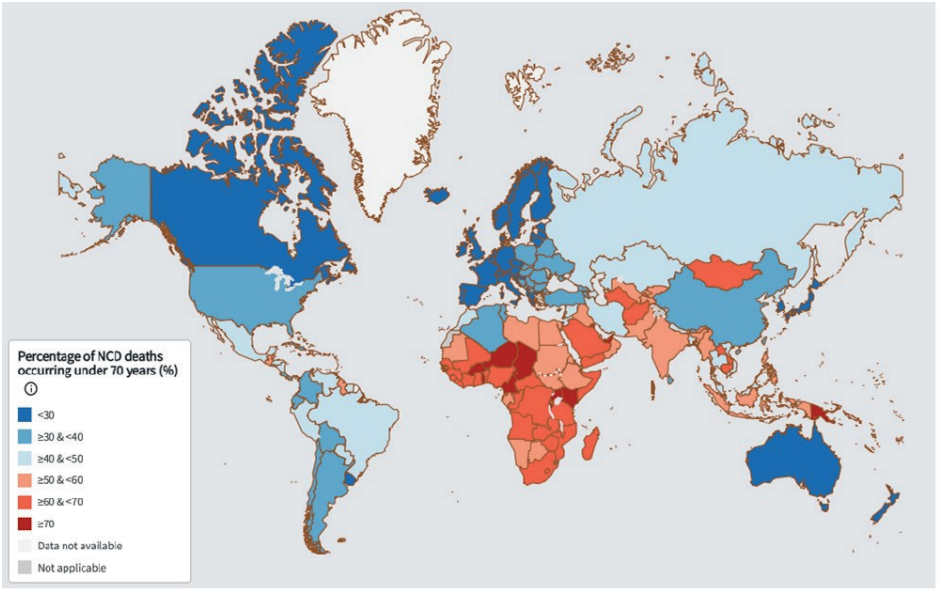

Figure 2: Percentage of Non-communicable disease deaths occurring under 70 years in 2019. Countries in the WHO African Region have the highest percentage of deaths (WHO Non-communicable Diseases Data Portal, 2023: https://ncdportal.org/))

Globally, an estimated 537 million adults live with diabetes, and over three-quarters reside in LMICs [19]. Already responsible for 6.7 million deaths annually, the International Diabetes Federation (IDF) estimates that 783 million people will be living with diabetes by 2045 [19]. An estimated 24 million adults live with diabetes in Sub-Saharan Africa, and 54% of these are undiagnosed [20]. In 2021, 416,000 diabetes-related deaths occurred in Sub-Saharan Africa [20]. Furthermore, the number of people living with diabetes in the region is projected to increase to 55 million by 2045 [20,21] (Figure 3).

This projected increase in diabetes cases will significantly burden diabetes control, increase healthcare costs, and impact residents' quality of life and socioeconomic status. Substantial expenses will go to diabetes care as most people in Sub-Saharan Africa pay out of pocket, thus elevating catastrophic costs for healthcare [22,23]. With weak health systems, limited health infrastructure, financing, and capacity for diabetes care compared to high-income countries, increased diabetes prevalence will increase the risks for diabetic complications and death in low-resource settings, particularly in Sub-Saharan Africa [24,25].

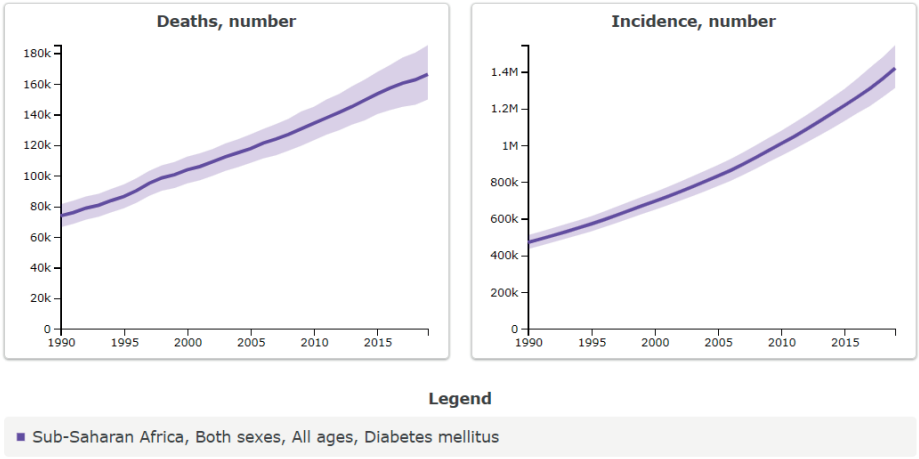

Figure 3: Incidence and death due to diabetes mellitus in Sub-Saharan African countries from 1990 to 2019 (Global Burden of Disease 2022; https://vizhub.healthdata.org/gbd-results/).

To mitigate the impending diabetes crises in Sub-Saharan Africa and other low-resource settings, understanding the drivers of diabetes and identifying other less-known risk factors can provide a critical starting point for designing context-specific interventions [21,26]. Another consideration is determining how the epidemiology of diabetes and other NCDs vary in the context of highly prevalent infectious diseases such as HIV, malaria, and TB. This can inform joint NCD-infectious disease intervention strategies and identify service integration points, lowering healthcare service delivery costs and increasing patient access to infectious diseases and NCD services.

Diabetes Mellitus – Tuberculosis Comorbidity

Diabetes is a known risk factor for TB. The risk of developing TB is two to three times higher in individuals with diabetes than in those without diabetes, and the risk of death during treatment and relapse after treatment is also higher in people with diabetes [27]. Globally, about 15% of people receiving treatment for TB have diabetes [28,29]. In Sub-Saharan Africa, the prevalence of DM–TB comorbidity is 6.7 – 15% [28–30]. In diabetes, there is impaired blood glucose regulation, limiting lymphocyte functions and rendering individuals susceptible to reactivation of latent TB and new infections [31]. Complications associated with diabetes, including renal impairment, may contribute to poor TB treatment outcomes in people with diabetes receiving treatment for tuberculosis [25].

Some patients without a previous history of diabetes have been diagnosed with impaired blood glucose or diabetes at TB diagnosis. This observation is termed transient or stress hyperglycemia; the blood glucose normalises a few weeks after the patient has commenced TB treatment [32]. An elevation in stress hormones and cytokines in response to TB infection is proposed as being responsible for this [32]. This thesis focuses on DM–TB epidemiology, not transient or stress hyperglycemia.

Rationale

TB burden and TB-related deaths are high in Sub-Saharan Africa, with TB diagnosis and treatment challenges. Concurrently, the highest increase in diabetes mellitus cases will occur in Sub-Saharan Africa by 2045. Available evidence indicates an ongoing epidemiological transition in Sub-Saharan Africa, with changes in lifestyle, inactivity, dietary patterns, smoking, alcohol, and ageing patterns, all contributing to increased diabetes risk with high burdens of tuberculosis and HIV.

With a limited understanding of DM–TB comorbidity in Sub-Saharan Africa, this thesis describes the epidemiology of DM–TB in a low-resource setting, the effect of blood glucose on TB treatment outcomes, the opportunities to improve TB patient management practices, the impact of COVID-19 on TB services and recommendations to improve integrated care for DM and TB.

Setting

The research described in this thesis was conducted in Eswatini (formerly Swaziland). Eswatini is a landlocked country in Southern Africa. It is surrounded by South Africa, except in the northeast, where it shares a border with Mozambique. It has a population of 1.2 million people [33] with four administrative regions – Hhohho, Lubombo, Manzini and Shiselweni (Figure 4).

It is classified as a lower middle-income country by the World Bank [33], with a GDP per capita of $3,987 [33]. It has one of the highest global HIV prevalence at 24.8% and an annual TB incidence of 348/100,000 population [34,35].

Figure 4: Map of Africa indicating the location of Eswatini where the study was conducted (http://www.vidiani.com/large-detailed-contour-political-map-of-africa/; https://www.worldatlas.com/ upload/92/63/d4/regions-of-Eswatini-map.png)

Eswatini and Switzerland were the first countries to achieve the Joint United Nations AIDS Program (UNAIDS) targets of 95-95-95 [36], indicating a robust response to the HIV epidemic. The government funds healthcare with additional support for different healthcare and development interventions from the United States Government, the Global Fund for AIDS, Tuberculosis and Malaria (GFATM), the World Bank and United Nations agencies. Private healthcare services are available and accessed through individual or employer-based medical aid or cash payments.

Thesis Outline

This thesis consists of eight chapters listed in the outline below:

Chapter 1: Introduction

Chapter 2: Scoping review of studies on the occurrence of abnormal blood glucose during tuberculosis treatment.

Chapter 3: Protocol for the prospective study of a cohort of patients on tuberculosis-diabetes comorbidity, treatment outcomes and opportunities to improve integrated care.

Chapter 4: Epidemiology of diabetes-tuberculosis comorbidity, tuberculosis treatment outcomes and predictors of poor tuberculosis treatment outcomes.

Chapter 5: Opportunities and recommendations for improving diabetes-tuberculosis integrated services in a low- and middle-income country.

Chapter 6: Impact of the COVID-19 pandemic on tuberculosis service delivery and approaches adopted by healthcare workers for continued service delivery.

Chapter 7: General Discussion

Chapter 8: Summary

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Chapter 2

Tuberculosis Treatment and Resulting Abnormal Blood Glucose: A Scoping Review of Studies from 1980 to 2021

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Global Health Action. 2022 Vol. 15, 2114146

Abstract

Background

Hyperglycaemia is a risk factor for tuberculosis. Evidence of changes in blood glucose levels during and after tuberculosis treatment is unclear.

Objective

To compile evidence of changes in blood glucose during and after tuberculosis treatment and the effects of elevated blood glucose changes on treatment outcomes in previously normoglycaemic patients.

Methods

Original research studies (1980 to 2021) were identified in PubMed, Web of Science, CINAHL and Embase databases.

Results

Of the 1,277 articles extracted, 14 were included in the final review. All studies were observational and 50% were prospective. Fasting blood sugar was the commonest clinical test (64%), followed by the glycated haemoglobin test and the oral glucose tolerance test (each 50%). Most tests were conducted at baseline and in the third month of treatment. Twelve studies showed that the prevalence of hyperglycaemia in previously normoglycaemic patients decreased from baseline to follow-up and end of treatment. Three studies showed successful treatment outcomes of 64%, 75% and 95%. Patients with hyperglycaemia at baseline were more likely to develop cavitary lung lesions and poor treatment outcomes and had higher post-treatment mortality. There was no difference in outcomes by human immunodeficiency virus (HIV) status.

Conclusion

Elevated blood glucose in normoglycaemic patients receiving treatment for tuberculosis decreased by the end of treatment. Positive HIV status did not affect glucose changes during treatment. Further research is needed to investigate post-treatment morbidity in patients with baseline hyperglycaemia and the effects of HIV on the association between blood glucose and tuberculosis.

Keywords

Diabetes, Hyperglycaemia, Impaired glucose tolerance, Human immunodeficiency virus

Introduction

The World Health Organization estimates that ten million people were infected with tuberculosis (TB) in 2020, with 1.5 million deaths in the same year [1]. Concurrently, the International Diabetes Federation estimates that 537 million adults aged 20 to 79 were living with diabetes mellitus (DM) in 2021, with 75% of these residing in low- and middle-income countries (LMICs) [2, 3]. An estimated 6.7 million people died from DM in 2021, with rising cases of type 2 diabetes mostly from LMICs [2, 3]. Different studies indicate that people with DM are more likely to develop TB with worse treatment outcomes when receiving treatment for TB [4-7]. Therefore, understanding the blood sugar changes in patients during TB treatment is essential to ensure good treatment outcomes. Globally the prevalence of TB amongst DM patients is estimated to be 15.3% [8]. This prevalence varies depending on the age and sex of the population, the burden of DM and TB in the population and human development index scores [8]. The prevalence of DM in active TB is highest in North America and the Caribbean (19.7%), Western Pacific (19.4%) and Southeast Asia (19.0%) compared with Africa (8.0%) [8]. A prevalence of 15%, 11% and 10% has been documented in Nigeria, Tanzania and Ethiopia, respectively [9].

While numerous studies indicate that diabetes is a risk factor for TB, it is not completely clear if TB or its treatment predisposes one to develop DM [10-12]. Available explanation points to an impaired glucose tolerance (IGT) during treatment with anti-TB drugs, which may or may not resolve once the treatment is completed [11, 13-17]. This IGT is thought to be due to underlying undiagnosed diabetes or stress response from infection, resulting in increased levels of stress hormones, interleukin-1, interleukin-6 and TNF-alpha, abnormal functioning of the pancreas and possible TB-induced pancreatitis offsetting endocrine function [10, 11, 18]. Though plausible, these explanations have not been fully verified. Also, a high TB burden has been associated with human immunodeficiency virus (HIV) infection, which results in an immunocompromised state. So, HIV co-infection in TB patients may result in varied immune and endocrine responses with untoward outcomes.

Although studies describing the effect of TB treatment on blood glucose are available, these are few in Africa and other LMICs. Additionally, DM-TB studies in resource-poor settings with high HIV burden are required to understand the intersection with HIV. Some available studies have methodological limitations such as small sample size and short follow-up post-TB treatment [19-21] and were conducted before the HIV epidemic. A search of PubMed and the Joanna Briggs Institute (JBI) Database of Systematic Reviews and Implementation Reports conducted on 25 July 2021 indicates few review articles and a systematic review protocol are available [10, 18, 22]. No scoping reviews were identified. The review articles presented useful information on the possible aetiology of abnormal glucose during TB treatment but none on the predictors. The available studies

also focused on blood glucose changes in people with known DM status, not those with a normal blood glucose level before commencing TB treatment. Patients with known blood glucose anomalies will receive special care during TB treatment, but those presumed to have normal blood glucose may have poor treatment outcomes if abnormal changes in blood glucose were missed during treatment.

Therefore, the objective of this scoping review was to identify and compile the available evidence on possible abnormalities in blood glucose in previously normoglycaemic patients during and after TB treatment, using studies published from 1980 to 2021.

Methods

This review was developed using the JBI reviewer's manual and the methodology is based on the framework developed by Arksey and O'Malley [23, 24].

Scoping review questions

The following questions were used as a guide to fully describe the topic of this scoping review and the articles included in the review:

1. What methodology has been employed in describing the abnormal blood glucose arising from TB treatment?
2. What approaches have been identified as appropriate for measuring blood glucose during TB treatment?
3. What is the TB treatment outcome for patients who develop abnormal blood glucose while on TB treatment?
4. What factors determine the occurrence of abnormal blood glucose during TB treatment?
5. What is the frequency of abnormal glucose tolerance or DM in patients receiving TB treatment?

Information sources and search strategy

A search was done for studies describing TB treatment's effect on patients' glucose levels from 1 January 1980 to 30 June 2021. This period was chosen to accommodate the increase in HIV infections that led to an increase in the number of new TB cases [25, 26]. We searched the PubMed, Web of Science, CINAHL and Embase databases. A three-step approach was used to identify articles for inclusion in the review [23]. The first step was a preliminary search that involved identifying index terms and MeSH

terms by searching PubMed and Embase using keywords from the scoping review's topic (e.g., *tuberculosis treatment, TB treatment, abnormal glucose/hyperglycemia/glucose intolerance, diabetes*). The second step was to search the databases for articles using all the identified text words and keywords. The PubMed search was done on 8 November 2021 and the search terms used include ("Tuberculosis"[MeSH Terms] OR "tuberculo*"[Title/Abstract]) AND ("treat*"[Text Word] OR "therap*"[Text Word] OR "drug*"[Title/Abstract] OR "medication*"[Title/Abstract] OR "medicine"[Title/Abstract] OR "therapeutics"[MeSH Terms] OR "drug therapy"[MeSH Subheading]) AND ("hyperglyc*"[Title/Abstract] OR "glucose intoler*"[Title/Abstract] OR "high blood glucose*"[Title/Abstract] OR "glucose tolerance"[Title/Abstract] OR "glycaemic"[Title/Abstract] OR "glycemic"[Title/Abstract] OR "hyperglycemia"[MeSH Terms] OR "blood glucose"[MeSH Terms] OR "Glucose Tolerance Test"[MeSH Terms]). Additional search criteria for other databases are available in ***Supplementary file 1***. The third step involved searching the reference list of the identified articles from the second step for additional articles for inclusion in the list of potential articles. Where there was a need, the authors of primary studies were contacted to obtain additional information regarding their study. A librarian from Utrecht University Library guided the search processes to ensure we used appropriate search terms and obtained relevant articles.

Inclusion criteria

Included articles were original studies (case-control studies, cross-sectional studies, cohort studies and clinical trials) with participants of all ages from any part of the world. The following additional inclusion criteria were applied: (a) studies that were published from 1 January 1980 to 30 June 2021, (b) articles in English, (c) studies that specifically indicated that blood glucose was done at baseline or before the start of TB treatment and non-diabetic patients were followed-up either during or after treatment or both, and (d) studies that had information on the country where the study was conducted or specifically stated the region covered.

Exclusion criteria

Excluded articles were those that were outside the study period, non-original studies (case reports, review papers, modelling studies, systematic reviews and meta-analyses, letters to the editor and opinion papers), studies for which the full texts were not accessible, studies with participants already known to be on treatment for DM, studies with no follow-up data and those with outcomes other than TB.

Study selection for inclusion

The study selection followed two steps. The first step was the title and abstract screening, and the second step was the full-text screening. All identified articles were compiled

and entered into EndNote (Clarivate Analytics, Philadelphia, USA) for deduplication. Once deduplication was complete, the remaining articles were uploaded into Rayyan software for title and abstract screening based on the inclusion criteria [27]. This was done independently by two reviewers (VW, CO). Where there was a conflict and the two reviewers could not agree, a third reviewer (AV) resolved the conflict. The full text of all the articles selected at the title/abstract stage was compiled and entered into EndNote for a full-text review and selection based on the inclusion criteria independently by two reviewers. Articles not meeting the inclusion criteria were excluded at this stage. The two reviewers first discussed and resolved disagreements and only invited the third reviewer when they did not agree. A PRISMA flow diagram (***Figure 1***) describes the steps adopted during article screening and selection for inclusion in the final study.

Data extraction (Charting the results)

The information extracted from each article is listed in ***Box 1*** and is based on the JBI reviewer's manual [23]. A standardised data extraction form to capture the required information was developed in REDCap as a survey [28] (***Supplementary file 2***). This was validated and updated by two reviewers (VW, CO) using five selected studies per JBI guidance [23]. They independently extracted data from each article into the REDCap survey (each reviewer assigned each study a predetermined code to enable comparison). At the end of data extraction, data from the REDCap spreadsheet were compared, and all discrepancies were resolved before using a merged file for data synthesis and subsequent analysis. For clarity, successful TB treatment outcome was defined as "cured or completed treatment", while a poor outcome was defined as "relapse/treatment failure, loss to follow-up or death".

Results

We identified 1,277 titles from our search (***Figure 1***). Of these, 945 unique titles were identified for screening after excluding duplicates. In the title and abstract screening, 916 articles did not meet the inclusion criteria, leaving 29 articles for a full-text review. Fourteen articles [13-15, 19-21, 29-36] were included in the final selection, while 15 articles were excluded. Two of five authors with contact information whose main text was unavailable were contacted but did not respond. Contact information was not available for the other three.

Description of included studies

The general characteristics of the 14 included studies are summarised in ***Table 1***. Studies were conducted between 1984 and 2020, mainly in Asian (50%) and African (36%) countries. One study was conducted in South America and Europe. The articles, though

varied, all aimed at studying or identifying IGT or hyperglycaemia during TB treatment. The studies were all observational, and 50% (n=7) were prospective cohort studies. Twenty-one per cent (n=3) were case-control studies, and 14% (n=2) were a combination of cross-sectional and prospective cohort studies. The sample size for the studies varied from 21 to 6,312, and participants from ten studies were patients receiving treatment for drug-sensitive TB. Of the remaining four studies, each used either multidrug-resistant TB patients (MDR-TB), HIV-TB co-infected patients, patients attending a private clinic or patients with respiratory symptoms. The participants were mostly males, with the proportion of males ranging from 49% to 78%, and the mean age of all participants ranged from 29.5 to 53 years.

Seven out of the 14 studies (50%) included HIV-co-infected participants. The proportion of HIV co-infection in four studies was less than 10%, then 26%, 61% and 100% in the remaining three studies. In ten studies, participants received first-line TB treatment, one was a second-line only and three were all types of treatment.

Method of glucose estimation

Four main types of glucose estimation tests were used either singly or in combination. These include FBS (64%), glycated haemoglobin test (HbA1c) (50%), oral glucose tolerance test (OGTT) (50%) and random blood sugar test (RBS) (14%). Some studies combined two or more tests to estimate glucose levels: 36% (FBS + OGTT), 21% (FBS + HbA1c), 14% (HbA1c + OGTT), 14% (RBS + HbA1c), 7% (FBS + HbA1c + OGTT) and 7% (RBS + HbA1c + OGTT).

Time of glucose estimation

Five described the time of glucose estimation in the studies: baseline, three months, six months, end of treatment and post-treatment (***Figure 2, Table 2***). Measurements were done at baseline in all 14 studies and a combination of time points thereafter. Two studies (14%) used all five parameters to describe the time of glucose estimation.

Glucose changes during tuberculosis treatment

Most of the studies defined DM and hyperglycaemia based on the guidance provided by the American Diabetes Association [37]. In this guide, DM is defined as glucose level ≥7.0 mmol/l, ≥11.1 mmol/l or ≥6.5% using FBS, OGTT or HbA1c, respectively. IGT is similarly defined as a glucose level of 5.6 to 6.9 mmol/l, 7.8 to 11.0 mmol/l or 5.7 to 6.4% using FBS, OGTT or HbA1c, respectively. The studies excluded patients with a known diagnosis of DM before conducting a baseline glucose test. With some variability, patients identified with glucose levels consistent with DM and hyperglycaemia had repeat tests at specified periods. ***Table 2*** describes the proportion of participants with DM and hyperglycaemia at baseline and during the follow-up period.

Twelve (86%) studies showed the proportion of previously normoglycaemic patients with glucose values in the DM and IGT range at baseline reduced during treatment follow-up and end of treatment, while only two studies [15, 35] showed an increase (***Table 2***). DM decreased from 11.9% at baseline to 9.3% at follow-up, while IGT decreased from 46.9% at baseline to 21.5% at follow-up [36] in one of the studies conducted in South Africa. On the contrary, an Iranian cohort study [15] showed that 24% of patients developed DM in the follow-up period, while the proportion with IGT increased from 31% to 34%. Similarly, another study in Pakistan [35] observed that the proportion of IGT increased from 32% at baseline to 42% at follow-up. Most of the follow-up was done at three months (71%) followed by end of treatment (43%). With follow-up at different times, most studies (86%) agree there is a reduction in the glucose level at follow-up compared to baseline and dysglycaemia observed at baseline normalised at follow-up or end of treatment. Glucose levels were higher in older patients, mostly above 40 years, compared to younger patients [13-15].

TB treatment outcome and glucose changes

A summary of results with TB treatment outcomes and glucose changes is presented in ***Table 3***. In three studies, 64%, 75% and 95% of the patients had a successful treatment outcome [15, 33, 34]. Two studies indicated that TB patients with DM or IGT were more likely to develop cavitary lung lesions, with one of the studies indicating a 54% prevalence [15, 30]. In one study where patients were followed up to one year after TB treatment, patients with hyperglycaemia had a 48.9% risk of mortality compared to 7.9% in those with euglycaemia [33]. While another study showed that hyperglycaemia at enrolment diagnosed using fasting capillary glucose was associated with poor treatment outcomes such as loss to follow-up, treatment failure or death (aOR 2.46; 95% CI: 1.08 to 5.57) [21], a 2019 study from Mali [34] indicates that blood sugar levels had no impact on TB treatment outcomes. Researchers in Nigeria [31] did not find any difference in HbA1c levels based on HIV status, but a 2017 study in China [32] showed an HIV positive status, DM, smoking cigarettes and presenting to a hospital instead of a clinic were associated with an unstable FBS during TB treatment.

Outcomes in TB-HIV co-infected patients

Of the seven studies that included HIV co-infected participants, six provided information on glucose changes or their association with TB treatment outcomes based on the HIV status of the participants. The different outcomes are presented in ***Table 4***.

Discussion

This scoping review has compiled findings from different studies on the changes in blood glucose levels of patients receiving treatment for TB. Most of the studies were conducted in Asia and Africa (***Table 1***), indicating locations with a high prevalence of TB. Consistent with the known epidemiology of TB, there were more male participants in the studies than females and glucose levels were higher in older participants. The FBG test was the commonest method for estimating blood sugar, followed by OGTT and HbA1c. There was no standardised approach to estimating blood sugar for patients, and most studies combined two or more approaches. In the studies where a combination of tests was used, HbA1c had higher values and patients with baseline values in the DM or IGT range were more likely to persist as hyperglycaemia throughout treatment [21]. This further indicates the use of HbA1c in identifying patients with long-term glucose abnormalities.

Although all studies conducted baseline blood glucose assessments, subsequent measurements were different across the studies. For glucose screening to identify DM comorbidity during treatment, the timing of blood glucose screening should be standardised to allow for comparison across different patients and country programmes. Some studies only repeated glucose measurements for patients who were not known DM patients but with glucose measurements in the DM or IGT range at baseline, excluding those with normal baseline values [20, 21, 35]. These studies could have primarily aimed at following up on patients with abnormal glucose measurements or adopted as a cost-saving measure. A limitation of this approach is that new cases of DM or hyperglycaemia during the follow-up period could be missed.

Findings from this review suggest the mean blood glucose levels in patients who were previously not known to have DM but with baseline values in the DM or IGT range decreased once they commenced treatment. The prevalence of elevated blood glucose also decreased during follow-up. This is consistent with earlier findings that the elevated blood glucose at diagnosis may be due to stress hormones' response to the disease process [10, 11, 18]. However, the elevated blood glucose did not always resolve following treatment, as some studies reported patients with persistent hyperglycaemia after TB treatment (***Table 2***). This could be people with undiagnosed DM before getting infected with TB or those already with IGT who develop DM due to the extra insulin resistance triggered by infection. Two studies conducted in Iran and Pakistan indicated an increase in blood sugar measurements after treatment [15, 35]. We are cautious of the interpretation of these studies as the number of patients screened at follow-up was lower than the baseline. This reduced number of follow-ups during TB treatment highlights a common problem encountered by TB programmes where patients are lost to follow-up or discontinue treatment due to various reasons such as distance to the health facility,

stigma, treatment fatigue, relocation or treatment costs. Another reason could be down referral of patients once they are stable on treatment from tertiary health facilities to lower-level facilities such as clinics.

The development of cavitary lung lesions indicates a severe abnormality in the immune response during TB infection and could be associated with hyperglycaemia [30, 38]. Two studies reported poor treatment outcomes (relapse, death, or loss to follow-up) in patients with DM or hyperglycaemia at enrolment and one-year post-treatment follow-up [21, 33]. This is consistent with a 2019 systematic review that showed the odds of death (OR 1.88, 95%CI 1.59–2.21) and relapse (OR 1.64, 95%CI 1.29–2.08) were higher in patients with DM receiving TB treatment compared to normoglycaemic TB patients [39]. Similarly, a 2022 multi-centre prospective cohort study from Brazil showed that poor TB treatment outcomes were associated with baseline dysglycaemia and higher HbA1c values [40]. From the studies, it is seen that glucose values improved over time with good TB treatment outcomes. A 2021 study from Ghana shows that though more patients with normoglycaemia had a sputum conversion at two months compared to those with hyperglycaemia, this difference became insignificant at six months, indicating that the observed dysglycaemia at the onset of treatment was temporary [41] and had no association with treatment outcomes. This implies that good treatment outcomes can often be achieved in DM patients with adequate glucose control.

This review assessed studies that included HIV-positive participants to ascertain if HIV status affected DM-TB association, but the findings were mixed, tending toward a reduction in hyperglycaemia or no difference based on HIV status (***Table 4***). This could be because we had only six studies reporting this, and it was not the primary outcome of our study. Despite this, conflicting findings have been reported on the effect of HIV on TB/DM or hyperglycaemia. Studies conducted in Tanzania and Nigeria [42-44] indicate a stronger association among HIV-negative participants, while another study conducted in South Africa [45] indicates a stronger association among people living with HIV. Further research is required to convincingly describe this association as the different blood glucose measurement approaches and medications taken by people living with HIV can influence outcomes [36].

Strengths and Limitations

A key strength of this scoping review is the rigorous methodological approach adopted at the different stages to ensure reproducibility, minimal errors and that the included studies met the inclusion criteria. The review team accessed four electronic databases to ensure relevant studies were not excluded. We also expanded the search to cover a period when HIV cases gradually increased and, more recently, to cover the period of the

COVID-19 pandemic where we expect more screening for diabetes would be done since it is a high-risk factor for COVID-19-associated mortality. Finally, our review team have diverse expertise (infectious disease epidemiologists, biostatisticians, clinicians, public health specialists and non-communicable disease epidemiologists), which served as a useful resource to guide the review process.

As a limitation, our review included relatively few articles as most studies in this field assessed glucose changes in known DM patients receiving treatment for TB. Since we did not extract records from all the databases, we may have missed some studies from the databases we did not search. For studies published during the COVID-19 pandemic, bias may likely have been introduced by elevated dysglycaemia from COVID-19 infections. But these are few and published in the early days of the pandemic. No risk of bias assessment was done to ascertain the methodological rigour of the included studies; therefore, recommendations cannot be provided based on the findings of this review. Nevertheless, we have been able to present findings from studies that describe glucose changes in non-DM patients receiving treatment for TB.

Conclusion

This scoping review aimed to identify and compile the available evidence on possible abnormalities in blood glucose during and after TB treatment. The studies indicated that dysglycaemia in patients receiving treatment for TB normalised after commencing anti-TB medication at the end of treatment, and a positive HIV status was not associated with glucose changes during TB treatment. There was no standardised method and time for testing or screening as the reviewed studies adopted different approaches. Further investigations on patient follow-up after TB treatment for possible signs of glucose changes that may result in high mortality and the impact of HIV on the association between DM and TB are required. This will enable definitive conclusions on the observed high mortality in persons with high glucose post-treatment and any effect of HIV on the association between DM and TB.

Paper context

Evidence of changes in blood glucose during tuberculosis treatment and the association with HIV is unclear. Our study shows that dysglycaemia identified at the onset of tuberculosis treatment is normalised at follow-up and end of treatment and patients with baseline dysglycaemia have poor outcomes post-treatment compared to normoglycaemic patients. HIV status was not associated with glucose changes during

treatment. Further research is required to understand morbidity post-tuberculosis treatment and its association with HIV.

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Box 1: Summary of information extracted from articles

Author(s)
Year of publication
Location the study was conducted (country, continent)
Aim/purpose
Study population (including mean/median age and sex)
Sample size
Study type (observational/experimental)
Study design used (including methods & time of glucose measurement)
Statistical method (descriptive/simple analysis/advanced)
Outcome details of the study (proportion with DM and hyperglycaemia, HIV status)

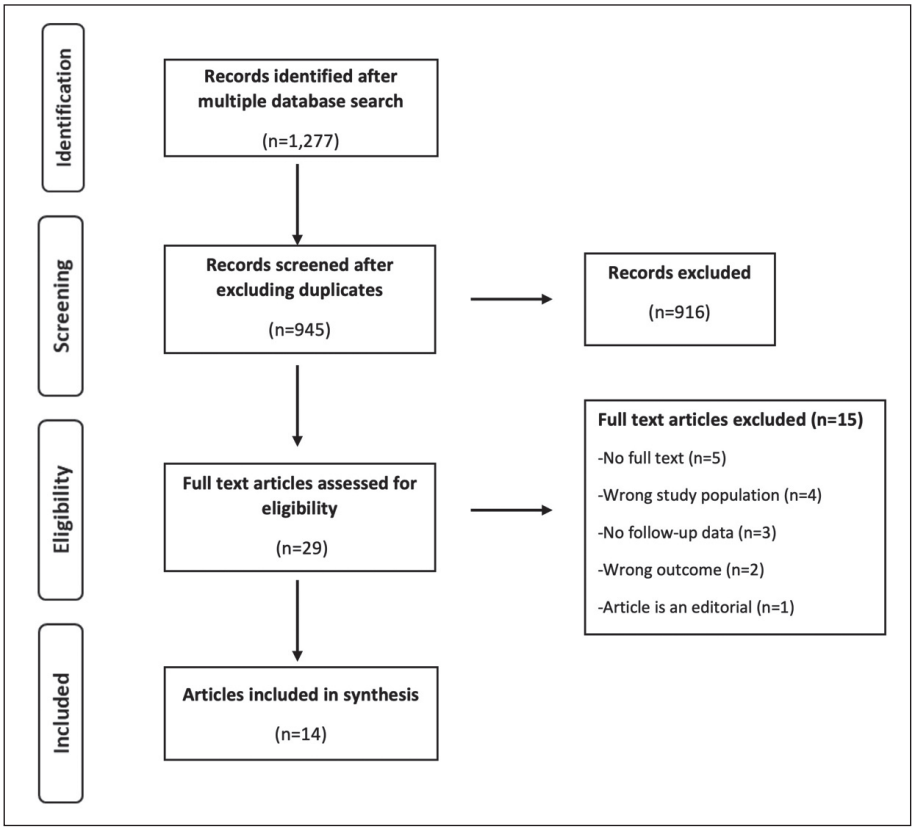

Figure 1: PRISMA flow diagram

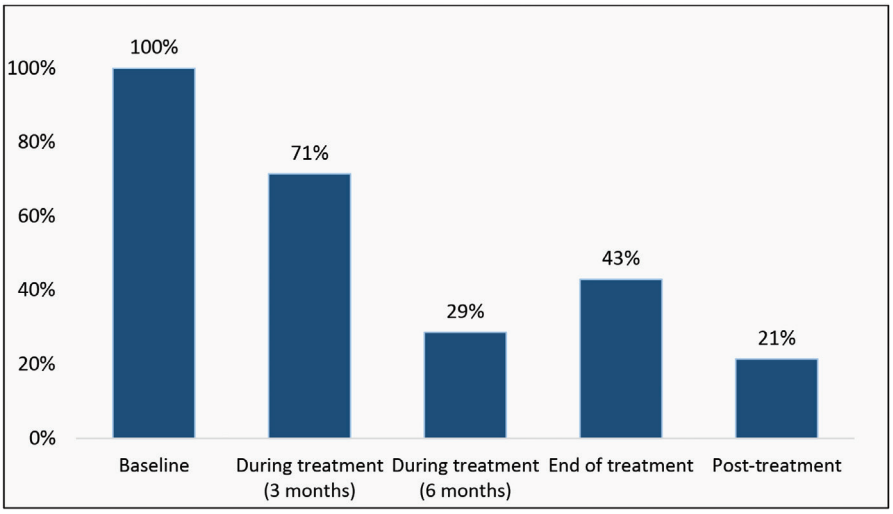

Figure 2: Timelines* for glucose estimation in different studies.
*Will not sum up to 100% since studies used a combination of timelines.

Table 1: Description of the included studies

First Author (Year/ Country)	Aim Of The Study	Study Design	Sample Size	Study Population	Sex (% Males)	Simple Analysis*	Advanced Analysis**
Purohit, S D (1984 / India)	To assess the effect of rifampicin therapy on glucose tolerance	Prospective cohort	57	TB patients	77	Yes	No
Singh, M.M (1984 / India)	To determine the prevalence of impaired glucose tolerance in active pulmonary TB patients and to determine the effect of anti-tuberculous chemotherapy on the glucose tolerance curves	Prospective cohort	52	TB patients	65	Yes	No
Oluboyo, P.O (1990 / Nigeria)	To determine the significance of glucose intolerance in TB	Case-control study	54	Pulmonary TB patients	63	Yes	No
Jawad, F (1995 / Pakistan)	To unmask glucose intolerance in patients with active pulmonary TB and to assess the effect of treatment on its reversal	Cross-sectional and prospective cohort	106	Outpatient pulmonary TB patients	59	No	No
Basoglu, O.K (1999 / Turkey)	To compare glucose tolerance test results of pulmonary TB patients with those of patients with community-acquired pneumonia	Case-control study	58	Pulmonary TB patients	78	Yes	No
Tarbasi, P (2014 / Iran)	To examine HbA1c of new TB patients and relate to if they complete TB treatment	Prospective cohort	158	New TB patients	49	Yes	No
Akinlade, K.S (2016 / Nigeria)	To assess changes in glycated haemoglobin levels in MDR-TB patients	Longitudinal study	21	MDR-TB patients	68	Yes	No
Boillat-Blanco, N (2016 / Tanzania)	To examine the association of TB and its outcome with the presence and persistence of hyperglycaemia in Tanzania, using three different DM screening tests.	Case-control study	530	Pulmonary TB patients	58	Yes	Yes
Lin, Y (2017 / China)	To understand if blood glucose levels were stable or fluctuated during TB treatment	Prospective cohort	270	TB patients	66	Yes	Yes
Moreira, J (2018 / Brazil)	To assess the impact/prevalence of hyperglycaemia on TB outcomes, comparison of treatment outcomes & one-year mortality rate based on the glycaemic status of patients during treatment	Retrospective cohort	473	HIV-TB coinfected patients	69	Yes	Yes

First Author (Year/ Country)	Aim Of The Study	Study Design	Sample Size	Study Population	Sex (% Males)	Simple Analysis*	Advanced Analysis**
Diarra, B[#] (2019 / Mali)	To determine the prevalence of DM in newly diagnosed TB patients	Cross-sectional and prospective cohort	201	TB patients	73	Yes	Yes
Krishnappa, D (2019 / India)	To determine the presence of hyperglycaemia (DM & IGT) in TB patients and assess outcomes after successful treatment	Prospective longitudinal study	582	TB patients	56	Yes	No
Habib, S.S (2020 / Pakistan)	To investigate the outcome of bidirectional TB-DM screening in the private sector	Cross-sectional	6312	All patients attending a private clinic	53	No	Yes
Kubjane, M (2020 / South Africa)	To assess the association between hyperglycaemia and TB, at TB diagnosis, and after three months of TB treatment	Prospective cohort	850	Patients with respiratory symptoms	53	Yes	Yes

[#] Patients without DM at baseline were followed-up at months two and five.
*Chi-square, t-test, ANOVA, Fisher's Exact, correlation, Mann-Whitney test, Kruskal-Wallis test
**Linear/Logistic/Multilinear regressions/Cox regression

Table 2: Glucose changes before and during treatment

First Author (Year)	Sample Size	Time of Glucose Estimation	Baseline DM (%)	Baseline IGT (%)	Participants at Follow-up (N)	% DM at Follow-Up	% IGT at Follow-up
Purohit, S D (1984)	57	0, 7, 30 days	-	10.0	0	0.0	0.0
Singh, M.M (1984)	52	0, 4, 8, 12 weeks	3.8	44.2	52	1.9	11.5
Oluboyo, P.O (1990)	54	0, 3, 3 months PT#	5.6	37.0	53	1.9	9.3
Jawad, F (1995)	106	0, ET	19.8	29.2	23	21.7	21.7
Basoglu, O.K (1999)	58	0, 3 months	8.6	10.3	58	0	0
Tarbasi, P (2014)	158	0, 3 months	0	31.0	158	24.0	34
Akinlade, K.S*(2016)	21	0, 2, 4, 6 months PT	-	-	-	-	
Boillat-Blanco, N (2016) **	530	0, ET	6.8	24.3	378	1.4	10
Lin, Y (2017)	232	0, 2, 6 months	0	7.3	232	0	3.0
Moreira, J (2018)	473	0, 3, 6 months, ET, PT	2.1	10.4	426	5.4	-
Diarra, B (2019)	201	0, 2, 5 months	5.5	3.0	190	0	-
Krishnappa, D (2019)	582	0, ET, PT	7.0	4	579	-	1.5
Habib, S.S (2020)	6312	0, 3 months	24	32	502	-	42.0
Kubjane, M (2020)	850	0, 3 months	11.9	46.9	276	9.3	21.5

*Two months follow-up showed a significant reduction in mean HbA1c. No values were indicated.
Reported values are for 2-hCG (two-hour capillary glucose). #In those with abnormal results. **ET – End of treatment; **PT** – Post-treatment.
Follow-up glucose at 30 days and two months was grouped with three months

Table 3: Summary of results from the different studies

First Author (Year/ Country)	Overall Summary and Treatment Outcome
Purohit, S.D (1984 / India)	The mean rise in glucose was lower on the 30th day compared to the pre-treatment rise. The mean rise in glucose was higher in the rifampicin group at different intervals compared to the baseline.
Singh, M.M (1984 / India)	54% (19/35) of those with cavities had an impaired glucose tolerance indicating an association between cavities and IGT. Only six out of 23 with initial impaired glucose tolerance continued to show impairment at 12 weeks.
Oluboyo, P.O (1990 / Nigeria)*	Only 3.7% of patients remained abnormal three months after full treatment compared to baseline. The result suggests glucose intolerance during TB treatment caused by infection and is reversible. All patients had improved symptomatic and radiographic features at the end of treatment.
Jawad, F (1995 / Pakistan)*	Glucose levels improved and returned to normal after TB treatment.
Basoglu, O.K (1999 / Turkey)*	OGTT results returned to normal in both TB and pneumonia groups after treatment. Cases with abnormal OGTT were older than 40 years and more likely to be males.
Tarbasi, P (2014 / Iran)*	95% had a successful treatment outcome. 24% developed DM, were older, had the highest level of FBG and had the highest prevalence of cavitary lung lesions.
Akinlade, K.S (2016 / Nigeria)	HbA1c decreased at two months post-treatment compared to baseline. There were no changes in glucose levels at months four and six of treatment compared to baseline. No difference was seen in HbA1c levels based on HIV status.
Boillat-Blanco, N (2016 / Tanzania)	DM or IGT at enrolment was significantly associated with adverse TB outcomes (i.e., loss to follow-up, treatment failure, or death).
Lin, Y (2017 / China)	HIV positive status, DM, smoking cigarettes and presenting at a hospital rather than a clinic increased the odds of association with unstable FBG.
Moreira, J (2018 / Brazil)*	75% successful treatment outcome. Hyperglycaemia was associated with an increased risk of mortality one year after TB treatment compared to euglycaemia (48.9% vs 7.9%).
Diarra, B (2019 / Mali)*	No elevated blood sugar was seen at follow-up for the two periods. 64% with DM had a good TB treatment outcome and blood sugar levels had no impact on treatment outcome.
Krishnappa, D (2019 / India)	Patients with hyperglycaemia (DM & IGT) were older. The blood sugar levels improved in all patients with DM following treatment of TB.
Habib, S.S (2020 / Pakistan)	42% (213/502) with previous normal HbA1c had an increased HbA1c at three months follow-up while 58% (141/244) with previous elevated HbA1c dropped to the normal range at three months follow-up.
Kubjane, M (2020 / South Africa)	2.6% (n=10) with DM at enrolment reverted to normal at follow-up; and 22.5% (n=105) of patients with IGR reverted to normal at follow-up.

*Studies with outcomes

Table 4: Summary outcomes in HIV-positive patients receiving TB treatment

First author (Year/ Country)	Study population	Sample size	% Hiv positive	Outcome based on HIV status
Tarbasi, P (2014 / Iran)	New TB patients	158	3.2	Not assessed.
Akinlade, K.S (2016 / Nigeria)	MDR-TB patients	21	26.3	No difference in baseline HbA1c between HIV-positive and negative participants (p=0.954).
Boillat-Blanco, N (2016 / Tanzania)	Pulmonary TB patients	530	32	Using HbA1c, HIV-positive participants had lower odds of DM (p=0.048). No difference between those receiving ART and those not receiving ART.
Lin, Y (2017 / China)	TB Patients	270	3.3	Only 9/151 with known HIV status were HIV positive and 6/9 HIV positive patients had unstable FBG. HIV-positive participants had higher odds of unstable FBG after adjusting for confounding (p=0.027).
Moreira, J (2018 / Brazil)	HIV-TB coinfected patients	473	100	***Successful treatment outcome*** - euglycaemic group (75%), hyperglycaemia group (28%), DM group (80%); ***Adverse event*** - euglycaemic group (25%), hyperglycaemia group (71%), DM group (20%); ***Death*** - euglycaemic group (7.5%), hyperglycaemia group (51%), DM group (10%); ***Lost to follow-up*** - euglycaemic group (17%), hyperglycaemia group (20%), DM group (10%).
Diarra, B (2019 / Mali)	TB patients	201	6.5	No HIV-positive participant developed DM during TB treatment.
Kubjane, M (2020 / South Africa)	Patients with respiratory symptoms	850	61	Significant positive association between DM and TB at baseline (OR, 2.4 [95% CI, 1.3–4.3]) and follow-up (OR, 3.3 [95% CI, 1.5–7.3]) regardless of HIV status.

Supplementary File 1: Additional Search Criteria for other databases

Web of SCIENCE
Date 8 November 8, 2021. Output: 570

ALL=(tuberculos*)
((((ALL=(treat*)) OR ALL=(drug therap*)) OR ALL=(therap*)) OR ALL=(medica*)) OR ALL=(medicine)
(((((((ALL=(hyperglyc*)) OR ALL=(glucose intoler*)) OR ALL=(high blood glucose*)) OR ALL=(glucose tolerance)) OR ALL=(glycaemi*)) OR ALL=(glycemi*)) OR ALL=(Hyperglycemia)) OR ALL=(Blood Glucose)) OR ALL=(Glucose Tolerance Test)

CINAHL
Date 8 November 8, 2021. Output:

TI tuberculos*

TI treat* OR TI drug therap* OR TI therap* OR TI medica* OR TI medicine

TI hyperglyc* OR TI glucose intoler* OR TI high blood glucose* OR TI glucose tolerance OR TI glycaemi* OR TI blood glucose OR TI glucose tolerance test

Embase
Date 9 November, 2021. Output: 356

1: 'tuberculosis'/exp OR tuberculo*
2: 'therapy'/exp OR therap*:ti,ab OR drug*:ti,ab OR medica*:ti,ab OR medicin*:ti,ab
3: hyperglyc*:ti,ab OR 'glucose intol*':ti,ab OR 'high blood glucose':ti,ab OR 'glucose tolerance':ti,ab OR glycemic:ti,ab OR glycaemic:ti,ab OR 'glucose tolerance test':ti,ab
1 AND 2 AND 3

Chapter 3

Epidemiology and Control of Diabetes-Tuberculosis Comorbidity in Eswatini: Protocol for the Prospective Study of Tuberculosis Patients on Predictive Factors, Treatment Outcomes and Patient Management Practices

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Abstract

Introduction

Previous studies indicate people with diabetes (DM) may have varying treatment outcomes when receiving treatment for tuberculosis (TB) and that TB infection or its treatment may predispose them to develop abnormal blood glucose or type 2 diabetes mellitus (T2DM). This has implications for Eswatini which is a high TB burden country and with increasing cases of non-communicable diseases including DM. This study will describe the epidemiology of DM-TB comorbidity in a prospective cohort of patients receiving TB treatment and identify best practices for integration of care for non-communicable diseases into TB services in Eswatini.

Methods and Analysis

This study will employ a mixed-methods approach. Data from a prospective cohort of newly enrolled TB patients at 12 health facilities from June 1 to September 30, 2022, and followed-up to February 28, 2023, will be used. For the qualitative, key informants who provide TB services at the health facilities will be interviewed. Quantitative data from patients will be analysed descriptively and by tests of association and multivariate modelling. Key informant interviews from healthcare workers will be analysed using content analysis.

Ethics and Dissemination

This research has been approved by the Eswatini Health and Human Research Review Board (EHHRRB) and participant confidentiality will be maintained. COVID-19 safety measures to reduce the risk of infection or transmission by researchers and participants have been instituted. Key programmatic findings and how they can impact healthcare delivery and access will be presented to the specific program in the Eswatini Ministry of Health and other relevant stakeholders.

Strengths and Limitations of the Study

- The use of a prospective cohort design allows for the collection of more accurate and complete data.
- Interview of key informants provides useful background to different factors which impact services access by TB patients.
- Reduced sample size due to a reduced number of new TB patients and a short follow-up period
- Information on the incidence of DM or hyperglycemia is limited due to a short follow-up period since DM may develop a few months after treatment.
- Healthcare workers may provide limited information during the in-depth interview due to fear of reprimand by the health authorities.

Keywords: Diabetes, Tuberculosis, COVID-19

Introduction

Background

The global pandemic caused by the novel coronavirus - severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected all countries and territories of the world (1, 2). High daily cases and mortality have been recorded in the United States of America, India and Brazil, closely followed by countries in Europe and Asia (3, 4). Mortality data indicated a high mortality rate in patients with comorbidities such as diabetes mellitus (DM), cardiovascular and respiratory diseases, kidney and liver diseases, those recovering from transplants and the critically ill (2, 4, 5). This indicates that non-communicable diseases (NCDs) have a propensity to coexist and complicate other disease conditions, most times, negatively altering the prognosis. Thus, the development of an appropriate context-specific method of managing commonly occurring non-communicable diseases is vital in the context of infectious disease.

In the last two decades, tuberculosis (TB) and HIV infection gained attention from global leaders, healthcare workers, researchers, and non-governmental organizations. This was due to their impact on the economy of high-burden countries, the health of individuals and pressure on the health system. With concerted efforts from different stakeholders, the prevalence of these two diseases has been controlled in high-income countries while some low and middle-income countries are gradually achieving epidemic control with stable infrastructures for a sustained response (6, 7).

While all efforts concentrated on curtailing the impact of HIV/TB with visible results of its reduction globally, the NCDs, diverse with insidious onset, gradually increased and are now the highest cause of mortality globally (8, 9). NCDs now account for about 71% of global mortality (10). This can partly be attributed to less-developed structures to combat NCDs with far less funding for NCD programs compared to TB and HIV, especially in low and middle-income countries which also have the highest incidence and prevalence of infectious diseases with high levels of poverty and social inequality (11). This neglect of NCDs has become evident as the countries with a high burden of infectious diseases now record high mortality from NCDs. This indicates that both conditions (NCDs and infectious diseases) coexist in the community with each disease acting as an enabler for the other (9, 11, 12). Major NCDs accounting for increased morbidity and mortality globally include cardiovascular diseases (17.9 million deaths - 44%), cancers (23%), respiratory diseases (10%) and DM (1.5%) (10, 13).

The coexistence of infectious diseases, particularly TB, with NCDs such as DM and hypertension has long been recognized by researchers with varying concepts of managing these conditions in the midst of dwindling resources for healthcare services

(14, 15). People with DM have a greater risk of developing TB. This increased risk is possibly due to poor glycemic control resulting in abnormal metabolism in macrophages and lymphocytes, which impacts the immune function of these cells. This predisposes to new TB infection or reactivation of latent TB in those who were previously infected (12, 14). On the contrary, the causes of impaired blood glucose during TB treatment are not clear. Current evidence points to an impaired glucose tolerance during TB treatment which may or may not resolve once treatment is completed (16-18). This may be due to undiagnosed DM, stress response from infection which elevates stress hormones or abnormal functioning of the liver which results in abnormal endocrine function (16, 19).

Among known diabetics undergoing treatment for TB, there have been concerns of DM delaying sputum conversion leading to a poor outcome. This is yet to be fully confirmed (12, 14). A recent study from Ghana shows significantly fewer patients with hyperglycemia had sputum conversion at two months of TB treatment compared to normoglycemic patients, but not at six months (20). Other factors that could impact TB treatment outcomes amongst people with DM include the non-integration of services that causes non-adherence, psychosocial factors such as stigma and increased economic burden of treatment for the two conditions which are paid for out-of-pocket in most low-income countries (12, 15). More recently, the COVID-19 pandemic impacted all service delivery and access to essential care. This was due to disruption in the supply of essential health commodities, widespread infection of healthcare workers with COVID-19 and restriction of movement which limited TB patients from visiting health facilities. The impact of the pandemic and the different measures adopted to limit COVID-19 infection on access to TB services and treatment outcomes is yet to be quantified.

The Syndemics concept has been used to describe the symbiotic coexistence of diseases with associated inequity in access to health and social services, poverty and malnutrition resulting in increased morbidity and mortality in at-risk populations (15, 21). The Syndemics concept originated from high-income countries' observations that different disease conditions coexist and affect the communities, notably the minority populations and those with low socioeconomic status. Meanwhile, the concept has been extended to describe the comorbid conditions which exist in low and middle-income countries, like TB/HIV and non-communicable diseases (15, 21). With a gradual increase in lifespan in low- and middle-income countries, the impact of NCDs particularly DM and hypertension, has become obvious. Morbidity and mortality due to TB and HIV have reduced because patients now access life-saving medications and observed morbidity and mortality is due to NCDs (22-24).

In Eswatini, literature on DM in the population and DM – TB comorbidity is scarce with easily accessible data being estimates by WHO and International Diabetes Federation (IDF) (25). Available studies have centred on HIV–NCD comorbidity and developing effective integration models to address the increasing cases of NCDs among HIV patients (26). A 2020 study on the prevalence of abnormal blood glucose metabolism in adults indicated a 3.9% prevalence of type 2 DM in adults who attended the outpatient department of a tertiary hospital but no data is available on associated co-morbidities with TB or HIV(25). Similarly, the International Diabetes Federation estimates the prevalence of DM in Eswatini is 3.6% in people aged 20-79 years while the age-adjusted prevalence for impaired glucose tolerance is 6.9% (27).

Significant progress has been made in the Kingdom of Eswatini in the provision of HIV/ TB services with HIV incidence in people 15 years and above reducing from 2.5% in 2011 to 1.4% in 2017 (28). Similarly, TB incidence reduced from 1069/ 100, 000 in 2009 to 363/100, 000 in 2019 (6). Despite these achievements in HIV/TB control, more is required to improve the quality of life of her citizens as more present with NCDs, notably cardiovascular diseases, DM and cancers (29). Data from the Eswatini Ministry of Health indicate DM accounted for 12% of outpatient department visits in 2018 and 5.9% of all in-patient mortality (29). Given the burden of TB in Eswatini, an increase in cases of DM due to lifestyle changes, obesity, and ageing may limit further successes in TB prevention activities. Further complicating the dilemma is the absence of reliable data on the prevalence of the common NCDs in the general population and diverse population groups, with the most recent reliable data on the burden of NCDs in Eswatini being the STEPS Survey, conducted in 2014 (30). Therefore, research on DM in people receiving treatment for TB will provide insight into the different factors that may impact DM and TB treatment outcomes and provide direction for effective health services delivery. This will help Eswatini achieve WHO's target of reducing by a third, the burden of NCDs by 2025 (9). In this research, reference to diabetes means type 2 diabetes mellitus (T2DM).

Rationale for the Research

1. There is a lack of reliable data on the burden of DM in Eswatini, both in the general population and different population subgroups. This study at its conclusion will generate reliable information on DM-TB comorbidity and the prevalence of DM and hyperglycemia in patients receiving treatment for TB.
2. With the availability of life-saving HIV/TB medications, people are living longer but are now exposed to developing diabetes due to changing lifestyles, ageing and possibly TB infection. This study will identify the risk factors for developing diabetes or hyperglycemia in people receiving treatment for TB.
3. There is an absence of evidence on factors hindering effective management of diabetes at healthcare facilities providing TB services in Eswatini. This research will identify these factors and propose context-specific solutions to improve the integration of TB and DM care.

Conceptual Framework

The study will be based on the Social-Ecological Model which examines different interactions which determine the health outcome of an individual (31). The different individual, interpersonal, community, organizational and policy/environmental contexts which can influence health outcomes in Eswatini in line with the social-ecological model will be considered. This will be contextualized to ascertain how these affect the services received by people while receiving treatment for TB and how service delivery can be improved.

The conceptual framework presented in Figure 1 highlights the possible interactions which determine the health outcome of an individual. The components of the social-ecological model have been unpacked to show the different direct and indirect relationships that exist between the components and the health outcome of an individual. Other determinants of the health outcome of an individual such as demand and supply factors are not included here. This is to enable easy interpretation and application of this framework to the context of Eswatini.

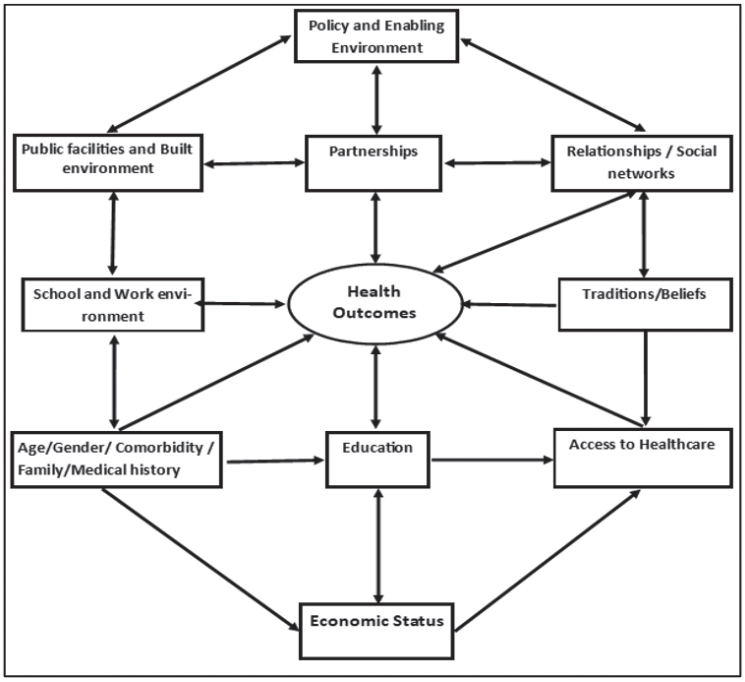

Figure 1: Conceptual framework for the study

Research Questions and Objectives

Research Question

The study research questions with the desired endpoint and required variables are presented in Table 1 below.

Table 1: Descriptive summary of different research questions and study requirements

S/n	Research question	Endpoint	Required variables	Proposed analysis method
	What is the prevalence and incidence of DM/ hyperglycemia in patients receiving treatment for tuberculosis in Eswatini?	-Prevalence of DM in diagnosed TB patients -Identified risk factors -Incidence of elevated blood glucose in those receiving treatment for TB -Identified predictive factors	- Sociodemographic variables -Clinical variables -Baseline and follow-up data	Descriptive: Frequency tables with percentages, Mean (SD) and/ or median (IQR) Comparative analysis: Pearson Chi-Square test ($\chi 2$) or Fischer's exact test for categorical variables. T-test or Mann Whitney for continuous variables. Statistical analysis: Univariate and multivariate logistic regression and mixed-effects model. Missing Data: If ≥10%, imputation of missing data will be done, and the results averaged across all the datasets imputed. Sensitivity analysis: Nested multilevel logistic regression analysis with random effects at two levels (region and individual) to account for clustering at regions. Model Fitness: Hosmer-Lemeshow goodness of fit test
	Does DM or hyperglycemia affect TB treatment outcome in patients receiving treatment for tuberculosis in Eswatini?	-Findings of comparative analysis of TB treatment outcome in patients with diabetics/ hyperglycaemia and those without	- Sociodemographic variables -Clinical variables -Baseline and follow up data	Descriptive: Frequency tables with percentages, Mean (SD) and median (IQR) Comparative analysis: Pearson Chi-Square test ($\chi 2$) or Fischer's exact test for categorical variables. T-test or Mann Whitney for continuous variables. Statistical analysis: Univariate and multivariate logistic or linear regression models. Missing Data: If ≥10%, imputation of missing data will be done, and the results averaged across all the datasets imputed. Model Fitness: Hosmer-Lemeshow goodness of fit test, Residual Sum of Squares (SSE)
	What factors limit the effective integration of diabetes care into TB Services provision at the health facilities providing TB care in Eswatini?	-Identified factors -Recommendations for effective services delivery	- All the variables from the qualitative questionnaire	Descriptive: Frequency tables with percentages, Mean (SD) and median (IQR) Qualitative analysis: Analysis of both deductive and inductive codes from healthcare worker's interviews.

Objectives

This research aims to describe the epidemiology, predictive factors, and control measures of diabetes in a prospective cohort of patients who will be treated for TB. The objectives are to:

1. Describe the epidemiology of diabetes-TB comorbidity in a prospective cohort of patients receiving TB treatment in Eswatini from 1 June 2022 to 30 April 2023.
2. Identify factors that predict the occurrence of diabetes (or hyperglycaemia) in patients receiving TB treatment in Eswatini from 1 June 2022 to 30 April 2023.
3. Describe the effect of blood glucose on TB treatment outcome in patients receiving treatment for TB in Eswatini from 1 June 2022 to 30 April 2023, and ascertain if diabetes is a precursor of first-line TB drug resistance.
4. Ascertain if there is a relationship between baseline BMI, HIV status, blood glucose level and TB treatment outcomes in patients treated for TB in Eswatini.
5. Identify factors that hinder effective DM care amongst diabetics receiving TB treatment in Eswatini and propose a context-specific approach to address these factors.

Methodology

Study Design

A mixed-methods prospective study design will be used for this study. For the quantitative part, a prospective cohort approach will be used to review data of consecutive newly diagnosed TB patients enrolled on care and followed up from June 1, 2022, to February 28, 2023. The qualitative part will involve the interview of select clinical healthcare workers who provide direct care to TB patients. Data from the prospective cohort will address objectives 1, 2, 3 and 4 while the healthcare worker's interview will address objective 5.

Setting

The study will be conducted at 12 health facilities providing TB services in the four regions of Eswatini (Mbabane Government Hospital, The Luke Commission, Phocweni Clinic, TB Center, Siphofaneni clinic, Mankayane Hospital, AHF Lamvelase Clinic, Raleigh Fitkin Memorial Hospital, AHF Matsapha, Pigg's Peak Government Hospital, Nhlangano Health Center, Hlathikulu Hospital TB Clinic). The health facilities are purposively selected because they see more TB patients at any given time and have medical officers who review TB patients with standard laboratories and x-ray facilities to aid patient investigations. Only complicated cases are referred to the National TB Referral Hospital. The National TB Referral Hospital is excluded from this study as it was converted into a COVID-19 isolation

and treatment centre and all patients relocated to one of these selected facilities. Eswatini is a landlocked country in Southern Africa with a population of about 1.2 million (29). It is surrounded by South Africa, except in the North-East which is bordered by Mozambique.

Patients on drug-susceptible TB treatment in Eswatini receive treatment for 6-9 months depending on if they have received the first-line drug before and are followed up monthly till after two consecutive sputum conversions (expected in the 2nd or 3rd month). Monthly follow-up continues after sputum conversion till they complete treatment. Sputum microscopy for Acid Fast Bacilli (AFB) and culture are reviewed on each follow-up visit. Drug-resistant tuberculosis (DRTB) patients are initially admitted until they have two consecutive negative sputum culture tests (sputum conversion) before discharge and monthly follow-up visits for clinical evaluation which includes medication review, sputum AFB and culture results review, and general assessment. The duration of treatment for DRTB is varied and can last 12-24 months depending on the drug regimen and response to treatment.

Patients receive routine laboratory assessments during their treatment including fasting blood glucose at baseline, twice during treatment and at the end of treatment before final discharge. Three follow-up visits post-discharge is advocated but most patients do not keep this appointment except those receiving antiretroviral medications from the same facility.

Study Population

From 2015 to 2020, about 19, 000 patients received treatment for tuberculosis in Eswatini and 6% of these were pediatric patients (32). The male-female ratio ranged from 1.4 to 1.6 within the same period and the TB/HIV co-infection rate in 2020 was 64% (32). Report of other comorbidities e.g., T2DM, or hypertension is not available. For the years 2015 – 2020, about 98% of all patients have a documented treatment outcome for all types of tuberculosis and the treatment success rate in 2019 and 2020 was 89% and 86% respectively (32). Different cadres of healthcare workers provide care for TB patients but those who will participate in the key informant interview will be nurses and doctors.

Sampling and Sample Size

A consecutive sampling approach will be used to enrol newly diagnosed TB patients on the study. Current TB program data indicate that on average, in a period of four months, about 410 patients are enrolled on TB care at the 12 selected health facilities. Therefore, it is estimated that a minimum of 380 – 430 participants will be enrolled on this study. Using an estimated diabetes prevalence of 3.6% in Eswatini (27), an effect size of 0.05

and an alpha of 5%, the estimated power of this study is 98%. A sample size range of 106 – 582 has been used in similar studies (18, 33-36) therefore this anticipated sample size will be adequate for the different outcomes.

One doctor and one nurse will be purposively selected and interviewed per health facility until saturation is achieved in each group and no more new information is obtained from the healthcare workers (37). Since the study will be conducted at 12 health facilities, there will be a minimum of 24 study participants for the qualitative study.

Inclusion Criteria

New patients aged 18 and above who will initiate treatment for any form of TB at any of the 12 selected health facilities from 01 June 2022 up to 30 September 2022 will be eligible for inclusion irrespective of sex. Patients meeting the above criteria who are able and willing to provide informed consent will be included.

Healthcare workers to be included in the study must have clinical training (doctors or nurses), regularly review patients' medical records, have worked at the health facility for a minimum of twelve months, and be willing to provide informed consent to participate in the study.

Data Collection

Data collection from patients (baseline and during follow-up) and interviews of healthcare workers will be conducted by two trained research staff conversant with TB data. Data from patients will be entered into an electronic form developed using Research Electronic Data Capture (REDCap). Patients' demographic and clinical information will be extracted at baseline and during follow-up visits (Month 2, Month 5/End of Treatment) till patients are discharged from care and have a treatment outcome documented in their case file per updated WHO guidance (38) (Supplementary file 1).

A structured questionnaire developed in REDCap will be administered electronically to healthcare workers to identify their views on DM-TB management and challenges to DM-TB services provision at the health facilities. This questionnaire has three sections that should take approximately 15 minutes to complete – demographic information, occupational information, and patient care-related questions. An interview will complement the electronically administered questionnaire (Supplementary file 2) to obtain healthcare workers' perspectives on service delivery and recommendations for improvement. An interview guide has been developed to assist the interviewers during

interviews (Supplementary file 3) to ensure the quality of the interview responses. The interview guide will be reviewed to ensure it is coherent and the questions asked directly operationalize the study research question. Before interviewing the healthcare workers, deductive codes will be discussed with the research team to act as a guide during the interviews and the final codes will include those raised by the participants. The interviewee will be allowed to respond with limited interruptions. Recorders will be used so that the correct information is transcribed once the interview is completed. The anticipated duration of the interview is 30 to 45 minutes.

Approach for Patient Data Collection

The TB units at the different health facilities where TB patients are enrolled and reviewed maintain patients' clinical information which will be available to the study team. Noting that some TB units may not have the facility for testing and recording baseline glucose measurements for patients and during follow-up, point of care Accu-Check Active Glucometer (Roche®) (with test strips and lancets) will be placed at the different TB Units for the measurement and documentation of blood glucose at baseline and during the 2nd and 5th month follow up visits. Based on this, baseline data will be collected at enrollment, while follow-up data for the 2nd-month visits will commence in the third month and that for the 5th-month visits will commence in the sixth month (Figure 2). This is consistent with the guidelines for the recording of patient information when receiving treatment for tuberculosis in Eswatini (Supplementary file 4). The provision of Accu-Check Active Glucometer (Roche®) is to ensure patients receive a blood glucose measurement at each visit and the study does not become an additional burden to the health facility. Study participants will not be required to fast before a blood glucose test as such a strict routine may not be achievable in programmatic conditions. All study participants with abnormal random baseline or follow-up glucose measurements will be referred to a clinician for further evaluation and care. At the end of the study, the glucometers will be donated to the TB unit for continued use with support from the health facility's laboratory.

Description	Timeline										
	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11
	Jun-22	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23
Baseline	Recruit	Recruit	Recruit	Recruit							
Follow up data 1 (Month 2)			Month 1 Recruits	Month 2 Recruits	Month 3 Recruits	Month 4 Recruits					
Follow up data 2 (Month 5)						Month 1 Recruits	Month 2 Recruits	Month 3 Recruits	Month 4 Recruits		
Follow up data for end of treatment								Month 1 Recruits	Month 2 Recruits	Month 3 Recruits	Month 4 Recruits

Figure 2: Schedule for data collection at baseline and during follow-up

The nurses in the TB unit will be oriented on how to use the Glucometer as a point-of-care test by a trained laboratory technician from the health facility's laboratory using a standardized guide (Supplementary file 5). The Glucometer will initially be calibrated by the health facility's laboratory technician at baseline, at the end of month 2 and at the end of month 4. This is to ensure the quality of the results produced by the Glucometer is standardized and possible calibration errors are identified and rectified. Additional baseline patient sociodemographic information – educational status, marital status, occupation, smoking and alcohol status which is not routinely collected will be obtained for this study.

Staff at the TB clinic will be oriented on the study and one healthcare worker at each of the 12 health facilities will be trained on how to approach and consent new patients into the study. Facilities will be visited monthly with a follow-up call weekly for updates.

Statistical Methods and Analysis

The baseline characteristics of variables in the patients' dataset will be presented in a table. The prevalence of DM or impaired glucose will be determined based on the number of patients with DM or impaired glucose at baseline and during the treatment period expressed as a proportion of all the patients treated in the same period. This will be determined overall and by the type of TB disease (drug-sensitive TB (DSTB), rifampicin-resistant TB (RRTB), DRTB or extra drug-resistant TB (XDR)). The occurrence of abnormal glucose during treatment will be determined based on the number of patients who had normal values at baseline but developed abnormal values during treatment or at the end of treatment. This will be determined overall, and by type of TB disease with additional analysis to estimate the mean and median time between TB diagnosis and identification of abnormal measurements. A logistic regression (or mixed effect model for repeated data) will be used to predict the occurrence of DM or hyperglycemia.

Statistical tests will be significant if $p<0.05$. Different sub-analysis, comparative and sensitivity analyses will be done to identify possible interactions which may exist between the different patient characteristics (e.g., age, sex, HIV status) and hyperglycemia e.g., testing to ascertain if there is an association between timing of culture conversion and blood glucose. The proposed statistical methods for the different research questions are presented in Table 1.

Qualitative analysis in form of analysis of identified codes will be done to identify factors that hinder the care of diabetics receiving TB treatment. Recommendations for improvement will be coded and similar codes will be analyzed and presented.

Study data entered into REDCap (39) will be extracted in Stata format and imported into Stata 15 (Stata Corp., College Station, TX) for analysis. The software NVivo (40) will be used for the analysis of transcribed information from healthcare workers' interviews.

Patient and Public Involvement

Patients and members of the public were not involved in the study design and the development of this protocol. However, TB program priorities were considered in the design of the study and protocol. Patients during their routine visits will be informed if their blood glucose measurement is within the normal values. Those with abnormal values will be referred for further review and care. Participating health facilities, healthcare workers, the TB program and relevant stakeholders will be provided with feedback on the outcome of the study with direct recommendations on how to improve access to TB services and integrate non-communicable disease care into TB services.

Ethics and Dissemination

Ethical Considerations

Approval for the study has been obtained from the Eswatini Health and Human Research Review Board (EHHRRB) (Protocol Reference Number: EHHRRB036/2021).

Participation in the study will be optional. Patients and healthcare workers who will be interviewed will be oriented and provided with a study information sheet (Supplementary files 6 and 7). They will be required to provide informed consent before participating (Supplementary files 6 and 7) and healthcare workers' consent will include consent for the recording of their comments. Researchers administering the interviews will be required to attest they read out the information sheet to the study participants and answered all questions to their satisfaction before commencing the interview.

Data will be de-identified to ensure confidentiality. Each patient record and healthcare worker interviewed will be assigned a unique identification code. This code will assist with retrieving information in case there is missing data during analysis or a follow-up question. Identifiable information will only be available to the Principal Investigator (PI) and the de-identified data will be accessible to the study team for monitoring of data quality. All project data will be stored in a password-protected hard drive to ensure data safety. Transcription will be done without linking names to comments to ensure confidentiality. Healthcare workers will be free to stop participating in the interview at any time without providing a reason. The risks to study participants are minimal and measures have been instituted to ensure the confidentiality and safety of data and information

from the patients and healthcare workers. Researchers who will access patient data and interview healthcare workers will be required to sign a confidentiality and non-disclosure document (Supplementary file 8).

Standard COVID-19 control measures will be adopted during data extraction and a virtual interview option will be available to limit infection and transmission of SARS-COV-2.

Dissemination

Several articles will be generated from this study for presentation either as a poster or oral presentation at local and international conferences and for publication in peer-reviewed journals.

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Supplementary file 1: Proposed variables list for the study

Facility name: _____
Date of visit: DD/MM/YY

Baseline*: Sociodemographic*
Assigned unique id
Age
Sex
Weight
Height
Educational status
Marital status
Occupation
Region
Smoking
Alcohol
Family history of DM

Baseline*: Clinical*
HIV status
Year HIV Diagnosis
Past TB Treatment
Date TB diagnosis
Type of TB (Drug Sensitive, Rifampicin Resistant, Drug-Resistant, Extra-Drug Resistant)
TB Drugs Regimen
HIV Drugs Regimen
Last Viral Load result
DM on admission
DM Treatment

Baseline and follow-up variables
Visit Date (DD/MM/YY)
Fasting Blood Sugar (FBS) (mmol/l)
Systolic Blood Pressure (SBP) (mmHg)
Diastolic Blood Pressure (DBP) (mmHg)
Sputum Acid-Fast Bacilli (AFB)
Sputum Culture

Adverse Event
Adverse Event Type
DM Diagnosis
Treatment Outcome

Supplementary file 2:
Healthcare Workers Interview Questionnaire

Date: _____

Health facility description (To be filled in by the researcher)

Questionnaire Identification Number: _____

Facility type: Hospital/Health centre/ Clinic

Facility location: Urban/Semi-urban/Rural

Section A: INTRODUCTIONS

The researcher introduces herself and confirms the healthcare worker is the right one who is scheduled for the interview.

The researcher gives an overview of the study to the healthcare worker and hands her a copy of the study information sheet (the healthcare worker would have received one by email some days before the interview).

If the healthcare worker accepts to participate in the study, s/he is given the consent form to review and endorse.

Section B: SURVEY

Sociodemographic Details

Date of Birth: _____

Gender: Male/Female/Other

Region of residence: Hhohho/Lubombo/Manzini/Shiselweni

Occupational History

1. Region hospital is located: Hhohho/Lubombo/Manzini/Shiselweni
2. Occupation/profession type e.g., a. Nurse b. Doctor
3. Nature of work a. direct patient care c. Other
4. Highest qualification a. Certificate b. Diploma c. Degree d. Post-graduate
5. Total number of years in your profession _____
6. Duration of years providing care for TB patients _____
7. Received training for Non-communicable diseases Yes/No
8. Received specific training in TB/NCD care. Yes/No
9. Received specific training in TB/Diabetes care. Yes/No
10. Number of in-service training received in the last twelve-months _____

Patient Care related Questions

1. In a month how many TB patients on the average present with a non-communicable disease (NCD) in your hospital e.g. of NCD – hypertension, diabetes, asthma, cancers

   _____ _____

2. What is the commonest NCD they present with? _____

3. In a month how many TB patients present with Diabetes Mellitus (This is baseline blood glucose >7.0 mmol/dl)? _____

4. Indicate Yes/No if the following are readily available at your health facility:

5. Policy document on TB care

6. Current National TB Treatment guidelines

7. Standard Operating Procedure (SOP) for the care of TB patients with diabetes mellitus

8. Training requirement for staff on non-communicable diseases

9. Essential medicines list

10. Describe the protocol or give a summary of the protocol followed if "Yes" to 4C above.

    _____

11. If a TB patient has DM, is the treatment offered at the same consultation room? Yes/No

12. Where a TB patient is HIV positive and has diabetes mellitus, is the treatment for the three conditions offered at the same consultation room? Yes/No

13. Does your facility provide Hba1c? Yes/No

14. If Yes to 8 above, describe the referral process:

15. Indicate Yes/No if the following services are offered to TB patients at baseline:
    a. HIV Testing
    b. Fasting/random blood glucose
    c. Blood Pressure measurement
    d. Indicate Yes/No if the following services are offered to TB patients during follow-up visits:
    e. HIV Testing
    f. Fasting/random blood glucose
    g. Blood Pressure measurement

16. Indicate if the following are available or not available for TB patient screening at your OPD:
    a. Sphygmomanometer
    b. Weighing scale
    c. Glucometer
    d. Urinalysis test strips
17. Indicate Yes/No if the following medications are available for dispensing at your facility:
    e. Insulin
    f. Oral DM drugs
    g. Antihypertensive medication
18. Indicate Yes/No if there has been a stock-out of the following medications at your hospital in the last six months:
    a. Glucometer test strips
    b. Urinalysis test strips
    c. Insulin
    d. Oral DM medication
    e. Antihypertensive medication
    f. At least one 1st line TB medication
19. How many clinical staff (doctors and nurses) provide care for TB patients in your hospital? _____

Section C: Qualitative Interview

Healthcare Providers Perspective

1. If your patient presents with symptoms of diabetes, what tests are available to help you and your team make a diagnosis?

Prompt – apart from Fasting blood glucose, do you have HbA1c test available? If yes, describe the procedure for referring a patient for this test.

2. Is Oral glucose tolerance test available? Can it be done?
3. If a TB patient has diabetes or develops abnormal blood glucose, describe the protocol or referral process adopted for the care of this patient.
4. Considering the number of TB Patients seen daily at your TB department, do you think your department has enough clinical staff? Prompt- How do you work to ensure continued services provision?
5. What best practices have your unit adopted that has improved the care of TB patients receiving treatment in general and those with Diabetes Mellitus?

6. What is your view of the current standard of care for TB patients? Prompt – do you think this can be improved? If yes, what can be done?
7. Do you feel you are well-trained and prepared to provide the required care for TB patients with DM? Prompt – if yes, what training have you received? How has it helped you? If no, what training do you specifically need?
8. Are there any challenges that hinder you from providing effective care to TB Patients in your hospital?
9. Are there any challenges that limit the provision of diabetes mellitus care to TB patients in your hospital?

Prompt for 7 & 8: What would you suggest that can improve services delivery for TB patients in general and those with diabetes mellitus?

10. In the last 18 months, how has the COVID-19 Pandemic affected your ability to provide care to TB patients with hypertension and diabetes mellitus?
    Prompt – is there anything that should have been done to improve care you provide? Which issue stands out for you that should be addressed? What best practice can you recommend to other facilities?

Additional comments:

Supplementary file 3: Interview guideline

This guideline provides an outline of the different questions the healthcare worker should be asked based on the different sections of the questionnaire. The researcher should adapt the questions and may not need to necessarily ask exactly the way it is written and should observe the healthcare worker for guiding cues during the interview.

This interview aims to obtain the healthcare workers perspectives on services accessed by the TB patients, those who are also being treated for DM, and those who develop DM during treatment. The interview will also identify best practices instituted by the healthcare workers to improve services, challenges they encounter during services delivery and some recommendations on what they think can be done to address the challenges.

Section A: Introduction

The first part of the interview aims to develop a rapport with the participant you are interviewing. It is important to develop a non-judgemental tone throughout the interview and to convey that there are no right or wrong answers.

Start by ensuring the participant is comfortable and at ease. Introduce yourself and confirm you have the right healthcare worker for an interview. Provide a recap about the study and give the healthcare worker a copy of the Study information sheet to review and the consent form to sign if they accept to participate in the study.

Turn the digital recorder on.
Example introduction – adapt as appropriate

Thank you for agreeing to be interviewed for our study today. As I explained earlier, we are studying the different processes involved in the provision of services for TB patients and, those with DM or those who develop DM during treatment. We are interviewing you to better understand this process and some challenges you encounter. This will enable us to develop recommendations that can help improve services delivery in the future.

We are interested in your opinion today; everything you say is very important to us. I will not talk much, but I want you to talk freely, and as much as you want. There are no "good" or "bad" answers.

Section B: Survey to provide a background on the healthcare worker and services delivery

This part of the interview aims to understand the background of the healthcare worker, processes adopted in the care of TB patients with TB, and availability of optimal work conditions which can enhance services provision.

Open the structured questionnaire on the tablet and allow the healthcare worker to respond to the short survey questions.

Provide clarity for any question that may not be clear.

Section C: Healthcare providers perspectives on services delivery

This part of the interview aims to understand how well equipped and confident health practitioners are in providing care for TB patients also receiving treatment for DM. This section will also elicit challenges encountered by health providers, innovative approaches adopted to solve problems and their recommendations for improving services delivery for TB patients and those also receiving treatment for DM. There will also be a further enquiry on the impact of the COVID-19 pandemic on the provision of TB services and how this has impacted services delivery for TB patients with DM.

Now, I would like to ask you some questions about your work, potential challenges, and some recommendations for improvement.

Considering the number of TB Patients seen daily at your TB department, do you think your department has enough clinical staff to attend to them?

Probes:
What is your view of the current standard of care for TB patients?

Probes: Any frustrations?
What best practices have your unit adopted that has improved the care of TB patients receiving treatment for Diabetes Mellitus?

Probes:
Do you feel you have adequate training to care for TB patients with DM?

Probes: Please elaborate on some areas you would like more training in.
What would you suggest that can improve services delivery for TB patients with DM?

Probes:
How has the COVID-19 Pandemic affected your ability to provide care to TB patients with DM?

Probes: Did you have to screen all your patients before attending to them?

Ending the Interview
Before closing the interview, allow the participant to make any further comments about the topics discussed or to ask questions.

Thank the participant for his/her time and for sharing experiences and views.

Supplementary File 4: TB Treatment Card

TB 01: Tuberculosis Treatment Card

Name:_____ Registration TB No.: _____
Physical Address:_____ Date of Registration: _____
_____ Health Facility: _____
_____
Sex: (M / F)_____Age:_____Contact Number:_____ Pregnant / Non Pregnant: _____
Name of Treatment Supporter:_____ FP Method:_____
Contact No.: _____ Height:_____

Anthropometrics (Monthly)				
	Baseline	Month 2	Month 5	End of Treatment
Weight				
BMI				
MUAC				
BP	/	/	/	/
RBS				
Alt				
HB				
Creatinine				

Baseline Xpert Ultra		Sputum Smear Microscopy				Culture		
Result	*Date/Lab No.*	*Month*	*Date*	*Result*	*Lab No.*	*Date*	*Result*	*Lab No.*
		0						
		2						
		5						
		End						

DST	X-RAY
Date:	*Date:*
R	*Results*
H	
E	
S	

Disease Classification	
Pulmonary ☐	Extrapulmonary ☐
Specify:	
Patient Registration Group	
New	
Relapse	
Previously Treated	
Previously Treated History unknown	
Other (Specify)	

Nutritional Support/Food by Prescription Start Date:	
Nutritional Support/Food by Prescription End Date:	

HIV Testing and Counselling			HIV Care		
Date of Test	*Result*	*Post-Test Counselling Date*	*CPT/Dapsone*	*Date Started*	
			CD4	*Date/at initiation*	
			VL	*Date/Most Recent*	
			ART	*Y/N/Unk*	
				Date Started ART	
				ART Number	
				ART Regimen/Doses	

Initial Phase:
1. Fill in prescribed regimen and dosage
2. Indicate number of tablets per dose and dosages in milligrams (mg)

Description of Drugs:
R: Rifampicin
H: Isoniazid
Z: Pyrazinamide
E: Ethambutol
Other

ADULT ☐	CHILD ☐	OTHER:
4FDC (HRZE)	HRZ | E	

ADMINISTRATION OF DRUGS: Use one row per month. Mark in the boxes copying from the treatment supporter card: √ = directly observed card; - = Not supervised; 0 = Not taken

Day / M	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Drugs given to supporter, date	

2. Continuation Phase: Prescribed regimen and doses

Day / M	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Drugs given to supporter, date	

Remarks:

Administration of IPT: *Use one row per contact, document date refill taken. *Dosage should be 30 tabs per month*

In case treatment has been interrupted, extend to month 7

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7
Contact 1							
Contact 2							
Contact 3							

Treatment Outcome *(document date outcome assigned)*

Cured		Completed	
Failed		Lost to follow-up	
Died		Not evaluated	

Is treatment supporter present at end of treatment? Y N

Post Treatment Follow-up										
Visits	Anthopometrics								Smear	Culture
	Weight	BMI	MUAC	BP	RBS	Alt	HB	Creatinine		
Visit 1										
Visit 3										
Visit 2										

Supplementary file 5: Guidelines for Capillary Blood Glucose (CBG) Testing

Preparation

Gather equipment required for the procedure
Gloves
Disposable lancet
Glucometer test strips
Glucose monitoring device (Glucometer)
Gauze/tissue
Sharps disposal box
Patients register and pen
Check the expiry dates on the glucometer test strips.
Ensure that the glucometer and the test strips have been calibrated together. Each batch of glucometer test strips will require calibration to the machine.

Patient preparation

Obtain informed consent from the patient for the procedure – explain the need for the test and the benefits to the patient.
Wash and dry hands to be tested.
Note: The recommended site is the side of the distal ends of fingertips to minimize pain and injury to the bone. Avoid the little finger as the tissue may not be deep enough to prevent injury to the bone. Avoid the index finger and thumb as these are highly sensitive areas compared to other fingers. Avoid the arm if an intravenous infusion is underway or is the side of the body where a recent mastectomy, if any, was performed.

Process

Bring out the glucometer from its packing and place it on the table
Remove the glucose testing strip without touching the sensor tip from the container and insert it into the glucometer. This often leads to the glucometer turning itself on.
Prime the lancet to no more than 2.0 mm to minimize the risk of bone injury.
Firmly apply lancet to the site of sample collection and release the trigger on the lancet to pierce the skin. Dispose of the lancet in the sharps box.
Wipe away the first drop of blood with a clean gauze or tissue as this drop of blood may contain intracellular or interstitial fluid, or is hemolyzed, both of which could affect the blood sample.
Apply a gentle downward pressure close to the puncture site to facilitate blood flow and collection of the second drop of blood.
Collect the second drop of blood as it forms by touching the tip of the glucose testing strip.
Place the glucometer down and cover the site of skin puncture with a clean tissue. Pressure may need to be applied to stop further bleeding from the puncture site.

The glucometer will provide a result at this stage unless there have been errors in collection; for example, insufficient sample, low battery, wrong code, or the machine times itself out.
If an error displays on the glucometer, troubleshoot as appropriate.
Document the patient's blood glucose measurement in the patient register and the date the test was conducted.
Dispose of the glucose test strip in the sharps box.
Wash hands and replace equipment in storage bag container.
Inform the patient if the results is within normal values
Where the reading falls outside the normal values, refer the patient to a doctor for immediate review.

Adapted from: Mathew TK, Tadi P. Blood glucose monitoring. In StatPearls [Internet] 2020 Aug 14. StatPearls Publishing.

Supplementary file 6: Patient information and consent form

Part 1: Study Information Sheet for Patients

Patient guidance: *Please read this document carefully and ask for clarity where it is required.*

Introduction

Previous studies conducted in other parts of the world have indicated that people with diabetes may have varying treatment outcomes when receiving treatment for tuberculosis and that treatment for tuberculosis may predispose them to develop diabetes. This study will verify the status of these claims in patients receiving TB treatment in Eswatini and also identify means of improving treatment outcomes for diabetic persons receiving treatment for tuberculosis. The title of this study is **"Epidemiology and Control of Diabetes-Tuberculosis Comorbidity in Eswatini: Protocol for the prospective study of tuberculosis patients on predictive factors, treatment outcomes and patient management practices"**. The principal investigator of this study, Dr Victor Williams will also utilise findings from this study to fulfil part of the requirement for the award of a Doctor of Philosophy degree (PhD) by the University Medical Centre, Utrecht University, Utrecht, Netherlands.

This research will be implemented at the different hospitals and health centres that provide TB services in Eswatini. These include Mbabane Government Hospital, The Luke Commission, Phocweni Clinic, TB Center, Siphofaneni clinic, Mankayane Hospital, AHF Lamvelase Clinic, Raleigh Fitkin Memorial Hospital, AHF Matsapha, Pigg's Peak Government Hospital, Nhlangano Health Center, Hlathikulu Hospital TB Clinic.

Aim of the research

The study aims to describe the epidemiology, predictive factors, and control measures of diabetes in patients who are being treated for tuberculosis in Eswatini. The study has four objectives and one of them is to identify factors that hinder effective Diabetes Mellitus care for diabetics receiving TB treatment in Eswatini and to propose a context-specific approach to address these factors. To achieve this objective, health care workers who directly provide care for these patients will be interviewed. As healthcare personnel who is experienced in the care of TB patients, you are invited to participate in this study.

If you agree to participate in the study, a convenient date and time will be arranged for you to be interviewed.

Potential benefits and risks

There will be no direct benefit for you from taking part in the interview. However, the information you provide will help the researcher understand the best practices and challenges in the care of TB patients with diabetes and provide recommendations that will help improve services delivery for these patients. Participating in the interview carry's a low risk for you as a participant if there is a breach of confidentiality but the researchers have been trained in research ethics to ensure your confidentiality. Comments you make will not be directly linked to your name in the final study report. Also, there is a possibility that the interview may evoke sad memories concerning your patients. Kindly let the interviewer know if you feel this way and would like to end the interview.

Voluntary participation

Your participation in this interview is voluntary. There are no right or wrong answers. You can at any time choose to withdraw from the study completely (including deletion of audio-recording and transcript of interview if you wish). You can decide not to take part or to stop taking part in this study at any time, without giving a reason, and without any impact on your work. We would like to record the interview, if you consent to this, solely for the study, to ensure we capture everything you say.

Confidentiality

The information you provide during the interview will be confidential and accessible only to the research team. The audio recording will only be heard by the research team. This will be transcribed onto paper and the original recording will be kept securely for the duration of the study. All written information collected (transcripts of interviews, notes, signed informed consent form) will be kept privately and anonymously (including password-protected storage) for about 10 years or as recommended by the Eswatini Health and Human Research Review Board (EHHRRB).

The researchers will make every effort to ensure that the information you provide as part of this study remains confidential. When using quotes from an interview, the researcher will make sure that the identity of the cited person cannot be revealed. Any information you share during the interview will be confidential and your privacy will be maintained. Also, the research assistants and interviewers conducting this research have been made to sign a confidentiality agreement to further ensure your confidentiality and privacy.

Contact for additional information

If you have any questions regarding this study, please contact the study's Principal Investigator Dr Victor Williams at +268 7618 4334; victormw55@gmail.com or P.O Box 9482, Mbabane, H100, Eswatini.

OR

The Secretariat of Eswatini Health and Human Research Review Board (EHHRRB) on (00268) 2404 0865 / (00268) 24044905.

Part 2: Patient Consent form

Thank you for considering taking part in this study. The person organising the interview must explain the study to you before you agree to take part. If you have any questions, from the information sheet above or the explanation given to you, please ask the researcher before you decide to take part. You will be given a copy of the information sheet to keep if you wish.

Informed consent

- I have been informed by the undersigned person of the purpose of this study, and the possible benefits and risks of my participation.
- Any questions, I had about my participation in this study have been answered to my satisfaction. I will receive a copy of the document I have signed if I wish.
- I was given enough time to decide if I will participate in the study.
- I am participating in this study voluntarily. I may withdraw at any time without giving a reason and my decision not to take part will not affect my access to health services.
- I permit the researchers and the Ethics Committee to see my anonymised data, with the understanding that this data will remain confidential.

I, _____ consent voluntarily to being a participant of this study.

I consent to this interview being recorded
Yes No
I consent to be contacted for a follow-up interview
Yes No

_____
Signature of the study participant with Date (**or thumbprint if cannot sign**)

_____
Name and Signature of researcher with Date

Supplementary file 7: Healthcare worker Information and consent form for qualitative interviews

Part 1: Study Information Sheet for participants

Guidance for study participants: *Please read this document carefully and ask for clarity where it is required.*

Introduction

Previous studies conducted in other parts of the world have indicated that people with diabetes may have varying treatment outcomes when receiving treatment for tuberculosis and that treatment for tuberculosis may predispose them to develop diabetes. This study will verify the status of these claims in patients receiving TB treatment in Eswatini and also identify means of improving treatment outcomes for diabetic persons receiving treatment for tuberculosis. The title of this study is ***"Epidemiology and Control of Diabetes -Tuberculosis Comorbidity in Eswatini: a prospective study of tuberculosis patients on predictive factors, treatment outcomes and patient management practices".*** The principal investigator of this study, Dr Victor Williams will also utilise findings from this study to fulfil part of the requirement for the award of a Doctor of Philosophy degree (PhD) by the University Medical Centre, Utrecht University, Utrecht, Netherlands.

This research will be implemented at the different hospitals and health centres that provide TB services in Eswatini. These include Mbabane Government Hospital, The Luke Commission, Phocweni Clinic, TB Center, Siphofaneni clinic, Mankayane Hospital, AHF Lamvelase Clinic, Raleigh Fitkin Memorial Hospital (RFM), AHF Matsapha, Pigg's Peak Government Hospital, Nhlangano Health Center, Hlathikulu Hospital TB Clinic.

Aim of the research

The study aims to describe the epidemiology, predictive factors, and control measures of diabetes in patients who are being treated for tuberculosis in Eswatini. The study has four objectives and one of them is to identify factors that hinder effective Diabetes Mellitus care for diabetics receiving TB treatment in Eswatini and to propose a context-specific approach to address these factors. To achieve this objective, health care workers who directly provide care for these patients will be interviewed. As healthcare personnel who are experienced in the care of TB patients, you are invited to participate in this study.

If you agree to participate in the study, a convenient date and time will be arranged for you to be interviewed.

Potential benefits and risks

There will be no direct benefit for you from taking part in the interview. However, the information you provide will help the researcher understand the best practices and challenges in the care of TB patients with diabetes and provide recommendations that will help improve services delivery for these patients. Participating in the interview carry's a low risk for you as a participant if there is a breach of confidentiality but the researchers have been trained in research ethics to ensure your confidentiality. Comments you make will not be directly linked to your name in the final study report. Also, there is a possibility that the interview may evoke sad memories concerning your patients. Kindly let the interviewer know if you feel this way and would like to end the interview.

Voluntary participation

Your participation in this interview is voluntary. There are no right or wrong answers. You can at any time choose to withdraw from the study completely (including deletion of audio-recording and transcript of interview if you wish). You can decide not to take part or to stop taking part in this study at any time, without giving a reason, and without any impact on your work. We would like to record the interview, if you consent to this, solely for the study, to ensure we capture everything you say.

Confidentiality

The information you provide during the interview will be confidential and accessible only to the research team. The audio recording will only be heard by the research team. This will be transcribed onto paper and the original recording will be kept securely for the duration of the study. All written information collected (transcripts of interviews, notes, signed informed consent form) will be kept privately and anonymously (including password-protected storage) for about 10 years or as recommended by the Eswatini Health and Human Research Review Board (EHHRRB).

The researchers will make every effort to ensure that the information you provide as part of this study remains confidential. When using quotes from an interview, the researcher will make sure that the identity of the cited person cannot be revealed. Any information you share during the interview will be confidential and your privacy will be maintained. Also, the research assistants and interviewers conducting this research have been made to sign a confidentiality agreement to further ensure your confidentiality and privacy.

Contact for additional information

If you have any questions regarding this study, please contact the study's Principal Investigator Dr Victor Williams at +268 7618 4334; victormw55@gmail.com or P.O Box 9482, Mbabane, H100, Eswatini.

OR

The Secretariat of Eswatini Health and Human Research Review Board (EHHRRB) on (00268) 2404 0865 / (00268) 24044905.

Part 2: Consent form for participants

Thank you for considering taking part in this study. The person organising the interview must explain the study to you before you agree to take part. If you have any questions, from the information sheet above or the explanation given to you, please ask the researcher before you decide to take part. You will be given a copy of the information sheet to keep if you wish.

Informed consent

- I have been informed by the undersigned person of the purpose of this study, and the possible benefits and risks of my participation.
- Any questions, I had about my participation in this study have been answered to my satisfaction. I will receive a copy of the document I have signed if I wish.
- I was given enough time to decide if I will participate in the study.
- I am participating in this study voluntarily. I may withdraw at any time without giving a reason and my decision not to take part will not affect my position, career or reputation as a healthcare worker.
- I permit the researchers and the Ethics Committee to see my anonymised data, with the understanding that this data will remain confidential.

I, _____ consent voluntarily to being a participant of this study.

I consent to this interview being recorded
Yes No
I consent to be contacted for a follow-up interview
Yes No

_____
Signature of the study participant with Date

_____
Name and Signature of researcher with Date

Part 3: Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and the best of my ability made sure that the participant understands that the following will be done:

1. The interview will be recorded in a tape recorder and later transcribed for use.
2. The information obtained from the interview will be used to provide recommendations for the improvement of health services delivery and care of TB patients.
3. All comments and responses by the participant will be confidential and when a reference is made to a statement, it will be anonymous.

I confirm that the participant was allowed to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability.

I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Name of Researcher/person taking the consent

_____

Signature of Researcher /person taking the consent_____

Date _____

Day/month/year

Supplementary File 8:
Confidentiality and Non-Disclosure Statement

As a member of this research team, I understand that I may have access to confidential information about research sites and study participants. By signing this statement, I am indicating my understanding of my responsibilities to maintain confidentiality and agree to the following:

I understand that names and any other identifying information about research sites and participants are completely confidential.

I agree not to divulge, publish, or otherwise make known to unauthorized persons or the public any information obtained during this research that could identify the persons who participated in the research.
I understand that all information about research sites or participants obtained or accessed by me during this research is confidential. I agree not to divulge or otherwise make known to unauthorized persons any of this information unless specifically authorized to do so by approved protocol or by the local principal investigator acting in response to applicable law or court order, or public health or clinical need.

I understand that I am not to read information about research sites or participants, or any other confidential documents, nor ask questions of research participants for my personal information but only to the extent and to perform my assigned duties on this research project.

I agree to notify the local principal investigator immediately should I become aware of an actual breach of confidentiality or a situation that could potentially result in a breach, whether this is on my part or the part of another person.

_____ _____ _____

Name of researcher Signature Date

_____ _____ _____

Name of principal investigator Signature Date

Chapter 4

Diabetes – Tuberculosis Comorbidity in a Low-Income Setting: Findings from a Prospective Cohort Study in Eswatini

Victor Williams, Alinda G. Vos-Seda, Marianne Calnan, Colani S. Ngwenya, Samson Haumba, Lindiwe Mdluli-Dlamini, Diederick E. Grobbee, Kennedy Otwombe, Kerstin Klipstein-Grobusch

Submitted

Summary

Background: The increasing burden of diabetes mellitus in low- and middle-income countries (LMICs) negatively impacts current tuberculosis control efforts. 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 used a prospective cohort study design at 11 purposively selected health facilities in Eswatini. Adults ≥18 years commencing tuberculosis treatment were recruited into the study and followed up until the end of treatment. Blood glucose measurements were taken at baseline and in months 2 and 5. Patients sociodemographic and clinical data were extracted from treatment cards and registers. We computed the prevalence of elevated blood glucose (random≥11.1mmol/l or fasting>5.5mmol/l) and used logistic regression to determine the predictors of elevated baseline blood glucose and unfavourable treatment outcomes.

Findings: We consecutively enrolled 369 patients. The mean age was 38.4 (SD: 12.9) years and 202 (54.7%) were males. The median baseline blood glucose was 5.5mmol/l (IQR 4.8, 6.7), reducing to 5.3mmol/l (IQR 4.8, 6.2) (p=0.0413) and 5.2mmol/l (IQR 4.8, 5.9) (p=0.0002) at months 2 and 5 respectively. 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); increased with age, highest at ≥55 years (13.6%; 95% CI: 6.2, 27.3); and more elevated in reactive HIV patients at 9.5% (95% CI: 6.5, 13.7). A family history of diabetes mellitus (Adjusted Odds Ratio (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), but not blood glucose, were associated with unfavourable treatment outcome.

Interpretation: 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.

Funding: This study was funded by the Global Health PhD Support Programme at the University Medical Center, Utrecht, The Netherlands.

Key Words: Diabetes; Tuberculosis; Comorbidity; Non-communicable diseases; Treatment outcome; Mortality; Low- and middle-income countries

Research in Context

Evidence before this study

We searched PubMed on the 20th of May 2022 using the search terms "diabetes"[Title/Abstract] AND "tuberculosis"[Title/Abstract] AND "comorbidity"[Title/Abstract] without date and language restrictions. There were no articles describing diabetes–tuberculosis co-morbidity in Eswatini. A further search generated one article, which showed a 6% prevalence of DM among HIV patients. Eswatini has a high burden of tuberculosis and HIV, with an increasing burden of diabetes. Studies from other locations indicate a rising burden of diabetes mellitus in low- and middle-income countries with a high burden of tuberculosis. Diabetes mellitus increases the risk of tuberculosis disease with unfavourable outcomes in those receiving treatment for tuberculosis, directly limiting tuberculosis control efforts.

Added value of this study

This study describes outcomes of blood glucose screening in patients receiving tuberculosis treatment, predictors of elevated baseline blood glucose and unfavourable treatment outcomes. We observed a higher prevalence of elevated baseline blood glucose in patients commencing tuberculosis treatment than the general population, slightly higher in males and those with a reactive HIV status. A family history of diabetes mellitus and reactive HIV status predicted elevated baseline blood glucose. Three-quarters of the patients had a favourable tuberculosis treatment outcome, and death was the most common unfavourable outcome. Hypertension and unemployment were predictors of unfavourable treatment outcomes, while high school education was protective.

Implications of all the available evidence

The higher prevalence of elevated baseline blood glucose in tuberculosis patients indicates the need to implement the framework for collaborative action on TB and comorbidities, as the World Health Organisation advocates. This can fast-track the timely diagnosis and treatment of diabetes and other non-communicable diseases among tuberculosis patients to limit unfavourable treatment outcomes. Additional evidence is required to identify and address the causes of death among tuberculosis patients 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 World Health Organization (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 programs on the bidirectional screening and integrated treatment for TB in NCD programs (including DM) [10] and the integration and prevention of NCDs in infectious disease programs [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 programs 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% have 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 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 is limited. The International Diabetes Federation (IDF) 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 is 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 the 1st of June to the 30th of September 2022. A description of the context and approach to TB services provision in Eswatini and the study setting has been published previously [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 TB services provision. The study was conducted at 11 health facilities providing TB services in Eswatini (12 sites were selected, but one 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 six 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 were expected but 352 participants were eventually enrolled in the study as one health facility did not participate in the study. A consecutive sampling approach was used to include all consenting patients newly enrolled on TB care.

Data management

Data sources and approach to data collection

The data used for this study was from routine patient care. Data from patients at baseline, during follow-up visits (2nd and 5th months) and at the end of treatment were extracted from patient treatment cards and registers for analysis (Supplementary 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 that 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 on using the glucometer, so there was no need for another 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, 2nd and 5th months. The Eswatini Ministry of Health requires all patients to have random blood glucose tests at baseline, months 2, 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, ³55 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, high blood pressure (HBP) stage 2) and hypertensive crises) [24]; HIV status, comorbidities, date of TB diagnosis, type of TB, baseline GeneXpert, baseline culture, TB lam; and follow-up variables – blood glucose measurement, systolic blood pressure, diastolic blood pressure, sputum microscopy, GeneXpert, TB treatment outcome and date of TB treatment outcome.

Blood glucose measurements were done at baseline, 2nd and 5th month using a glucometer. They were reclassified as normal (random <11.1mmol/l or fasting≤5.5mmol/l) or elevated (pre-DM: fasting >5.5 to 6.9 mmol/l or DM: random ≥11.1mmol/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 standard deviation or median with interquartile range 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). 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 sub-analysis 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 to 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 diastolic and systolic blood pressure changes between baseline, 2nd, and 5th 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/BMI (selected apriori) 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 (LASSO) 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 multi-level 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, re-initiated 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 apriori) 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.

Ethical review and approval

Ethical review and approval for the study were done by the Eswatini Health and Human Research Review Board (EHHRRB) (Ref: EHHRRB 036/2021). The Eswatini Ministry of Health also granted permission to ease access to health facilities.

Results

Descriptive characteristics of participants

We enrolled 369 participants in the study, and the baseline blood glucose was available for 352 participants. For the 2nd and 5th month visits, 235 and 262 participants had documented blood glucose, respectively (Figure 1). At baseline, more males were included compared to 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%.

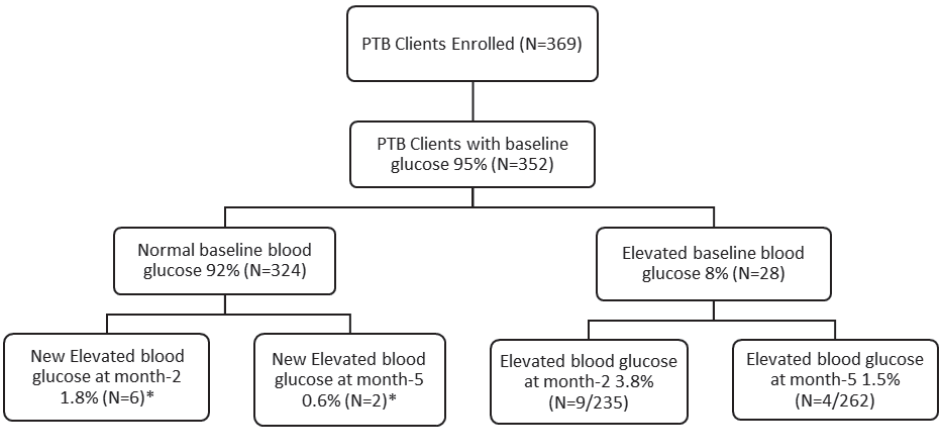

Figure 1: Flow chart describing patient enrollment and blood glucose status during follow-up.
*This number is included in the total for elevated blood glucose during follow-up.

The median baseline blood glucose was 5.5 mmol/l (IQR 4.8, 6.7), 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 (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%). Few participants had comorbidities at baseline – DM 2.4% (N=9), hypertension 4.3% (N=16) and hypertension & DM 0.5% (N=2).

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) 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).

Table 1: Descriptive characteristics of participants in the study

	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			
<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%)

	Normal glucose (N=324)	Elevated glucose* (N=28)	Total (N = 369)**
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(mmHg)#			
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(mmHg)##			
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%)
Region			
Hhohho	94 (29.0%)	10 (35.7%)	106 (28.7%)
Lubombo	21 (6.5%)	1 (3.6%)	22 (6.0%)
Manzini	146 (45.1%)	14 (50.0%)	173 (46.9%)
Shiselweni	63 (19.4%)	3 (10.7%)	68 (18.4%)
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%)
Tertiary	33 (10.2%)	2 (7.1%)	37 (10.0%)
Occupation			
Employed	149 (46.0%)	10 (35.7%)	160 (43.4%)

	Normal glucose (N=324)	Elevated glucose* (N=28)	Total (N = 369)**
Unemployed	175 (54.0%)	18 (64.3%)	209 (56.6%)
Alcohol			
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			
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 ≥11.1mmol/l & fasting >5.5mmol/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

Sub-analysis of 33 patients with a fasting blood glucose

In a sub-analysis 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

Two hundred and thirty-five (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 to baseline median blood glucose, the median blood glucose at month two and month five reduced to 5.3mmol/l (IQR 4.8, 6.2) (p=0.041) and 5.2mmol/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. Amongst those with normal blood glucose at baseline (N=324), 6 (1.8%) had an elevated measurement during month two visit and 2 (0.6%) at month 5 (Figure 1).

Overall, 43.3% and 33.8% of participants had elevated baseline systolic and diastolic blood pressure, respectively. The median baseline systolic blood pressure was 117.0

mmHg (IQR 109, 128 (with no significant change during follow-up). The median diastolic blood pressure at baseline increased from 74 mmHg (IQR 67, 82) to 76 mmHg (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 mmHg (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 diastolic blood pressure (OR 1.03; 95% CI: 0.99, 1.07; p=0.085) were marginally statistically significant. A positive family history of DM (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 multi-level logistic model was not different from the final multivariate logistic model (Supplementary file 2), and the intra-cluster 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

Variable	Univariate			Multivariate		
	Odds	95% CI	P-Value	Odds	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 DM						
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 two 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 (N=19, 5.2%), transferred out (N=13, 3.5%), active (N=6, 1.6%), re-initiated (N=6, 1.6%), DRTB on treatment (N=3, 0.8%) and stopped treatment (N=2, 0.5%) (Supplementary 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 to 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). Thirty-four patients (9.2%) died, and more than half were males (N=20, 59%). More males were lost to follow-up (N=16, 84%), were re-initiated for any reason (N=5, 83%) and were transferred out (N=9, 69%) compared to 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 outcome

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 patients with elevated baseline blood glucose had a favourable TB treatment outcome. Five (17.9%) died, 2 (7.1%) were lost to follow-up, and one each stopped treatment and was transferred out.

Table 3: Predictors of unfavourable tuberculosis treatment outcome

Variable	Univariate			Multivariate		
	Odds	95% CI	P-Value	Odds	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

Predictors of Unfavourable Tuberculosis Treatment Outcome

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 to 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.

Comparison with other studies

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% have been reported in Benin [34] and Brazil [35], respectively. Our reported DM prevalence of 12% from a sub-analysis 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 further scrutiny [39–41]. Older age (>45 years), female and male sex, BMI, poor glycemic control, elevated diastolic blood pressure 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 diastolic blood pressure. 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 stress hyperglycemia [44] or the treatment of patients with elevated blood glucose with metformin as mandated by MOH. The high prevalence of elevated systolic and diastolic blood pressure 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 loss to follow-up, is a challenge for TB programs across Sub-Saharan Africa. A recent systematic review indicated the contribution of death and loss to follow-up to unfavourable treatment outcomes was 48% (95% 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 five 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.

Strength and Limitation

This study is the first to report on the prevalence of elevated blood glucose among TB patients 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, utilising 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. Secondly, one health facility did not respond to a request to participate in the study, which also impacted our final sample size. Thirdly, 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. 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 three 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 fro the clinic.

Conclusion

This study reveals a high prevalence of elevated baseline blood glucose in patients commencing TB treatment compared to the general population, higher in males, older age groups and HIV-positive patients. A concurrent high prevalence of elevated systolic and diastolic blood pressure 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 programs (TB, HIV and STIs) as recommended by WHO [10,11] can help accelerate timely diagnosis and treatment of NCDs to limit unfavourable treatment outcomes for TB patients.

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Supplementary Files

Supplementary file 1: TB Treatment Card

TB 01: Tuberculosis Treatment Card

Name:_____ Registration TB No.: _____
Physical Address:_____ Date of Registration: _____
_____ Health Facility: _____
_____
Sex: (M / F)_____Age:_____Contact Number:_____ Pregnant / Non Pregnant: _____
Name of Treatment Supporter:_____ FP Method:_____
Contact No.: _____ Height:_____

Anthropometrics (Monthly)				
	Baseline	Month 2	Month 5	End of Treatment
Weight				
BMI				
MUAC				
BP	/	/	/	/
RBS				
Alt				
HB				
Creatinine				

Baseline Xpert Ultra		Sputum Smear Microscopy				Culture		
Result	*Date/Lab No.*	*Month*	*Date*	*Result*	*Lab No.*	*Date*	*Result*	*Lab No.*
		0						
		2						
		5						
		End						

DST		X-RAY	
Date:		*Date:*	
R		*Results*	
H			
E			
S			

Disease Classification	
Pulmonary ☐ Extrapulmonary ☐	
Specify:	
Patient Registration Group	
New	
Relapse	
Previously Treated	
Previously Treated History unknown	
Other (Specify)	

Nutritional Support/Food by Prescription Start Date:	
Nutritional Support/Food by Prescription End Date:	

HIV Testing and Counselling			HIV Care	
Date of Test	*Result*	*Post-Test Counselling Date*	*CPT/Dapsone*	*Date Started*
			CD4	*Date/at initiation*
			VL	*Date/Most Recent*
			ART	*Y/N/Unk*
				Date Started ART
				ART Number
				ART Regimen/Doses

Initial Phase:
1. Fill in prescribed regimen and dosage
2. Indicate number of tablets per dose and dosages in milligrams (mg)

Description of Drugs:
R: Rifampicin
H: Isoniazid
Z: Pyrazinamide
E: Ethambutol
Other

ADULT ☐ CHILD ☐ OTHER:

4FDC (HRZE)	HRZ	E

ADMINISTRATION OF DRUGS: Use one row per month. Mark in the boxes copying from the treatment supporter card: √ = directly observed card; - = Not supervised; 0 = Not taken

Day / M	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Drugs given to supporter, date	

2. Continuation Phase: Prescribed regimen and doses

Day / M	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	Drugs given to supporter, date	

Remarks:

Administration of IPT: *Use one row per contact, document date refill taken. *Dosage should be 30 tabs per month*

In case treatment has been interrupted, extend to month 7

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7
Contact 1							
Contact 2							
Contact 3							

Treatment Outcome *(document date outcome assigned)*

Cured		Completed	
Failed		Lost to follow-up	
Died		Not evaluated	

Is treatment supporter present at end of treatment? Y | N

Post Treatment Follow-up										
Visits	Anthopometrics								Smear	Culture
	Weight	BMI	MUAC	BP	RBS	Alt	HB	Creatinine		
Visit 1										
Visit 3										
Visit 2										

Supplementary File 2: Multi-level model of individual risk factors of elevated blood glucose accounting for clustering of individuals within regions.

Variable	Univariate			Multivariate		
	Odds	95% CI	P-Value	Odds	95% CI	P-Value
Age	1.02	0.99, 1.05	0.111			
Baseline HIV Status						
Non-Reactive	1					
Reactive	3.01	0.89, 10.23	0.077	4.62	1.06, 20.1	0.042
Sex						
Female	1					
Male	1.33	0.61, 2.93	0.476			
Family history of DM						
No	1					
Unknown	2.71	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
Duration of treatment	0.86	0.72, 1.02	0.093			
Diastolic blood pressure	1.03	0.99, 1.07	0.085	1.02	0.99, 1.05	0.132
Baseline weight	0.98	0.96, 1.01	0.283			
Education						
None	1					
Primary	0.68	0.23, 1.99	0.477			
High School	0.40	0.15, 1.05	0.064			
Tertiary	0.39	0.08, 1.93	0.247			

Random effects Standard Deviation = 3.46e-08; Prob >= chibar2 = 1.0000

Supplementary File 3: Tuberculosis Treatment Outcome disaggregated by sex

Treatment outcome	Female (N=167)	Male (N=202)	Total (N=369)
Active	3 (1.8%)	3 (1.5%)	6 (1.6%)
Completed	79 (47.3%)	71 (35.1%)	150 (40.7%)
Cured	55 (32.9%)	71 (35.1%)	126 (34.1%)
DRTB on Treatment	2 (1.2%)	1 (0.5%)	3 (0.8%)
Died	14 (8.4%)	20 (9.9%)	34 (9.2%)
LTFU	3 (1.8%)	16 (7.9%)	19 (5.1%)
Not Evaluated	1 (0.6%)	0 (0.0%)	1 (0.3%)
Re-initiation	1 (0.6%)	5 (2.5%)	6 (1.6%)
Stopped	1 (0.6%)	1 (0.5%)	2 (0.5%)
Transferred out	4 (2.4%)	9 (4.5%)	13 (3.5%)
Treatment Failure	4 (2.4%)	5 (2.5%)	9 (2.4%)

Chapter 5

Diabetes – Tuberculosis Care in Eswatini: A Qualitative Study of Opportunities and Recommendations for Effective Services Integration

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Abstract

Objective

This study describes the availability of basic services, equipment, and commodities for integrated DM–TB services, best practices by healthcare workers, and opportunities for better integration of DM–TB care in Eswatini.

Methods

A qualitative design was used. Twenty-three healthcare workers participated in a survey and key informant interview.

Results

Most respondents indicated DM and TB care are integrated and patients access blood pressure and fasting/random blood glucose assessment. Few respondents indicated they provide visual assessment, hearing assessment, and HbA1c testing. Respondents experienced stockouts of urinalysis strips, antihypertensive drugs, insulin, glucometer strips, and DM drugs in the previous six months before the interview. Four main themes emerged from the qualitative interviews – quality and current standards of care, best practices, opportunities, and recommendations to improve integrated services delivery.

Conclusion

While DM care is provided for TB patients, the implementation of integrated DM–TB services is suboptimal as the quality and current standards of care vary across health facilities due to different patient-level and health system challenges. Some identified opportunities must be utilized for a successful DM–TB integration.

Keywords

Diabetes mellitus; tuberculosis; non-communicable diseases; services integration; primary healthcare

Contribution to the field

The Collaborative framework for care and control of tuberculosis and diabetes recommended by the WHO/TB Union in 2011 has been implemented in some high TB burden countries, including India, China, and Pakistan. In Sub-Saharan Africa (SSA), studies from Angola, Benin, Ethiopia, Nigeria, and Zimbabwe highlight some context-specific challenges and opportunities that when harnessed, can improve outcomes for DM patients receiving treatment for TB and TB treatment outcomes.

Our study provides evidence on the extent of integration of DM and TB care in Eswatini and highlights different health facility-specific opportunities that when optimised, can further improve TB treatment outcomes. Our findings indicate integration of DM care and TB services is achievable, and healthcare workers are aware of the advantages of integrated services but are constrained by different factors. Considering NCD cases (including DM) are increasing annually in most SSA, integrating TB and DM care will mitigate the impact of this increase on favourable TB treatment outcomes. However, multiple opportunities for improvement exist across different countries and will need to be addressed to fully maximize the benefits of integrated DM and TB care. Finally, this study provides baselines for future studies in Eswatini and other low- and middle-income countries.

Introduction

The World Health Organization (WHO) recommends bidirectional screening for diabetes mellitus (DM) and tuberculosis (TB) [1]. In this approach, DM patients are screened for TB while TB patients are screened for DM to identify cases of each condition that could have been missed. Bidirectional screening is vital in low- and middle-income countries (LMIC) with a high TB prevalence and surge in non-communicable diseases (NCD), including DM [2–4]. The International Diabetes Federation (IDF) estimates that in 2021, 537 million adults were living with diabetes; 50% of these are undiagnosed, while 75% reside in LMICs [4]. This indicates every opportunity for screening should be maximized for improved case finding and treatment as the number of cases is expected to increase to 643 million by 2030 [4]. Similarly, TB accounted for 1.5 million deaths in 2020 [5]. Before 2020, significant progress was made in the global TB response and countries were on track to eradicate TB by 2035, however, the COVID-19 pandemic reversed this progress [6–8].

DM is a recognised risk factor for TB [9–11]. Conversely, TB disease process or its treatment is recognised to alter glucose metabolism resulting in impaired blood glucose [9,12,13]. Hence, the recommendation for bidirectional screening and integrated management by WHO [1]. Different LMICs have integrated bidirectional screening and treatment services for the two conditions with varying outcomes [14–17]. WHO defines integrated services delivery as "the management and delivery of health services so that patients receive a continuum of preventive and curative services, according to their needs over time and across different levels of the health system" [18]. Services integration offers several benefits. First, in the early identification of cases to limit the spread of infection and development of complications; second, early identification and treatment of DM can reduce the risk for TB infection; third, integration can help optimise the treatment outcomes and retention in care for the different conditions; fourth, integration can improve documentation, monitoring, and reporting of DM and TB, and finally, it can limit resource requirement for health services delivery [19].

In Eswatini, the HIV prevalence is 24.8% in adults aged 15 years and above [20]. Consistent with the high HIV prevalence is the TB incidence of 319/100,000 as of 2021 [21]. Available data from IDF indicates the prevalence of DM is 3·6% in adults, and the age-adjusted prevalence of impaired glucose tolerance is 6·9% [22]. A recent study among outpatient attendees at a tertiary health facility in Eswatini indicates the prevalence of DM and impaired glucose tolerance is 7·3% and 6·5% respectively [23], and 6% and 30% respectively in HIV patients [24]. An estimated 15% of outpatient visits in 2020 were for NCDs, and 4% of these were related to DM [25]. Data on the prevalence of DM in TB patients is not available.

Before the COVID-19 pandemic, there was a limited effort at integrating DM–TB, but in 2021, tools for the screening of TB patients for NCDs including DM became available. This process is still in its infancy with limited data available to assess the level of implementation or guide practice and policy for TB patient care. This study assesses the integration of DM care into TB services at select health facilities in Eswatini and describes the availability of basic services, equipment, and commodities for integrated TB–DM services delivery, best practices by healthcare workers, key challenges, and recommendations on how services can be improved.

Methods

Study design, setting, and participants

This qualitative study (with a pilot survey) is part of an ongoing prospective cohort study of newly enrolled patients in TB care in Eswatini from June 2022 and is based on the social-ecological model. The social-ecological model explores various relationships – individual, interpersonal, community, organisational, and policy/environmental factors which determine the health outcome of an individual [26,27]. Healthcare workers from twelve health facilities were purposively selected to participate in the study – a pilot survey followed by a semi-structured interview. The health facilities were selected from the four regions of Eswatini based on the highest average number of new tuberculosis patients enrolled in the two quarters before this study. These consisted of five hospitals, one health centre, and six primary care clinics.

The healthcare workers were invited to participate if they were doctors or nurses, worked in the TB clinic for at least one year, and directly provided routine care to TB patients. A minimum of two healthcare workers (one doctor and one nurse) who met the above criteria were purposively selected from the TB clinic for interview per health facility. It was expected saturation would be achieved after interviewing 20 – 30 participants [28].

Data collection and interviews

Healthcare workers who met the selection criteria and consented to participate were interviewed between May and June 2022. They were requested to respond to a short survey administered through REDCap [29] before the interview. The survey obtained basic demographic details of the healthcare worker, the availability of certain services, and basic requirements for DM-TB care at their health facilities (Supplementary file 1). A semi-structured interview guide was used to obtain healthcare workers' views on DM–TB care, challenges during service delivery and recommendations for improvement (Supplementary file 2). A trained research assistant fluent in English and Siswati conducted

the interviews which were also recorded. Healthcare workers expressed themselves in either English or Siswati. Interviews were conducted face-to-face or telephonically and lasted 30–45 minutes. The study was approved by the Eswatini Health and Human Research Review Board (EHHRRB-036/2021). Informed consent by participants also covered the interview recording. Identifiable details of participants were not taken to maintain privacy and confidentiality.

Qualitative analysis

Recordings from the interviews were transcribed verbatim in English immediately after each interview. The study Principal Investigator (PI) and the research assistant reviewed each interview recording and transcript for accuracy before analysis. The PI documented predefined codes (deductive) and those identified by the participants during the interview (inductive) in a codebook (VW). Analysis of each interview transcript was used to refine the different codes (VW). Four co-authors (SH, MC, AV, and KO) reviewed samples of the transcripts with the identified codes for accuracy and consistency of the identified codes. A consensus resolved any disagreement on the codes. VW and AV independently grouped the codes into themes and all the authors approved the themes once the coding was complete. Themes were categorised and presented using text and summary tables. NVivo 12 software was used for qualitative analysis [30]

Results

Of the twenty-five healthcare workers from 11 health facilities invited to participate in the survey, 23 (92%) accepted to be interviewed. One health facility did not respond, and one healthcare worker was unavailable for the interview. *Table 1* summarizes the sociodemographic details of the healthcare workers while other findings from the pilot survey of the healthcare workers who were interviewed are summarized in Figure 1 and Figure 2.

Table 1: Demographics and experiences of healthcare workers in the study (Eswatini, 2022)

Variable	Doctors (n = 10)	Nurses (n = 13)	Overall (n = 23)
Age			
Mean (SD)	40·80 (8·4)	36·77 (8·6)	38·52 (8·6)
Min, Max	32·0, 59·0	26·0, 56·0	26·0, 59·0
Gender of healthcare worker			
Female	2 (20·0%)	8 (61·5%)	10 (43·5%)
Male	8 (80·0%)	5 (38·5%)	13 (56·5%)
Highest qualification attained			
Certificate	0 (0·0%)	1 (7·7%)	1 (4·3%)
Degree	4 (40·0%)	6 (46·2%)	10 (43·5%)
Diploma	0 (0·0%)	4 (30·8%)	4 (17·4%)
Postgraduate	6 (60·0%)	2 (15·4%)	8 (34·8%)
Total years of experience in the profession			
Mean (SD)	13·70 (9·3)	13·08 (8·7)	13·35 (8·8)
Min, Max	4·0, 34·0	4·0, 34·0	4·0, 34·0
Number of years providing care for TB patients			
Mean (SD)	6·80 (4·4)	4·00 (2·1)	5·22 (3·5)
Min, Max	1·0, 15·0	1·0, 7·0	1·0, 15·0
Number of in-service training in the last 12 months			
Mean (SD)	3·00 (4·1)	3·46 (3·0)	3·26 (3·5)
Min, Max	0·0, 11·0	0·0, 12·0	0·0, 12·0
Received training for non-communicable diseases?			
No	2 (20·0%)	5 (38·5%)	7 (30·4%)
Yes	8 (80·0%)	8 (61·5%)	16 (69·6%)
Received training in TB-NCD care?			
No	4 (40·0%)	6 (46·2%)	10 (43·5%)
Yes	6 (60·0%)	7 (53·8%)	13 (56·5%)
Received specific training on TB/Diabetes?			
No	6 (60·0%)	9 (69·2%)	15 (65·2%)
Yes	4 (40·0%)	4 (30·8%)	8 (34·8%)

Facility description and availability of guiding documents

About half of the respondents (n=12) indicated they worked at a hospital while 11 worked at a primary care clinic. Fourteen indicated their health facility was in an urban area, 5 in a semi-urban, and 3 were in a rural area. All (n=23) indicated they had the current national TB treatment guideline, 11 had a Standard Operating Procedure (SOP) for the care of TB patients with DM, 21 indicated there was a requirement for staff of the TB clinic to be trained on NCDs and 20 stated they had the essential medicines list.

Baseline services for TB patients

Figure 1 describes NCD-related services provided at baseline in addition to the routine services for TB care.

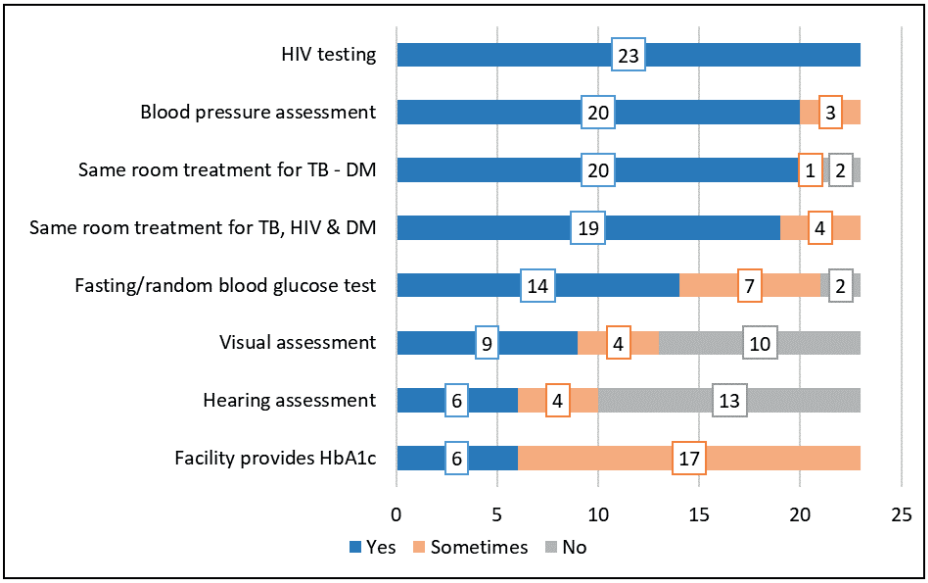

Figure 1: NCD-related services provided at baseline in addition to routine TB services (Eswatini 2022)

Availability of essential commodities in the previous six months

Respondents provided information on the availability of essential commodities and medication for the screening, treatment, and monitoring of NCDs. Availability was determined by the occurrence of stock-outs within the previous six months before the interview date (Figure 2).

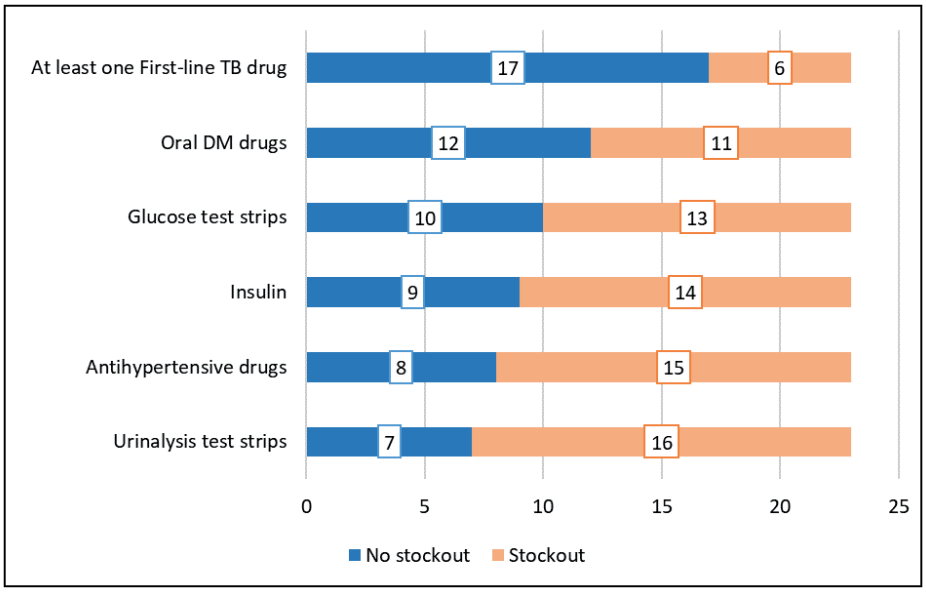

Figure 2: Availability of essential commodities and medication for the management of NCDs within the last six months before the interview (Eswatini, 2022)

Qualitative

Four broad themes emerged from the data. These were obtained from several sub-themes based on codes from the healthcare workers' interviews (*Table 2*).

Table 2: Themes and sub-themes derived from different codes in the study (Eswatini, 2022)

Themes	Sub-themes
Quality and current standards of care	Treatment guidelines
	Screening for DM
	HbA1c and Oral glucose tolerance test
	Care of TB – DM patients
	Pill burden for DM patients
	COVID-19 affected services delivery
Best practices	Staff rotation
	Synchronized clinic visits
	Health education
	Integrated services
	Fast track services
	Bidirectional screening and screening for COVID-19
Opportunities to improve integrated services delivery	Patient support
	HR and staffing
	Staff training
	Reporting tools
	DM and TB diagnosis
	Availability of drugs
Recommendations	NCD management guidelines
	Healthcare worker training
	Patient documentation tools
	Improve diagnostics
	Improve drugs supply
	Patient Support and Health Education

Quality and current standards of care

Treatment guidelines

More than half of the participants (n=12) indicated Standard Operating Procedures (SOP) or documents to guide the care of TB patients with DM or other non-communicable diseases were not available.

"The guidelines (TB and HIV) are clear and good for me, but we need a clear guideline on the NCDs aspect because for now, much attention is given to TB and ART forgetting about NCDs." R3

"We do not have a proper protocol (for TB-DM). We just manage the patient based on what we are doing as our routine practice." R22

Screening for DM

The random blood glucose or fasting glucose test was commonly used by healthcare workers to screen and diagnose DM, and 14 respondents indicated they screen patients at baseline.

"We check the fasting or random blood sugar using a glucometer depending on if the patient has eaten or not… If it was random blood sugar, I can ask the patient to come the following day not eaten so we can do a fasting blood sugar and further review" R10

HbA1c and Oral glucose tolerance test

Participants were aware of the HbA1c and the oral glucose tolerance tests, but these were either not available or had a long turnaround time. Only 6 respondents stated they screened patients at baseline with HbA1c.

"…In our facility, we do not perform the HbA1c test and again we do not do the oral glucose tolerance test" R1

"…the HbA1c test is available, but we do not have the reagents, so we are not doing it currently" R11

"The HbA1c test is not run here but in Mbabane, we are usually allocated a day wherein they come and collect the sample. So, if a patient comes on Monday, she has to wait for Friday so that the specimen can be collected" R14

Care of TB – DM patients

The participants had different approaches to providing care for TB patients with DM. A common practice was to refer the patient to a hospital or a doctor if the facility was

a clinic or the healthcare worker was a nurse. Additional care includes counselling for lifestyle modification and assessment for complications.

"If the patient has already been diagnosed with DM and is on treatment, we continue with the treatment. But if I test a patient and find that he/she has abnormal blood glucose and is not a known DM patient, I refer that patient to the doctor for review" R10

Pill burden for TB patients with DM

There was a concern associated with adherence due to the pill burden, and the fact DM care was previously not prioritized until the COVID-19 pandemic.

"…diabetes mellitus needs more attention than HIV these days. HIV is well funded, patients are now taking one pill per day, but with DM, patients are taking 3-4 tablets" R8

"If I can be precise, there has been poor sensitization of DM, it only gained much attention during the COVID-19 era… we knew about DM but there was no clear guidance and proper management." R7

COVID-19 affected services delivery

The participants also described how the different health measures adopted during the COVID-19 pandemic affected healthcare services resulting in sub-optimal patient care.

"If you were living with TB, hypertension or DM during the COVID era, follow-up was poor, because there was an instance where we lowered the volume of people visiting the facility for infection control purposes, hence we were giving patients 3 months, thus in the 3 months no one was following if you have been doing well or if your blood sugar was controlled, so by the end of the 3 months most patients were elevated." R8

"Patients were not coming to the clinic for monitoring and check-ups due to fear of contracting COVID, this led to other patients being severely attacked by TB and others had their DM escalated" R7

Best practices

Participants described some of the best practices they adopted to continue providing healthcare services (*Table 3*). These include staff rotation, a process where they are routinely reassigned to work in different units and departments within the health facility; synchronizing patients' clinic visits so they can receive care for multiple health conditions on the same day; routinely providing health education for their patients; and integrating

services where they provide multiple services for patients at one service point, so patients do not queue at other service points.

Table 3 – Sub-themes describing best practices by healthcare workers with illustrative quotes (Eswatini, 2022)

Sub-themes	Illustrative quote
Staff rotation	"To ensure continual service provision we do staff rotation, if a TB nurse is not available, one is always assigned to the TB department" R4 "We do have enough clinical staff because we rotate the nursing staff working on the chronic care site, we provide training to our staff so that they can familiarize themselves on HIV and TB care, this is the same staff that we normally use for the rotation" R7
Synchronized clinic visits	"We allow the patients to start at the DM clinic and then come to the TB clinic so that we can assign the very same date as that of DM refill, this is a way of avoiding an instance whereby the patient has to come for TB/DM treatment at different dates, hence we are treating TB and DM as one package together with ART" R12
Health education	"Health education is important to both the patient and the nurse. On the patient aspect, we need to teach the patient about the importance of insulin treatment for the good control of blood sugar and a good response to the TB drug …we are having a challenge of adherence when it comes to the patients that is why the health education is important" R5 "We then discuss with the patient what is expected and see if we can start on oral medication, we also articulate on the diet issue." R14
Integrated services	"...we have integrated the services, such that an ART patient, who has DM and TB is going to get all the services at our department even his/her medication. There is no need of going to the pharmacy or laboratory, we do everything here at our department" R3 "We have also integrated all the services at one consultation room such that ART, DM, TB and hypertension patients or any NCD patient receive all the services at one point." R18
Fast-track services	"We do NCDs screening and highlight if that patient has one and then fast-track the patient, this helps us to easily check and manage the patient monthly to avoid complications" R7 "…we normally fast-track them because we don't want them to queue, everything is provided at one place, and we don't want them to go here and there for their services." R20 "But one challenge that we normally face is that patients are not honest when giving such information, they tend to say they have no history or family history of DM, such that when a patient has no family history of, we don't fast-track that patient" R7
Bidirectional TB – DM screening and COVID-19	"…now we have adopted at least to screen all TB patients for DM and so far, we have started picking some that we were missing all along. So, in our diabetic clinic we were not screening our DM patients for TB but now we have started screening all our DM patients when they come for a refill, and we are picking patients who are TB positive, but we have been missing them all along" R11 "COVID-19 was severe for DM patients, thus in our facility we are now screening every patient above 40 for DM if they are found to be positive, we fast track them to the focal person for NCDs" R20

Opportunities to improve integrated services delivery

Patient support

The study participants identified some patient-related factors which may result in poor outcomes. These include non-adherence to medication, late presentation at a health facility for review and diagnosis, denial, limited knowledge and understanding of the disease process, and poor economic status.

"Some of the patients do not accept the diagnoses, hence it becomes difficult to assist the patient who has not accepted his/her condition" R17

"…coming to the dietary control, patients do not have money to buy a healthy diet, thus this has an impact on the blood sugar, because when you are not eating a proper diet the blood sugar goes up" R21

HR and staffing

Most participants indicated inadequate clinical staff and would require additional staff to ease the workload and ensure quality care. They indicated this led to prolonged waiting times for patients who visit the TB clinic for different services.

"…we do not have enough clinical staff, it is only one nurse and one doctor wherein we have to take care of ART, hypertension, DM, and TB… hence we appoint patients to different dates in an attempt to control the patient flow" R18

Staff training

While most of the participants (n=13) stated they have received training for TB – NCD, few (n=8) indicated they have specifically been trained to provide care for DM – TB patients.

"With TB I am well equipped, but I am not with diabetes mellitus, hence I require more training and sensitization in that aspect." R1

"On the part of DM yes, because I am a focal person for D.M., but I cannot say the same for TB For instance if I initiate a patient on TB treatment and the patient complicates, I normally do not know what to do and when to switch the drugs, I do not have enough exposure to TB" R4

Reporting tools

A few participants indicated they did not have the required patient information sheets. They indicated different versions of the patient documentation card were available, requiring varying patient detail and timelines for documentation.

"The standard of care is okay, there are only issues with the white card, one is detailed, and the other is not, now we do not have the detailed white card which I guess it's the new one, it is very simple and straightforward" R15

DM and TB diagnosis

Most participants agreed they had challenges screening for and diagnosing DM due to recurrent stockout of glucometer test strips, absence of a glucometer, variable access to the HbA1c due to lack of reagents, and an unfavourable schedule for specimen submission. For instance, only 6 and 14 respondents reported providing baseline HbA1c and a fasting/random blood glucose test for patients respectively. In addition, 16 and 13 respondents reported stock out of urinalysis and blood glucose test strips respectively in the previous six months. Additional concerns were the absence of GeneXpert cartridges, the long turnaround time for sputum culture, and the limited availability of TB-lam.

"We do face numerous challenges, taking for instance, last month we had challenges with cartridges in the laboratory which made it difficult to transition a patient from an intensive phase to a continuation phase…" R2

"… we do not have a glucometer and a BP cuff such that when a patient comes, you need to run around borrowing from other departments and we end up not doing the proper routine care" R10

"We normally run out of glucose strips..." R16

Availability of drugs

The participants acknowledged frequent stock-out of medication for the treatment of NCDs and tuberculosis. From the survey, the participants indicated a stockout of antihypertensive medication, insulin, and oral DM drugs within six months of the date they were interviewed.

"… shortage of insulin; some patients who are taking the 500mg doses (Metformin) are sometimes given the 850mg doses due to shortage of stock" R3

"…for the past 2 months we did not have metformin 500mg which is a drug that we normally give to TB patients who are diabetic, hence this is a rural area patients cannot afford private pharmacies" R17

Recommendations

Participants provided recommendations on how DM – TB services integration can be improved. This is summarized in *Table 4*.

Table 4 - Sub-themes describing recommendations by healthcare workers with illustrative quotes (Eswatini, 2022)

Sub-themes	Illustrative quote
NCD management guidelines	"The guidelines (TB and HIV) are clear and good for me, but we need a clear guideline on the NCDs aspect because for now much attention is given to TB and ART forgetting about NCDs" R3 "I think the national guidelines of TB care are really good, and we refer to them a lot, and they have been updated I think around 2019, but we are struggling on the management of TB and, I feel like if there can be proper guidance to that aspect" R9 "… there should be a proper guideline on the NCDs aspect" R21
Healthcare worker training	"… I am more equipped in DM; I think more training needs to be done in the area of NCDs since it is where most of us are lacking" R1 "I wouldn't say I am well equipped on balancing TB and DM, my knowledge is mostly on TB hence I am lacking training on the DM aspect, thus I suggest that more training must be done on the DM aspect since I only know the general aspect of DM such that if I can face a patient who is critical with DM I wouldn't know how to assist." R2 "I suggest that there should be more training for healthcare workers, more in-service training is also important as well. I strongly suggest that facilities must be visited by the doctor at least twice a month" R17
Patient documentation tools	"… the MoH needs to ensure that all the required tools (documentation) are available in the facilities as stipulated in the national guideline." R6
Improve diagnostics	"One can advise that screening TB patients for DM is important but not only using the random or fasting blood sugar but using the oral glucose tolerance test" R5 "I would also strongly suggest that the HbA1c test be made available to facilities, it is very accurate for diagnosing DM and also to monitor patients who are living with DM" R11 "… we also need the HbA1c test because for now, we are not doing the best care whether for TB or DM patients" R21
Drugs	"…also availing the medication because it's one of the many challenges that we see, one drug being available then the next day it's not then you are supposed to use another drug that won't help" R21
Patient support and Health Education	"I think it (standard of care) can be improved, especially supporting the patients with food since some of them are facing diet issues" R13 "… health education, regardless of the shortage of drugs we have also noticed that patients are not eating well, and they must be taught about the importance of a balanced diet and that of exercise" R5

Discussion

Most of our survey respondents (n=20) indicated they have integrated DM care into TB services, but the implementation varies as some services are not routinely available with frequent stock-out of essential medication and commodities required for the care of TB patients with NCD comorbidities (Figures 1 & 2). The participants indicated there are no standardized guidelines and SOPs for the management of TB patients with any of the NCDs including DM. The random/fasting blood glucose test was commonly used for screening and diagnosis, while there is limited access to HbA1c required to estimate glucose regulation in the past three months and follow-up. Participants were concerned

the different limitations they encountered may impact patient outcomes and hinder Eswatini from achieving the goal of ending the TB epidemic.

Some opportunities and recommendations for improvement by the participants include the provision of a uniform guideline and documentation card for the management of TB patients with NCDs, patient support to address adherence and economic burden, additional human resources, training, and capacity building of healthcare workers on the management of TB patients with NCDs, increased access to and availability of TB and DM diagnostics, and improved supply chain management processes to limit the stock out of essential drugs and commodities. The participants also indicated some best practices they adopted to ensure efficient services.

A 2021 study assessing the implementation of recommendations from WHO's Collaborative Framework for Care and Control of Tuberculosis and Diabetes [14] indicates evidence is available from only 35 countries (out of 194 countries registered with WHO). The authors observed bidirectional screening for the two conditions is possible but that there was limited integration with a parallel care system for the two conditions, absence, and limited knowledge of guidelines for healthcare workers, limited knowledge of DM – TB care amongst healthcare workers, and more emphasis on screening than management. These findings are similar to our research findings, except that, in Eswatini, the services are integrated though the implementation is varied.

An Ethiopian study to explore health system challenges and opportunities for integration of DM – TB care indicates healthcare workers had the motivation to provide integrated DM – TB services but encountered challenges with the continuity of care for DM – TB patients, limited knowledge, and skills in providing care, recurrent stock-outs of supplies for DM care, limited attention to DM, poor data management, and the inability of patients to pay for services [31]. Another study from India to explore stakeholder perspectives on challenges and opportunities for integrated DM – TB care indicates that integrated DM – TB care requires improvement in laboratory and diagnostics, drug management, human resources and training of healthcare workers, data infrastructure, and higher-level coordination [32]. Findings from our study highlighted the need to also address these gaps.

Patient factors reported in Ethiopia were also reported in studies conducted in Zimbabwe and Pakistan, where transportation costs or long distances to the health facility to access a test and the cost of the test hindered patients from visiting a health facility for a repeat test [33,34]. This is particularly important as TB is more prevalent in people of low socioeconomic status (SES) which has been shown to negatively impact

treatment outcomes [35]. In our study, the participants expressed concerns as the patient's economic status limits their access to proper nutrition. This emphasizes the need for continued patient support and the adoption of the patient-centred care model in planning integrated DM – TB services [36].

Studies from Malawi and Angola indicate that integrated DM – TB services can be beneficial [15,17]. In Malawi, they observed no loss to follow-up where services are integrated compared to where there is none or limited integration (14·8%) with higher retention in care of 62·5% after two years for people with diabetes where there is integration compared to 41·8% in sites with no integration [17]. The study from Angola aimed to assess the burden of NCDs amongst TB patients and pilot the integration of diabetes and hypertension screening within the TB program. They observed a high burden of NCDs amongst TB patients and noted that the absence of screening guidelines and protocols to guide patient management limited the implementation of integrated TB – NCD services [15].

Using a qualitative design enabled the collection of comprehensive information on the DM – TB integration. We selected health facilities and healthcare workers across the four regions to ensure adequate representation. To ensure findings will be useful for TB programming, the study focused on the TB program's key priorities following engagement with the TB program. Finally, the study team consists of diverse expertise, including qualitative research and TB programming.

Our study has some limitations. First, healthcare workers from non-selected sites (including some private health facilities) may have had different views based on their training and experiences. Secondly, we did not include community-based organizations that mainly see patients on an outreach basis. Healthcare service delivery in community settings is different from facility-based care and presents different opportunities that could have been included for improvement. Finally, we did not include other healthcare workers who support patient care such as pharmacists, laboratory scientists, adherence, and psychosocial officers, etc. These staffs provide vital services along the care continuum and interact with patients. Their views could have added to describing the care processes and some opportunities that could be improved overall. Nevertheless, we believe the evidence provided in this study will be vital to improving DM – TB care in Eswatini and other LMICs.

Recommendations

The healthcare workers have identified different opportunities but some of these e.g., additional human resources, and new laboratory equipment are resource intensive and may require long-term planning to achieve. However, some immediate actions can be taken to ensure improved service delivery. First, is developing a standardized treatment algorithm to guide healthcare workers on how to care for TB patients with NCDs including hypertension and DM. This can be adapted from the guidelines provided by TB Union while ensuring the local context is incorporated [37]. Healthcare workers can be trained on this standardized algorithm with more experienced clinicians serving as mentors. Secondly, the TB program collaborating with the health promotion unit can develop standardized information, education, and communication (IEC) materials for comprehensive patient education that will include information on NCDs and nutrition based on the staple food in Eswatini.

Third, indicators for monitoring NCDs amongst TB patients should be tracked in the national reporting system. This will ensure the availability of NCD data for TB patients, and a routine review of this data by the program and stakeholders will identify program needs and guide interventions. Finally, stock out of drugs and other commodities hinders effective care for patients. The procurement process for pharmaceutical commodities can be complex and prolonged. This became worse as the COVID-19 pandemic impacted global supplies. One way of addressing this is to train and mentor healthcare workers to keep accurate records and timely orders of supplies once they have the recommended minimum stock. Issues around financing for the procurement of drugs and laboratory supplies are complex and require multisectoral engagement.

Conclusion

There is limited implementation of DM–TB integration at health facilities included in this study as the quality and current standard of care varies across health facilities. While challenges and opportunities exist to improve the implementation of DM–TB integration, healthcare workers currently adopt different practices to ensure continued service delivery. Addressing the different patient-level and health system challenges and utilizing the available opportunities is vital for successfully implementing the DM–TB services integration.

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Chapter 6

Tuberculosis Services during the Covid-19 Pandemic: A Qualitative Study on the Impact of Covid-19 and Practices for Continued Services Delivery in Eswatini

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Abstract

Objectives: To describe the impact of the COVID-19 pandemic on tuberculosis services and the different approaches healthcare workers adopted to ensure continued service delivery.

Study design: This is a qualitative study with a cross-sectional design.

Methods: Thirteen nurses and 9 doctors who provide tuberculosis care from 10 health facilities participated in an indepth interview to describe how the COVID-19 pandemic affected tuberculosis services and the approaches adopted to ensure continued patient care. Twenty in-person and 2 telephone interviews were conducted. The participating facilities were selected based on a ranking criterion of the number of patients seen. Data were analyzed using thematic content analysis. NVivo 12 software was used for qualitative analysis, and the Consolidated Criteria guided the study for Reporting Qualitative research (COREQ).

Results: Two major themes emerged: COVID-19 impacted services delivery and access; and best practices that ensured healthcare services delivery. Six sub-themes describe how COVID-19 impacted services; all attention focused on COVID-19; COVID worsened the health system challenges; COVID hindered patients from accessing care; patients defaulted due to the lockdown; COVID impacted the quality of care and increased the risk of infection among healthcare workers. Five sub-themes describe best practices that ensure continued service delivery: Home-based care, Patient support, Patient Education, Integrated Services, and Staff rotation.

Conclusion: While various strategies were adopted globally to mitigate the impact of the COVID-19 pandemic, these strategies need contextualization to be effective and sustainably incorporated into routine care to ensure continuity of and access to TB and other healthcare services.

Keywords: Tuberculosis, Pandemic, COVID-19, Primary care, Tuberculosis Outcomes

1. Introduction

At the peak of the COVID-19 pandemic in 2020, tuberculosis (TB) case notifications dropped by as much as 47%.[1] Many TB high-burden countries continue struggling to recover as newer COVID-19 variants arise and impact resource allocation and service delivery.[2,3] Impacts include the closure of health facilities and laboratories, healthcare workers becoming sick, stock out of medical supplies, and repurposing of existing facilities and staff. Additionally, an impact modelling study demonstrated there could be an increase of up to 20% in TB-related deaths due to delayed diagnosis over the next five years.[4]

Data from different WHO regions indicate access to other health services including HIV, malaria, vaccination, non-communicable diseases, and mental health were affected.[5–8] The responses to address the impact of COVID-19 on these services including TB varied by country, especially noting wide differences in health systems and existing infrastructure before the pandemic. Associated with the public health response was the economic meltdown caused by the global shutdown and restriction in both local and international movements to limit new infections.[9]

Like other countries, the declaration of COVID-19 as a global pandemic in March 2020 by WHO activated a national response in Eswatini which mandated the use of face masks, hand washing and sanitization, closure or limited operations at some institutions and the general restriction in movement.[10] These measures affected access to healthcare including TB services. In this paper, we describe the impact of the COVID-19 pandemic on TB service delivery and different practices adopted by healthcare workers in Eswatini to ensure continued services.

2. Methods

2.1 Context

TB services in Eswatini are coordinated by the ministry of health (MOH) through the National Tuberculosis Control Programme (NTCP).[11] The NTCP oversees TB services through a network of primary care clinics, health centres and regional hospitals where every patient is screened for TB regardless of the primary complaint. Drug-sensitive TB patients are managed at the primary care clinics while those with multi-drug resistant TB are initially treated at one of the regional hospitals and down referred to the primary care clinic when they achieve sputum conversion.

2.2 Study design and setting

This qualitative study, evaluated cross-sectionally, is based on the socio-ecological framework and is part of a prospective cohort study which has been described earlier [12]. Healthcare workers from eleven health facilities in Eswatini were interviewed to identify barriers to TB and integrated TB–DM services, the effect of COVID-19 on TB and TB-DM services and the practices adopted to ensure sustained services delivery. This article focuses on the effect of COVID-19 on TB services and the different practices adopted by healthcare workers to ensure sustained TB services. The research team consists of specialist physicians and epidemiologists (AV, MC, SH, DEG, VW), a nurse practitioner in the national TB program (LM), a biostatistician experienced in quantitative and qualitative TB research (KO), an epidemiologist and global health researcher (KKG).

2.3 Data collection

The eleven health facilities selected for this study consist of five hospitals, one health centre and five primary care clinics across the four regions in Eswatini. The facilities were purposively selected based on a ranking criterion of the highest number of patients two quarters before the study. Doctors and nurses were invited to participate if they had worked at the health facility for a minimum of one year and provided care for TB patients. Those who met the inclusion criteria and provided informed consent were included.

Interviews were conducted between May and June 2022 by a trained research assistant assisted by the principal investigator at the clinic. Participants informed consent included consent to record the interviews. One participant declined to consent to the recording and interview notes were taken. Participants received an orientation on the study and a study information sheet. In-person interviews were conducted with 20 participants and two participants were interviewed telephonically. A semi-structured interview guide (Supplementary file 1) was used for the interview. Each interview lasted 30–45 minutes and healthcare workers used the language of their preference (English or Siswati). The study was approved by the Eswatini Health and Human Research Review Board (EHHRRB-036/2021).

2.4 Data analysis

Each interview was transcribed immediately afterwards without linking it to the healthcare worker. The research assistant and the study principal investigator reviewed each transcript against the interview recording to ensure the accuracy of the transcript. Inductive and deductive codes were identified from the transcripts and documented in a codebook (VW). Similar codes in the codebook were grouped into

sub-themes and similar sub-themes were grouped into major themes for the study (VW, MC). Three research team members reviewed the code book and the themes for accuracy and consistency. Inaccuracies in the codes, sub-themes, and themes were resolved in a study meeting. Reviewing the codes was iterative to ensure the finalized themes were accurate. The results were presented using text analysis. NVivo 12 software was used for qualitative analysis and the Consolidated Criteria for Reporting Qualitative research (COREQ) guided the reporting of this study.[13,14] (Supplementary file 2).

Results

3.1 Characteristics of respondents

Twenty-two healthcare workers from ten healthcare facilities participated in the interview (Table 1). Although two participants from one health facility were not available for interviews, data saturation was achieved.

Data from the interviews indicate two themes which describe the healthcare worker's perspectives on the impact of COVID-19 on TB services delivery and access and best practices which enabled services delivery during the COVID-19 pandemic. The different themes and subthemes are summarized in Table 2.

3.2 COVID-19 impacted services delivery and access

3.2.1 All attention focused on COVID

Most participants stated many aspects of healthcare delivery were deprioritized at the start of the COVID-19 pandemic. Services were implemented partially or suspended.

"More attention was given to COVID-19, sputum was not collected due to COVID-19 hence many patients who were TB+ were lost in the process since patients were only screened mostly for COVID-19. Many patients who came with NCDs during the COVID-19 phase missed out because we were afraid of conducting some of the tests" R1

"Sputum induction was stopped due to the pandemic since we were in fear of the exposure to COVID-19" R2

3.2.2 COVID worsened the health system challenges

Respondents observed that existing health system-related challenges worsened during the pandemic including disruptions in the supply of drugs and consumables and shortages of healthcare workers (Table 3).

3.2.3 COVID hindered patients from accessing care

With the uncertainty around COVID-19, most chronic care patients stopped visiting health facilities to avoid infection, hindering routine care, and increasing their risks of poor treatment outcomes.

"… but they (patients) were afraid to come to the clinic because they thought they would contract COVID-19 from the facility" R5

"Patients were not coming to the clinic for monitoring and check-ups due to fear of contracting COVID, this led to other patients being severely attacked by TB and others had their DM escalated" R7

3.2.4 Patients defaulted due to the lockdown

The respondents observed that some patients, besides not visiting the health facilities, stopped taking their medications while others could not be reached or contacted (Table 3). These losses to follow-up were, attributed to the different COVID-19 prevention measures and limited resources at some health facilities to provide alternative means of care such as home visits.

3.2.5 COVID impacted the quality of care

Some of the COVID-19 infection prevention measures instituted at different health facilities may have impacted the quality of care provided by healthcare workers (Table 3). Limiting the services available, restricting the number of patients that are reviewed daily and increased time before accessing a service due to patient screening and triaging contributed to decreased quality of care.

3.2.6 Increased risk of infections in healthcare workers

Respondents had reservations about interacting with patients as they were at an increased risk of infection with COVID-19. Some of their colleagues nonetheless got infected, reducing the number of staff available for patient care, and further impacting the quality of care negatively.

"Sputum induction was stopped due to the pandemic since we were in fear of the exposure to COVID-19" R2
"We were afraid of the patients because we were afraid of contracting COVID-19 from them" R10

"One can also talk about the issue of human resources during COVID-19 since many of our staff were affected (infected) this affected the standard of care for patients" R19

3.3 Some practices ensured healthcare services delivery

3.3.1 Home-based care

An adaptation to ensure continuity of services for patients was community and home-based care. Patients received essential medical care and medication refill for chronic conditions within their community, at home, or at a pre-arranged service delivery point.

"We usually do community and home visits wherein we do TB contact tracing and TB history; this helps us to uncover TB presumptive cases" R6

"…we are doing home visits to deliver their medication to relieve them with the transport fare…" R21

3.3.2 Patient support

The respondents also provided different types of support for patients during the pandemic to encourage them and to ensure they continue with their treatment (Table 3). Some of these include providing counselling, transport reimbursement to the clinic, follow-up calls, drug refills near their homes and food supplies.

3.3.3 Patient Education

The respondents felt health education was important to empower their patients to become responsible for their health and minimize TB infections within the community.

"We have dedicated our Wednesdays… for teaching and review of the patients. TB treatment also involves teaching the patient about health education and how to prevent the spread of TB even at home" R10

3.3.4 Integrated services

Offering services at different sections of a health facility can prolong the time a patient spends at a health facility and requires more personnel. This may discourage some patients from accessing care. To avoid this, the respondents indicated they introduced a system where possible services a TB patient will require during a visit are provided at one service point. This will reduce waiting time, encourage patients to keep their appointments and minimize required staff.

"*We have introduced the one-stop-shop, wherein we have integrated all the services at one point*" R15

3.3.5 Staff rotation as a best practice

Limited staffing and skillset are challenges at most health facilities. This was obvious at the peak of the pandemic when several healthcare workers were infected and had to isolate. The respondents stated they had a process where staff were intermittently moved to provide services at other units to avoid delay or suspension of services.

"*To ensure continual service provision we do staff rotation, if a TB nurse is not available, one is always assigned to the TB department*" R4

"Yes, we have enough clinical staff. We normally rotate so that whenever there is a gap someone can cover it up" R9

Discussion

Based on the views of healthcare workers, we describe some of the impacts of the COVID-19 pandemic on TB service delivery and access in Eswatini; and describe some approaches by healthcare workers to ensure the continuity of TB services. At the height of the pandemic, COVID-19 took priority over other conditions, worsening health system challenges which were already in a precarious state. Different measures adopted to limit the spread of COVID-19 infection hindered patients from accessing care as some services were suspended or limited. This affected the number of patients accessing care and the quality of services provided by healthcare workers. Healthcare workers were equally affected by the pandemic, resulting in reduced number of staff for patient care. Despite these challenges, healthcare workers adopted different methods to ensure patients continued receiving care. These included providing care for patients within their communities or at home; providing additional support to patients such as counselling, transport, food packages, and health education; making different services available at one service point and adopting staff rotation to ensure a healthcare worker is always available to attend to patients.

4.1 Comparison with other studies

Available evidence at the onset of the pandemic indicated that COVID-19 would adversely affect TB services delivery resulting in reduced access by different population groups with poor outcomes.[15–17] This was corroborated by the WHO Global Tuberculosis Report 2021 on COVID and TB which showed that different TB targets were missed between 2019 and 2020 when the pandemic commenced compared to the years 2017 to 2019. For instance, there was an 18% reduction in global TB case notification with a lower mean TB case notification in most TB high-burden countries notably in Gabon (80%), the Philippines (37%) and Lesotho (35%).[7] There were also reductions in people commencing MDR/RRTB

treatment, people being initiated on TB preventive therapy, a reduction in coverage of the bacille Calmette-Guérin (BCG) vaccine in children and a reduction in spending for TB prevention, diagnostics and treatment services.[7,18] A recent study from Eswatini shows TB case notifications decreased during the pandemic compared to the period prior. Death rate increased to 21.3% compared to 10.8% and the odds of unfavourable outcomes were higher (aOR 2.91, 95% CI: 2.17–3.89) during the pandemic compared to the period prior.[19]

Findings from this study indicate a complex interaction of patient-level, socioeconomic, and health system factors with limited emergency response capability. These coupled with the urgent need to control a pandemic caused by a pathogen whose epidemiology was not fully understood vastly accounted for the reduced access to TB services; further contributing to the global reduction in TB achievement. A Nigerian survey describing TB and COVID-19 screening by healthcare workers during the lockdown indicates that 54% of healthcare workers were not screening patients for TB during this period.[20] Similarly, a review of TB services in India during the COVID lockdown indicates there was a widespread disruption in services at both the primary and secondary health facilities; and that different health guidelines aimed at limiting COVID virus transmission limited access to TB services.[21] This is similar to what we have reported as some services were temporarily suspended while others operated at half capacity. Reports from Sierra Leone [22], the United States [23] and Portugal [24] confirm similar findings. In a multi-country cross-sectional survey, about 40% of respondents indicated it was more difficult for HIV and TB patients to access a health facility during the COVID pandemic and another 31% indicated access to TB patient support such as food and counselling was interrupted. [25]

Another critical factor was the repurposing of TB resources for COVID-19 including the equipment GeneXpert used for TB diagnosis.[18,26] This negatively impacted TB diagnosis, access to treatment and follow-up care as the number of TB samples that can be processed was reduced. Available human resources and clinic spaces were also reassigned in some instances to provide COVID-19 services. When combined with other related factors such as stock-outs of medications, reduced facility operational hours and movement restrictions, fewer patients access services.[18] Several healthcare workers who were also the first responders got infected with COVID-19.[27] While some died, others suffered different forms of physical, mental and psychological impact including fear, anxiety and depression.[28–30] This was similarly reported in our study as healthcare workers were afraid of seeing patients due to fear of infection. This also contributed to a reduction in the quality and number of services provided. While the reduced number of healthy staff could have been responsible for the reduced quality of care, limited availability of personal protective equipment (PPE) and limited support to healthcare workers contributed to sub-optimal service delivery.[18,31]

Due to the pandemic, more people globally have become poorer. [9] TB already being a disease associated with poverty means more TB patients are disadvantaged. In addition to the increased poverty level, measures aimed at controlling the pandemic hindered patients from accessing care and basic support including food and psychosocial services; and transport to health facilities by both patients and healthcare workers.[18,25] Patients in Eswatini also encountered these different challenges and healthcare workers adopted different measures to continue providing services. While these measures – home-based care, patient support services and patient education may not be completely new, their adaptation within limited resources ensured patients remained in care. This is different compared with some high-income countries where patients could easily access healthcare through telemedicine consultations, virtual consultation and monitoring.[31]

4.2 Strength and Limitations

Our qualitative study presents healthcare workers' perspectives on how COVID-19 impacted TB service delivery at the peak of the pandemic and the different steps they took to ensure continued service delivery in Eswatini. This will provide insight into the reduced performance in key TB outcomes in Eswatini and other LMICs and guide TB program implementers on measures that can increase access to TB services. Our study participants were drawn from health facilities across Eswatini so our findings are representative of how COVID-19 impacted TB services. As a limitation, our study does not present data to quantify the impact of the pandemic on key TB indicators. This would have provided a more objective view of the problem. Secondly, we interviewed only doctors and nurses. We did not include other healthcare workers such as community TB officers responsible for active TB case finding, TB treatment supporters, and laboratory and pharmacy technicians. These healthcare workers could have presented a more complete perspective of how the pandemic affected TB service delivery and patients. Finally, we did not interview TB program staff. They would have offered an additional explanation for observations by our participants.

Conclusion

The COVID-19 pandemic affected health systems globally, even in advanced economies. The different approaches that sustained services must be standardized so patients can continue receiving care. In the future, tailored and hybrid approaches to care should be developed where patients can access care either at the health facility or remotely with the freedom to visit a health facility if necessary. Due to limited infrastructure, approaches such as telemedicine for consultation may not be feasible immediately in most LMICs but telephone calls, SMS and home-based services can be used for medication dispensing, testing, follow up and psychosocial support. Finally, bidirectional screening and integration of care for different comorbidities can increase access to care.

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Table 1: Characteristics of study participants

Variable	Overall (n = 22)
Age (years)	
Median (Q1, Q3)	36.0 (33.0, 43.0)
Min, Max	26.0, 59.0
Gender of healthcare worker	
Female	9 (41.0%)
Male	13 (59.0%)
Highest qualification attained	
Certificate	1 (5.0%)
Degree	10 (41%)
Diploma	4 (18.0%)
Postgraduate	8 (36.0%)
Occupation	
Medical Doctors	9 (41.0%)
Nurses	13 (59.0%)
Number of years providing care for TB patients	
Median (Q1, Q3)	4.0 (3.0, 7.0)
Min, Max	1.0, 15.0

Table 2: Summary of themes and subthemes in the study

Themes	Subthemes
COVID-19 impacted services delivery and access	All attention focused on COVID COVID worsened the health system challenges COVID hindered patients from accessing care Patients defaulted due to the lockdown COVID impacted the quality of care Increased risk of infections among healthcare workers
Some practices ensured healthcare services delivery	Home-based care Patient support Patient Education Integrated services Staff rotation as a best practice

Table 3: Illustrative quotes from the participants in the study

Sub-theme	Quotes
3.2.2 COVID worsened the health system challenges	"… much attention was given to COVID-19 such that other medications were out of stock which hampered the control of the chronic conditions, at times patients were getting their medications at the comfort of their homes without a medical practitioner to ensure if their condition is getting better or worsening" R5 "The availability of drugs during COVID-19 was also a challenge from the suppliers as well." R11 "…most patients who screened positive for COVID-19 were also sent to the TB department, hence they were flooding the department... both the confirmed and the presumptive TB cases are seen by the same person due to the associated symptoms of TB and COVID-19… we were seeing that challenge of the shortage of staff during COVID-19 surge …" R21
3.2.4 Patients defaulted due to the lockdown	"… what happened is that patients were not coming to the facility hence we were missing cases, and some patients were defaulting." R9 "During COVID-19 many of our patients defaulted and we had many lost to follow-up due to lockdown and the travel restrictions which were put in place. There was no transport to do home-based care visits" 17 "When COVID-19 started, movement was restricted hence it affected the patients who were coming *to our facility" R20*
3.2.5 COVID impacted the quality of care	"Due to COVID-19 we were limiting the amount of time the patient would spend in the facility, such that we were not checking the blood pressure, even some processes that were followed before were not followed in the COVID era such that it was easy to miss a TB patient who has COVID or even misdiagnose a patient." R3 "The standard of care to patients declined especially if a patient was diagnosed with COVID-19, thus the time spent with the patient was reduced" R7 "Since COVID and TB almost share the same symptoms, all the TB and COVID patients are reviewed by one nurse which has increased the volume (of patients) seen by the nurse thus increasing the waiting period as well." R20 "We normally face delayed transportation of samples to the national lab... The ambulance is not always available for emergencies which can affect the standard of care" R19 "… we sometimes have a problem with our GeneXpert machine and sometimes we run out of TB-lam… There is no proper follow-up on culture, sometimes we send, and the results do not come back" R20
3.3.2 Patient support	"… we have our treatment supporter who also provides counselling to our patients… we do provide transport money to our patients so that they cannot be frustrated when it's time for refills..." R8 "COVID-19 did affect us but not that much, most of our TB patients were coming and if they didn't come, we call them, and if they are far, we used their nearest facility for refills" R12 "…We are also giving food parcels to our patients who are both TB and HIV positive to improve their nutrition because most of our patients are struggling with nutrition" R21

Chapter 7

General Discussion

Diabetes – Tuberculosis Comorbidity

This thesis described diabetes mellitus (DM) and tuberculosis (TB) comorbidity in a low-resource setting, the effect of blood glucose on TB treatment outcomes, the impact of COVID-19 on TB services, and recommendations to improve integrated DM-TB care. Given the high burden of TB and DM-related mortality in Sub-Saharan Africa, urgent attention is required to limit mortality from the two conditions and to promote health [1–3]. As most cases of DM are undiagnosed [4], and countries in Sub-Saharan Africa still struggle to find TB cases [3], innovative approaches for screening, timely diagnosis, and managing DM and TB are essential.

Although the association between DM and TB has been described previously [5–9], there are few studies on blood glucose changes during TB treatment in non-diabetic individuals. In our scoping review to assess the available evidence on this subject, we noted that the observed high prevalence of diabetes and pre-diabetes at diagnosis reduced or normalized during TB treatment, with only a few patients remaining with elevated blood glucose at the end of treatment. This transient increase in blood glucose has been linked to unfavourable TB treatment outcomes, emphasizing the importance of integrating blood glucose monitoring with TB care during TB treatment for every patient, not just those with diabetes. Abnormalities in blood glucose during TB treatment will be missed if patients without diabetes are not monitored, contributing to unfavourable TB treatment outcomes.

The described epidemiology of DM-TB presented in this thesis is similar to what is reported in the general literature, with some variations given the differences across Sub-Saharan African populations. Our prevalence of 8% elevated baseline blood glucose is similar to the reported prevalence from studies conducted in Tanzania and Uganda and a pooled prevalence of studies from Sub-Saharan Africa [8]. We conducted our study in Eswatini, which has a largely homogeneous population with similar dietary patterns and risks for TB infection. So, prevalence across regions in the country did not vary as expected in a more densely populated country with diverse cultures, nutritional habits, risks of TB infection and access to health services [9,10]. The prevalence was higher in people aged 40 and above and those with a reactive HIV status than in younger people and those with a negative HIV status. This finding is consistent with the general literature, as people aged 40 and above are more likely to have an NCD. Metabolic and inflammatory changes and medication taken by HIV-positive patients may also contribute to their diabetes risks [5,9,11,12]. A family history of diabetes and a positive HIV status predicted elevated blood glucose, while hypertension and unemployment were associated with unfavourable TB treatment outcomes. High school education was protective against unfavourable TB outcomes. The effect of HIV status on blood glucose is conflicting

and requires further investigation. Unconfirmed reports on the effect of dolutegravir on blood glucose indicate it impairs blood glucose metabolism, resulting in elevated blood glucose or even diabetes in some patients [13]. Dolutegravir is part of a three-drug regimen currently recommended by WHO for the treatment of HIV and has been adopted by different countries, including Eswatini [14,15]. It has been implicated in weight gain, which is associated with blood pressure; hence, it could explain the association between hypertension and unfavourable outcomes [16]. Hypertension as a predictor of unfavourable TB treatment outcomes indicates the need for continuous monitoring and treatment of patients for comorbid conditions, as hypertension can impair different organ functions, limiting outcomes [17]. Unemployment limits access to basic needs, including housing, food and healthcare, thus lowering the quality of life and negatively impacting treatment outcomes. The protective effect of education has been reported in the literature, increasing employment opportunities and access to health education and healthcare [18]. Consistent with findings from Sub-Saharan Africa, most patients with unfavourable treatment outcomes died [19], indicating the need to identify and address the different causes of TB-related mortality beyond HIV. Compared to other studies [20–22], elevated baseline blood glucose was not associated with unfavourable TB treatment outcomes in our study.

Health services integration

The integration of DM–TB care, access to DM-TB services by patients and opportunities for improved service provision varies across Sub-Saharan Africa. A review describing the adoption of the WHO Collaborative Framework for Care and Control of Tuberculosis and Diabetes indicates that evidence of implementation is available in only 35 out of 94 registered countries, mainly emphasizing screening for both conditions [23]. From our qualitative study, most healthcare workers provide integrated DM-TB care, although with challenges that hinder effective service delivery. These include limited staffing, the absence of guidelines, limited knowledge of DM and TB amongst healthcare workers, limited availability of testing kits for screening, diagnosis and monitoring of DM and TB, and frequent stockouts of DM and TB medications. These findings are similar to those from Ethiopia, India and Zimbabwe, where, in addition to health system-related issues, some patient-related factors such as socioeconomic status and availability of psychosocial support also hindered access to care [23–25]. The cost of managing diabetes is enormous for most patients, often requiring repeat hospital appointments for different services and out-of-pocket payments for medication and laboratory investigations [26]. A comorbid TB infection with diabetes only adds more expenses for the patient, who may need additional financial, psychosocial, and nutritional support to complete TB treatment. However, this extra support may not always be available.

To promote access to quality health services by patients at risk of DM–TB comorbidity, the World Health Organisation (WHO) advocates bidirectional screening and treatment for both conditions [27]. Through this approach, patients who present for either condition will receive screening for the other condition and treatment. To strengthen this, WHO has also provided guidelines for integrating NCD services in infectious disease programs (TB, HIV and STI) [28]. Integrating different services will limit parallel services in primary care settings, multiple clinic visits, long waiting times, and timely diagnosis and management of clinical conditions. While our study mainly assessed the level of integration of DM care at health facilities providing TB services, we note the operational status of health facilities may hinder the provision of DM-TB services in the same consultation room but allow for bidirectional screening and referral for treatment. This can be the case in a tertiary health facility with dedicated DM and TB clinics with separate staffing, unlike primary care clinics where one nursing staff provides care for all the patients. Existing health system gaps offer the opportunity to improve DM-TB care.

Impact of COVID-19 on TB services

Healthcare workers who were the first respondents during the COVID-19 pandemic were frequently infected and had to isolate, creating staff shortages with specific services either suspended or provided at half capacity to limit contacts while prioritizing patients with signs and symptoms of COVID-19 [29,30]. Restriction in movement and economic activities similarly impacted supplies of essential health commodities, including DM and TB drugs, test kits and reagents. Stringent measures adopted to limit the spread of the virus limited access to health services and worsened health outcomes across all patient groups. Admittedly, besides fewer patients accessing TB services, HIV, Malaria, non-communicable diseases, and other specialized services also observed a drastic decline in the number of patients served [30]. Despite these limitations, healthcare workers adopted different approaches to ensure continued service delivery to meet patient's needs. Not only peculiar to Sub-Saharan Africa, the COVID-19 pandemic disrupted healthcare services globally. To mitigate this, less-used innovations pre-pandemic, such as telemedicine, teleconsultation and virtual monitoring, became a standard for accessing health care [31]. In contrast, these technology-enabled services are not readily available in Sub-Saharan Africa. Contextualized approaches, including health outreaches, community-based service points and home visits by healthcare workers, were used for HIV testing, screening for diabetes and hypertension, and medication refills.

Health systems improvement will improve DM–TB Care

The infrastructures in most Sub-Saharan African countries will not sustain the projected increase in DM and TB cases [32,33]. Currently, most country health systems cannot meet health needs; hence, urgent improvement across the different health system components is required [34,35]. Some of the gaps in DM-TB care identified in our study have been described. A comprehensive needs assessment by the local health authority to identify gaps provides a good starting point to better plan for health system improvement. When conducted based on the projected population growth and projected prevalence of communicable and non-communicable disease, this will identify approximate resource needs to achieve different country health targets. The WHO's analytical framework on the health system has divided it into six components for consideration during health planning [36]. These include leadership and governance, service delivery, health system financing, health workforce, medical products, vaccines and technologies and health information systems. While frequently overlooked, leadership and governance, which coordinate the overall implementation of changes and how the other health system components function, should have sufficient expertise to efficiently allocate and utilize available resources for optimal health outcomes while remaining accountable [37,38].

Commitment from relevant stakeholders to address NCDs is vital

Globalization, with advancements in healthcare technology and different healthcare funding models, has significantly changed planning, delivery and access to healthcare interventions [39–41]. With projected increases in diabetes and other NCDs, infectious diseases and future pandemics, key stakeholders' active participation in planning and delivering healthcare interventions is pivotal to the success of any intervention [39,42]. Policymakers, funders of public health interventions, academia, the private sector, pharmaceutical and biotech companies, non-governmental organizations, and community and civil rights organizations are some of the key stakeholders who should commit to partnering with host governments to address NCD risk factors [39]. Stakeholder participation can range from planning an intervention to address modifiable NCD risk factors in high-risk populations to developing and testing new drugs or medical equipment to treat NCDs.

Frequently omitted during planning for health interventions are the recipients of the planned intervention. This omission has dire consequences, as the planned intervention may not be suitable or acceptable to the intended beneficiaries. One approach to overcome this is utilizing the human-centred design (HCD) concept when planning an intervention. HCD, as a concept, uses an iterative engagement process with the

beneficiaries of an intervention during planning and implementation to ensure the intervention continuously meets the needs of the beneficiaries [43,44].

A significant limitation encountered by NCD programs globally and more in Sub-Saharan Africa is limited commitment to funding, implementation of the NCD strategy and health system support as they are not an immediate risk and require a multisectoral approach for its control [45,46]. For instance, low-income countries spent 51% of their health budget on infectious and parasitic diseases compared to only 13% for NCDs [47]. In addition, only 37% of all spending on NCDs in low-income countries is from public funds, while domestic private sources and foreign aid account for 48% and 15%, respectively [47]. Globally, despite being the largest funding country, only 0.48% of the US and 1.66% of the UK government funding was for bilateral portfolios targeting NCD interventions [48]. NCD programs in most Sub-Saharan African countries depend on limited government grants to implement their activities. Public-private partnerships can close the NCD funding gap in healthcare. At the same time, collaborations with academic institutions, public health funders and non-governmental organizations can enhance research [49] and build the capacity of healthcare workers to provide improved NCD-related healthcare services.

Future Studies

Although DM and TB are well-known diseases with standardized treatment guidelines, some gaps still exist.

Estimates of DM burden in Eswatini with associated risk factors are not reliable. Currently, prevalence is based on estimates provided by the International Diabetes Federation. The WHO STEPwise approach to NCD risk factor surveillance, last conducted in Eswatini almost a decade ago (2014), may provide unreliable estimates to guide future interventions. Therefore, addressing the challenges of diabetes care will require a survey to determine the correct estimates of the burden of diabetes mellitus and diabetes risk factors in Eswatini.

As >90% of the people living with HIV in Eswatini are on antiretroviral therapy (ART), a study to determine the effect of commonly used ART drugs, particularly Dolutegravir, on blood glucose is required. This will clarify a concern for clinicians and patients if it is associated with diabetes and guide patient care.

Patients' socioeconomic status affected how they accessed TB and DM care. So, a study to determine the catastrophic cost of TB treatment for patients and those with TB and DM or another non-communicable disease in Eswatini can evaluate the treatment burden on patients and guide interventions to support patients.

About 10% of patients receiving TB treatment died, and this was not associated with HIV. This outcome is a cause for concern and requires additional study to determine the predictors of mortality in people receiving TB treatment apart from HIV and how these can be addressed.

Some patients in our study had abnormal baseline blood glucose during treatment. A cohort study post-TB treatment would help determine the DM risk of these patients. The outcome of this study can guide future DM prevention interventions.

The scope of this thesis did not accommodate patient perspectives, which could have provided more insight into different factors that impact how they access DM-TB care. Therefore, a future qualitative study targeting patients will clarify the dynamics influencing access to health care from their point of view, with recommendations on how provided services could better meet their needs.

Dissemination of key learnings

The key lessons from this thesis will be summarised and presented to the Eswatini Ministry of Health and participating health facilities with contextualised recommendations on improving DM-TB services. Additional feedback to stakeholders will be done during the national technical working group meeting for TB/HIV care.

Conclusion

This thesis has described the risks of DM-TB comorbidity and different opportunities that could improve service delivery for this comorbid condition. Despite technological advancements and significant global progress in diagnosing and treating diabetes and tuberculosis, avoidable deaths still occur. Ministries of health and health program implementers must engage all relevant stakeholders to identify and address funding, research, infrastructure, and service delivery gaps in DM-TB services. Most importantly, a comprehensive improvement in health system planning and service delivery is necessary to overcome disease-specific challenges as they rely on infrastructure from the overall system. In essence, sustaining quality services in one program area will be difficult when the system is dysfunctional. Therefore, a systemwide improvement is required and needs advocacy and commitment by different stakeholders.

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Chapter 8

Summary
Nederlandse Samenvatting

Summary

This thesis has described DM-TB comorbidity in a low-income country, the different opportunities to improve DM-TB care and the impact of COVID-19 on TB services.

Chapter 1 provides insight into the diabetes and tuberculosis burden globally and in Sub-Saharan Africa. Over 500 million people have diabetes globally, with an estimated 6.7 million deaths annually. More than three-quarters of people living with diabetes reside in low- and middle-income countries, and the number of people living with diabetes is projected to increase to 783 million by 2045. In 2022, 10.6 million people were ill with tuberculosis, with 1.3 million tuberculosis-related deaths. The COVID-19 pandemic impacted TB control efforts, and significant effort is required to revive TB services globally to the pre-pandemic levels. Globally, an estimated 15% of people receiving treatment for TB have comorbid diabetes. Diabetes increases the risk of developing TB disease and death during TB treatment and relapse after TB treatment. To address diabetes-tuberculosis comorbidity, the World Health Organisation advocates bidirectional screening and treatment for diabetes and tuberculosis.

Chapter 2 reviews studies on blood glucose changes in people without diabetes receiving treatment for tuberculosis. We searched PubMed, Web of Science, CINAHL and Embase for original research articles between 1980 and 2021. Out of 1,227 articles identified, we included 14 in the final analysis. All the studies were observational, and the fasting blood glucose test was the most common. Most tests were conducted at baseline and in the third month. Twelve out of the 14 included studies indicated the prevalence of elevated blood glucose was lower at follow-up and end of treatment compared to baseline. Patients with baseline hyperglycemia were more likely to develop unfavourable tuberculosis treatment outcomes and death. Findings from this review indicate the importance of blood glucose screening and monitoring for patients commencing TB treatment, even if they are not known to have diabetes mellitus.

In **Chapter 3,** we describe a protocol for a mixed methods study – the prospective study of a cohort of patients commencing tuberculosis treatment and interviews of healthcare workers. The prospective study of patients aims to describe the epidemiology of diabetes-tuberculosis comorbidity, predictors of elevated baseline blood glucose and unfavourable tuberculosis treatment outcomes. The healthcare worker's interviews aimed to describe the availability of diabetes services at TB clinics, essential equipment and commodities, opportunities to improve integrated care for DM-TB and the impact of COVID-19 on tuberculosis service delivery.

Chapter 4 presents findings from the prospective cohort study of patients who commenced TB treatment. Three hundred and sixty-nine patients were enrolled into TB care from 11 purposively selected health facilities from the four regions of Eswatini from 01 June to 30 September 2022. The median baseline blood glucose was 5.5mmol/l, and the baseline prevalence of elevated blood glucose was 8%. A family history of diabetes and a reactive HIV status predicted elevated baseline blood glucose. Three-quarters of the patients had a favourable TB treatment outcome, and the most common unfavourable treatment outcome was death. Hypertension and unemployment were positive predictors of unfavourable treatment outcome, while high school education and education in general was protective from unfavourable treatment outcome. The blood glucose of patients was not associated with unfavourable outcomes. Large cohort studies are required to identify the causes of death in patients receiving TB treatment and recommendations on how to prevent these deaths.

Chapter 5 identifies opportunities and recommendations for improving diabetes-tuberculosis integrated services in a low- and middle-income country. Most of the healthcare workers indicated they provide integrated diabetes–tuberculosis services, although with different challenges, including staff shortages, limited availability of reporting tools, limited knowledge on care for TB patients with comorbid conditions, frequent stockouts of laboratory testing commodities (glucose test strips, HbA1c, GeneXpert Cartridges, TB-Lam and culture) for screening and monitoring of patients for diabetes and tuberculosis, and frequent stock out of drugs for treatment of diabetes and tuberculosis. Non-adherence to treatment, late presentation and low socioeconomic status of some patients are the patient-level factors identified by the healthcare workers. Despite the limitations, healthcare workers used fast-track services, bidirectional screening, staff rotation, synchronized clinic visits and health education to improve their patients' services. This study emphasizes the need to ensure healthcare workers are trained and provided with updated treatment guidelines with appropriate systems to ensure the availability of pharmaceutical and laboratory supplies. Standardizing patient support services to provide counselling and psychosocial support, health education, treatment adherence counselling, transport and nutritional support can increase treatment adherence and improve treatment outcomes.

Chapter 6 describes the impact of the COVID-19 pandemic on TB service delivery and approaches adopted by healthcare workers for continued service delivery. At the pandemic's peak, services other than those targeting COVID-19 were limited, health system challenges worsened, and patients defaulted treatment due to movement restrictions to control infections. Increased risk of COVID-19 infection amongst healthcare workers with limited availability of personal protective equipment negatively impacted

the quality of care. Illness and deaths of healthcare workers from COVID-19 also led to health workforce shortages. However, healthcare workers adopted staff rotation to address staff shortages, integrated patient-centred care, community outreaches and home-based care to ensure patients continue receiving care. A hybrid approach should be adopted to better prepare for future pandemics and disruptions in routine service delivery. In this approach, patients can be followed up and supported through phone calls and short message service (SMS) with community outreaches and home visits to provide medication refills, screening and testing for communicable and non-communicable diseases. Implementing this, however, requires resource mobilization and effective coordination.

In Chapter 7, we discussed the different results and their implications for diabetes-tuberculosis care in Sub-Saharan Africa with recommendations on areas for further research. We conclude that a comprehensive improvement in health systems with infrastructure to address NCD risk factors and TB services with contributions from all relevant stakeholders is necessary for sustained improvement in diabetes-tuberculosis services to match future increases in both diseases.

Nederlandse Samenvatting

Dit proefschrift beschrijft de epidemiologie van diabetes mellitus (DM)- tuberculose (TB) co-morbiditeit in een land met een laag inkomen. Hiernaast beschrijft het de verschillende mogelijkheden om de DM-TB-zorg te verbeteren en tot slot de impact van COVID-19 op de TB-zorg.

Hoofdstuk 1 geeft inzicht in de epidemiologie van DM en TB wereldwijd en in Sub-Sahara Afrika. Wereldwijd hebben meer dan 500 miljoen mensen DM, met naar schatting 6,7 miljoen sterfgevallen per jaar. Meer dan driekwart van de mensen met DM woont in lage- en middeninkomenslanden en het aantal mensen met DM zal naar verwachting toenemen tot 783 miljoen in 2045. In 2022 waren 10,6 miljoen mensen ziek door TB en stierven er 1,3 miljoen mensen ten gevolg van deze ziekte. De COVID-19-pandemie heeft de inspanningen voor TB-bestrijding negatief beïnvloed en er is een aanzienlijke inhaalslag nodig om TB-diensten wereldwijd weer op het niveau van vóór de pandemie te brengen. Wereldwijd heeft naar schatting 15% van de mensen die voor TB worden behandeld ook DM. DM verhoogt het risico op het ontwikkelen van TB, sterfte tijdens en terugval na de TB-behandeling. Om de comorbiditeit tussen DM en TB te verminderen, pleit de Wereldgezondheidsorganisatie voor bidirectionele screening op en behandeling van DM en TB.

Hoofdstuk 2 bevat een overzicht van de literatuur over veranderingen in bloedglucose bij mensen zonder DM die worden behandeld voor TB. We zochten in PubMed, Web of Science, CINAHL en Embase naar artikelen die origineel onderzoek presenteren in de periode tussen 1980 en 2021. Van de 1.227 geïdentificeerde artikelen namen we er 14 op in de uiteindelijke analyse. Alle onderzoeken waren observationeel en de nuchtere bloedglucosetest was de meest gebruikte test om het glucose gehalte te meten. De meeste tests werden uitgevoerd bij start van de TB behandeling en in de derde maand na start van de TB behandeling. Twaalf van de 14 geïncludeerde onderzoeken gaven aan dat de prevalentie van verhoogde bloedglucose lager was bij follow-up en aan het einde van de behandeling in vergelijking met de uitgangswaarde. Patiënten met hyperglykemie bij aanvang hadden een grotere kans op een ongunstige uitkomst van de TB behandeling en op overlijden. De bevindingen van dit onderzoek wijzen op het belang van screening en controle van bloedglucose bij patiënten die beginnen met de TB behandeling, zelfs als ze niet bekend zijn met DM.

In hoofdstuk 3 beschrijven we een protocol voor een mixed methods studie: een prospectieve studie van een cohort patiënten die met TB behandeling beginnen en interviews met hulpverleners. Het prospectieve onderzoek onder patiënten is gericht op het beschrijven van de epidemiologie van de DM-TB comorbiditeit, voorspellers

van verhoogde bloedglucose bij aanvang en ongunstige uitkomsten van de TB behandeling. De interviews met hulpverleners waren gericht op het beschrijven van de beschikbaarheid van DM diensten in TB klinieken, waaronder essentiële apparatuur en producten, mogelijkheden om geïntegreerde zorg voor DM-TB te verlenen en de impact van COVID-19 op de TB zorg.

Hoofdstuk 4 presenteert de bevindingen van de prospectieve cohortstudie van patiënten die begonnen met een TB behandeling. Tussen 1 juni en 30 september 2022 werden 369 patiënten geïncludeerd. Deze patiënten waren geworven uit 11 vooraf geselecteerde TB klinieken uit de vier gezondheidregios van Eswatini. De mediane bloedglucose voor start van de TB behandeling was 5,5 mmol/l, en de prevalentie van verhoogde bloedglucose bij aanvang was 8%. Het voorkomen van DM in de familie en een reactieve HIV status voorspelden een verhoogde bloedglucose bij aanvang. Driekwart van de patiënten had een gunstige uitkomst van de TB behandeling en de meest voorkomende ongunstige uitkomst was overlijden. Hypertensie en werkloosheid waren positieve voorspellers van een ongunstige uitkomst van de behandeling, terwijl een hoge opleiding en opleiding in het algemeen beschermend waren. De bloedglucose van patiënten was niet geassocieerd met ongunstige uitkomsten. Er zijn grote cohortonderzoeken nodig om de oorzaken van overlijden te identificeren bij mensen die TB behandeling krijgen, en om aanbevelingen te doen hoe deze sterfgevallen voorkomen kunnen worden.

Hoofdstuk 5 identificeert mogelijkheden en aanbevelingen voor het verbeteren van geïntegreerde DM-TB diensten in een land met een laag en gemiddeld inkomen. De meeste hulpverleners gaven aan dat ze geïntegreerde DM-TB diensten verlenen, hoewel met verschillende uitdagingen. De volgende uitdagingen werden genoemd: personeelstekorten, beperkte beschikbaarheid van medische dossiers en behandelregistratie, beperkte kennis over zorg voor TB patiënten met comorbide aandoeningen, en het frequent niet voorradig zijn van laboratoriumtestproducten (glucoseteststrips, HbA1c, GeneXpert-cartridges, TB-Lam en kweek) en medicatie voor DM en TB. Op patiënt niveau werden de volgende factoren geïdentificeerd door de hulpverleners: onvoldoende therapietrouw, late presentatie en lage sociaal-economische status. Ondanks de beperkingen maakten hulpverleners gebruik van fast-track diensten, bidirectionele screening, personeelsroulatie, gesynchroniseerde kliniekbezoeken en gezondheidsvoorlichting om de dienstverlening aan hun patiënten te verbeteren. Dit onderzoek benadrukt de noodzaak om ervoor te zorgen dat hulpverleners worden opgeleid en voorzien van up-to-date behandelrichtlijnen. Hierbij zijn systemen nodig om de beschikbaarheid van laboratoriumbenodigdheden en medicatie te garanderen. Het standaardiseren van verschillende aspecten in de keten van zorg kan helpen om de therapietrouw vergroten en de behandelresultaten verbeteren. Hierbij kan gedacht

worden aan voorlichting, counseling, psychosociale ondersteuning, en praktische hulp met betrekking tot transport en voeding.

Hoofdstuk 6 beschrijft de impact van de COVID-19-pandemie op de TB dienstverlening en de methodes die hulpverleners gebruikten om de dienstverlening voort te zetten. Op het hoogtepunt van de pandemie was er nauwelijks aandacht voor aandoeningen anders dan COVID-19. Hierdoor namen reeds bestaande uitdagingen in andere programma's, zoals TB zorg, toe. Patiënten misten behandeling door de mobiliteitsbeperking die er was om de verspreiding van COVID-19 tegen te gaan. Het verhoogde risico op COVID-19-infectie onder hulpverleners door afwezigheid van persoonlijke beschermingsmiddelen had een negatieve invloed op de kwaliteit van de zorg. Ziekte en sterfgevallen van hulpverleners als gevolg van COVID-19 leidden ook tot een tekort aan personeel. Hulpverleners hebben echter personeelsrotatie ingevoerd om het personeelstekort aan te pakken, verleenden geïntegreerde zorg, en werkten met mobiele klinieken en zorg aan huis om ervoor te zorgen dat patiënten zorg bleven ontvangen. Ter voorbereiding op toekomstige pandemieën moet een hybride aanpak worden geïmplementeerd ter voorkoming van verstoringen van de routinematige dienstverlening. Bij deze aanpak kunnen patiënten worden gevolgd en ondersteund via telefoontjes en SMS berichten. Dit kan gecombineerd worden met mobiele klinieken en huisbezoek met als doel het tijdig bijvullen van medicijnen en screening en testen op overdraagbare en niet-overdraagbare ziekten. Om dit te implementeren moeten er echter middelen gemobiliseerd worden en is effectieve coördinatie nodig.

In Hoofdstuk 7 bespraken we de verschillende resultaten met betrekking tot DM-TB in Sub-Sahara Afrika, implicaties voor de zorg en aanbevelingen voor verder onderzoek. We concluderen dat een verbetering van de gezondheidszorgsystemen en infrastructuur nodig is om risicofactoren voor leefstijlgerelateerde ziekten en TB aan te pakken. Participatie van alle stakeholders is nodig voor een duurzame verbetering van de DM-TB zorg om de toekomstige toename van beide ziekten het hoofd te kunnen bieden.

Appendices

Acknowledgement
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Victor Williams received his primary medical degree from the College of Medical Sciences, University of Calabar, Nigeria, and postgraduate training in Infectious Disease Epidemiology, Biostatistics and Research Project Management from the University of the Witwatersrand School of Public Health, Johannesburg, South Africa. He has received additional training in Global Health, Quality Improvement in Healthcare and monitoring and evaluation.

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Williams V, Vos-Seda AG, Calnan M, Mdluli-Dlamini L, Haumba S, Grobbee DE, Klipstein-Grobusch K, Otwombe K. Tuberculosis services during the COVID-19 pandemic: A qualitative study on the impact of COVID-19 and practices for continued services delivery in Eswatini. Public Health in Practice. 2023 Jul 1:100405. https://doi.org/10.1016/j.puhip.2023.100405

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Sukoluhle Khumalo, Yves Mafulu, **Victor Williams**, Normusa Musarapasi, Samson Haumba, Nkululeko Dube. Secondary Syphilis presenting with alopecia and leukoderma in a stable HIV-positive patient in a resource-limited setting: A case report.

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