PREVALENCE OF PULMONARY TUBERCULOSIS IN DIABETIC PATIENTS ATTENDING DIABETIC CLINIC AT TEMEKE REGIONAL REFERRAL HOSPITAL IN DAR ES SALAAM

Gerald Jamberi Makuka, MD

Masters of Medicine in Internal Medicine

Muhimbili University of Health and Allied Sciences

October, 2021

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

DEPARMENT OF INTERNAL MEDICINE

PREVALENCE OF PULMONARY TUBERCULOSIS IN DIABETIC PATIENTS ATTENDING DIABETIC CLINIC AT TEMEKE REGIONAL REFERRAL HOSPITAL IN DAR ES SALAAM

By

Gerald Jamberi Makuka

A Dissertation submitted in Partial Fulfillment of Requirement for the Degree of Masters of Medicine in Internal Medicine Muhimbili University of Health and Allied Sciences

October, 2021

CERTIFICATION

The undersigned certifies that, they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled: **"Prevalence of pulmonary tuberculosis in diabetic patients attending diabetic clinic at Temeke Regional Referral Hospital in Dar es Salaam**" in partial fulfillment of requirement for the degree of Master of Medicine in Internal Medicine Muhimbili University of Health and Allied Sciences.

_____

Dr. Patricia Munseri
(Supervisor)

_____

Date

_____

Dr. Emmanuel Balandya

(Co- Supervisor)

_____

Date

DECLARATION

AND

COPYRIGHT

I, **Dr. Gerald J. Makuka**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature:…… Date:……..

ACKNOWLEDGEMENTS

I am eternally grateful to Almighty God for His grace, love and mercy in enabling me to complete my dissertation. I am utmost thankful and appreciative to my supervisors Prof Patricia Munseri and Dr. Emmanuel Balandya for their advice and guidance throughout my dissertation journey.

I would like to thank the Department of Internal medicine MUHAS for their advice and guidance during development of this research.

I would like to thank the staff at MUHAS Genetic Laboratory in particular Dr. Teddy Mselle and Harvest Marick; Lillian Nkinda, Donatus Mwambete and Dr. Frank Msafiri of MUHAS Microbiology and Immunology department; George Bwire of the School of Pharmacy; and the Department of Epidemiology Biostatistics in particular Heavenlight Ayubu, Professor Gideon Kwesigabo and Dr. Candida Moshiro for their technical support; Dr. Gerald Mpembe and Dr. Frederick Lymo of the Muhimbili National Hospital department of radiology and Peter Kunambi for his technical support.

I would like to thank Temeke Regional Referral Hospital; Dr. Ikupa and Dr. Mneney of the radiology department, Pius Mayembe of laboratory department, tuberculosis clinic, HIV clinic, diabetic clinic and the patients for being co-operative and enabling me to conduct this study.

To my mentors Professor Ben Hamel and Dr. Sabina Mtweve I am continual grateful for their endless guidance since the first step of my academic career.

To my family and friends I have always leaned on your strong pillar of support during my entire academic journey.

ABSTRACT

Background: There is undeniable evidence that diabetes is a major risk factor for tuberculosis. However, despite this fact there has been a long lapse of time of about 30 years since the last survey of TB among diabetics in Tanzania therefore warranting the need for recent studies.

Objective: To determine the prevalence, associated factors and chest radiographic findings for TB among diabetic patients attending the diabetic clinic at Temeke Regional Hospital in Dar es Salaam, Tanzania.

Methodology: A descriptive cross-sectional study was conducted at Temeke Regional Referral Hospital diabetes clinic from September to November 2020. A structured questionnaire was used to collect socio-demographic (age, sex, level of education, number of rooms and people in the house, number of people per room, housing floor material, cigarette smoking, alcohol consumption) and clinical characteristics (body mass index, fasting blood glucose, glycated haemoglobin, auscultatory findings on chest examination, previous history of tuberculosis, presence of tuberculosis symptoms, bacilli Calmette-Guerin scar, duration with diabetes, family history of diabetes, Human Immunodeficiency virus status and type of anti-glycaemic agent). Blood samples were taken for fasting blood glucose and glycated haemoglobin analysis. Tuberculosis was confirmed using sputum for GeneXpert and chest radiography was performed for participants with confirmed tuberculosis or symptoms suggestive for tuberculosis. Logistic regression was used to examine for association and control confounders and effect modifier whereby p value of < 0.05 was considered statistically significant.

Results: Among 623 patients screened, 11 (1.8%) had tuberculosis disease (95% CI 0.9-3.1). Age groups 45-64 years {aOR 0.39, 95% CI (0.11-0.42)} and > 65 years {aOR 0.34, 95% CI (0.15-0.96)}, cough > 2 weeks {aOR 10, 95% CI (2.42-172.87)}, normal auscultatory findings on chest examination {aOR 0.02, 95% CI (0.01-0.15)} were found to

be independently associated with tuberculosis disease. The predominant chest radiographic findings were opacification affecting upper and mid-lung zones on the right lung and bilateral involvement.

Conclusion: Our study findings indicate that although there is a decline in the burden of tuberculosis in the diabetic population, the prevalence is still much higher than in the general population, signaling the need for routine screening of tuberculosis in diabetic patients. The association of tuberculosis and diabetes is strongest in the young, with crackles/ bronchial breath sounds and cough >2 weeks. Diagnosing tuberculosis in diabetes mellitus requires a high index of suspicion; therefore, chest radiographic imaging is warranted in all patients who present with suggestive symptoms for tuberculosis regardless of GeneXpert result.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AIDS	Acquired Immunodeficiency Syndrome
AMO	Assistant Medical Officer
BMI	Body Mass Index
CO	Clinical Officer
COVID-19	Corona virus disease 2019
DM	Diabetes Mellitus
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
HBA1c	Haemoglobin A1c (glycated haemoglobin)
HIV	Human Immunodeficiency Virus
IDF	International Diabetes Federation
MOHCDGEC	Ministry of Health, Community Development, Gender, Elderly and Children
MTB/RIF	Mycobacterium tuberculosis/ Rifampicin
MUHAS	Muhimbili University of Health and Allied Sciences
NCDs	Non- Communicable Diseases
NTLP	National Tuberculosis and Leprosy Program
PITC	Provider Initiated Treatment and Counselling
RBG	Random Blood Glucose
TB	Tuberculosis
TBDM	Tuberculosis Diabetes Mellitus
TBNDM	Tuberculosis without Diabetes Mellitus
TRRH	Temeke Regional Referral Hospital
T1D	Type 1 diabetes
T2D	Type 2 diabetes
WHO	World Health Organization

DEFINITION OF TERMS

Our primary case definition for TB disease was based on the National TB guidelines [1–3]. According to these guidelines, TB disease was defined as an individual who is: Gene- Xpert sputum positive and/or chest X-ray suggestive of TB and supported by clinical symptoms.

CHAPTER ONE

1. INTRODUCTION

1.1 BACKGROUND

1.1.1 Burden of Tuberculosis

Tuberculosis (TB) an infectious disease caused by the bacillus *Mycobacterium tuberculosis* is regarded as the single most infectious organism and one of the top ten causes of death worldwide [4]. TB is transmitted mainly by droplet infections that are airborne. TB primarily affects the lungs resulting into pulmonary TB, but can also affect other sites resulting into extrapulmonary TB [4]. Risk factors for TB include; age above 40 years and children less than two years, alcoholism, smoking, undernourishment, comorbidities such as human immunodeficiency virus (HIV) infection and diabetes mellitus (DM) [5–7].

There were about 10 million people who developed TB in 2019 worldwide and 1.4 million died [4]. There was an estimated 8.2% incidence of TB in people living with HIV. The highest burden of TB disease was in men who accounted for 56% of the TB cases [4]. South- East Asia region contributed to 44% of the TB cases that ranked the highest that was followed by Africa that contributed 24% of the TB cases [4]. Tanzania with a reported incidence of TB of 237 per 100, 000 is still among the 30 high TB burden countries with a mortality rate of 47 per 100,000 population and a case fatality of 4% [4].

1.1.2 Pathogenesis of TB

The cycle of TB infection starts when the bacilli are spread from one person to another via air droplets into the lungs. The bacilli are phagocytized by alveolar macrophage cells and invade the underlying epithelium. The monocytes from surrounding blood vessels form a granuloma that is a hallmark feature of the disease. Within the granuloma foamy macrophages, mononuclear phagocytes and lymphocytes surround the infected macrophages. This forms a caseous debris (necrotic tissue resembling cheese) in the centre of the granuloma. Although, it seems to be contained immunologically, the caseous centre usually liquefies and cavitates releasing thousands of M. tuberculosis

bacilli into the airway. The cycle is complete as the infected lungs produce a cough that once again contains the highly transmissible infectious droplets [8]. Diabetes, HIV and other risk factors that result in immune suppression may predispose to reactivation [9,10].

1.1. 3 Burden of DM

DM is defined as a group of shared metabolic disorders with a common outcome of hyperglycaemia [11]. DM is largely classified as type 1 and type 2 diabetes (Fig 1). However, other forms of diabetes are recognised such as gestational diabetes. Usually diabetes progresses from normal glucose tolerance to impaired glucose tolerance followed by full blown diabetes [12].

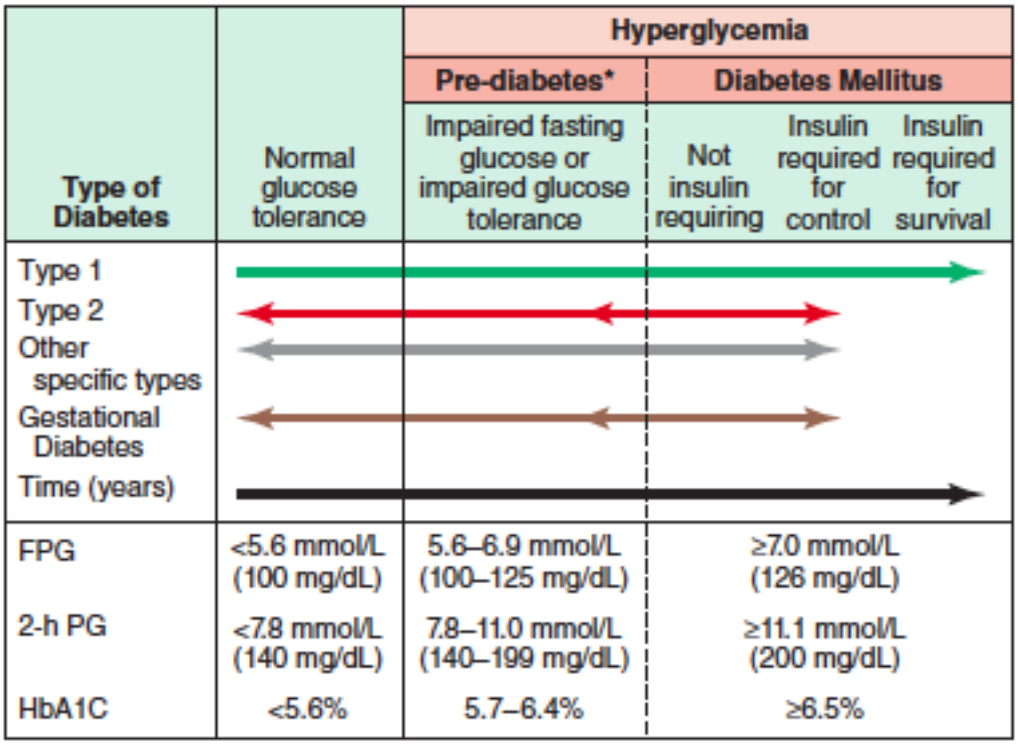


Figure 1: Spectrum of glucose homeostasis and DM. Adopted from Harrison's Principles of Internal Medicine 19th Edition.

According to the IDF, the estimated prevalence of diabetes (type 1 and type 2 diabetes combined, both diagnosed and undiagnosed) was at 463 million people (9.3%) in the year 2019 [13]. It is predicted that without sufficient efforts to address the growing

burden 578 million people (10.2%) will have diabetes by 2030 [13]. It will further escalate to a frightening 700 million (10.9%) by 2045 [13]. The burden of DM among adults in Tanzania was estimated to be 3.6% in 2017 [13]. Type 2 DM more commonly results from inadequate insulin regulation while type1 1 DM results from an autoimmune destruction of the insulin-producing beta cells of the pancreas [14]. In sub-Saharan Africa, type 2 diabetes is more prevalent accounting for more than 90% of diabetes [15].

1.1. 4 Pathogenesis of Tuberculosis in Diabetes Mellitus

Due to that diabetes is an immune suppressive disease; it alters the natural disease progression of tuberculosis including a higher risk of a person progressing to TB disease [5]. Diabetes is linked with impaired cellular immunity as a result of decreased number and function of T- lymphocytes as well as a reduced number of neutrophil counts.

The level of cytokine responses of tumour necrosis factor alpha, TNF- beta, interleukin-1, and interleukin- 6 production are reduced in diabetics when compared to non-diabetics [16,17] thus diabetics are prone to diseases including TB. Diabetics are mainly susceptible to TB due to decreased number and function of T- lymphocytes, particularly Th1 cytokine that is responsible for inhibition of Mycobacterium tuberculosis. Diabetics also have macrophage dysfunction that results in impaired production of reactive oxygen species, phagocytosis and chemotactic function [18,19]. It is postulated that hyperglycaemia may impair effectiveness of respiratory defense and clearance mechanisms of getting rid of pathogens [20].

1.2 LITERATURE REVIEW

1.2.1 Impact of Diabetes Mellitus in Tuberculosis

Although there has been some dispute with respect to cause and consequence, it is widely accepted that diabetes usually comes first in the occurrence of combined disease [5]. The increase in DM incidence in low and middle-income countries poses a significant threat towards the control of TB and could result in hindrance towards achieving the sustainable development goal of ending TB by the year 2030 [21]. Consequently, this has renewed new interest in the TBDM topic [22]. In 2018, WHO reported that diabetes was responsible for 0.4 million TB cases worldwide [21]. Studies revealed that about 10-15% of TB cases are attributable to diabetes [5] (Fig 2). These findings underline that diabetes is a moderate to strong risk factor for active tuberculosis [5]

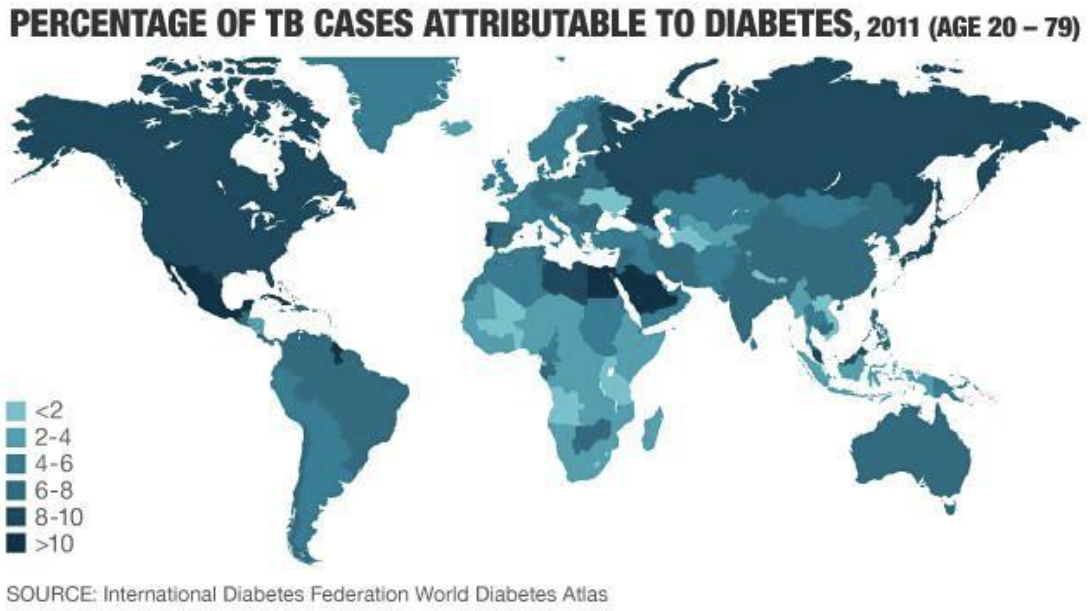


Figure 2: Global percentage of TB cases attributable to diabetes

A study done by Workneh revealed that patients with TBDM comorbidity are more symptomatic compared to those with TB without DM (TBNDM) [23]. Several studies have revealed that patients with TBDM had a three times more mortality compared to patients in the TBNDM group while in Tanzania, it is estimated that it could be slightly higher at about fourfold [1]. It is suggested that this is related to poor blood sugar control and compromised cell-mediated immunity [16,24–26].

1.2.2 Prevalence of Tuberculosis in patients with Diabetes Mellitus

A meta- analysis study done by Jeon et al revealed that patients with DM were at a higher risk of TB [relative risk (RR)= 3.11, 95% CI 2.27- 4.26] [27]. Dobler et al conducted a large whole population historical cohort study in Australia that revealed a higher risk of TB in patients with DM (RR= 1.48, 95% CI 1.04 to 2.10) and in people with DM using insulin therapy (RR= 2.27, 95% CI 1.41 to 3.66) [28]. However, these studies were conducted in high-income countries that have different settings and disease burden compared to low-income countries.

A systematic review study conducted by Workneh et al in 2017 found that the prevalence of TB among diabetic patients was 0.38% in Taiwan and 14% in Pakistan with an overall median prevalence of 4.1% [29]. Despite TBDM comorbidity being a global issue studies in sub- Saharan Africa and even so in Tanzania are limited [5]. The few conducted studies done between 2013 and 2018 reported differing prevalence's that varied between 3% in South Africa [30] to 6.2% in Ethiopia [6]. A study done by Swai et al in 1990 on a follow up of 1250 patients at Muhimbili Medical Centre in Dar es salaam, Tanzania revealed a prevalence of 5.4% [31]. The most recent study in Tanzania by Mtwangambate et al in 2014 reported a prevalence of 1.3% of TB prevalence in diabetics [32]. However, this study focused only on symptomatic patients who presented with cough.

1.2.3 Factors associated with Tuberculosis in patients with Diabetes Mellitus

It is not known if there is a gender predilection to the impact of DM on TB. Although some reports show it is more among men above the age of 40 compared to women [6,33]. Other studies have found no difference in gender and TB prevalence in patients with diabetes [30]. A recent large prospective cohort study done in China showed that being underweight is an independent risk factor for TB [34]. A study done in Ethiopia revealed that place of residence, presence of TB in the family, past TB contact, past history of TB and duration of diabetes were independent risk factors for TB [6].

1.2.4 Clinical characteristics of Tuberculosis in patients with Diabetes Mellitus

There are significant differences in patients with TBDM compared to patients with DM only whereby, patients with TBDM the mean BMI was lower [30,35], had a higher number of patients with longer duration of diabetes (> 10 years) and were on combined oral medication and insulin [35]. Furthermore, classic TB symptoms such as cough, fever, noticeable weight loss, night sweats and blood stained sputum have been shown not to be statistically different between TBDM patients and non-TB patients [30].

1.2.5 Chest radiographic patterns of Tuberculosis in patients with Diabetes Mellitus

Patients with TBDM have been found to have atypical changes seen on imaging. It was seen that these patients could present with atypical radiographic patterns that were more prominent in the lower lobes compared to the upper lobes that is usually observed in classical immuno-competent TB [5]. This has important clinical repercussions as the disease can be mistaken for pneumonia and wrongly treated as a pneumonia case. Not to forget that this also could have public health consequences since early detection and diagnosis of TB plays an important role in TB control [5].

1.2.6 Glycaemic control in TB patients with diabetes mellitus

Studies have shown that poor glycaemic control is associated with TB occurrence in patients with DM [35,36]. In these studies, it was revealed that patients with poor glycaemic control of HBA1c $\geq$ 7% had a twofold risk of active TB. However, it is worthwhile mentioning that other studies have not found similar results [30,37].

1.2.7 Practices in approaching Tuberculosis in diabetes

Studies have concluded that there is a strong tuberculosis diabetes relationship and recommended early screening for diabetes and TB, particularly the early diagnosis of TB as this will have significant global and public health impact and play an important role in TB control [5,38].

CHAPTER TWO

2.0 PROBLEM STATEMENT

2.1 Problem statement

Tanzania being one of the countries with a high burden of TB and DM [30] routine screening for TB in diabetics is still not practiced, despite that fact that DM is a known to be a strong risk factor for acquiring TB. Nevertheless, there has been a long lapse of time of about 30 years since the last survey of TB was carried out among diabetics in Tanzania.

2.2 Conceptual framework

The development of tuberculosis disease is to two-step process, starting with exposure to infection by *Mycobacterium tuberculosis* followed by progression to disease [39]. Any sort of impairment, which increases either susceptibility to infection and/or affects the rate of M. tuberculosis multiplication once infected, may increase the risk of developing TB disease. Studies show that diabetes mellitus increases both the susceptibility to infection and the disease itself [40]. The effect of diabetes mellitus on tuberculosis varies, and can be modulated by other risk factors, which may confound the diabetes tuberculosis association. These include socio-demographic and clinical factors such as age, sex, level of education, crowding, housing floor material, cigarette smoking, alcohol consumption, body mass index, fasting blood glucose, glycated haemoglobin, findings on chest examination, previous TB contact, previous history of TB, presence of TB symptoms, BCG scar, duration with diabetes, family history of DM, HIV status and type of anti-glycaemic agent.

Below is the conceptual framework (Fig 3), which shows the relationship between diabetes and tuberculosis done in context of other confounding variables. Our study only focused on the relationship between diabetes mellitus and tuberculous disease.

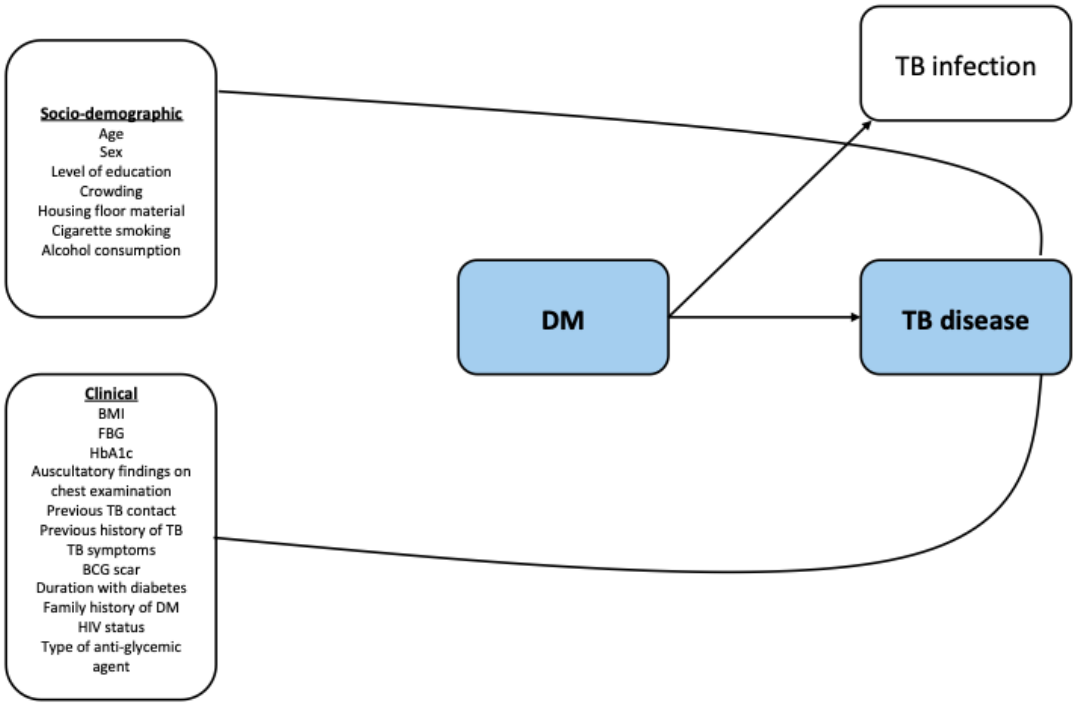


Figure 3: Conceptual framework

2.3 Rationale of the study

Due to the fact that only a few studies have been conducted in the country there is limited data on the prevalence of TB in patients with DM. Our study serves to determine the current prevalence and establish the burden of TB disease in patients with DM. Our study delineates the determinants for TB disease among patients with DM, thus enable timely identification and linkage of patients to appropriate treatment options.

2.4 Research questions

What is the prevalence of TB disease among diabetics attending Temeke Regional Hospital (TRH) diabetic clinic in Dar es Salaam, Tanzania?

What are the associated factors for TBDM patients attending Temeke Regional Hospital diabetic clinic in Dar es Salaam, Tanzania?

2.5 Objectives

2.5.1 Broad objective

To determine the prevalence, associated factors and describe chest radiographic findings for TB among diabetic patients attending diabetic clinic at Temeke Regional Hospital in Dar es Salaam, Tanzania.

2.5.2 Specific Objectives

1. To determine the prevalence of TB disease among patients with diabetes attending Temeke Regional Hospital diabetes clinic
2. To describe the clinical characteristics of TB disease in patients with diabetes attending Temeke Regional Hospital diabetes clinic
3. To describe the chest radiographic findings of TB disease in patients with diabetes attending Temeke Regional Hospital diabetes clinic
4. To determine factors associated with TB disease among patients with diabetes attending Temeke Regional Hospital diabetes clinic

CHAPTER THREE

3. METHODOLOGY

3.1 Study design

This was a descriptive cross sectional study

3.2 Study area

The study was conducted at TRRH in Dar es salaam, Tanzania. The diabetic clinic is a public facility within TRH that operates four days a week Monday, Wednesday, and Friday for adults and Tuesday for children and adolescents. The diabetic clinic receives about 600 patients in a month. The clinic receives both insured and none insured diabetic patients within Temeke region. About a tenth of the patients attending the clinic have health insurance and the rest without health insurance receive services at a subsidized fee. A Physician, Assistant Medical Officer (AMO), a Clinical officer (CO) and nursing officers run the clinic. The clinic provides routine diabetic services such as FBG/RBG, vital sign check, weight and height assessment, medications and education on prevention and control of diabetes.

3.3 Study duration

Data was collected over three months duration from September 2020 to November 2020.

3.4 Study population

Adult patients with DM who attended diabetic clinic at TRRH between September and November 2020

3.5 Inclusion criteria

- Diabetic patients aged 18 years and above attending diabetic clinic at Temeke hospital
- Able to provide written informed consent

3.6 Exclusion criteria

- None

3.7 Sample estimation

Sample size and calculation:

$$n = \frac{z^2 p(1-p)}{\varepsilon^2}$$

Where: n = minimum sample size

z = standard normal deviate (1.96)

p = 5.4% Swai et al, Tuberculosis in diabetic patients in Tanzania [31].

Ɛ = boundary of error (2%), Arya and Antonisamy, Sample size calculation in prevalence studies [41].

None response= 10%

Therefore,

$$n = \frac{1.96^2 \times 5.4\ (100-5.4)}{2^2}$$

n= 491

Taking a none response of 10%

$$n' = \frac{n \times 100\%}{100\%-10\%}$$

$$n' = \frac{491 \times 100\%}{100\%-10\%}$$

= 545

The minimal sample size obtained was 545 people. However, in this study, a total number of 623 participants were recruited in the study.

3. 8 Study variables

In this study, the following study variables will be used:

3.9 Dependent variables

TB disease

4.0 Independent variables

Age, sex, level of education, crowding (number of people per house and room; number of rooms), housing floor material, cigarette smoking, alcohol consumption, body mass index, fasting blood glucose, glycated haemoglobin, auscultatory findings on chest examination, previous TB contact, previous history of TB (ever had TB prior to DM diagnosis; ever had TB after DM diagnosis), presence of TB symptoms (fever, cough > 2 weeks, night sweats, haemoptysis and weight loss), BCG scar, duration with diabetes, family history of DM, HIV status and type of anti-glycaemic agent

4.1 Sampling technique and study procedures

Convenience sampling technique with consecutive enrollment of study participants was used whereby all consenting adult DM patients attending the Temeke diabetic clinic were recruited into the study as outlined in the flow chart (Fig 4) below. The recruitment process was conducted on every clinic visit until the required sample size was met.

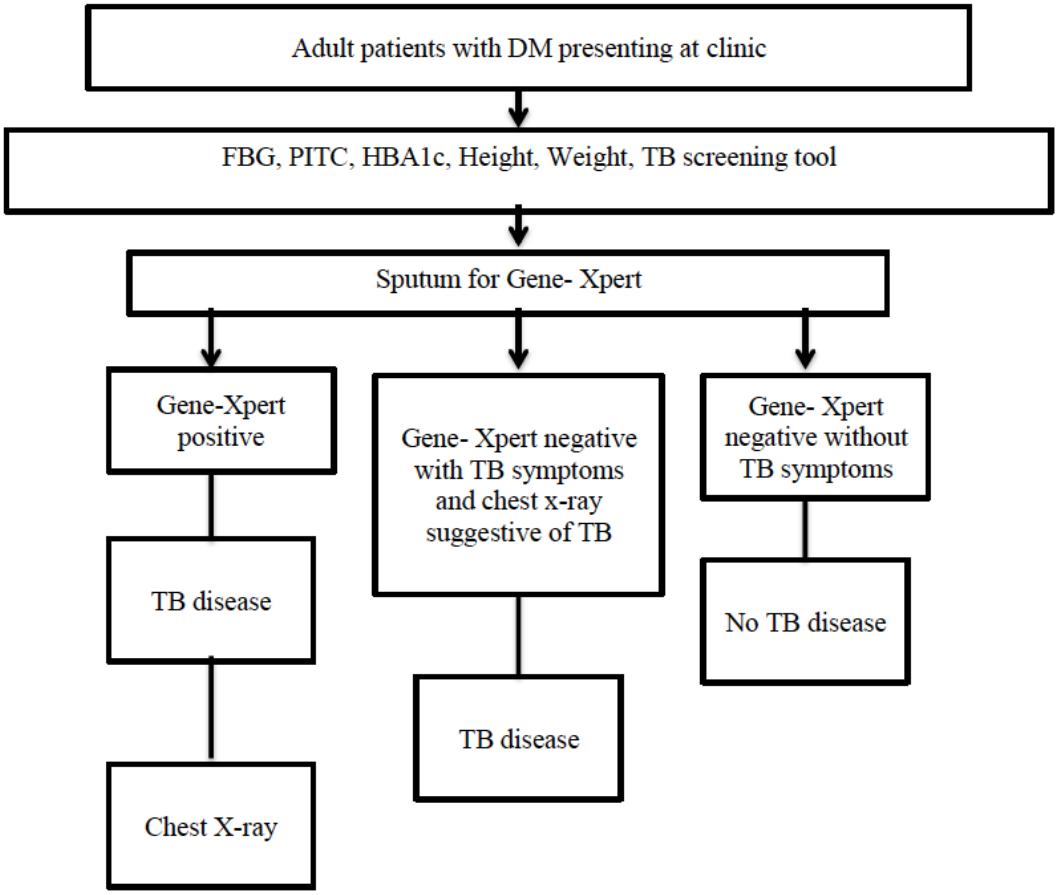


Figure 4: Flow chart illustrating the recruitment procedure of the study participants

4.2 Data collection

4.2.1 Patient interview

1. Each study participant was administered a structured interviewer-based questionnaire.
2. The questionnaire was divided in to the following sections socio- demographic characteristics, clinical characteristics, TB screening, history of previous TB treatment, date of DM diagnosis, treatment for DM, any other co-morbidities, physical examination findings including weight, height, presence of a BCG scar and any chest examination findings.

4.2.2 Clinical examination

Anthropometric measurement:

- Patients' height was measured using the height-measuring rod without shoes, caps and recorded to the nearest 0.5 centimetres.
- Weight was measured without shoes or heavy clothing using a SECCA weighing scale and readings recorded to the nearest 0.5 kilograms.
- BMI was calculated by taking the weight in kilogram and dividing it by height in meters squared (m^2). BMI results were categorized as normal if it was between 20 kg/m^2 to 24.9kg/m^2, overweight if BMI >25kg/m^2 and obesity if BMI $\geq$ 30kg/m^2, and under-weight if below 18 kg/m^2.

4.2.3 Investigations

Fasting blood glucose

A capillary fingertip blood glucose measurement was collected from each study participant on attendance at the clinic. The blood measurement for FBG was done using a GlucoPlus machine. If the patient had not fasted then he/she was asked to come on a separate day after having fasted for FBG testing. The FBG levels were categorized as follows:

- FBG $\geq$ 7mmol/l was considered elevated
- FBG < 7mmol/l was considered normal

HBA1c

About 3mls of blood was collected from the ante-cubital vein, and on the same day serum separated and stored at -20°C at MUHAS Genetic laboratory until the day of the analysis. Serum was tested for Human Glycated haemoglobin A1c by enzyme-linked immunosorbent assay (ELISA), using human-specific ELISA kits (Qayee Biotec, Shanghai, CN) according to the manufacturer's instructions.

Briefly, all reagents, including serum samples to be tested was brought to room temperature prior to the assay. About 50µL of the standard and serum samples to be tested were added in duplicate to the 96 well-plate. Thereafter 50µL of horseradish (HRP) was added into each well except blank well, immediately shaken and mix, and thereafter incubated for 1 hour at 37°C. The plate was then aspirated and washed 5 times, before 50µL of detection chromogen solution A and B were added and incubated for 10 minutes at 37°C. Finally, 50µL of stop solution was added and absorbance read at 450 nm. The standard curve was plotted as the relative optical density (OD 450) of each standard solution (*y-axis*) against the respective concentrations of the standard solution (*x-axis*). The human HbA1c concentrations of the samples were then interpolated from the standard curve. The results were reported in ng/ml with the following cut-off points as per manufacturer's instructions:

- HBA1c 12.5- 800ng/ml were categorized as well controlled DM
- HBA1c > 800 ng/ml were categorized as poorly controlled DM

Sputum for GeneXpert

How collection of sputum was done:

- Ensuring that no one is standing in front of the patient in an open area, the patient was instructed to cough deeply and expectorate sputum amounting 3-5mls into the sputum container. One sputum sample was collected per participant.
- The patient was instructed to avoid contaminating the outside of the container with sputum. If the outside of the container was contaminated the container was discarded and a fresh sputum container obtained.

- If the specimen was not suitable the patient was asked to repeat the sputum collection procedure. Induction for sputum increases the risk of aerosol transmission of COVID-19 [42], therefore following WHO recommendation during the ongoing COVID-19 pandemic sputum induction was avoided [42].

Xpert MTB/RIF

The collected sputum sample was appropriately labelled and taken for Xpert MTB/RIF at TRRH laboratory. Xpert MTB/RIF is a semi- automated PCR test that combines detection of TB and Rifampicin resistance. Expected time of Xpert MTB/RIF results was between 24- 48 hours. The patients were asked to come after two days to collect their sputum results.

HIV testing

HIV testing was done at the diabetic clinic according to Tanzanian HIV treatment guidelines[43]. Pre- testing counselling was done for all consenting participants followed by post- testing counselling. SD bioline HIV 1/2 was done and if negative the patient was recorded as having no HIV infection but if positive then this was followed with a confirmatory Uni-Gold HIV test, if positive then the patient was recorded as being HIV infected.

Radiology

Chest X- rays (CXR) posterior- anterior view was obtained from participants who were found to have TB disease (GeneXpert positive or GeneXpert negative but with symptoms). Based on the patient clinical history two independent radiologists who were blinded to the patient information interpreted the chest radiographic imaging to come up with the chest radiographic findings and conclusion with any discordant results resolved by a third radiologist.

4.2.4 Outcomes

Study outcome was recorded as TB disease.

4.3 Data management and analysis

Data was entered in KoboTool box software and extracted in form of Microsoft Excel and imported into R version 3.5.0 statistical software (https://cran.r-project.org/) for cleaning and analysis. Descriptive statistics was conducted to describe the socio-demographic (age, sex, level of education, number of rooms and people in the house, number of people per room, housing floor material, cigarette smoking, alcohol consumption) and clinical characteristics (body mass index, fasting blood glucose, glycated haemoglobin, auscultatory findings on chest examination, previous history of TB, presence of TB symptoms, BCG scar, duration with diabetes, family history of DM, HIV status and type of anti-glycaemic agent) of study participants. Frequencies were calculated for categorical variables and median and interquartile ranges were used to summarize numerical variables. Prevalence of TB disease was calculated as total number of TB cases divided by the total number of DM patients.

Binary logistic model were used to estimate odds ratio in crude analysis. Multivariable logistic regression were used to control confounders and effect modifier where the variables with p value of < 0.2 in bivariate analysis were included in multivariable logistic model. All tests were two sided and significance level was set at 5%. Parsimonious model was selected based on the lowest akaike information criteria.

4.4 Ethical approval

Ethical approval was sought from the MUHAS research ethical committee. Informed written consent was obtained from all participants prior to the data collection. Permission to conduct the study was obtained from the administration of Temeke Regional Referral Hospital. Only patients who agreed to participate in the study were enrolled and confidentiality of their information maintained through study identification numbers and not sharing the data with any third parties. All patients with uncontrolled DM were counselled and managed according to the standard of care. The patients found to have TB disease were referred to the NTLP clinic for treatment. The patients found to have new HIV infection were referred to the HIV clinic for care and treatment.

4.5 Data dissemination

Findings of this study will be presented to the department of Internal Medicine and a final report will be available at MUHAS library. A manuscript will be prepared and published in a peer-reviewed medical journal.

CHAPTER FOUR

5.0 RESULTS

We screened 623 DM patients at the diabetic clinic (Fig 5). Table 1 shows the socio-demographic characteristics of the study participants. The median age of study participants was 50.0 years ± IQR (36,61). Majority of patients were in the age category of 45-64 years 273 (43.8%), were female 331 (53.1%) and married 382 (61.3%). Majority of participants had completed primary education 306 (49.1%) and were unemployed 571 (91.7%).

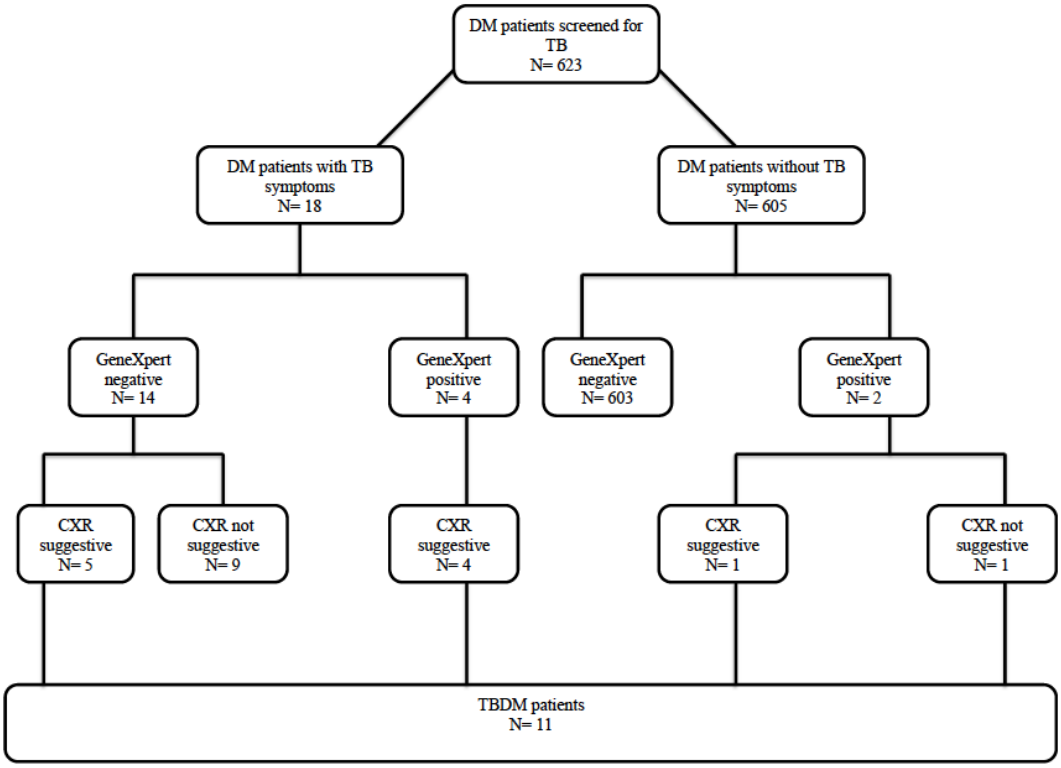


Figure 5: Consort flow diagram of recruitment process and results of DM patients screened for TB

Table 1: Socio-demographic characteristics of the study participants N= 623

Variables	Categories	n (%)
Age (years)	18 - 44	240 (38.5)
	45 - 64	273 (43.8)
	≥ 65	110 (17.7)
Sex	Male	292 (46.9)
	Female	331 (53.1)
Marital status	Single	241 (38.7)
	Married/Cohabiting	382 (61.3)
Education	No education	110 (17.7)
	Primary	306 (49.1)
	Secondary	180 (28.9)
	College/University	27 (4.3)
Occupation	Employed	357 (57.3)
	Unemployed	266 (42.7)
Residence	Temeke	513 (82.3)
	Outside Temeke	110 (17.7)
Active cigarette smoking	Yes	9 (1.4)
	No	619 (99.4)
Alcohol consumption	Yes	148 (23.8)
	No	475 (76.2)
Number of people in house	One	17 (2.7)
	Two	83 (13.3)
	Three and more	523 (83.9)
Number of sleeping rooms	One	56 (9.0)
	Two	172 (27.6)
	Three or more	395 (63.4)
Number of people per room	One	90 (14.4)
	Two	435 (69.8)
	Three or more	98 (15.7)
House floor material	Carpet/ceramic/cement	568 (91.2)
	Dung/earth/sand	55 (8.8)

5.1 Prevalence of Tuberculosis disease among diabetic patients

Active TB prevalence was 11/623 (1.8%) (95% CI 0.88-3.13) (fig 6). Xpert MTB/RIF diagnosed TB in 6/623 (0.96%) and by chest radiographs in 5/623 (0.80%).

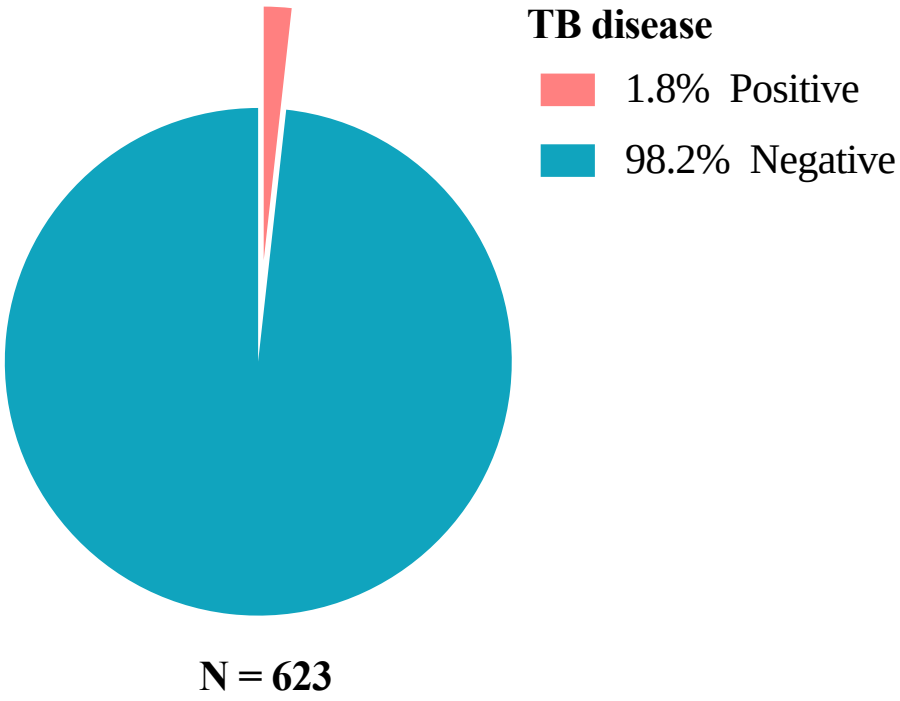


Figure 6: Prevalence of TB in patients with diabetes

5.2 Clinical characteristics of Tuberculosis disease in patients with diabetes

Table 2 shows the clinical characteristics of the study participants. The median duration of diabetes was 4.0 years ± IQR (2,8). Of note, is that 2/11 (18.2%) patients with TB were asymptomatic. In terms of glycaemic level all eleven patients with TB had well-controlled glycaemia. All patients with TB were HIV- negative. Majority of patients with TB were on insulin therapy (61.5%) followed by metformin (15.4%) (Fig 7).

Table 2: Clinical characteristics of Tuberculosis disease in patients with diabetes N= 11

Variables	Categories	n (%)
Family history of DM	Yes	6 (54.5)
	No	5 (45.5)
Cough for 2 weeks or more	Yes	6 (54.5)
	No	5 (45.5)
Fever	Yes	2 (18.2)
	No	10 (90.9)
Night sweats	Yes	5 (45.5)
	No	6 (54.5)
Weight loss	Yes	8 (72.7)
	No	3 (27.3)
Haemoptysis	Yes	0 (0.0)
	No	0 (0.0)
Auscultatory findings on chest examination	Yes	8 (72.7)
	No	3 (27.3)
BMI	Underweight	4 (36.4)
	Normal	5 (45.5)
	Overweight/obesity	2 (18.2)
BCG scar	Present	9 (81.8)
	Absent	2 (18.2)
Fasting blood glucose	Elevated	10 (90.9)
	Normal	1 (9.1)
HBA1C	Well controlled	11 (100)
	Poorly controlled	0 (0.0)
HIV status	Positive	0 (0.0)
	Negative	11 (100)
Duration of diabetes	≤ 10 years	10 (90.9)
	> 10 years	1 (9.1)
Previous TB contacts	Yes	4 (36.4)
	No	7 (63.6)
Ever had TB prior to DM diagnosis	Yes	3 (27.3)
	No	8 (72.7)
TB after DM diagnosis	Yes	2 (18.2)
	No	9 (81.8)

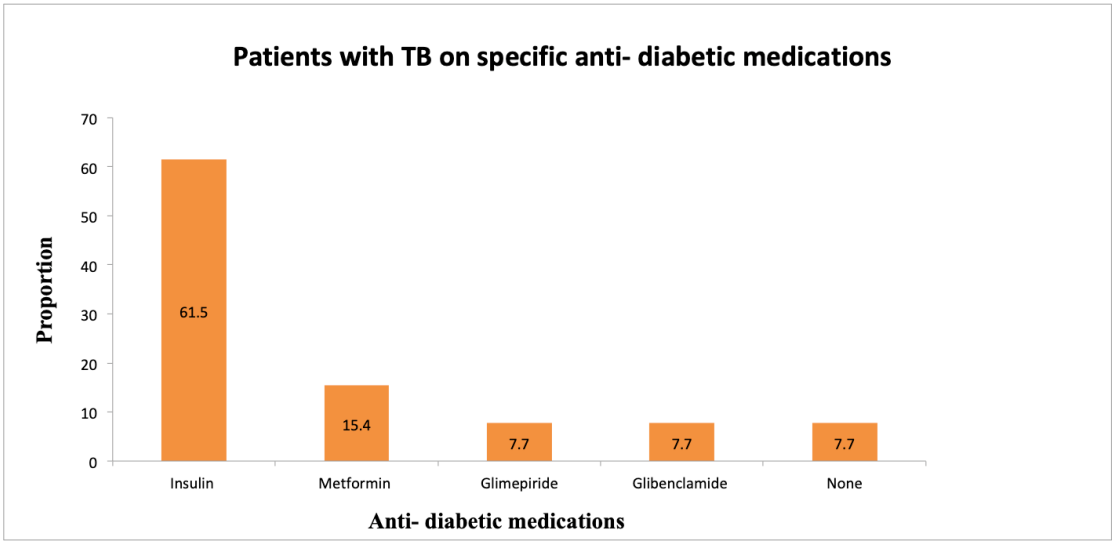


Figure 7: Patients with TB on specific anti- diabetic medications

5.3 Chest radiographic findings of Tuberculosis disease in patients with diabetes

In most TB cases, the most affected lung was found to be the right lung and bilateral involvement 4 (36.4%). Radiographic imaging largely revealed findings of opacification 9 (81.8%) followed by cavitations 4 (36.4%) equally affecting the upper and mid-lung zones 6 (54.5%) respectively (Fig 8). Amongst, patients with abnormal chest radiograph 4 (36.4%) presented with both opacification and cavitation. Of note, 1 (9.1%) patient with TB had a normal chest radiograph.

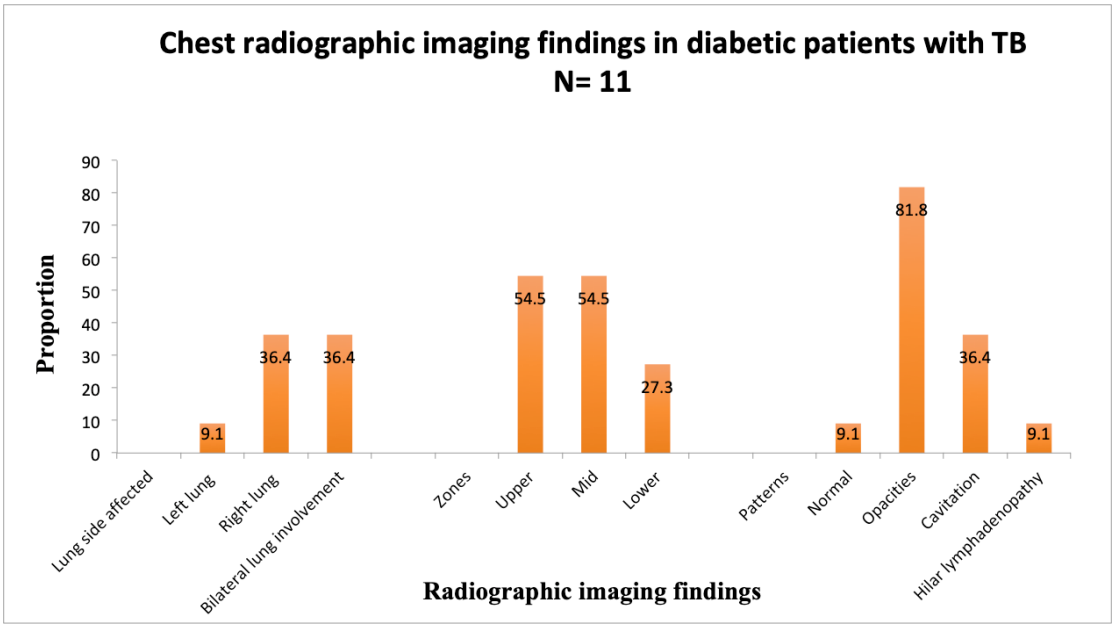


Figure 8: Chest radiographic imaging findings in diabetic patients with TB N= 11

5.4 Factors associated with TB disease in patients with diabetes

On univariate analysis cough > 2 weeks (cOR 66.8, 95% CI 20.4,218.8), normal auscultatory findings on chest examination (cOR 0.01, 95% CI 0.00,0.25), BMI (underweight) (cOR 6.79, 95% CI 1.74, 26.50), having ever had TB prior to DM diagnosis (cOR 5.83, 95% CI 1.48, 22.91), having ever had TB after DM diagnosis (cOR 0.10, 95% CI 0.19,0.50) and metformin (cOR 0.08 95% 0.01,0.64) and insulin therapy (cOR 0.16, 95% CI 0.04,0.60) were found to be associated with TB disease. In the adjusted model, age (45-64 years) (aOR 0.39 95%, CI 0.11-0.42) and (> 65 years) (aOR 0.34, 95% CI 0.15-0.96) respectively, cough > 2 weeks (aOR 10, 95% CI 2.42-172.87), normal auscultatory findings on chest examination (aOR 0.02, 95% CI 0.01-0.15) were found to be independently associated with TB disease (table 3) and (table 4).

Table 3: Socio- demographic characteristics associated with TB

Variable	cOR(95%CI)	p value	aOR(95%CI)	p value
Age				
18-44	1		1	
45-64	0.21(0.05, 1.02)	0.053	0.39(0.11,0.42)	**0.001**
65 and above	0.27(0.33, 2.15)	0.215	0.34(0.15,0.96)	**0.048**
Sex				
Male	1		1	
Female	0.32 (0.09, 1.24)	0.099	0.25(0.01,7.81)	0.431
Marital status				
Single	1		1	
Married/cohabiting	0.52(0.16, 1.72)	0.288	0.12(0.01,1.39)	0.09
Alcohol consumption				
No	1		1	
Yes	2.73(0.82, 9.10)	0.101	1.42(0.45,4.46)	0.55
House floor material				
Dung/Earth/sand	1			
Carpet/ceramic/cement	0.43(0.09,2.03)	0.284		
Residence				
Outside Temeke	1			
Temeke	0.57(0.15,2.17)	0.405		
People per room				
One	1			
Two	0.72(0.15,3.52)	0.685		
Three or more	0.92(0.13,6.65)	0.931		

Key: cOR: Crude Odd Ratio, aOR: Adjusted Odd Ratio, 1: Reference group
aOR: Adjusted for cough > 2 weeks, chest examination findings, ever had TB prior to DM diagnosis, ever had TB after DM diagnosis, BMI, metformin and insulin therapy

Table 4: Clinical characteristics associated with TB

Variable	cOR (95%CI)	p value	aOR (95%CI)	p value
Family history of DM				
No	1			
Yes	2.11(0.64,6.99)	0.222		
DM duration				
≤10 years	1			
> 10 years	0.45(0.05, 3.54)	0.445		
Cough > 2 weeks				
No	1		1	
Yes	66.8(20.4,218.8)	**<0.01**	10(2.42,172.87)	**<0.01**
Auscultatory findings on chest examination				
Crackles/bronchial breath sounds	1		1	
None	0.01(0.00,0.25)	**<0.01**	0.02(0.01,0.15)	**<0.01**
Metformin				
No	1		1	
Yes	0.08(0.01,0.64)	**0.017**	0.18(0.02,1.43)	0.105
Insulin				
Yes	1		1	
No	0.16(0.04,0.60)	**0.007**	0.31(0.04,2.71)	0.29
BMI status				
Normal	1		1	
Obesity/overweight	0.63(0.07,5.49)	0.677	3.72(0.57,24.2)	0.17
Underweight	6.79(1.74, 26.50)	**0.006**	1.17(0.33,4.15)	0.805
FBG				
Normal	1			
Elevated	2.26(0.29,17.87)	0.438		
Previous TB contact				
No	1		1	
Yes	2.89(0.83,10.07)	0.095	5.58(1.00,33.31)	0.05
Ever had TB prior to DM diagnosis				
No	1		1	
Yes	5.83(1.48, 22.91)	**0.012**	0.13(0.01,1.80)	0.128
Ever had TB after DM diagnosis				
Yes	1		1	
No	0.10(0.19,0.50)	**0.005**	0.04(0.01,4.99)	0.187
BCG scar				
Absent	1			
Present	0.86(0.18,4.03)	0.846		

Key: cOR: Crude Odd Ratio, aOR: Adjusted Odd Ratio, 1: Reference group aOR: Adjusted for age, sex, marital status and alcohol consumption

CHAPTER FIVE

6.0 DISCUSSION

The main finding of this study was that the prevalence of active TB in DM patients was 1.8%. Furthermore, we show that TB in DM was more common among younger patients below 45 years of age as well as those with cough for more than 2 weeks and crackles or bronchial breathing upon chest auscultation, and presented as opacification of the right lung and bilateral lung involvement.

The prevalence of active TB in DM patients at 1.8% was higher than the national estimate of 237 per 100, 000 (0.2%) in the general population [4]. The prevalence rate of active TB reported in our study was within the range of 0.1%- 6.2% that has been reported in previous screening studies [6,30–32]. Although, our reported prevalence was much lower than the previous screening study in the country by Swai et al that found a prevalence of 5.4% [31]. It should be noted though that their study was a follow up study of 1250 participants for a period of 1-7 years. Secondly, the long lapse of time of 30 years since the previous study is another factor as Tanzania has made great strides towards tuberculosis control having achieved the 2020 WHO global TB milestone of 20% reduction in new TB cases, although it still remains among the top thirty TB burdened countries [4]. Despite this our study differs from other conducted studies in that all diabetic patients were screened for active TB regardless of presence of symptoms. In most studies sputum was only collected from symptomatic patients suspected of having TB [32,35,44]. Although, guidelines in our setting have not specified frequency of TB screening in patients with diabetes, literature suggests that these patients be screened every 2 years [45].

TB risk has been found to vary within populations. Studies have revealed that young adults are at a higher risk than older persons to be infected with TB [46]. Studies have also found males to have a higher TB risk compared to females [46]. The present study is in agreement with these findings; younger DM patients were found to be significantly associated with TB. Although, sex was not significantly associated with TB but majority of patients with TB were males. However, more studies with follow up design are required to ascertain these findings as other findings indicated that DM patients with

TB tended to be older [35].

Noteworthy, in our study is that majority of diabetic patients with TB were not on metformin therapy. A national based study conducted in Taiwan revealed that patients who are on metformin had a lower risk to TB with recommendation that newly diagnosed diabetic patients should be prescribed metformin due to its increased TB protective effects [47]. A large systematic review study revealed that the protective effect of metformin is through multiple effects in the immune system; it enhances the host cell production of mitochondrial oxygen species and enhancing acidification of mycobacterial phagosome and inhibits intracellular growth of Mycobacterium through the adenosine monophosphate activated protein kinase pathway (AMPK) [48].

Our study done in a large sample size demonstrated that TB in diabetic patients was significantly associated with cough > 2 weeks. Thus, diabetic patients are likely to present with cough > 2 weeks than any other symptom. Previous studies have had varying results with regard to the effects of DM on symptoms presentation in patients with TB. Alisjahbana et al and Wang et al reported that majority of DM patients presented with more TB symptoms [49,50]. However, Park et al demonstrated that there was no difference in TB symptoms between TB diabetic and non- TB diabetic patients [51]. The varying results could be due to differences in sample sizes as most of these studies were conducted using small sample sizes. Interestingly, few patients were asymptomatic and this further stresses the need for routine screening in diabetic patients. The asymptomatic nature of the disease in some of the patients can be explained due to low bacterial load in diabetic patients [52].

In contrast to study done by Berkowitz et al in South Africa that revealed a high prevalence of HIV among TB cases with diabetes [30], our study findings did not discover a similar finding. The perceived difference can be attributed to the global decline in new HIV infections over the past decade [53]. In addition, there is a higher HIV prevalence among adults of 19% in South Africa compared to the meagre 4.8% in Tanzania [53]. However, larger studies such as population-based studies are needed to ascertain these associations and come up with scientific explanations.

There is an ongoing debate concerning the atypical radiographic presentation of TB in diabetic patients. Some scientists reported that TB affects mostly the lower lung zones [5,54,55] while others state that there was no difference with the lower lung zones only being affected in older patients [56]. Our study findings support that tuberculosis mostly affects the upper and mid- lung zones. We also found bilateral involvement of the lung and this finding is supported by Patel et al [54]. Previous studies showed that diabetic individuals presented mostly with cavitations in the lungs [5,54] . Our study revealed that tuberculosis in diabetic patients presented predominantly with opacification. Similarly, a study done by Bacakoglu et al revealed that diabetic patients with TB presented mostly with opacification similarly to non- diabetic patients [56]. The similar radiographic presentation of tuberculosis in diabetic versus non- diabetic patients could easily result in misdiagnosis of tuberculosis for pneumonia [5]. However, there is a need to ascertain these findings in larger epidemiological studies.

Stress induced hyperglycaemia is a state of dysglycemia resulting from an array of acute illnesses such as infections, trauma, surgery and usually resolves with the resolution of the precipitant condition. It is presumed to occur in patients with TB is as a result of changes in the host immune, metabolic and endocrine mechanisms during TB disease. However, in the context of TB disease effects of stress induced hyperglycaemia may be activated during subclinical TB disease, symptomatic TB disease, during anti- TB treatment and after even TB treatment [57]. Our study findings revealed discordant glycaemic levels obtained by FBG and glycated haemoglobin tests. We attribute this discordance possibly due to stress induced hyperglycaemia that is presumed to play a role [57,58].

Furthermore, high HBA1c represents glycation of proteins in the body secondary to high blood glucose [59]. Therefore, high HBA1c is only seen subsequently to an increase in high blood glucose, but there is scarcity of data on how long the delay is (weeks, months) [59]. Irrespective, of the length of this delay, diagnosis of diabetes using HBA1c would occur later than with blood glucose assessment and in many situations result in negative clinical outcome [59]. Blanco et al in there study conducted

in Tanzania echoed this phenomena as they found out that FBG tests at the time of tuberculosis detection was more preferable to HBA1c testing as HBA1c testing failed to detect hyperglycaemic patients and consequently those at risk of adverse outcome due to TB [58]. Our study findings are in agreement with the previous studies were we found that in patients with TB, FBG had high glycaemic levels compared to those detected by HBA1c who had well- controlled glycaemic levels.

Several studies have identified alcohol misuse and cigarette smoking as risk factors for TB [60,61]. Surprisingly, we did not find similar findings in our study despite that some patients with TB consumed alcohol but this did not achieve statistical significance. The overall low smoking and alcohol consumption habits in the Tanzania population could attribute to this effect. Also, one of the lifestyle modifications in diabetics is to limit cigarette smoking and alcohol consumption. Therefore, this would result in less proportion of patients with these habits.

Several studies have reported that TB patients tended to be underweight and that overweight/ obesity is associated with lower risk of TB [62,63]. Obesity is a known risk factor for DM and DM is a strong risk factor for TB. In people with DM it is expected that who are obese are supposedly more at risk for TB but available public health data are contradictory as it has been found that patients with DM who were obese had a reduction in tuberculosis hazard ratio [64]. In the present study underweight was associated with TB but only at univariate level. More larger scale studies are required to ascertain the interplay that exists between obesity, diabetes and TB. So far, this interplay can be explained by leptin a hormone found in obese individuals that has immune protective effects [62,65]. Leptin has been demonstrated to enhance T- cell mediated immunity resulting in an upturn in the numbers of T-helper type 1 lymphocytes thus lowering the risk to TB [62,65].

Previous history of TB does not bestow one with immunological protection against future TB disease [66]. This was evident in our study whereby history of having TB was associated with TB in diabetic patients but did not achieve statistical significance at multivariate level.

A large study of 7083 participants done by Kumpatla et al found that longer duration DM of > 10 years is associated with TB [35]. However, probably owing to the smaller sample size in our study we did not find this association.

It is known that patients with TB present with abnormal chest auscultatory findings such as crackles/ bronchial breath sounds on chest [12]. Our study is in support of this whereby crackles/ bronchial breath sounds were independently associated with TB.

Type 2 diabetes is most prevalent in sub- Saharan Africa affecting more than 90% of the population [15]. Limited studies have shown that type 1 diabetes has a stronger association with TB than type 2 [46] due to poorer glycaemic control [67].

6.1 Strengths of the study

Our study was a large hospital based cross sectional study adequately powered to accurately determine the prevalence of tuberculosis in the diabetic population in a health facility setting. Our study screened for tuberculosis routinely in all diabetic patients and not only in symptomatic patients as compared to previous studies [32,35,68]. This was an important aspect of the study as we were also able to diagnose tuberculosis in a few asymptomatic patients thus underscoring the significance of routine screening of tuberculosis in diabetes. Furthermore, glycaemic levels were based on FBG and HBA1c according to WHO, IDF and ADA diagnostic guidelines [11,13,69].

6.2 Limitations of the study

We acknowledge that our study had limitations. As our study targeted patients who attended diabetic clinic we risked missing on undiagnosed or non- adherent diabetic patients. We did not do sputum induction in our study and this could have underestimated the tuberculosis prevalence among diabetic patients found in our study. Despite this our study was still able to detect prevalent tuberculosis cases in diabetic patients. There is also a possibility of recall bias in participants trying to remember their diabetes diagnosis date that could have resulted in inaccurate estimation of diabetes

duration. Finally, due to laboratory challenges we were unable to determine HBA1c levels for a few (eighteen) study participants but we do not think this gravely affects our study findings, as this happened to be patients without tuberculosis.

CHAPTER SIX

7.0 CONCLUSION AND RECOMMENDATIONS

7.1 Conclusion

Our study findings indicate that although there is a decline in the burden of tuberculosis in the diabetic population, the prevalence is still much higher than in the general population, signaling the need for routine screening of tuberculosis in diabetic patients. Our study was able to pick the eleven patients who would have otherwise been missed. Consequently, this could have had an impact on disease transmission and progression, effect on glycaemic control and adverse outcome. The association of tuberculosis and diabetes is strongest in the young, with crackles/ bronchial breath sounds and cough > 2 weeks. Diagnosing tuberculosis in diabetes mellitus requires a high index of suspicion; therefore, chest radiographic imaging is warranted in all patients who present with suggestive symptoms for tuberculosis regardless of GeneXpert result.

7.2 Recommendations

In view of our study findings, we recommend that all diabetic patients attending diabetic clinic be routinely screened for tuberculosis disease after every two years. We recommend to MoHCDGEC to emphasize hospital administration on routine screening for tuberculosis among diabetic patients and education to diabetic patients on the dangers of TB amongst diabetics.

REFERENCES

1. Tanzania National Tuberculosis And Leprosy Programme. Ministry Of Health, Community Development GE. TB and Leprosy Manual Final draft Master Copy. 2019.
2. National Tuberculosis and Leprosy Program (NTLP). National Guidelines for Tuberculosis Infection Control. 2017.
3. Tanzania National Tuberculosis and Leprosy Programme (NTLP), Ministry of Health and Social Welfare. Manual for the Management of Tuberculosis and Leprosy. 2013.
4. World Health Organization. Global TB report. 2020.
5. Wang Q. A Double Burden of Tuberculosis and Diabetes Mellitus and the Role of Vitamin D Deficiency [Internet]. Wageningen University, Wageningen, the Netherlands; 2019.
6. Amare H, Gelaw A, Anagaw B, Gelaw B. Smear positive pulmonary tuberculosis among diabetic patients at the Dessie referral hospital, Northeast Ethiopia. Infectious Diseases of Poverty. 2013.
7. Narasimhan P, Wood J, MacIntyre CR, Mathai D. Review Article Risk Factors for Tuberculosis. Risk Factors for Tuberculosis. 2013.
8. Pathogenesis of tuberculosis (TB) infection [Internet]. [cited 2021 Mar 17]. Availablefrom:https://www.labce.com/spg631661_pathogenesis_of_tuberculosis_tb_infection.aspx
9. Young DB, Gideon HP, Wilkinson RJ. Eliminating latent tuberculosis. Trends in Microbiology. 2009;17(5):183–8.
10. Golden BM. T lymphocyte inhibitory/exhaustion marker expression in chronic HIV-1 infection and the impact of TB co-infection. Stellenbosch University; 2016.
11. American Diabetes Association. Standard of Medical Care In Diabetes-2019. 2019.
12. Harrison TR. Harrison's Principles of Internal Medicine. 19th ed. Kasper DL, Hauser StephenL, Larry JJ, Antony FS, Dan LL, Joseph L, editors. Harrison's principles of Internal Medicine. McGraw Hill Education; 2015.p2399

13. IDF. International Diabetes Federation (IDF) Atlas. International Diabetes Federation. 2019.
14. Khawandanah J. Double or hybrid diabetes: A systematic review on disease prevalence, characteristics and risk factors. Nutrition & diabetes. 2019;9(1):33.
15. Victoria H, Reimar W, Ole H, Nicoli L. Diabetes in Sub Saharan Africa 1999-2011: Epidemiology and public health implications. a systematic review. BMC Public Health. 2011;
16. Geerlings SE, Hoepelman AIM. Immune dysfunction in patients with diabetes mellitus. Immunology and Medical Microbiology. 1999;26(1999):259–65.
17. Yorke E, Atiase Y, Akpalu J, Sarfo-Kantanka O, Boima V, Dey ID. The Bidirectional Relationship between Tuberculosis and Diabetes. Tuberculosis Research and Treatment. 2017;2017:1–6.
18. Geerlings SE, Hoepelman AIM. Immune dysfunction in patients with diabetes mellitus. Immunology and Medical Microbiology. 1999;26(1999):259–65.
19. Yorke E, Atiase Y, Akpalu J, Sarfo-Kantanka O, Boima V, Dey ID. The Bidirectional Relationship between Tuberculosis and Diabetes. Tuberculosis Research and Treatment. 2017;2017:1–6.
20. Ljubić S, Balachandran A, Pavlić-Renar I, Barada A, Metelko Ž. Pulmonary infections in diabetes mellitus. Diabetologia Croatica. 2005;33(4):115–24.
21. World Health Organization. Global tuberculosis Report 2019. 2019.
22. Dobler CC, Flack JR, Marks GB. Risk of tuberculosis among people with diabetes mellitus: An Australian nationwide cohort study. BMJ Open. 2012;2(1):1–6.
23. Workneh MH, Bjune GA, Yimer SA. Diabetes mellitus is associated with increased mortality during tuberculosis treatment: A prospective cohort study among tuberculosis patients in South-Eastern Amahra Region, Ethiopia. Infectious Diseases of Poverty. 2016;5(1):1–10.
24. Chiang CY, Bai KJ, Lin HH, Chien ST, Lee JJ, Enarson DA, et al. The influence of diabetes, glycemic control, and diabetes-related comorbidities on pulmonary tuberculosis. PLoS ONE. 2015;10(3):1–15.
25. Kansal HM, Srivastava S, Bhargava SK. Diabetes mellitus and tuberculosis. Journal International Medical Sciences Academy. 2015;28(1):58–60.

26. Kapur A, Harries AD. The double burden of diabetes and tuberculosis - Public health implications. Diabetes Research and Clinical Practice. 2013;101(1):10–9.
27. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: A systematic review of 13 observational studies. PLoS Medicine. 2008;5(7):1091–101.
28. Dobler CC, Flack JR, Marks GB. Risk of tuberculosis among people with diabetes mellitus: An Australian nationwide cohort study. BMJ Open. 2012;2(1):1–6.
29. Workneh MH, Bjune GA, Yimer SA. Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: A systematic review. PLoS ONE. 2017;12(4):1–25.
30. Berkowitz N, Okorie A, Goliath R, Levitt N, Wilkinson RJ, Oni T. The prevalence and determinants of active tuberculosis among diabetes patients in Cape Town, South Africa, a high HIV/TB burden setting. Diabetes Research and Clinical Practice. 2018;138:16–25.
31. Swai ABM, Mclarty DG, Mugusi F. Tuberculosis in diabetic patients in tanzania. Tropical Doctor. 1990;20(4):147–50.
32. Mtwangambate G, Kalluvya SE, Kidenya BR, Kabangila R, Downs JA, Smart LR, et al. "Cough-triggered" tuberculosis screening among adults with diabetes in Tanzania. Diabetic Medicine. 2014;31(5):600–5.
33. Pal R, Ansari MA, Hameed S, Fatima Z. Diabetes Mellitus as Hub for Tuberculosis Infection : A Snapshot. 2016;2016.
34. Soh AZ, Chee CBE, Wang YT, Yuan JM, Koh WP. Diabetes and body mass index in relation to risk of active tuberculosis: A prospective population-based cohort. International Journal of Tuberculosis and Lung Disease. 2019;23(12):1277–82.
35. Kumpatla S, Sekar A, Achanta S, Sharath BN, Kumar AM V., Harries AD, et al. Characteristics of patients with diabetes screened for tuberculosis in a tertiary care hospital in South India. Public Health Action. 2013;3(1):23–8.
36. Leung CC, Lam TH, Chan WM, Yew WW, Ho KS, Leung GM, et al. Diabetic control and risk of tuberculosis: a cohort study. American journal of epidemiology. 2008;167(12):1486–94.
37. Blanca RI, Schlesinger LS. Host-pathogen interactions in tuberculosis patients with type 2 diabetes mellitus. NIH Public Access. 2013;93.

38. Jeon CY, Harries AD, Baker MA, Hart JE, Kapur A, Lönnroth K, et al. Bi-directional screening for tuberculosis and diabetes: A systematic review. Tropical Medicine and International Health. 2010;15(11):1300–14.
39. Kelly D. Tuberculosis and epidemics: convergence of two epidemics. Lancent Infectious disease. 2009;9(12):737–46.
40. Awad SF, Dargham SR, Omori R, Pearson F, Critchley JA, Abu-Raddad LJ. Analytical Exploration of Potential Pathways by which Diabetes Mellitus Impacts Tuberculosis Epidemiology. Scientific Reports. 2019;9(1):1–12.
41. Arya R, Antonisamy B, Kumar S. Sample size estimation in prevalence studies. Indian Journal of Pediatrics. 2012;79(11):1482–8.
42. World Health Organization. Clinical management of COVID-19. 2020.
43. Ministry of Health, Community Development, Gender E and C. National Guidelines For the Management of HIV and AIDS. 2017.
44. A. Kumar et al. Screening of patients with tuberculosis for diabetes mellitus in India. Tropical Medicine and International Health. 2013;18(5):636–45.
45. Ji Y, Cao H, Liu Q, Li Z, Song H, Xu D, et al. Screening for pulmonary tuberculosis in high-risk groups of diabetic patients. International Journal of Infectious Diseases. 2020 Apr 1;93:84–9.
46. Stevenson CR, Critchley JA, Forouhi NG, Roglic G, Williams BG, Dye C, et al. Diabetes and the risk of tuberculosis: A neglected threat to public health? Chronic Illness. 2007;3(3):228–45.
47. Lee MC, Chiang CY, Lee CH, Ho CM, Chang CH, Wang JY, et al. Metformin use is associated with a low risk of tuberculosis among newly diagnosed diabetes mellitus patients with normal renal function: A nationwide cohort study with validated diagnostic criteria. PLoS ONE. 2018;13(10):1–15.
48. Yu X, Li L, Xia L, Feng X, Chen F, Cao S, et al. Impact of metformin on the risk and treatment outcomes of tuberculosis in diabetics: A systematic review. BMC Infectious Diseases. 2019;19(1).
49. Alisjahbana B, Sahiratmadja E, Nelwan EJ, Purwa AM, Ahmad Y, Ottenhoff THM, et al. The effect of type 2 diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis. Clinical Infectious Diseases. 2007;45(4):428–35.

50. Wang CS, Yang CJ, Chen HC, Chuang SH, Chong IW, Hwang JJ, et al. Impact of type 2 diabetes on manifestations and treatment outcome of pulmonary tuberculosis. Epidemiology and Infection. 2009;137(2):203–10.
51. Park SW, Shin JW, Kim JY, Park IW, Choi BW, Choi JC, et al. The effect of diabetic control status on the clinical features of pulmonary tuberculosis. European Journal of Clinical Microbiology and Infectious Diseases. 2012;31(7):1305–10.
52. Nair A, Guleria R, Kandasamy D, Sharma R, Tandon N, Singh UB, et al. Prevalence of pulmonary tuberculosis in young adult patients with Type 1 diabetes mellitus in India. Multidisciplinary Respiratory Medicine. 2016;11(1):1–7.
53. UNAIDS. UNAIDS Data 2020. 2020.
54. Patel AK, Rami KC, Ghanchi FD. Radiological presentation of patients of pulmonary tuberculosis with diabetes mellitus. Lung India. 2011;28(1):70.
55. Perez-Guzman C, Torres-Cruz A, Villarreal-Velarde H, Vargas MH. Progressive age-related changes in pulmonary tuberculosis images and the effect of diabetes. American Journal of Respiratory and Critical Care Medicine. 2000;162(5):1738–40.
56. Bacakoglu F, Basoglu ÖK, Çok G, Sayıner A, Ates M. Pulmonary Tuberculosis in Patients with Diabetes mellitus. International Journal of Tuberculosis and Lung Disease. 2001;595–600.
57. Magee MJ, Salindri AD, Kyaw NTT, Auld SC, Haw JS, Umpierrez GE. Stress Hyperglycemia in Patients with Tuberculosis Disease: Epidemiology and Clinical Implications. Current Diabetes Reports. 2018;18(9).
58. Boillat-Blanco N, Ramaiya KL, Mganga M, Minja LT, Bovet P, Schindler C, et al. Transient hyperglycemia in patients with tuberculosis in Tanzania: Implications for diabetes screening algorithms. Journal of Infectious Diseases. 2016;213(7):1163–72.
59. Bonora E, Tuomilehto J. The pros and cons of diagnosing diabetes with A1C. Diabetes Care. 2011;34(SUPPL. 2).

60. Lönnroth K, Castro KG, Chakaya JM, Chauhan LS, Floyd K, Glaziou P, et al. Tuberculosis control and elimination 2010-50: cure, care, and social development. The Lancet. 2010;375(9728):1814–29.
61. Uplekar MW, Creswell J, Ottmani SE, Wei D, Sahu S, Lönnroth K. Programmatic approaches to screening for active tuberculosis. International Journal of Tuberculosis and Lung Disease. 2013;17(10):1248–56.
62. Yen YF, Hu HY, Lee YL, Ku PW, Lin IF, Chu D, et al. Obesity/overweight reduces the risk of active tuberculosis: A nationwide population-based cohort study in Taiwan. International Journal of Obesity. 2017;41(6):971–5.
63. Leung CC, Lam TH, Chan WM, Yew WW, Ho KS, Leung G, et al. Lower risk of tuberculosis in obesity. Archives of Internal Medicine. 2007;167(12):1297–304.
64. Lin H, Wu C, Wang C, Fu H, Lönnroth K, Chang Y, et al. Association of Obesity , Diabetes , and Risk of Tuberculosis : Two Population-Based Cohorts. 2018;66.
65. La Cava A, Matarese G. The weight of leptin in immunity. Nature Reviews Immunology. 2004;4(5):371–9.
66. Restrepo BI, Schlesinger LS. Impact of diabetes on the natural history of tuberculosis. 2015;106(2):191–9.
67. Shen TC, Lin CL, Wei CC, Liao WC, Chen WC, Chen CH, et al. Increased risk of tuberculosis in patients with type 1 diabetes mellitus: Results from a population-based cohort study in Taiwan. Medicine (United States). 2014;93(16):e96.
68. Reid MJA, Oyewo A, Molosiwa B, Mcfadden N, Tsima B, Ho-Foster A. Screening for tuberculosis in a diabetes clinic in Gaborone, Botswana. International Journal of Tuberculosis and Lung Disease. 2014;18(8):1004.
69. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. 2011.

APPENDICES

Appendix 1: Questionnaire

Prevalence of Pulmonary Tuberculosis In Diabetic Patients Attending Diabetic Clinic At Temeke Regional Referral Hospital In Dar es Salaam

SOCIODEMOGRAPHIC CHARACTERISTICS OF STUDY PARTICIPANTS

1. Study number: _____
2. Date of enrolment: _____
3. Sex: M ☐ F ☐
4. Date of birth (dd/mm/yy): _____

4b. Age of participant: _____

5. Address: _____
6. Mobile number: _____
7. Marital status:
    a. Single
    b. Married
    c. Divorce
    d. Cohabiting
    e. Widow
    f. Widower
8. Level of education:
    a. No education
    b. Primary incomplete
    c. Primary complete
    d. Secondary
    e. College/ University
9. Occupation:
    a. Unemployed
    b. Formal employment

c. Self- employed (business owner)
d. Casual labourer
e. Peasant

10. Place of residence: _____

11. Type of flooring material in the house:

a. Earth, sand
b. Dung
c. Wood/planks
d. Cement
e. Ceramic tiles
f. Carpet
g. Other

12. Number of people in the house:
a. One
b. Two
c. Three or more

13. Number of sleeping rooms:
a. One
b. Two
c. Three or more

14. Number of people per sleeping room:
a. One
b. Two
c. Three or more

15. Do you currently smoke cigarettes? Yes ☐ No ☐

a. If yes:
i. For how long have you been smoking? ……..
ii. How many cigarettes per day?.....
b. If no
Have you ever smoked cigarettes in the past? Yes ☐ No ☐

a. If yes:
i. For how long in years?.....
ii. How many cigarettes per day?.....

16. Have you ever consumed alcohol in a lifetime? Yes ☐ No ☐
a. If yes:
i. Are you currently consuming alcohol? Yes ☐ No ☐

b. If yes: specify amount:
i. Once/week
ii. Twice/week
iii. More than twice/week

c. If no: specify amount consumed in the past:
i. Once/week
ii. Twice/week
iii. More than twice/week

CLINICAL CHARACTERISTICS

17. When were you diagnosed with diabetes? ……

18. Family history of diabetes (first degree relative):
Yes
No

19. What medications are you on?
a. Metformin
b. Glibenclamide
c. Chloropropamide
d. Insulin
e. Others specify_____
f.

20. Tuberculosis screening
a. Cough for ≥ 2 weeks Y ☐ N ☐
☐ ☐

b. Coughing blood stained sputum Y N
If yes: specify duration in days…….

c. Fever Y ☐ N ☐
If yes: specify duration in days.....

d. Excessive night sweats Y ☐ N ☐

If yes: specify duration in days.....

e. Noticeable weight loss Y ☐ N ☐

If yes: specify duration.....

f. Have you been on any antibiotics Y ☐ N ☐
If yes for how long in days? .....

TB suspect (if participant answered yes {Y} to any question)
Not a TB suspect (if participant answered No {N} to all questions)

21. Previous TB contact Yes ☐ No ☐

22. History of TB status:

a. Ever had TB Yes ☐ No ☐

b. TB since diagnosis with diabetes Yes ☐ ☐
No

23. Last normal menstrual period for women (dd/mm/yr) ……

24. Ever tested for HIV in your lifetime or in the past 3 months? Yes ☐ No ☐

If yes specify result:
a. Positive
b. Negative

PHYSICAL EXAMINATION

ANTHROPOMETRY

25. Height…….cm

26. Weight……kg

GENERAL EXAMINATION

27. Cervical lymph nodes:

c. Present
d. Absent

28. BCG scar:

a. Present
b. Absent

SYSTEMIC EXAMINATION

29. Any chest examination findings:

a. Bronchial breath sounds
b. Crackles
    i. Fine
    ii. Coarse
c. None

INVESTIGATIONS

30. Fasting blood glucose…….. mmol/l

31. HBA1c …… %

32. HIV test

a. Positive
b. Negative
c. Indeterminate

33. IGRAs

    a. Positive
    b. Negative
    c. Indeterminate
    d. Borderline
    e. N/A

34. Gene- Xpert

    a. Positive
    b. Negative

35. Chest radiographic findings suggestive of TB (Only for participants found to be gene Xpert negative but with symptom(s) of TB mentioned in question 20 above or gene Xpert positive):

    a. Cavitation
    b. Hilar lymphadenopathy
    c. Pleural effusion
    d. Opacification
    e. Consolidation
    f. Infiltration
    g. Upper lung zone
    h. Lower lung zone
    i. Mid lung zone
    j. Right lung
    k. Left lung
    l. Bilateral
    m. Normal
    n. Others specify _____

Appendix 2: Consent to participate in research

Prevalence of Pulmonary Tuberculosis in Diabetic Patients Attending Diabetic Clinic At Temeke Regional Referral Hospital In Dar es Salaam

Introduction and Purpose

My name is Gerald Makuka. I am a resident doctor at Muhimbili University of Health and Allied Sciences (MUHAS). We are conducting a research study to screen for tuberculosis in patients with diabetes. I would like to invite you to take part in our research study. We are conducting this study because diabetes mellitus is a risk factor for acquiring TB infection that can progress to TB disease. Therefore, the information we learn from this research will be useful in determining the magnitude of TB- diabetes co-morbidity in our setting and improving diabetes medical care so as to prevent TB infection and disease in Tanzania. Your participation is important for this study.

Participation in research is completely voluntary. You are free to decline to take part in the study. You can decline to answer any questions. You are free to stop taking part in the research study at any time. There will be no penalty to you or loss of services if you do decide not to answer any questions or decide to stop being in the study.

Procedures

If you agree to be part of this research, I will conduct an interview with you now at this service location (Temeke Regional Hospital). The interview will involve some questions and also investigations such as fasting blood glucose level and rapid HIV test by pinprick. We will collect about 3mls of blood for HBA1c and 5mls of blood for IGRAs test. We will collect about 3- 5mls of sputum for Gene X-pert and for those unable to produce sputum we will induce them using nebulization with hypertonic saline. We expect that the whole activity should take about 45 minutes. You will be required to return after 2 days to collect your TB results. If you will be found to have TB disease you will be referred for TB treatment.

Benefits

There is no direct benefit to you from taking part in this study. We hope the research study will help us improve care for diabetes patients and prevent TB infection and disease.

Risks/Discomforts

Some of the research questions may make you uncomfortable or upset. You are free to decline to answer any questions, or to stop the interview at any time. As with all research, there is a small chance that your privacy could be breached; however, we are taking precautions to minimize this risk.

Confidentiality

Your study data will be handled as confidentially as possible. If results of this study are published or presented, individual names and other individual information will not be used. All study records will be stored on a password protected, encrypted computer. All paper survey forms will be kept in a locked cabinet at the study office, which is not at the clinic.

Questions

If you have any questions concerning your right as a participant, you may contact Dr. Patricia Munseri, Supervisor of the study, MUHAS, PO Box 65000, Dar es Salaam, Tanzania.
Mobile phone: +255 744 562 784. E mail: pmunseri@yahoo.com

Dr. Bruno Sunguya, Director of Research and Publication (DRC) of MUHAS, contacts P. O. Box 65001, Dar es Salaam, Tanzania. Tel: +255-022-2152489, Fax: +255-022-2152489, Email: drp.muhas.ac.tz.

****

CONSENT

Do you agree to participate in this study?

YES/NO

Name of person obtaining consent:_____

Signature of person obtaining consent:_____Date:_____

Appendix 3: Informed consent - Swahili Version

UKUBWA WA UGONJWA WA KIFUA KIKUU KWA WAGONJWA WENYE KISUKARI WANAOHUDHURIA KLINIKI YA KISUKARI KATIKA HOSPITALI YA RUFAA YA MKOA WA TEMEKE, DAR-ES-SALAAM

Dibaji na Lengo la utafiti

Jina langu ni Gerald Makuka.Ni daktari ninayesoma masomo ya uzamili, chuo kikuu cha Muhimbili (MUHAS). Tunafanya utafiti wa kuangalia ugonjwa wa kifua kikuu kwa wagonjwa wenye kisukari,hivyo nakuomba uweze kuwa mshiriki katika utafiti huu. Tunafanya utafiti huu kwasababu kisukari ni moja ya sababu ya kupata ugonjwa wa kifua kikuu. Kwa maana hiyo, matokeo ya utafiti huu yatatusaidia kuona ukubwa wa tatizo la ugonjwa wa kifua kikuu kwa wenye kisukari na kutusaidia kuboresha huduma zetu za kisukari ili kuweza kujikinga na ugonjwa wa kifua kikuu kwa wenye kisukari,ushiriki wako ni wa muhimu sana katika utafiti huu.

Ushiriki katika utafiti huu ni wa hiari. Uko huru kukataa kushiriki kwenye utafiti huu,na endapo umekubali kuanza kushiriki na baadaye ukaghairi unaruhusiwa kuacha, hakutokuwa na adhabu yoyote kama ukikataa kushiriki.

Taratibu

Ukiridhia kushiriki utafiti huu,nitakuwa na mahojiano na wewe sehemu ya kituo chako cha huduma(Hospitali ya Rufaa ya Temeke). Mahojiano hayo yatahusisha maswali machache na kuchukuliwa vipimo mbalimbali, kama kiwango cha sukari (FBG) na hali ya maambukizi ya virusi vya ukimwi (rapid HIV test). Tutatumia kadiriyo la damu 3mls kupima HBA1c na 5mls kupima IGRAs test. Tutatumia kadiriyo la 3-5mls za makoozi kwa ajili ya kupima kifua kikuu kupitia kipimo kiitwacho GeneXpert na kwa wale ambao hawataweza kutoa makohozi tuta wa chokonoa upatikinaji wa makohozi kwa kutumia maji maalumu yaliyochanganywa na chumvi kitaalam. Vinginevyo, shughuli yote ya mahojiano na kuchukua vipimo itachukua dakika 45 tu. Kila atakayechukuliwa vipimo hivi atahitajika kurudi baada ya siku 2 kupewa majibu ya kipimo cha kifua kikuu kitakachokuwa kimechukuliwa. Kwa wale wote watakaodhihirika kuwa na kifua kikuu, watapewa matibabu.

Manufaa ya utafiti

Ni matumaini yetu kuwa matokeo ya utafiti huu yatasaidia kuboresha huduma zetu kwa wagonjwa wenye kisukari,na kusaidia kukinga ugonjwa wa kifua kikuu kwa wenye kisukari.

Adha ya utafiti huu

Baadhi ya maswali utakayoulizwa yanaweza kukuudhi/kukukela,ni hiari kujibu au kukataa kujibu swali lolote utakaloulizwa, au kukataa kuendelea na mahojiano hayo,pia tutajitahidi kutunza taarifa zako kama siri.

Usiri

Taarifa zako zote zitakuwa siri na ,kama matokeo ya utafiti huu yatachapishwa taarifa zako binafsi hazitajumuishwa. Taarifa zako zote zitatunzwa kwa usiri wa hali ya juu.

Maswali

Kama una swali lolote kuhusiana na haki zako kama mshiriki wa utafiti huu waweza kuwasiliana na; Dr. Patricia Munseri, supervisor of the study, MUHAS,
PO Box 65000, Dar es Salaam, Tanzania.
Mobile phone: +255 744 562 784. E mail: pmunseri@yahoo.com

Dr. Bruno Sunguya, Director of Research and Publication (DRC) of MUHAS, contacts P. O. Box 65001, Dar es Salaam, Tanzania. Tel: +255-022-2152489, Fax: +255-022-2152489, Email: drp.muhas.ac.tz.

****

IDHINI

Je,unakubali kushiriki katika utafiti huu?

NDIYO/HAPANA

Jina la mshiriki:_____

Sahihi ya mshiriki:_____ Tarehe:_____

Appendix 4: Ethical clearance letter

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR OF POSTGRADUATE STUDIES

P.O. Box 65001
DAR ES SALAAM
TANZANIA
Web: www.muhas.ac.tz

Tel G/Line: +255-22-2150302/6 Ext. 1015
Direct Line: +255-22-2151378
Telefax: +255-22-2150465
E-mail: dpgs@muhas.ac.tz

Ref. No. HD/MUH/T.99/2018 06th May, 2020

IRB#: MUHAS-REC-04-2020-238

Gerald Makuka,
MMed. Internal Medicine,
School of Medicine,
MUHAS.

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED: " PREVALENCE OF TUBERCULOSIS IN DIABETIC PATIENTS ATTENDING DIABETIC CLINIC AT TEMEKE REGIONAL REFERRAL HOSPITAL IN DAR ES SALAAM."

Reference is made to the above heading.

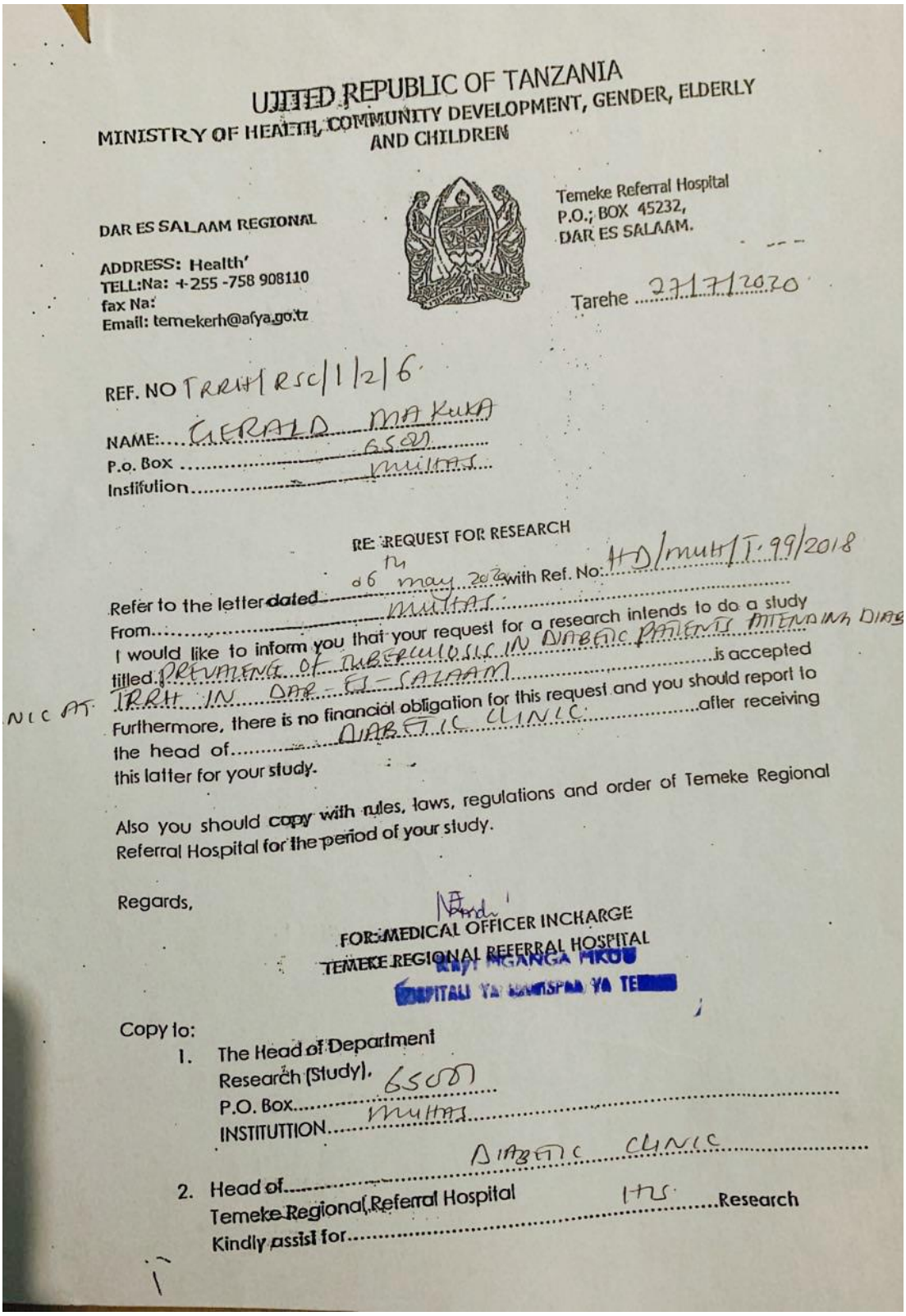
I am pleased to inform you that, the Chairman has, on behalf of the Senate, approved ethical clearance for the above-mentioned study. Hence you may proceed with the planned study.

The ethical clearance is valid for one year only, from **06th May, 2020 to 05th May, 2021.** In case you do not complete data analysis and dissertation report writing by **05th May 2021,** you will have to apply for renewal of ethical clearance prior to the expiry date.

Dr. Emmanuel Balandya
ACTING: DIRECTOR OF POSTGRADUATE STUDIES

cc: Director of Research and Publications
cc: Dean, School of Medicine, **MUHAS**

Appendix 5: Permission letter



UNITED REPUBLIC OF TANZANIA
MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT, GENDER, ELDERLY AND CHILDREN

DAR ES SALAAM REGIONAL

ADDRESS: Health'
TELL:Na: +255 -758 908110
fax Na:
Email: temekerh@afya.go.tz

Temeke Referral Hospital
P.O.; BOX 45232,
DAR ES SALAAM.

Tarehe 27/7/2020

REF. NO TRRH/RSC/1/2/6

NAME: GERALD MAKUKA
P.o. Box 65001
Institution MUHAS

RE: REQUEST FOR RESEARCH

Refer to the letter dated 06 may 2020 with Ref. No: HD/MUH/T.99/2018
From MUHAS
I would like to inform you that your request for a research intends to do a study titled PREVALENCE OF TUBERCULOSIS IN DIABETIC PATIENTS ATTENDING DIAB NIC AT TRRH IN DAR-ES-SALAAM is accepted
Furthermore, there is no financial obligation for this request and you should report to the head of DIABETIC CLINIC after receiving this latter for your study.

Also you should copy with rules, laws, regulations and order of Temeke Regional Referral Hospital for the period of your study.

Regards,

FOR: MEDICAL OFFICER INCHARGE
TEMEKE REGIONAL REFERRAL HOSPITAL
[illegible] MGANGA MKUU
[illegible]

Copy to:
1. The Head of Department
   Research (Study).
   P.O. Box 65001
   INSTITUTTION MUHAS
2. Head of DIABETIC CLINIC
   Temeke Regional Referral Hospital
   Kindly assist for ITS Research