ACTIVE CASE FINDING OF TUBERCULOSIS AMONG PATIENTS WITH DIABETES MELLITUS ATTENDING DIABETES CLINIC AT WEBUYE COUNTY HOSPITAL

BY

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A THESIS SUBMITTED TO THE SCHOOL OF MEDICINE IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR AWARD OF MASTER OF MEDICINE IN FAMILY MEDICINE DEGREE (MMED FM) OF MOI UNIVERSITY

DECLARATION

Declaration by the Student

I declare that this research thesis is my original work and that it has not been presented to any training institution as a research paper for the award or conferment of any academic degree. No part of this work may be produced without prior written permission of the author and/or Moi University.

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We, the undersigned, confirm that this thesis has been submitted for review with our approval as the university supervisors

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DEDICATION

I dedicate this work to my wife Sharon Boit and son Kalya Kiplang'at

for their love, support and patience.

To my parents for giving me encouragement during the entire process.

God bless you.

ABBREVIATIONS

ACTH – Adrenocorticotrophic Hormone

AIDS – Acquired Immunodeficiency Syndrome

AMPATH - Academic Model Providing Access to Health

DOPC – Diabetes Out-Patient Clinic

DM – Diabetes Mellitus

EPTB – Extrapulmonary Tuberculosis

ESR – Erythrocyte Sedimentation Rate

HbA1c – Glycosylated Haemoglobin

HIV – Human Immunodeficiency Virus

IDF - International Diabetes Federation

MDR-TB - multidrug-resistant tuberculosis

MOH – Ministry of Health

NCD – Non-communicable Disease

NLTD-P - National Tuberculosis, Leprosy and Lung Disease Programme

PTB –Pulmonary Tuberculosis

RES – Reticulo-endothelial System

TB – Tuberculosis

WHO – World Health Organisation

ZN - Ziehl-Neelsen staining technique

ABSTRACT

Background: Tuberculosis (TB) is the leading cause of death from a single infectious agent above Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome (HIV/AIDS) and it is one of the top ten causes of death with millions of people getting sick from the disease each year. Diabetes Mellitus (DM) is now one of the most common non-communicable diseases. DM increases the risk of TB by at least two to three fold. In Kenya and Webuye in particular, little is known about the prevalence of TB among the population with DM. This study therefore, tries to provide insights into the prevalence of TB among patients with DM and to outline associated risk factors at Webuye County Hospital (WCH).

Objective: To assess the prevalence of tuberculosis among patients with diabetes, the proportion of TB cases among presumptive TB cases and association between the occurrence of TB and socio-demographic factors among adult patients with diabetes at WCH.

Methods: This was a hospital-based cross-sectional study in which 975 adult patients attending diabetes out-patient clinic at WCH who were recruited using a consecutive sampling method between January 2021 and August 2021. Peduzzi et al. formula for sample size calculation was used to arrive at the sample size. Patient socio-demographic characteristics and co-morbidities were collected using a pretested structured, interviewer administered questionnaire. TB symptoms screening questionnaire was used to identify presumptive TB patients. Sputum samples were collected from presumptive TB cases and subjected to GeneXpert test for TB confirmation. Data was entered in Statistical Package for Social Sciences (SPSS) version 19 software and analysed using STATA statistical software for data science. Categorical and continuous variables were summarized using proportions, medians and interquartile ranges. Bivariate and multivariate analysis were done to test for association between TB diagnosis and socio-demographic characteristics and comorbidities. A p-value <0.05 was considered statistically significant.

Results: Of the 975 patients with DM sampled, 27.1% were male and 72.9% were female. The mean age of the participants was 57.527 (SD=12.34). A total of 83participants reported to have one of 8 symptoms that were suggestive of TB thus the prevalence of presumptive TB was 8.5% (95%CI: 6.8, 10.4). The prevalence of TB among those subjected to GeneXpert was 16.7% (95%CI: 9.2, 26.8), while for the whole study sample, prevalence was 1.3 % (95%CI: 0.7, 2.3). Male gender and smoking were associated, p-values of 0.05, 0.02 respectively, with confirmed TB and patients with DM in WCH. Among the comorbidities, having asthma was associated with having TB among patients with DM (p-value=0.01).

Conclusion: The prevalence of TB among presumptive TB patients with DM was 16.7% (13, N=78) and the prevalence of bacteriologically confirmed TB using GeneXpert among patients living with DM in WCH was 1.3% (13, N=975). Male gender, smoking, and having asthma were associated with increased risk of developing TB among patients with DM at WCH

Recommendation: Routine active case finding among DM patients should be strengthened to reduce the risk of TB infection among patients with DM. Male patients, those who smoke, and those with asthma should be closely monitored for TB.

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CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Worldwide, Tuberculosis (TB) is the leading cause of death from a single infectious agent above HIV/AIDS and it is one of the top ten causes of death with millions of people getting sick from the disease each year (WHO, 2018). Most cases of TB are in adults and of those co-infected with HIV the majority are found in Africa. About a third of the world's population are estimated to have latent TB and are at risk of developing active TB in their lifetime. This is a public health concern worldwide and WHO reports that the financing of TB prevention, diagnostic and treatment services has more than doubled from 2006 but this is still not enough (WHO, 2018).

It is estimated that one-third of the world's population are infected with tuberculosis. The World Health Organization (WHO) declared TB a world emergency in 1993. There were almost 9 million new and relapsed cases of TB worldwide in 2010. Its incidence had been increasing by around 1% per year to a peak in 2005, but since then the global incidence per capita has started to decline slowly. The majority of cases of TB are seen in Africa and Asia (Kumar & Clark, 2017).

TB is a disease that can affect anyone and anywhere, however, most of those affected are adults with the disease being more prevalent among men than women. WHO recognises TB as a disease of poverty, distress and vulnerability, therefore, stigma and discrimination is often faced by patients with TB (*Global Tuberculosis Report 2020*, n.d.)

Tuberculosis (TB) is an airborne infection that is spread via respiratory droplets and caused by four main mycobacterial species collectively known as *Mycobacterium tuberculosis complex* (MTb).

The outcomes of exposure is dictated by a number of factors including the hosts' immune response. Immune deficiency states including diabetes has been associated with the risk of developing tuberculosis (Kumar & Clark, 2017).

The first infection with *Mycobacterium tuberculosis* also known as primary tuberculosis is symptomless and most infected people never become ill because the human immune system usually contains the infection. However, the bacteria remain dormant within the body and can cause the disease many years later to manifest if host immunity declines because of increasing age or because of other medical conditions that lower the body's immune defence such as HIV infection and diabetes (Jeon & Murray, 2008)

TB is a curable and preventable disease. TB can be treated with a 6 month drug regimen with about 85% of those infected getting cured, thus curtailing the spread of the disease. Prevention of TB should have a multi-sectorial approach to TB determinants such as poverty, smoking, HIV infection as well as diabetes. (*Global Tuberculosis Report 2020*, n.d.)

In Kenya, TB remains a major cause of morbidity and mortality. Kenya is ranked 10th among the top 20 countries in the world with a high burden of tuberculosis based on an absolute number of incident cases (WHO, 2018). It affects all age groups, but has its greatest toll in the most productive age group of 15 to 44 years.

Globally, diabetes is now one of the most common non-communicable diseases. It is the fourth or fifth leading cause of death in most developed countries and there is substantial evidence that it is epidemic in many developing and newly industrialized nations.

The second edition of the Diabetes Atlas estimated that around two-thirds of these people live in developing countries (Diabetes Atlas Committee, 2003).

Diabetes mellitus (DM) is a syndrome of chronic hyperglycaemia due to relative insulin deficiency, resistance or both. The International Diabetes Federation (IDF) estimated that 8.3% of the global population had diabetes in 2013, and estimates an increase to 10.1% in 2035 (Kumar & Clark, 2017).

There is no evidence that diabetic patients with good glycaemic control are more prone to infection than normal subjects. Poorly controlled diabetes entails increased susceptibility to infections to skin, gastrointestinal tract, urinary tract, and lungs. In the lungs, diabetes predisposes the patient to pneumonia and tuberculosis. One reason why poor control leads to infection is that chemotaxis and phagocytosis by polymorphonuclear leucocytes are impaired because, at high blood glucose concentrations, neutrophil superoxide generation is impaired. Conversely, infections may lead to loss of glycaemic control and precipitate hyperglycaemic emergencies (Kumar & Clark, 2017).

Since the early 20th century, there have been clinical observations of the association between DM and TB, although they were often unable to determine whether DM was a risk factor for TB disease or whether TB led to the clinical manifestations of DM (C. Jeon & Murray, 2008)

The association between tuberculosis (TB) and diabetes mellitus (DM) was well known in the early 20th century, but somewhat forgotten in the second half of the 20th century with the advent of widely available treatment for both diseases. In the last decades, with the current global growth of diabetes, the link between TB and DM is re-emerging.

The epidemic growth of DM especially occurs in developing countries, where TB is highly endemic. As a result, DM and TB will increasingly present together, and this calls for renewed interest in this topic.(Ruslami et al., 2010)

Co-morbidity of Tuberculosis and diabetes worsen the prevalence, presentation, control and treatment outcomes of diabetes and the converse is true. Diabetes increases the risk of tuberculosis by at least two to three fold, while impaired glucose tolerance (IGT) and DM have been found to be higher among TB patients (Owiti et al., 2017).

According to Tatar et al, DM is a condition that can predispose previous Tb patients to reactivated infection. Diabetic ketosis provide suitable conditions for the reactivation of tuberculosis disease. Reduced immunological response to TB among DM patients is through over synthesis of adrenocorticotrophic hormone (ACTH), vitamin A deficiency, overproduction and deposition of lipids in the reticulo-endothelial system (RES). (Tatar et al., 2009)

A study by Lin et al. showed that patients with TB who have DM also have worse treatment outcomes compared to those without DM, with delays in sputum culture conversion, an increased risk of death and an increased risk of recurrent disease after successful completion of treatment. (Lin et al., 2012)

The World Health Organisation (WHO) and the International Union against Tuberculosis and Lung Disease (Union) recognised the need for international guidelines regarding the joint management of TB and DM and published a provisional Collaborative Framework for the Care and Control (CFTB/DM) of both diseases. (Castellanos-Joya et al., 2014) This framework emphasized establishment of mechanisms of collaboration between national programs of TB and DM, bidirectional screening of TB and DM, and integration of TB and DM management

1.2 Problem Statement

Kenya has a high disease burden, with the principal challenges coming from communicable diseases such as malaria, human immunodeficiency virus (HIV) and TB, which accounted for 64% of deaths in 2014. (World Health Organization, 2018).

Non-communicable diseases were responsible for more than 50% of all hospital admissions and over 55% of deaths in the same year. According to the International Diabetes Federation (IDF) it is estimated that the prevalence of diabetes adults is 4.6% although this rate is likely an underestimate due to the many undiagnosed cases in the country (Ministry of Health; Kenyan National Bureau of Statistics; World Health Organization, 2015).

There is a three-fold risk of developing active tuberculosis among diabetic patients because of impaired innate and adaptive immune responses that are necessary to counter the progression of the infections (Mburu et al., 2018).

In 2011 WHO and International Union against Lung Disease launched a Collaborative Framework for the Management of TB and DM with the aim of outlining TB-DM co-management strategies to be used by policymakers and implementers in order to reverse the TB-DM co-epidemic. The framework for the clinical management and control of TBDM comorbidity is designed to complement the core systems setup for the prevention and management of both diseases. The three strategies that were namely, establishing mechanisms of collaboration between TB and DM control programs, detection and management of TB in patients with DM, and detection and management of DM in TB patients(Quist-Therson et al., 2020)

Despite the guidelines for collaborative framework for care and control of TB and DM by WHO, most sub-Sahara African countries still lag behind in screening all TB patients seeking care for DM. (Mburu et al., 2018). Given the public health implications of a correlation between DM and TB, there is a clear need for assessment of the association between the two conditions.

In Kenya, TB-DM co-morbidity data is scarce and is not readily available (Mburu et al., 2018).

Previous studies have identified an important association between diabetes mellitus and tuberculosis in that diabetes is a risk factor for the development of tuberculosis.

In Kenya and Webuye, in particular, little is known about the prevalence of TB among the population with diabetes. Therefore, in this study we set to estimate the prevalence of TB among patients with diabetes and associated socio-demographic factors at Webuye County Hospital in Bungoma County, Kenya.

1.3 Broad Objective

To assess the prevalence of tuberculosis among patients with diabetes, the proportion of TB cases among presumptive TB cases and association between the occurrence of TB and socio-demographic factors among patients with diabetes at Webuye County Hospital

1.4 Specific Objective

1. To determine the proportion of TB patients among presumptive TB cases in patients with diabetes at Webuye County Hospital
2. To assess the prevalence of TB among patients with diabetes using TB screening tool and Xpert MTB/RIF at Webuye County Hospital

3. To determine the association between the occurrence of TB and socio-demographic factors, if any, among adult patients with diabetes at Webuye County Hospital

1.5 Justification of the Study

According to Kenyan tuberculosis prevalence survey of 2016, Kenya had a TB prevalence of 558 per 100000 in the adult population. The report noted that there was a detection gap for tuberculosis and recommended that there should be more involvement in the screening for active TB including involving private practitioners. Xpert MTB/RIF was also recommended as the first test for TB diagnosis should be universally made available. (MOH, 2016)

The National TB Leprosy and Lung Disease Program (NTLD-P) has moved from relying on passive case finding to identify TB cases to active case finding, (*TB Control In Kenya – National Tuberculosis, Leprosy and Lung Disease Program*, n.d.)

Kenya in its strategic plan for tuberculosis intends to scale up TB/DM collaborative management by establishing, implementing and monitoring a comprehensive TB/DM framework that will include monitoring and evaluating systems (MOH, 2019).

In a systematic review of 13 studies it was found that diabetes increases the risk of TB as DM impairs the immune response needed to control bacterial infections. The study also concluded that the increased risk of TB was regardless of study design and population. Therefore people with DM may be important targets for interventions such as active case finding and treatment of DM may have a beneficial impact on TB control (Jeon & Murray, 2008).

With an aim of actively finding cases of tuberculosis among diabetic patients and association between the occurrence of TB and socio-demographic factors among adult patients with diabetes in Webuye County Hospital, the researcher will be able to establish a prevalence of TB/DM comorbidity for the hospital and associated socio-demographic characteristics.

This will also provide the county and national programme managers and their staff with the fundamental information needed to make strategic decisions and improve both TB and DM management

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Introduction

In this section, a background of evidence will be evaluated from the existing literature on the occurrence of TB in diabetic patients. First, an understanding of the two diseases with an evaluation of factors contributing to their development, the pathogenesis, management, prevention, and complication will be covered. After that, the infection of TB in diabetic patients will be evaluated with a key emphasis on their prevalence and risk factors and active case findings of TB in diabetics based on findings, strategies, and recommendations from other studies. Also, this section will present evidence-based management of TB in diabetic patients, challenges, or obstacles in identifying TB among diabetic patients, and the impact of TB in diabetic patients.

Literature review provides a critical section of research by presenting evidence gathered from the work of others, thus bringing a deeper understanding of the study topic. An effective literature review is done by aligning the identification and analysis of materials with the study objectives and questions. The objectives of carrying out a literature review include providing a deeper understanding of the concepts, vocabularies, theories, and innovative or variant perspectives of the study field. Also, a literature review assists in identifying history in the specific study field to assist in the expansion of expertise. Lastly, the review helps create a focal point of argument for the study, adding to the significance of the rationale.(Mudavanhu, 2017)

2.2 Tuberculosis

2.2.1: Overview

Tuberculosis is a chronic disease that has infected and affected humans for over 4,000 years. It is caused by a bacillus known as *Mycobacterium tuberculosis*.

The mode of transmission is through the air. The disease is known to affect most parts of the human body, with symptoms dependent on the part of the body affected (Zaman, 2010).

While the history of the timing of the discovery of tuberculosis varies, Prabhu and Singh indicated that evidence of body tuberculosis was found as early as 8000 BC, with evidence from spinal cord fragments of Egyptian mummies as early as 2400 BC. Also, Hippocrates is described as having advised doctors against treating persons with stage 4 tuberculosis due to the fatal nature of the disease around 460 BC (Prabhu & Singh, 2019).

According to Churchyard et al., *Mycobacterium tuberculosis* was discovered in 1882 by Robert Koch (Churchyard et al., 2017). *Mycobacterium* is believed to have originated more than 150 million years ago with *Mycobacterium ulcerans,* the earliest known organism to cause infections since ancient times. Francis Sylvius described the exact anatomical and pathological characteristics of the disease in 1679, while Robert Koch was able to isolate the causative organism of the disease, tubercle bacillus, in 1882 (Barberis et al., 2017).

2.2.2: Epidemiology

Tuberculosis is caused by the bacteria *Mycobacterium tuberculosis,* which most often affects the lungs and is spread through the air from person to person.

Tuberculosis mostly affects adults in their most productive years. However, all age groups are at risk of contracting the disease (Turner & Bothamley, 2015).

Worldwide, Tuberculosis (TB) is the leading cause of death from a single infectious agent above HIV/AIDS and is one of the top ten causes of death, with millions of people getting sick from the disease each year.

Most cases of TB are in adults and about a quarter of the world's population are estimated to have latent TB and are at risk of developing active TB in their lifetime.

This is a public health concern worldwide is the financing of TB prevention, diagnostic and treatment services which has more than doubled from 2006 but this is still not enough (WHO, 2018).

In 2016 approximately 10.4 million were sick from tuberculosis disease worldwide with an estimated 1.6 million deaths from the disease according to W.H.O. The risk factors that contribute to the development of TB disease following an infection include malnutrition, immunosuppressive diseases such as HIV/AIDS, cancers, and diabetes, excessive alcohol intake, and smoking. The risk factors for TB infection include poor economic status, overcrowding, family TB history, males, single marital status, and absence of a B.C.G. scar (Shimeles et al., 2019; Narasimhan, Wood, Maclntyre and Mathai, 2013).

Other risk factors include chronic steroids use, chemotherapy, renal failure, reinfection in previously treated TB cases, the young and older adults, and use of tumor necrosis factors inhibitors (Singer-Leshinsky, 2016). Also, occupational exposure is a risk factor among health care workers (Loddenkemper, Lipman & Zumla, 2016).

According to Narashimhan et al., an estimated 5% of individuals will progress to develop TB disease within the first two years following TB infection. While the risk of TB disease increases with time, it is postulated that about 10 – 15% of cases with TB infection will develop active TB disease at some point in their lives. However, persons with HIV and other immunocompromising diseases have a 10% per year risk of developing TB disease (Narasimhan et al., 2013).

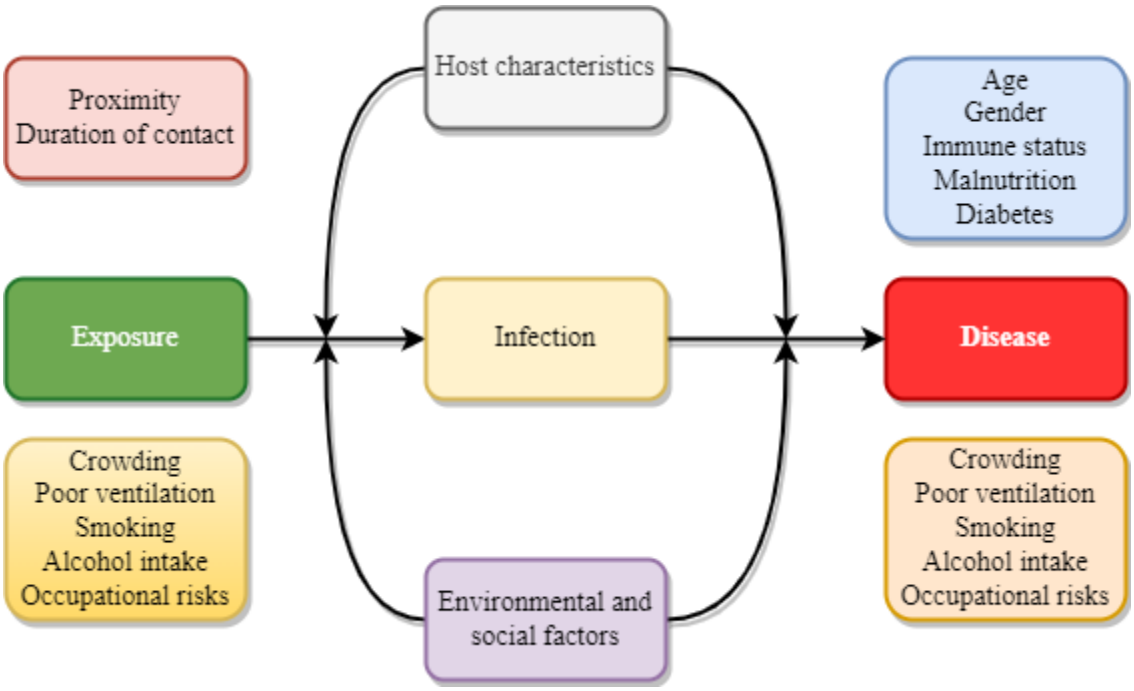


Figure 1: Risk factors for tuberculosis infection and disease (Narasimhan et al., 2013).

Despite there being effective therapies for the management of tuberculosis disease, TB continues to infect about one third of the world's population with an estimated 8.8 million people being infected each year across the world (Jeon & Murray, 2008). TB remains a major cause of morbidity and mortality in Kenya. Kenya is ranked 10th among the top 20 countries in the world with a high burden of tuberculosis based on an absolute number of incident cases (WHO, 2018).

In a study in, Addis Ababa, Ethiopia by Shimeles et al. among 520 participants above 15 years, 260 bacteriologically positive cases and 260 TB negative outpatient clinic attendees, the risk factors for tuberculosis were demonstrated (Shimeles et al., 2019). In the study, about a fifth (21.9%) of the TB cases recruited reported to be living in overcrowded areas. Almost a third of the TB cases (29.6%) were found to have low income levels of less than 1000 Birrs a month. Over half of the TB cases (53.8%) in the study revealed to be living in a single roomed house.

A majority 69.6% of the cases revealed to be living in a poorly ventilated house considered where the only one window or no window in the house. On history of contact, about one-sixth of the respondents reported to have history of TB contact in the household. On marital status, over half of the TB cases (51.9%) among the respondents were found to be single while among the genders, more males (55.8%) than females (44.2%) were found among the TB cases evaluated. Three quarters of the TB cases in the study had not history or mark of B.C.G. vaccination.

2.2.3: Pathophysiology

Mycobacterium tuberculosis is a rod-shaped, aerobic acid-fast bacterium that causes TB Infection with TB occurs when the tiny bacterium from a contagious host is expelled through cough, sneezing, speaking, and laughing, leading to droplet nuclei that may be suspended in the air for hours. An infective droplet with as few as ten bacilli can cause infection (Singer-Leshinsky, 2016). In addition to the above contributing factors, dust that is generated when shaking the beddings of a contagious host, sweeping, surgeries, and autopsies may generate viable Mycobacterium tuberculosis can lead to infection (Nardell, 2016).

Latent TB develops when a person comes into contact with the droplet nuclei and the alveolar macrophages contain them. In contrast, TB disease occurs when the body cannot contain them. It should be noted that only persons with active TB disease are contagious. The cell-mediated response to TB infection takes approximately 2 – 12 weeks in normal immunity contacts, which can be determined by a positive tuberculin skin test. Only an estimated 45% of persons with close contact with contagious persons develop TB infection(Singer-Leshinsky, 2016)

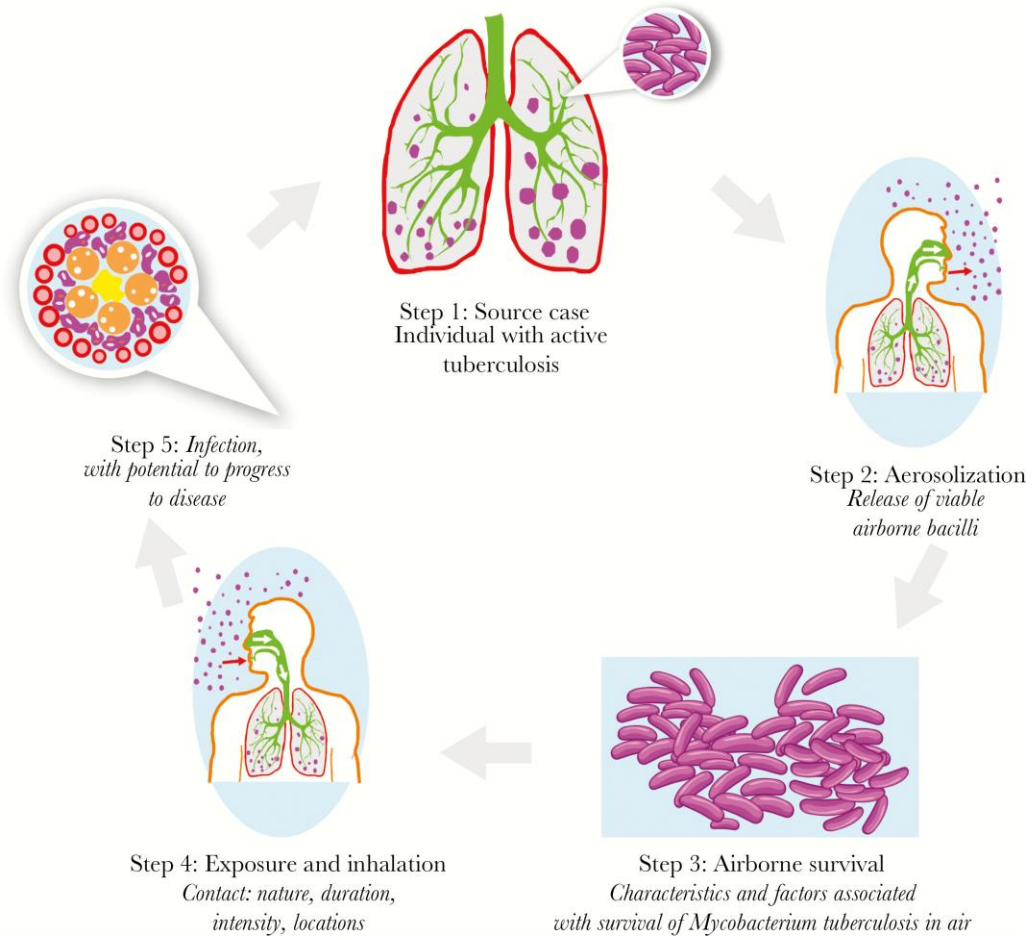


Figure 2: Cascade of TB transmission (Churchyard et al., 2017)

Individuals with poor immunity, the young and older adults, possess an impaired immune response, anergy, to TB infection leading to a negative tuberculin skin test (Singer-Leshinsky, 2016; Yan et al., 2013). TB infection in such cases leads to primary TB infection with the development of cavities at primary infection sites. Extra pulmonary TB occurs when bacteria drain into the blood vessels (Singer-Leshinsky, 2016).

The symptoms of TB disease depend on the stage of infection, from asymptomatic patients to fully symptomatic patients. Para tracheal lymph node swelling occurs in patients with a subclinical disease with lymphatic bacterial spread.

Cough of more than two weeks, fever, night sweats, shortness of breath, bloody sputum, unintentional weight loss, and chest pains are key symptoms of pulmonary TB disease requiring testing for TB The disease can affect almost all body parts, with symptoms dependent on the affected organ (Singer-Leshinsky, 2016; Loddenkemper, Lipman & Zumla, 2016).

National Tuberculosis, Leprosy, and Lung Disease Program, Kenya adds that tuberculosis infects all body organs except the nail, hair, and teeth (Kenya: Ministry of Health, 2021).

2.2.4: Management of TB

The global priorities for TB care and control are to improve case detection and to detect cases earlier, including cases of the smear-negative disease, which are often associated with coinfection with the human immunodeficiency virus (HIV) and young age. Another priority is to enhance the capacity to diagnose multidrug-resistant tuberculosis (MDR-TB). WHO current policies and guidelines recommend that Xpert MTB/RIF assay be used as an initial diagnostic test in all suspected individuals and those suspected of having MDR-TB or HIV-associated TB.

Xpert MTB/RIF is used in detecting *Mycobacterium tuberculosis* and detecting mutations that confer the organism resistance to Rifampicin. The guidance also provides a conditional recommendation that Xpert MTB/RIF be used as a follow-on test to smear microscopy in settings where MDR-TB or HIV are of lesser concern, especially for further testing of smear-negative specimens (WHO, 2014; WHO, 2015).

Singer-Leshinsky and WHO (2020) opine that the first step of making a TB diagnosis is clinical suspicion based on the history of symptoms.

While there is no gold standard test for the diagnosis of latent TB, a tuberculin skin test or interferon-gamma release assay (IGRA) have been widely used with satisfactory results.

Xpert MTB/RIF is the recommended test for M. tuberculosis with a test turnaround time of 2 hrs. Also, Xpert MTB/RIF has the ability to test for Rifampicin and Isoniazid resistance (*Global Tuberculosis Report 2020*, n.d.; Singer-Leshinsky, 2016).

According to National Tuberculosis, Leprosy, and Lung Disease Program, Kenya, other testing modalities include clinical diagnosis in smear-negative patients, chest X-ray, urinary L.A.M., sputum smears, and sputum cultures (Kenya: Ministry of Health, 2021).

The treatment of TB is premised on several goals, such as providing a cure and preventing disease transmission and death. Also, treatment is aimed at preventing complications, relapse, and the development of drug resistance. Four drugs are used in first-line TB treatment: Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol.

The six months treatment is divided into two phases; the 2 – month intensive treatment phase using four drugs (Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol) and a four-month continuation phase using two drugs (Rifampicin, Isoniazid) (Singer-Leshinsky, 2016; National Tuberculosis, Leprosy, and Lung Disease Program, Kenya, 2021).

2.2.5: TB prevention

The prevention of TB is focused on the prevention of TB infection, progression of TB infection to TB disease, and detection and treatment of active TB disease to avoid transmission (Nardell, 2016).

Li et al. conducted a scoping review study to assess TB prevention strategies with evidence gathered from 19 articles.

From the evidence gathered, strategies to avoid TB infection included good ventilation, avoiding overcrowding, and rapid detection, treatment, and isolation of infectious patients.

Other strategies include improved nutrition, economic empowerment, stopping smoking, a targeted approach to TB detection in high-risk areas, and infection prevention measures in health facilities. Prevention of spreading TB infection to TB disease includes avoiding risk factors described in the previous section (Li et al., 2017).

World Health Organization also provides guidelines for treating latent TB infection (LTBI) in at-risk populations, such as HIV-infected patients prevent the advancement of TB disease (WHO, 2020).

2.2.6: TB complications

Absence of early detection and treatment of TB lead to complications that are often life threatening. In addition, effectiveness of treatment also contributes to complications. TB complications include spontaneous pneumothorax, bronchiectasis, lung fibrosis, lung abscess, massive hemoptysis, and chronic pulmonary aspergillosis. Factors that affect the effectiveness of TB treatment include age, presence of co-morbidities, immunosuppressive states, malnutrition, alcoholism, and adherence which may be attributed to behavior or drug tolerance. Also, the organisms' virulence and drug resistance and radiological extent of the disease influence treatment outcomes. The development of multidrug resistance (MDR-TB) and extensive drug-resistant TB (XDR-TB) as complication presents major challenges to individuals and health care systems (National Tuberculosis, Leprosy, and Lung Disease Program, Kenya, 2021; Jeon & Murray, 2008; Rabahi et al., 2017).

2.3: Diabetes Mellitus

2.3.1: Overview

Diabetes mellitus is a multifactorial metabolic disease with considerable heterogeneity which disease results from the body's deficiency or resistance to insulin (Grundlingh et al., 2022).

As early as 1500 BC, Egyptian manuscripts described a disease characterized by "too great emptying of the urine." Diabetes was described in India in 400 – 500 AD as a disease with "honey urine or *madhumeha*" because it attracted ants with identificati9n of two types of the disease which would later be known as type I and II (Lakhtakia, 2013).

The word *"diabetes"* (Greek, 'Siphon') was first coined by Aretaeus the Cappadocian in the first century A.D. Aretaeus stated about diabetes that; "no essential part of the drink is absorbed by the body while great masses of the flesh are liquefied into the urine." John Rollo, a British Surgeon-General in 1798, coined the word "mellitus" (Latin, 'sweet like honey). Mellitus was used to help distinguish the specific type of diabetes with diabetes insipidus, which is characterized by tasteless urine. Perhaps the boldest diagnosis method for the detection of diabetes was by Willis, a London-based physician, who tasted his patient's urine (Lakhtakia, 2013; Karamanou et al., 2016).

2.3.2: Epidemiology

Diabetes mellitus (DM) is a syndrome of chronic hyperglycemia due to relative insulin deficiency, resistance, or both. The International Diabetes Federation (I.D.F.) estimated that 8.3% of the global population had diabetes in 2013 and estimates an increase to 10.1% in 2035 (Kumar & Clark, 2017). Diabetes mellitus is one of the four major non-communicable diseases causing about 4 million deaths in 2017.

It is projected that by 2040, low-income countries will experience a 92% increase in mortality from diabetes mellitus (Mohamed et al., 2018).

Diabetes mellitus can now be found in almost every population in the world. Epidemiological evidence suggests that diabetes will likely continue to increase globally without effective prevention and control programs. Diabetes constitutes a major public health problem because of the increased risk of developing cardiovascular disease (Diabetes Atlas Committee, 2003).

Al Mansour indicates that diabetes mellitus is estimated to affect about 5 – 10% of the global population. The chronic endocrine disorder is forecasted to have a 20 – 69% increase in prevalence by the year 2030 based on the 2010 prevalence. Among 20 – 79 years of age, the prevalence is estimated to increase by 7.7% leading to 439 million cases by 2030 (Al Mansour, 2020). Zeru et al. notes that the prevalence of diabetes mellitus has been on the rise in developing countries with a subsequent increase in mortality rates (Zeru et al., 2021).

According to Grundlignh et al., the global prevalence of diabetes had risen to 463 million 18 years and above individuals in 2019 from 108 million in 1980. This increase showed an above double prevalence rate of 9.8% in 2019 from 4.7% in 1980 (Grundlingh et al., 2022).

According to the International Diabetes Federation (I.D.F.), Kenya is estimated to have a 2.5 % of its adult population affected by diabetes. In 2017, it was reported that Kenya had 458.900 cases of diabetes. However, the I.D.F. estimates are based on a combination of several data sources, including health facility data, small population studies, and modeling that may not provide robust estimates.

There is a need for empirical data at the population level to accurately determine the true burden of diabetes in Kenya (Mohamed et al., 2018).

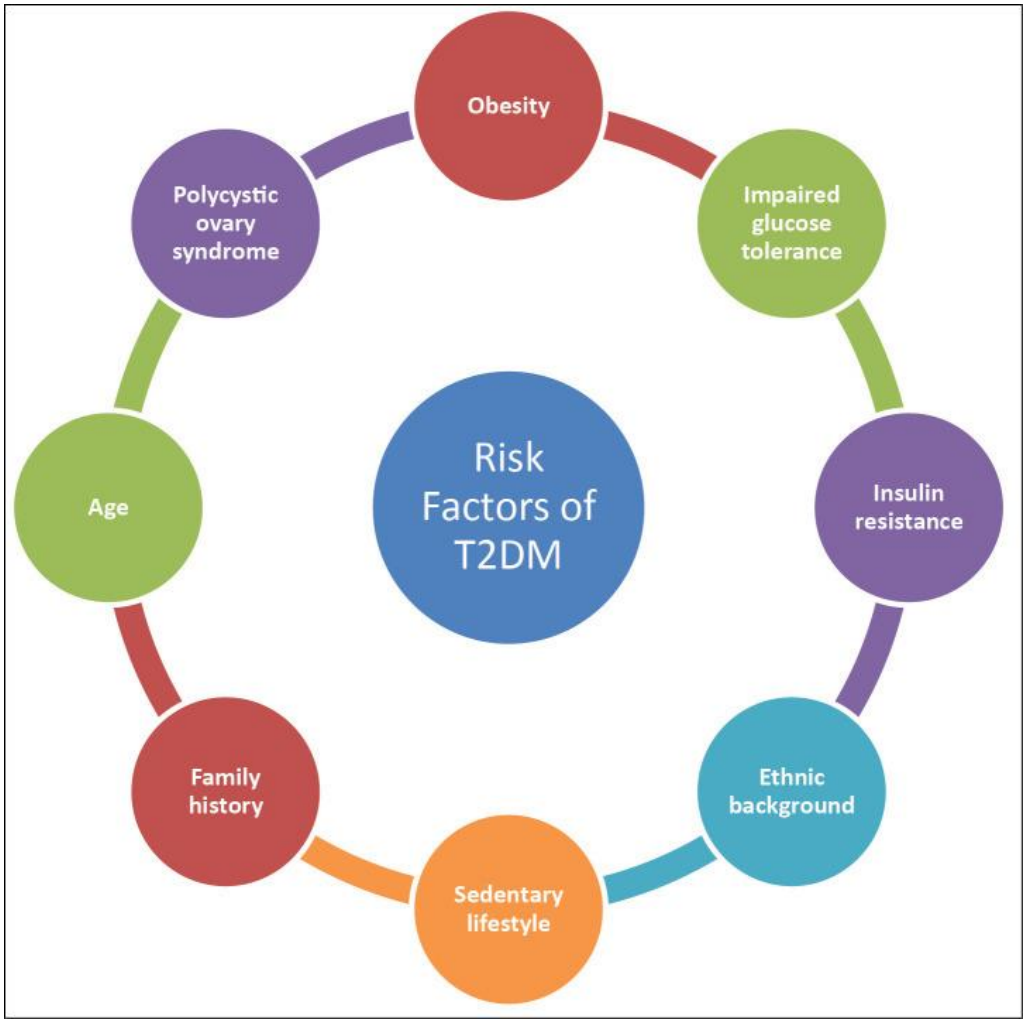


Figure 3: Some of the risk factors for diabetes (Banday, Sameer & Nissar, 2020).

Al Mansour conducted a study in Saudi Arabia to determine type 2 diabetes risk factors among a semi-urban population in Majmaah City in Riyadh among 353 respondents from five primary health centers. The study found over a third of the respondents (34.6%) had diabetes.

Being female showed a slightly higher non-statistical significant prevalence (34.9%) as compared to males (34.2%); the elderly, over 40 years, had almost average (44%) while those with low income had almost similar prevalence levels (42.4%).

Respondents who were overweight and obese, those who did not engage in regular physical exercises, and high consumption of fatty foods had a significantly high prevalence of diabetes mellitus of 42.3%, 31.1%, and 35.6%, respectively.

In addition, a history of cigarette smoking was not found to increase the prevalence, with those with a smoking history having a prevalence rate of 25.7% compared to 35.5% in those who were non-smokers. Hypertensive patients demonstrated a prevalence rate of 42.3% compared to normotensives (33.9%) (Al Mansour, 2020).

A study in Ethiopia found age (>40 years), poor literacy levels, cigarette smoking, and high body mass index (>25kg/m^2) as significant risk factors for the development of diabetes mellitus. Other risk factors deduced from the study are family history of diabetes mellitus with odds of 6.14 in persons with family history. Also, a history of hypertension and lack of physical exercise or sedentary lifestyles conferred an increased risk of the development of type II diabetes mellitus (Zeru et al., 2021). Type I diabetes is a genetic autoimmune disease that results from insufficient insulin production leading to poor regulation of blood sugars. Type 2 diabetes accounts to over 90% of diabetes mellitus cases (Grundlingh et al., 2022).

2.3.3: Pathophysiology

Type I diabetes mellitus is an autoimmune disorder accounting for 5 – 10% of all diabetes cases and has also been referred to as insulin-dependent diabetes mellitus. The disease occurs due to the destruction of the β-cells of the pancreas by a T-cell-mediated autoimmune reaction.

A cascade of genetic and environmental factors is thought to contribute to the immune reaction.

The rate of destruction is often fast, leading to the onset of type I DM in infants and children. In some circumstances, gradual destruction leads to the late onset of the disease in adults, referred to as *"latent autoimmune diabetes in adults (LADA),"* which often masquerades as type II DM. Sudden destruction and failure of the β-cells lead to diabetes ketoacidosis (DKA). This is often the initial and common presentation of type I DM. Slow-progressing destruction leads to diabetes being noted when individuals have psychological stress, severe infections, or develop other conditions (Banday, Sameer & Nissar, 2020).

Type II DM is a non-insulin-dependent disease resulting from the resistance to insulin or dysfunction of the β-cells. These occurrences of these two factors are intertwined. Initially, peripheral body tissues, particularly the muscles, liver, and adipose tissue, become resistant to insulin. As a result, the circulating glucose levels become high, leading to β-cells hyper function to produce more insulin to maintain normoglycemia. Consequently, the β-cells cannot meet the increased insulin production and their function begins to decline. As in type I diabetes, a combination of genetic predisposition such as family history and environmental factors as described above contribute to the occurrence of the disease. Type II DM's typical symptoms include increased urination, excessive thirst, weight loss, growth impairment, and blurred vision (Banday, Sameer & Nissar, 2020; Galicia-Garcia et al., 2020).

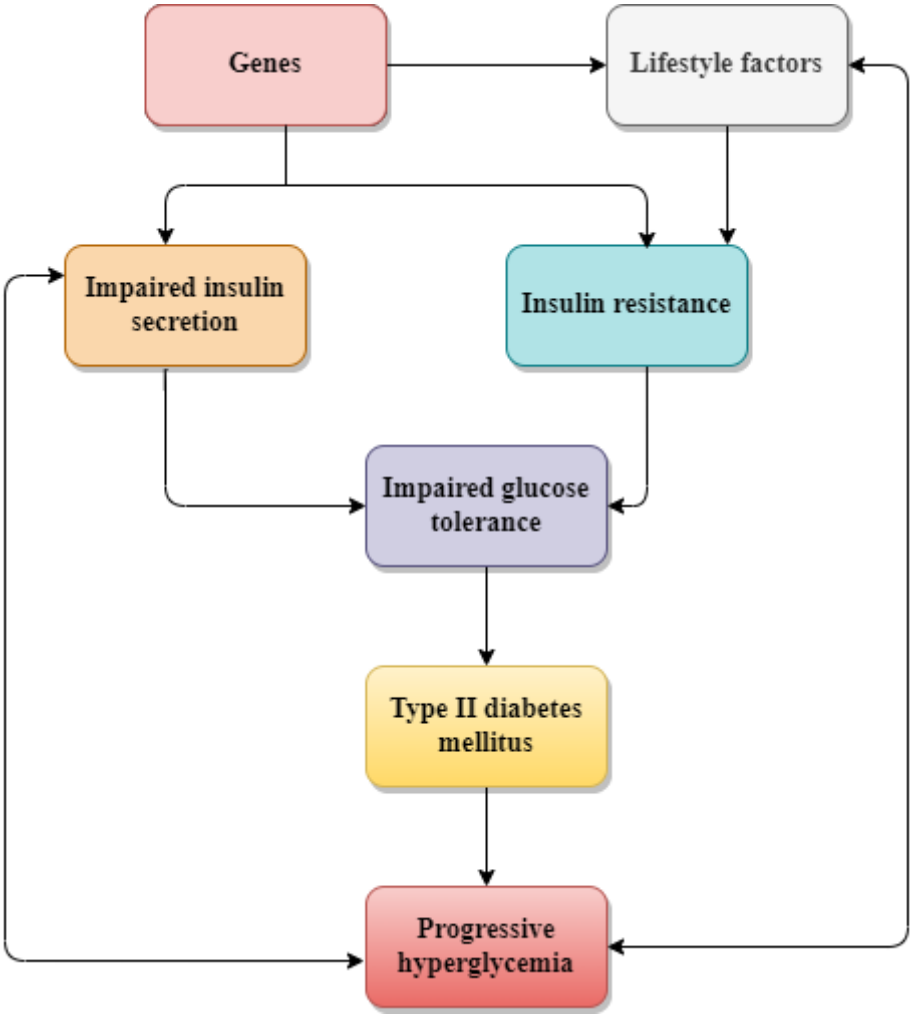


Figure 4: Pathophysiology of type II DM (Ozougwu et al., 2013).

2.3.4: Diabetes management

In addition to classical symptoms, the diagnosis of diabetes is considered when there is a fasting blood sugar of above 7.0mmol/L (126mg/dL) or a random blood sugar of above 11.1mmol/L (200mg/dL). Also, an abnormal result in an oral glucose tolerance test and an HbA_{1c} (glycated hemoglobin) level of above 6.5% can be used to diagnose DM About a third of patients with type I DM present with DKA and may be used in further classifying the type of diabetes. Over 50% of type I DM occur in childhood. Biomarkers such as pancreatic autoantibodies can be used to classify type I DM coupled with clinical factors such as the age of onset and body mass index.

Low C-peptide concentration is also a marker of severe endogenous insulin insufficiency (DiMeglio et al., 2018; Kahanovitz et al., 2017). The treatment of type I DM is insulin therapy. On the other hand, type II DM is managed by lifestyle modifications and drugs such as metformin and sulfonylureas and may sometimes require insulin supplementation (Ozougwu et al., 2013)

2.3.5: Diabetes prevention

Prevention of diabetes is anchored on two goals; primary and secondary prevention. Primary prevention is aimed at identifying the risks for diabetes among individuals and implementing strategies for modifying them. In addition to modifying risks described in the previous section, other recommendations include a 5 – 10% weight loss target, reduced fat intake to <30% of calories, and increased fiber intake to >15g/1000kcal. Also, exercising for at least 30min per day at least three times a week is essential in primary prevention. Secondary prevention is aimed at preventing the development of complications in diabetic patients. Strategies include upholding primary prevention strategies in confirmed diabetic patients, maintaining good glycemic control, and early detection and management of complications (National Diabetes Control Programme, 2010).

2.3.6: Diabetes complications

Acute complications of diabetes are diabetes ketoacidosis (DKA), hyperosmolar hyperglycemic state (H.H.S.), hypoglycemia, and hyperglycemia. DKA and H.H.S. are the most common and life-threatening acute complications of diabetes (DiMeglio et al., 2018; Zeleke Negera et al., 2020).

Persistent hyperglycemia contributes to the occurrence of complications in diabetic patients as a result of vascular damage. Damage to the medium and large-sized vessels lead to heart disease, cerebrovascular accident, and peripheral vascular diseases. Damage to the small vasculature leads to renal failure and neuropathies that result in loss of sensory and autonomic nervous function. Also, small vasculature damage leads to blindness due to retinopathy. Patients with diabetes are at an increased risk of hypertension and abnormalities of lipoprotein metabolism (DiMeglio et al., 2018; Kahanovitz et al., 2017).

2.4: TB infection in Diabetes

2.4.1: Prevalence

It is evident that patients with diabetes have an increased of developing TB Diabetes increases the risk of latent TB infection progression to active disease that would have otherwise been contained by the body (Crevel & Critchley, 2021). It is hypothesized that diabetic patients have an increased risk of infection and subsequent TB disease when TB contact occurs, as evidenced in a cross-sectional study in Bandung, Indonesia. In the study, following household contact, diabetic patients had a 4.2% prevalence of TB disease compared to 1.2% of those without diabetes (Crevel & Critchley, 2021; Koesoemadinata et al., 2017).

In diabetes, TB has been found to lead to more severe TB, more cavitation, and a high prevalence of positive pulmonary TB sputum smear and culture. DM patients are considered less likely to develop extrapulmonary TB (Riza et al., 2016; Jeon & Murray, 2008).

According to Crevel and Critchley, diabetes lengthens the time during TB treatment which smears or culture turn bacteriologically negative to between 2 – 3 months. TB disease in diabetes doubles the risk of death, increases the recurrence rate, and doubles the risk of developing MDR-TB, as depicted in the figure below:

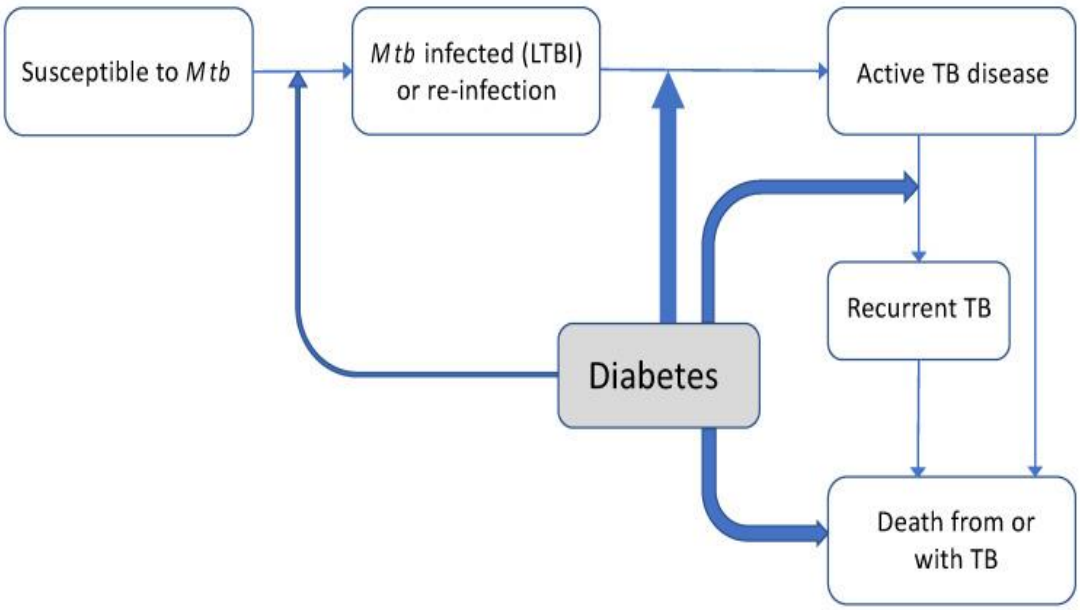


Figure 5: Effects of diabetes on the natural history of TB (Crevel & Critchley, 2021).

Historically, research into the association between TB and DM started early in the 19th Century with publication in New England Journal of Medicine reported as early as 1934 (Root, 1934). Association between DM and pulmonary TB is well established, and the prevalence of TB among patients with diabetes is increased 4-5 times. Impairment of host defenses plays an important role in changing the clinical, radiological, and bacteriological presentation of TB in diabetes (Kant et al., 2013).

The historical focus of previous research has been on the impact of type 2 diabetes mellitus on TB, with numerous studies showing that DM increases the rate of TB disease among patients. (Magee et al., 2022) Diabetes is a metabolic disease that weakens the body's immune system.

With the weakened immune system, diabetic patients have been found to exhibit a tendency to be more affected by pulmonary TB and fungal pulmonary infections than those in the general population (Tatar et al., 2009).

A systematic review found the prevalence of TB among DM patients ranging between 0.38% to 14%, with a relatively higher prevalence observed in studies in countries in Asia and Africa. The review also found that the prevalence of TB among DM patients is lower globally compared to DM among TB patients (Workneh et al., 2017). A hospital-based study in Pakistan looking at the prevalence of pulmonary tuberculosis among people with diabetes found a 7.5% higher risk of developing tuberculosis among patients with diabetes compared to non-diabetic patients (Qayyum et al., 2004). This concurs with another hospital-based study in Mirpur, Pakistan, which found a higher prevalence of pulmonary TB among people with diabetes (4.1%) but did not find confounding factors such as age or sex statistically significant in TB/DM co-morbidity (Masood et al., 2016).

These two studies recommended regular screening be done for DM patients. A study in Vietnam showed a higher prevalence of diabetes among TB patients and recommended regular screening for diabetes among TB patients (Hoa et al., 2018). This shows that TB/DM co-morbidity worsens the clinical outcomes of both TB and DM In a study done in china, the frequency of TB among DM patients was higher than that of the general population. The study recommended active TB screening in patients with diabetes to increase early detection and facilitate better treatment of TB Moreover, this will improve the clinical outcomes with anti-TB treatment and DM routine care (Wang et al., 2014).

A European study noted that Non Communication Disease (N.C.D.) risk factors like diabetes, malnutrition, smoking and chronic lung disease have increased TB infection. It recommended integrating TB care for N.C.D. services to enhance public health response efficiency (Bates et al., 2015). A systemic review of 13 studies found that diabetes increases the risk of TB as DM impairs the immune response needed to control bacterial infections. The study also concluded that the increased risk of TB was regardless of study design and population. Therefore, people with DM may be important targets for interventions such as active case findings, and treatment of DM may benefit TB control (Jeon & Murray, 2008).

In a study conducted in Hong Kong among the elderly population above 65 years, diabetes was associated with a modest increase in the risk of active pulmonary TB It was found that patients with diabetes with HBA1c less than 7%, were not at an increased risk (Leung et al., 2008).

Good glycemic control was shown to decrease the risk of developing tuberculosis. In a meta-analysis of observational studies of the prevalence of diabetes among tuberculosis Patients in Sub-Saharan Africa. The reviewed studies recommended special emphasis on early screening of DM among TB/HIV co-infected patients (Alebel et al., 2019). With this in mind, there should also be an active TB screening among DM patients in relation to TB and DM A study done in South Africa to screen DM patients for TB (using Xpert MTB/RIF irrespective of symptoms) and HIV found a high prevalence of active TB with over half of the study participants asymptomatic. The study also showed that DM patients with HIV or hemoptysis had a greater TB risk and should be targeted for active TB screening. The study also concluded that given the high sub-clinical active TB prevalence, the screening should be irrespective of symptoms for DM patients (Berkowitz et al., 2018).

Harries et al. found that the occurrence of DM and HIV lead to adverse outcomes on the treatment of TB. The two diseases lead to increased fatality rate among TB patients during treatment. They also led to the recurrence of TB even after successful completion of treatment. The immune compromise in DM/HIV diseases lead to granuloma formation, smear positive form *Mycobacterium tuberculosis*, lung cavities, and commonly upper lobe disease. However, further immune compromise in DM/HIV lead to occurrence of atypical TB disease with presence of negative smears and infiltrative and lower lung disease. Also, the advanced compromise leads to disseminated TB disease or extra pulmonary TB (Harries et al., 2011).

In studies cited in the study by Harries et al. in 2011 the odds of death from TB during treatment in patients with DM was high at 1.89 while the risk among those with DM/HIV was significantly higher with pooled odds ratio of 4.95. The pooled risk of TB relapse was also high in DM with other co morbidities such as HIV was found to be 3.89. The findings on the prevalence of TB among DM and HIV border showed that about a quarter of the TB cases were contributed by DM (25%) and approximately 5% in HIV leading to a cumulative prevalence of over a third of the cases identified in the border (Harries et al., 2011).

A study of risk factors for PTB among DM patients found that the mean age of 52 years was associated with TB/DM co-morbidity. The study identified poor glycemic control, lower hemoglobin levels, and elevated HBA1c and E.S.R. as statistically significant factors for the development of TB among DM patients. However, it showed no statistical significance regarding gender, smoking, and DM treatment compliance (Khalil & Ramadan, 2016).

An Ethiopian study noted that patients with a history of contact with TB and prolonged diabetes were more prone to have pulmonary TB. Diabetes mellitus, in the study, was found to cause a three times risk of developing TB than those without diabetes. Among the 225 diabetic patients suspected to have TB, positive smear were found in 6.2% as compared to a 0.39% prevalence in general population. Factors such as urban residence, previous history of TB, family TB contact, and long duration of DM were found to exacerbate the occurrence of TB disease in patients with DM. notably, urban residence conferred a 6 times risk of TB development than rural DM patients, previous history of TB presented a significantly high risk of TB (AOR = 13.4). Also, family TB contact presented a 9 times more risk and having diabetes for more than 10 years presented a high risk (2.7%) as compared to less than 5 years of DM (1.3%). Therefore, the study recommended screening DM patients for pulmonary TB during follow-up visits (Amare et al., 2013).

A study in Kisii showed a positive association of DM with getting TB, and other factors, such as malnutrition, were associated with the likelihood of getting tuberculosis among those exposed (Kasera et al., 2015). In a study in two counties in Kenya looking at prognostic factors among TB and TB/DM co-morbidity, the prevalence of DM among TB-infected patients, was 37.2%. The study also found patient's regimen, employment status, alcohol intake, smoking, age, and household size were some of the factors associated with DM among TB patients. The study was limited in that it was done in select facilities in 2 counties (Mburu et al., 2018).

In another study in western Kenya assessing diabetes among tuberculosis patients, the researchers found the prevalence of diabetes (HbA1c >6.5%) to be 5.1% and those with prediabetes (HBA1c 5.7-6.4%) to be 37.5%.

With these higher rates of diabetes and prediabetes, the authors supported the need to routinely screen for diabetes in patients with TB (Owiti et al., 2017). With this in mind and the TB/DM association, there is also a need to actively screen for TB among DM patients. The studies analyzed show that diabetes drastically affects the clinical course of tuberculosis, with more severe clinical manifestations and poorer prognosis and treatment efficacy. In the absence of international guidelines on managing and controlling comorbid tuberculosis and diabetes, experts must establish a strategy for treating both diseases simultaneously and take preventive action by introducing strategic measures to prevent co-morbidity in developing countries such as Mexico (Rodríguez-Rodríguez et al., 2015).

A study done in National Massan Tuberculosis Hospital in Republic of Korea was aimed at assessing the impact of diabetes mellitus and smoking on the mortality in TB. The study sample of 657 respondents comprised of patients with first episode of TB or retreatment. The study findings revealed that diabetes was implicated in occurrence of greater radiographic severity, TB recurrence of relapse.

Patients with diabetes who were also smoking had their risk of death increased in the first 12 months of enrolment. In relation to the occurrence of TB, the study revealed that smoking in diabetes conferred to individuals a hazard ratio of 5.78 as opposed to those who were not smoking. The study concluded that smoking and diabetes increased the risk of developing active TB disease and occurrence of adverse outcomes from the TB disease (Reed et al., 2013).

While assessing the impact of smoking on the occurrence of TB, Wen at al. in 2010 evidenced that smoking playing a significant role in the whole spectrum of TB disease.

Notably, history of smoking was found to be significant factor in increased mortality from TB by 9 – fold while cessation of smoking reduced the risk of mortality more than half (65%) (Wen et al., 2010). In the study, it was revealed that of all the TB mortalities in Taiwan, smoking accounted to over one third of all TB related death (37.7%).

Therefore, based on the findings of Reed et al. (2013) and Wen at al. (2010), it is clear that smoking and diabetes are of great influence on TB occurrence.

According to Silva et al. (2014) cigarette smoking plays a role on the pathogenesis of TB. It is known to play an important part in the TB pathogenesis. Some mechanisms include causation of ciliary dysfunction and reduced immune response. Also, cigarettes smoking leads to defects macrophage immune response with related normal or reduced CD4 count. These effects on the immune system present an increased susceptibility to mycobacterium tuberculosis infection and allowing a favourable environment for development of TB disease and its continuum (Silva et al., 2014).

According to Gunaserkaran et al. chronic obstructive pulmonary disease (COPD) is a lung disease resulting from chronic inflammation leading to progressive airway obstruction and is not fully reversible.

In a study examining the impact of DM on COPD using the National Inpatient Sample (NIS) in the United States, it was shown that the two diseases have an impact on morbidity and mortality among patients. Among other study findings using 7,498,577 patients cases over the years 2002 - 2014, it was noted that the occurrence of DM and COPD lead to occurrence of pneumonia and respiratory failure including the occurrence of TB (Gunasekaran et al., 2021).

An Iranian 6 year retrospective study of patients diagnosed with TB at Ghaem Hospital and outpatient clinics found that predisposing factors to development of TB were more prevalent in the elderly (mean age = 69.6 years ± 6.1) population who had a significantly higher frequency of chronic pulmonary disease, ischemic heart disease, congestive heart failure, malignancy and diabetes (Towhidi et al., 2008)

2.4.2: Diagnosis of TB in DM

The screening for latent tuberculosis infection (LTBI) in diabetes is done using a tuberculin skin test (T.S.T.) or the interferon-gamma release assay (IGRA). Latent TB is screened in diabetic patients, especially those with poor glycemic control, and when confirmed, preventive treatment may be offered as per the WHO guidelines. A positive T.S.T. is determined when a skin induration occurs following an intra-dermal tuberculin injection. It has a sensitivity and specificity of 77% and 97%, respectively. The T.S.T. in LTBI diagnosis in DM is low test costs but has various shortcomings in that follow-up in 2 – 3 days is required and requires training to administer. An IGRA test is more sensitive (85%) and specific (96%) in LTBI diagnosis from detection of immune reactivity in a blood sample with a diagnosis made within the same day but presents high costs of the tests and requires a laboratory capacity. Due to reduced immunity in diabetic patients, there may be reduced test sensitivity, and there is poor evidence for use in diabetes for T.S.T. and IGRA (Deuffic-Burban et al., 2020; Trajman, Steffen & Menzies, 2013; Riza et al., 2016).

The screening and diagnosis of TB disease in diabetes is determined using various tests as those without diabetes. However, in diabetes, screening and diagnosis modalities have various pitfalls in their application to diabetic patients.

Clinical assessment by carrying out a symptomatic screen and clinical examination is low-cost and takes less time but has low sensitivity (77%) and specificity (67%), and diabetes differs TB clinical presentation characteristics making it less reliable (Riza et al., 2016).

A chest radiograph is useful in detecting TB suggestive lesions, especially in asymptomatic individuals, and has a medium cost and low turnaround time. A radiograph has a 98% sensitivity and 75% specificity. A radiograph application may be restricted in areas with high rates of non-tuberculosis abnormalities and the possibility of differing findings in patients with diabetes (Riza et al., 2016; Lin et al., 2015).

Sputum microscopy is used in TB diagnosis by detecting the acid-fast bacilli in a sputum smear, has a medium cost, may take days in turnaround time, and is less sensitive than culture. On the other hand, a sputum culture is the gold standard in detecting *M. tuberculosis* as it allows diagnosis and resistance tests. Sputum culture has high costs, a turnaround time of up to 8 weeks, requires training and skills, and it may be impossible to do for all diabetes patients due to their high numbers. The downside of both sputum tests is the requirement for a laboratory that may not be available in most diabetes clinics and the reluctance of diabetic patients to provide sputum samples. Xpert/MTB/RIF test is a high-cost polymerase chain reaction (PCR) test that detects *M. tuberculosis* and rifampicin resistance with hours in turnaround time. W.H.O recommends it as the initial diagnostic test for all TB suspects, including diabetic patients. Xpert/MTB/RIF has an 88% sensitivity and 98% specificity and uses a closed automated system, thus requiring less skills (Riza et al., 2016; WHO, 2014; WHO, 2015; Crevel & Critchley, 2021).

2.4.3: Evidence Based Management of TB in DM

Since TB treatment is standardized, its treatment in DM is not different. It follows the recommended six months treatment course for drug-susceptible TB; two months of rifampicin, isoniazid, pyrazinamide, and ethambutol (RHZE) and four months of rifampicin and isoniazid (RH). A key consideration should be made on TB treatment in DM due to the increased risk of treatment failure, relapse, treatment failure, and death.

Therefore, it is imperative to maintain optimal glycemic control not only to prevent TB infection and disease but also during treatment. However, TB disease in DM often causes challenges in maintaining good glycemic control. Some of the causes of treatment failure in diabetes include extensive disease, immune compromise in DM, and/ or reduced anti-TB drug concentration in DM patients (Riza et al., 2014; Crevel & Critchley, 2021).

In Indonesia, Nijland et al. found a decreased rifampicin level in the continuation phase in people with diabetes. In DM patients, the rifampicin levels were 50% less than those without diabetes in the same age and sex cohort (Nijland et al., 2006). DM patients who were overweight or obese showed reduced plasma rifampicin concentration even after correcting body weight. Also, reduced rifampicin concentrations in plasma were found in patients with profound hyperglycemia. However, in the intensive phase, no pharmacokinetic difference was found in the same weight cohort of DM patients and those without DM for rifampicin, pyrazinamide, and ethambutol. Also, there was no evidence of a difference in oral rifampicin bioavailability in DM patients, which correlated with a Peru study findings where 2 and 6 hours rifampicin plasma concentrations were similar to TB/DM and TB only in the intensive phase (Ruslami et al., 2010). It is, therefore, evident that DM affects TB drugs' bioavailability.

It is important that more evidence and studies be done to optimize TB treatment in DM outside the standard treatment protocols to avoid treatment failure and other complications (Requenza-Mendez et al., 2012; Ingen et al., 2011).

2.4.4 Active Case Finding of TB in DM

Active case findings for TB in DM follows similar protocols to those without diabetes. However, it is important to emphasize screening patients with diabetes due to the effects TB presents (Crevel & Critchley, 2021). Active case finding is recommended by W.H.O.s' End TB Strategy as an approach that assists in detecting persons with active TB missed by the health service.

W.H.O defines A.C.F. as *"the systematic identification of people with presumed active TB, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly."* Active case finding has proven benefits in detecting TB early in the disease. As opposed to active case finding, passive case finding concentrates on finding TB among the people seeking health care services due to signs and symptoms of TB (Biermann et al., 2021).

Crevel and Critchley note that screening for TB in diabetic patients is important in detecting active disease, thus helping in TB elimination in this group (Crevel & Critchley, 2021). In South Africa, Berkowitz et al. found that about 50% of the patients who had TB using sputum culture and GeneXpert were asymptomatic (Berkowitz et al., 2018). In the study, 440 patients with diabetes were screened for TB, finding a 3% TB prevalence among the study group. Relying on the presence of symptoms to test for TB in DM may lead to many missed cases underscoring the importance of active case finding as opposed to passive case finding, as evidenced in the South African study (Biermann et al., 2021).

According to Ji et al., the target group for active case finding for TB in DM is those at highest risk, including low B.M.I. individuals, poor glycemic control, and low triglyceride levels. Also, a history of smoking and old age individuals may form a cohort of individuals for TB testing with or without symptoms (Ji et al., 2020).

2.5 Conceptual Framework

Conceptual framework is applied in research to provide an understanding of how the research problem will be explored. It provides a picture or visual display of the relationship between the ideas in the study (Adom et al., 2018). The framework provides the key variables to be studied and their presumed relationship. For this study's purposes, the independent variables were demographic, behavioral, and disease-related factors.

The intervening variables were known diabetes patients and TB symptoms. Lastly, the dependent variables were Xpert/MTB/RIF positive results contributing to the TB prevalence in DM patients.

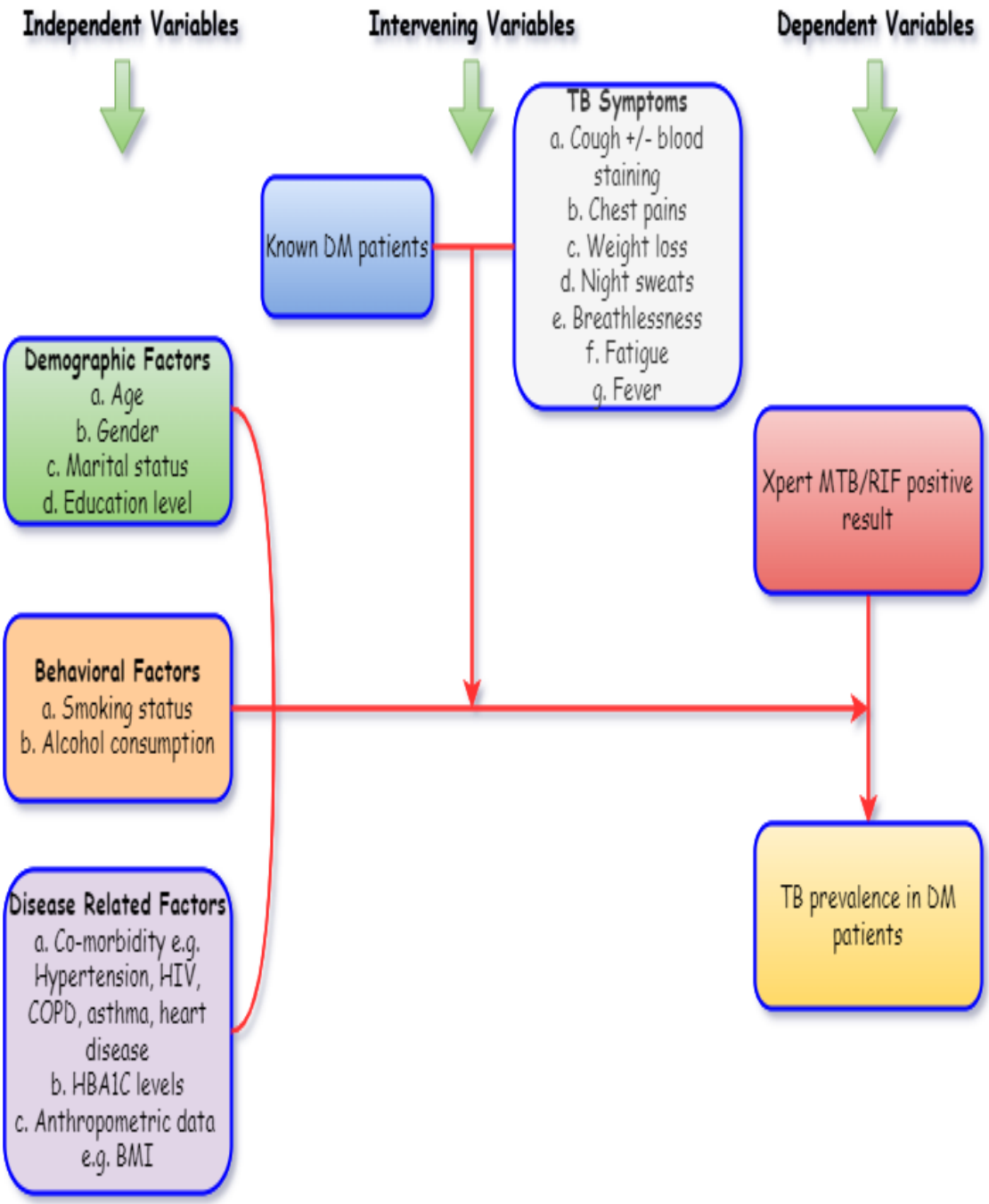


Figure 6: Conceptual framework

CHAPTER THREE

3.0 METHODOLOGY

3.1. Study Design

This was a hospital based cross-sectional study. The study was conducted over a period of eight months from January 2021 to August 2021 in a rural setting in Webuye, Bungoma County, in Western Kenya. Participants above the age of 18 years who were diagnosed with diabetes and attending the diabetes outpatient clinic were recruited. These participants were recruited and enrolled after they signed the consents forms and screened for presumptive TB Structured questionnaires were administered including sputum collection.

3.2. Study Site

The study was carried out at Webuye County Hospital's diabetes outpatient clinic (DOPC). Webuye is located in Bungoma East Sub-County of Bungoma County and is situated at 0° 36' 27.04" N; 34° 46' 10.78" E. According to the national census of 2019, Bungoma East sub-county covers an area of 163.3KM^2 with a population of 114,548 persons (Kenya National Bereau of Statistics, 2019). The sub-county is predominantly rural with the economic backbone being agriculture. The county has an efficient communication network and good road network.

The diabetes outpatient clinic (DOPC) is conducted every Friday and patients report to the clinic except when it falls on a public holiday. The average attendance of the clinic was 30 patients on a typical clinic day. Most patients were revisits but on average the clinic received 4 new patients on the clinic day. All patients who attend DOPC are captured in the regular clinic attendance list kept at the clinic and the records departments at Webuye County Hospital.

The Xpert MTB/RIF molecular essay for the sputum specimens was done at the AMPATH reference laboratory at Webuye County Hospital.

Patients were also advised to visit the casualty department anytime they felt unwell. Webuye County Hospital runs general and specialist outpatient services. The majority of the general outpatient were walk-in without appointments while those attending specialist clinics were mostly seen on appointment.

3.3. Target Population

The target population comprised a heterogeneous population of all patients aged 18 years and above with diabetes in Western Kenya attending the DOPC. Webuye County Hospital has a catchment population of over 250,000 patients (UN HABITAT, 2017) from Bungoma, Trans-Nzoia and Uasin-Gishu Counties which are bordering Webuye.

3.4. Study Population

The study population included all diagnosed patients with diabetes mellitus who were aged eighteen (18) years and above, registered with and attending the Diabetes Out-Patient Clinic (DOPC) between January 2021 and August 2021 at Webuye County Hospital. They included those who met the eligibility criteria within the study period and who gave informed consent. Nine hundred and seventy five (975) consenting adults (18years and over) who were registered for treatment at the DOPC were enrolled in the study.

3.4.1. Inclusion Criteria

1. All patients with diabetes registered at the diabetes outpatient clinic (DOPC) at Webuye County Hospital aged 18years and above
2. The patients were able and willing to give an informed consent

3.4.2. Exclusion Criteria

1. Clinically unstable patients who required urgent attention e.g. those who had diabetic ketoacidosis (DKA), hyperosmolar hyperglycaemic state (HHS), severe hypoglycaemia or those who had a concurrent acute infections
2. All respondents who refused to consent

3.5. Sample Size Determination

The objectives of the study was to determine the prevalence of TB among patients with diabetes and also to determine the association between socio-demographics factors and TB occurrence among patients with diabetes. A systematic review of the prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity found an overall median prevalence of TB among patients with diabetes to be 4.1% (Workneh et al., 2017). Using this prevalence considering accessible population of 1583 in our settings a sample size of 377 was arrived at for objective one using Fisher's formula (Charan & Biswas, 2013).

$$N = \frac{Z^2 p(1-p)}{e^2}$$

Where:

N = Sample size [Webuye County Hospital DOPC] - 1583

Z = Normal deviation at the desired confidence interval. In this case it will be taken at 95%, Z value at 95% is 1.96

P = Prevalence of TB among patients with diabetes – 4.1% (Workneh et al., 2017)

1-p = Proportion of the population without the desired characteristic.

e^2 = margin of error at 5% (0.05)

To estimate the sample size required for objective 3, the Peduzzi formula was used (Newsom, 2016):

$$n \geq \frac{k \times 10}{p}$$

Where:

n=minimum sample size

p= prevalence of TB among patients with diabetes globally (4.1%)

k= the number independent variables (factors) that were considered were four (4) – this include: HBA1c, alcohol use, cigarette smoking, and comorbidities

Substituting for the above formula a sample size of 975 patients with diabetes was arrived at and since it's higher than that of objective one, then it was considered as the sample size for the study.

3.6. Sampling Technique

Permission was sought and obtained from the Hospital management and granted to conduct the study and access the attendance list of all patients seen at the DOPC. Eligible participants were informed of the study and their consent sort. Those who decline were reassured and normal clinic services were offered. For those who consented, normal clinic services was offered first before data collection was done.

The respondents were recruited from recorded patients who were in attendance at the DOPC over the study period of 8 months. A consecutive sampling method was used to screen for presumptive TB cases among patients with diabetes who met the inclusion criteria until the required sample size was achieved.

The screening questionnaire was administered to all the diabetic clients attending DOPC who consented and met the eligibility criteria to screen for TB presumptive cases at the triage area.

The study questionnaire was then administered to the presumptive TB cases after being attended to in the normal diabetes clinic and then they were be asked to visit the TB clinic for sputum collection. The presumptive TB participants were then sent to the TB clinic for a sputum sample for Xpert MTB/RIF.

Participants were asked whether they had participated in the study during a previous visit, if they had, they were then excluded during the study period. The procedure was repeated every data collection day until the sample size was achieved.

Recruitment Flowchart

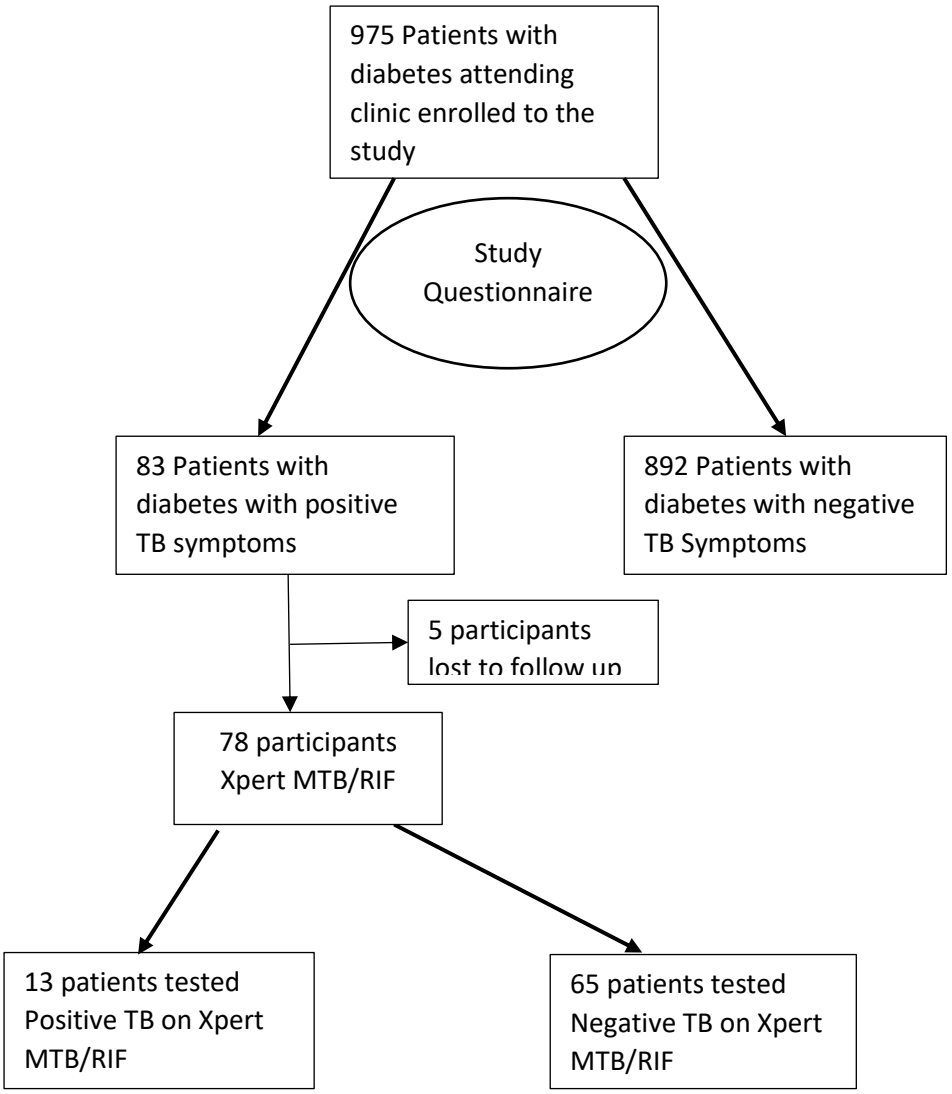


Figure 7: Recruitment flowchart for TB screening among patients with diabetes attending diabetes clinic

3.7. Demographic and Other Information

The questionnaire collected information about the participant's age, gender, marital status education, smoking status, alcohol consumption, TB comorbidity and symptoms of tuberculosis.

Information on other comorbidities, and HbA1c levels and anthropometric data was extracted from the patient's file. The questionnaire was further developed to suit the target population in this study, pre-tested, and administered to the respondents.

The modified questionnaire was pre-tested on 90 diabetic patients who were not included in the final study group and was done at Bungoma County Hospital diabetes clinic.

3.8. Criteria for Identifying Presumptive TB Cases

A TB screening tool developed using world health guidelines on TB screening(WHO, 2015). which incorporated signs and symptoms such as fatigue, breathlessness, chest pain, and night sweats was used and additional questions were added to the structured survey which were found to be important predictors in Kenya tuberculosis prevalence survey of 2016 (Enos et al., 2018). This was used to screen for presumptive cases of TB and those with TB/DM comorbidity.

3.9. Referral of Identified Presumptive TB Cases (among DM patients) to TB Clinic

Trained research assistants worked in collaboration with the staff at the DOPC to conduct a symptomatic TB screening for all eligible patients living with diabetes using the study screening tool. The identified presumptive TB cases among those screened for TB were linked with Webuye County Hospital TB clinic for Sputum collection for Xpert MTB/RIF analysis. Those who were found to be positive for Xpert MTB/RIF were diagnosed with TB Patients who were confirmed to have TB were referred to TB clinic for treatment and results were record in the study tool and the recommended government data tools. Good cooperation was established between the staff working in DOPC and TB clinic at Webuye County Hospital

3.10. Sputum Samples

Once a patient with diabetes attending the DOPC was identified to have symptoms in the questionnaire, he/she was taken to the TB clinic at Webuye County Hospital where personal details and contact information were taken. They then went to the AMPATH lab at Webuye County Hospital where the patient was given two sputum bottles for the samples. A spot sputum sample was taken on first contact and the second sample bottle was for morning sputum. The second sample was delivered at the lab by the patient the following day after collecting the morning sample. The TB clinic collected the results for patients once Xpert MTB/RIF had been performed on the sputum samples and contacted the patient to inform them about their results.

3.11. Data Management

A purposefully designed data collection form and questionnaire was used to collect demographic and screening data. The demographic and other general patient information such as gender, weight, height, systolic/diastolic blood pressure, HbA1c, schooling, marital status, smoking status, and HIV status was extracted from the DM patients register used at the DOPC. A validated screening tool was used to collect screening data. The interpreted GeneXpert (Xpert MTB/RIF) results were also captured in a specifically designed data collection form. All the data were captured by a trained research assistant and checked by the principal investigator to ensure good quality data. Double entry was done to ensure accuracy. IBM Statistical Package for Social Sciences (SPSS) Version 19 was used for data entry and editing.

3.12. Data Analysis

Data was analysed using STATA statistical software for data science. The primary outcome of the study was prevalent TB Secondary outcomes were frequency of TB risk factors among DM. Categorical and continuous variables were summarized using proportions and medians with inter- quartile range (IQR), respectively, and compared using chi square test, Fisher's exact test or Wilcoxon rank-sum test as appropriate between adults with DM and confirmed TB and also between presumptive TB cases and confirmed TB

To determine the association between socio-demographics factors and TB occurrence among diabetic patients at bivariate level Chi-square test of association was done. If any of the cell had counts less than 5 Fisher's exact test was done instead. Chi-square statistic and corresponding p-value was reported. A p-value <0.05 was considered statistically significant.

3.13. Ethical Consideration

Ethical approval was obtained from Moi University and Moi Teaching and Referral Institutional Research Ethics Committee (MU/MTRH-IREC). Approval was granted under approval number FAN: 0003512.

Permission to conduct the study was also be sought from the management of Webuye County Hospital. Participation in the study was purely voluntary and informed written consent was obtained from all individual participants included in the study. There was no reward offered to participants who chose to enrol in the study.

All significant findings were discussed with the patients and those found to have tuberculosis were linked with the TB clinic at Webuye County Hospital for treatment and follow-up. Patients were also advised on the importance of compliance to medication and routine clinic follow-up.

The results of the study will be disseminated through presentations to the clinicians and hospital management. This will collaboratively explore how research findings fit with current practice and policy, and can inform on improvements to the practice. Additionally, findings may be published through articles in peer-reviewed journals

3.14. Confidentiality

All participants' information was kept confidential and was not used for other purposes other than this study. Filled questionnaires were kept safe under safe custody of the principal investigator. All electronic data was handled confidentially and were password protected. No names or personal identifiers were included in the final report.

CHAPTER FOUR

4.0 RESULTS

This study used data from a total of 975 adult patients with diabetes attending diabetes clinic at Webuye County Hospital, Bungoma County.

4.1 Socio-demographic and Co-morbid Characteristics of Patients with Diabetes Mellitus at Webuye County Hospital

Table 1 and Table 2 shows the means and standard deviation of continuous variables and proportions of categorical variables together with the dispersion. The mean age of the participants was 57.5 years (SD=12.34). Majority of the participants 711 (72.9%) were female and half of the respondents were either overweight or obese. The proportion of legally married participants was 3 times the number of those who were either divorced or widowed. About 99% of the participants had at least a primary education qualification. Other baseline variables and comorbidities that had noticeable differences included; smoking (9.2%), HIV+ (15.6%), hypertension (74.8%), COPD (7.7%), asthma (7.2%), heart disease (9.4%).

Table1: Socio-demographic characteristics

Variable	Overall (N=975)
Age (yrs)	
Mean (SD)	57.53 (12.34)
Range	18.00 - 99.00
Sex	
Male	264 (27.1%)
Female	711 (72.9%)
BMI	
Missing	1
Underweight	29 (3.0%)
Normal	461 (47.3%)
Overweight	296 (30.4%)
Obese	188 (19.3%)
Marital status	
Single	31 (3.2%)
Married	722 (74.1%)
Divorced	26 (2.7%)
Widowed	195 (20.0%)
Missing	1 (0.1%)
Education level	
No school	15 (1.5%)
Primary	436 (44.7%)
Secondary	360 (36.9%)
College	142 (14.6%)
University	22 (2.3%)
Ever Smoked	
Yes	90 (9.2%)
No	885 (90.8%)
Consume alcohol	
Yes	275 (28.2%)
No	700 (71.8%)

Table 2: Co-morbidities Characteristics

Co-morbidities	Overall (N=975)
HIV	
Yes	152 (15.6%)
No	798 (81.8%)
Never been tested	25 (2.6%)
Hypertension	
Yes	729 (74.8%)
No	246 (25.2%)
Never been tested	0 (0.0%)
Ever been told have COPD	
Yes	75 (7.7%)
No	892 (91.5%)
Never been tested	8 (0.8%)
Ever been told have asthma	
Yes	70 (7.2%)
No	903 (92.6%)
Never been Tested	2 (0.2%)
Ever been told have heart disease	
Yes	92 (9.4%)
No	882 (90.5%)
Never been tested	1 (0.1%)

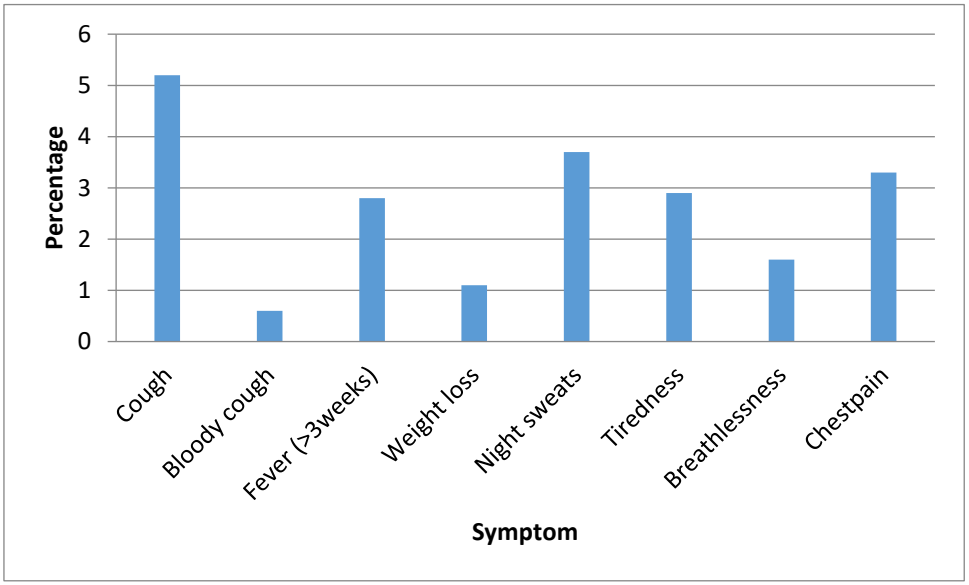
4.2 Objective 1: Prevalence of Presumptive TB among DM patients

A total of 83 (8.5%) participants reported to have one of the 8 symptoms that were suggestive of TB thus the prevalence of presumptive TB was 8.5% (95%CI: 6.8, 10.4). Figure 2 shows the distribution of the symptoms that were used to asses for presumptive TB The most common symptom was cough followed by night sweats while least common symptom was having a cough with blood stained sputum.

Table 3: Prevalence of presumptive TB and among those GeneXpert done

Variable	Overall (N=975)
Presumptive TB (any 8 symptoms)	
No	892 (91.5%)
Yes	83 (8.5%)
GeneXpert done	
Yes	78 (8.0%)
No	897 (92.0%)

Figure 8: Distribution by TB symptoms



4.3 Objective 2: Prevalence of TB among diabetic patients in Webuye County Hospital

Of the 83 participants who had symptoms of presumptive TB, a total of 78 (94%) had GeneXpert done of which 13 (16.7%) had confirmed TB positive. Hence, the prevalence of TB among those subjected to Gene expert was 16.7% (95%CI: 9.2, 26.8). While for the whole study sample was 1.3 % (95%CI: 0.7, 2.3).

Table 4: Prevalence of TB among Patients with DM

	Overall (N=975)
GeneXpert results	
Negative	65 (83.3%)
Positive	13 (16.7%)
Other - invalid, error, no result	0 (0.0%)

4.4 Association between Socio-demographic Characteristics and TB Results

Table 5 shows the associations between socio-demographic characteristics, comorbidities and confirmed TB among the 78 presumptive cases who had a GeneXpert done. The socio-demographic characteristics did not differ between presumptive TB group and confirmed TB group. Smoking was the only characteristic that showed some difference albeit not significant (p-value=0.08). Among the comorbidities, having asthma showed some significant difference (p-value=0.023). The rest of the comorbidities including being HIV+, hypertension, COPD and having a heart disease did not show any difference.

Table 5: Association between Socio-demographic and TB results: GeneXpert

Variable	No (N=65)	Yes (N=13)	p value
Age (yrs)			0.888[1]
Count	65	13	
Median	62.00	57.00	
Q1,Q3	51.00, 66.00	52.00, 66.00	
Sex			0.101[2]
Male	18 (72.0%)	7 (28.0%)	
Female	47 (88.7%)	6 (11.3%)	
BMI			0.427[2]
Underweight	4 (66.7%)	2 (33.3%)	
Normal	30 (88.2%)	4 (11.8%)	
Obese	13 (86.7%)	2 (13.3%)	
Overweight	18 (78.3%)	5 (21.7%)	
Marital status			1.000[2]
Married	48 (82.8%)	10 (17.2%)	
Not married	17 (85.0%)	3 (15.0%)	

Variable	No (N=65)	Yes (N=13)	p value
Education level			0.540[2]
None/primary	36 (80.0%)	9 (20.0%)	
Secondary/higher	29 (87.9%)	4 (12.1%)	
Ever Smoked			0.080[2]
Yes	7 (63.6%)	4 (36.4%)	
No	58 (86.6%)	9 (13.4%)	
Consume alcohol			0.164[2]
Yes	13 (72.2%)	5 (27.8%)	
No	52 (86.7%)	8 (13.3%)	
HIV			0.107[2]
No	57 (86.4%)	9 (13.6%)	
Yes	8 (66.7%)	4 (33.3%)	
Hypertension			0.443[2]
No	13 (92.9%)	1 (7.1%)	
Yes	52 (81.2%)	12 (18.8%)	
Ever been told have COPD			0.693[2]
No	54 (84.4%)	10 (15.6%)	
Yes	11 (78.6%)	3 (21.4%)	
Ever been told have asthma			0.023[2]
No	61 (87.1%)	9 (12.9%)	
Yes	4 (50.0%)	4 (50.0%)	
Been told have heart disease			1.000[2]
No	51 (83.6%)	10 (16.4%)	
Yes	14 (82.4%)	3 (17.6%)	

1. Ruskal-Wallis rank sum test
2. Fisher's Exact Test for Count Data

4.5 Objective 3: Association Socio-demographic Characteristics and TB among Patients with Diabetes Mellitus

Table 6 shows the associations between socio-demographic characteristics, comorbidities and confirmed TB cases via GeneXpert among all the 975 patients with diabetes.

Gender and smoking showed some association with p-values of 0.05 and 0.02 respectively between the confirmed TB patients and diabetic patients attending DOPC at Webuye County Hospital.

The other socio-demographic characteristics including age and gender did not did not show any association between the two groups. Among the comorbidities, having asthma was associated with having TB (p-value=0.01). The rest of the comorbidities including being HIV+, hypertension, COPD and having a heart disease did not show any difference.

Table 6: Association between Socio demographic and TB results: All DM patients

	No (N=962)	Yes (N=13)	p value
Age (yrs)			0.699[1]
Count	962	13	
Median	58.00	57.00	
Q1,Q3	50.00, 66.00	52.000, 66.00	
Sex			0.052[2]
Male	257 (97.3%)	7 (2.7%)	
Female	705 (99.2%)	6 (0.8%)	
BMI			0.079[2]
Underweight	27 (93.1%)	2 (6.9%)	
Normal	457 (99.1%)	4 (0.9%)	
Obese	186 (98.9%)	2 (1.1%)	
Overweight	291 (98.3%)	5 (1.7%)	
Marital status			1.000[2]
Married	712 (98.6%)	10 (1.4%)	
Not married	250 (98.8%)	3 (1.2%)	
Education level			0.159[2]
None/primary	442 (98.0%)	9 (2.0%)	
Secondary/higher	520 (99.2%)	4 (0.8%)	
Ever Smoked			0.025[2]
Yes	86 (95.6%)	4 (4.4%)	
No	876 (99.0%)	9 (1.0%)	
Consume alcohol			0.534[2]
Yes	270 (98.2%)	5 (1.8%)	
No	692 (98.9%)	8 (1.1%)	
HIV			0.130[2]
No	814 (98.9%)	9 (1.1%)	
Yes	148 (97.4%)	4 (2.6%)	
Hypertension			0.203[2]
No	245 (99.6%)	1 (0.4%)	

	No (N=962)	Yes (N=13)	p value
Yes	717 (98.4%)	12 (1.6%)	
Ever been told have COPD			0.071[2]
No	890 (98.9%)	10 (1.1%)	
Yes	72 (96.0%)	3 (4.0%)	
Ever been told have Asthma			0.011[2]
No	896 (99.0%)	9 (1.0%)	
Yes	66 (94.3%)	4 (5.7%)	
Been told have heart disease			0.116[2]
No	873 (98.9%)	10 (1.1%)	
Yes	89 (96.7%)	3 (3.3%)	

CHAPTER FIVE

5.0 DISCUSSION

5.1 Prevalence of TB among Presumptive Patients with Diabetes at Webuye County Hospital

This study noted that 83 (8.5%) presumptive TB patients were identified with any of the eight symptoms that were studied, i.e., cough lasting more than 2 weeks, coughing up blood, fever that lasted more than 3 weeks, weight loss in the last year, night sweats, fatigue, breathlessness, and chest pain, among diabetic patients who were attending DOPC in Webuye County Hospital. These presumptive TB symptoms are not specific to patients with diabetes only but are present in all probable TB cases, as described in Singer-Leshinsky, 2016 and Loddenkemper, Lipman, and Zumla (2016). The presence of these symptoms leads to a high index of suspicion. Diabetic patients having a higher risk of diabetes are more likely to have TB if they develop the symptoms.

Xpert MTB/RIF was done on a total of 78 (94%) participants, of which 13 (16.7%) patients had confirmed TB-positive results. The prevalence of TB among presumptive TB patients was 16.7% (95%CI: 9.2, 26.8), using Xpert MTB/RIF test. The Xpert/MTB/RIF test was chosen as it is the W.H.O recommended test for confirmation of all suspected TB cases (WHO, 2014; WHO, 2015) and due to its availability in the study facility.

This finding of 16.7% is comparatively higher than a study done in 2012 in Ethiopia by Amare et al. found a prevalence of 6.2% in TB suspected diabetic patients.

The study was a cross-sectional hospital study where sputum specimens were collected from the study participants and examined for acid-fast bacilli using direct microscopy by the Ziehl-Neelsen (ZN) staining Technique (Amare et al., 2013).

The difference in the prevalence could be attributed to the testing techniques employed as Xpert MTB/RIF is a newer rapid diagnostic test approved by WHO in December 2010 (WHO Report 2011, 2011).

Xpert MTB/RIF has been demonstrated to have a higher level of performance than ZN microscopy, with a sensitivity of 93.75% and 50.00%, respectively (Ejeh et al., 2019). Also, Riza et al. (2016) and Crevel and Critchley (2021) found that Xpert/MTB/RIF had a test sensitivity rate of 88% and a sensitivity rate of 98% higher than other tests.

Another study done in 1999 in Ethiopia by Feleke et al. using retrospective data analysis on TB in diabetic patients found a prevalence of 36.6% when sputum for AFB was tested. This prevalence was higher than that found in our study, which could also be attributed to the study design and test employed for the diagnosis of TB (Feleke et al., 1999).

In a study done in Tanzania by Swai et al. in 1990 with a seven-year follow-up, 45.7% of patients on follow-up were diagnosed with TB after the diagnosis of diabetes. This is significantly higher than what was found in this study. This difference can be explained by the time period and advances in the diagnostic, prevention measures, and treatment of tuberculosis in that the follow-up period was before 1990 (Swai et al., 1990)

5.2 Prevalence of TB among Patients with Diabetes Mellitus in Webuye county hospital

This study found Xpert MTB/RIF positive TB prevalence of 1.3% (95%CI: 0.7, 2.3) among the diabetic patients attending DOPC in Webuye County Hospital. This prevalence is 2.3-fold higher than the 2016 national estimate of 558 (95%CI 455-662) per 100,000 adult population (Enos et al., 2018).

This is also higher than the WHO estimates of the burden of tuberculosis for Kenya for the year 2020 of 259 (160-381) per 100,000 population. (Global Tuberculosis Report 2020, n.d.).

However, this study found a comparatively lower prevalence of TB among DM patients compared to the WHO global estimate of the number of TB cases attributable to DM of 3.1% for Kenya (Global Tuberculosis Report 2020, n.d.)

A study done in Muhimbili Medical Centre, Tanzania, by Swai et al. had a prevalence of 5.4% for pulmonary tuberculosis. The study followed 1250 diabetic patients for 1-7 years. (Swai et al., 1990). This prevalence is higher than what was found in this study. The variance can be explained by the study method used in the Tanzania study.

However, the prevalence of 1.3% found in this study is similar to a study done in Tanzania, which also found a prevalence of 1.3%. The study in Tanzania, however, employed a 'cough triggered' strategy for case finding among patients with diabetes (Mtwangambate et al., 2014). A study done in Cape Town, South Africa, found a prevalence of active tuberculosis at 3.0% (95% CI 1.72–5.03) among diabetic patients. The study also employed GeneXpert (Xpert MTB/RIF) test together with sputum for microscopy. The higher prevalence could be explained by the multiple methods of testing employed in that study (Berkowitz et al., 2018).

In this study, presumed TB cases for further evaluation using Xpert/MTB/RIF sputum test were determined by the presence of at least one of the eight symptoms evaluated. However, the use of symptoms could lead to missed TB cases, as demonstrated in Cape Town, South Africa (Berkowitz et al., 2018). In the study, out of the 3% cases found, about 50% had no symptoms negating the reliability of symptoms in determining presumptive cases.

An even higher prevalence of 29.8% (95%CI 24.2 – 35.4) was found in a study done in the Western Cape Province, South Africa, by Machingaidze et al. However, this study was done on children and adolescents with type 1 diabetes.

The study also used the Mantoux Tuberculin skin test for the diagnosis of *Mycobacterium tuberculosis* infection, the organism that causes TB (Machingaidze et al., 2012). The age of study participants, type 1 diabetes, and the test used for diagnosis could be used to explain the difference in prevalence between this study and the study by Machingaidze et al. A study in Korea by Kim et al. noted a smear-positive prevalence of 231 per 100,000 population.

The study was done by looking at the medical records of health insurance claimants (Kim et al., 1995). The methodology in the study could explain the low prevalence of 0.231%.

To underscore the significance of diabetes in increasing the risk of TB and in concurrence with this study's findings, a study in Bandung, Indonesia, found a difference in TB prevalence among household contacts. The study revealed that diabetic patients had a 4.2% prevalence of TB after household contact as opposed to a 1.25 prevalence in those who did not have diabetes (Koesoemadinata et al., 2017). A higher prevalence among diabetic patients for TB disease was found in a systematic review by Wokneh et al. (2017). The prevalence levels in African and Asian studies in the review showed levels ranging from 0.38 – 14%.

While it is evident that diabetes increases the risk of TB infection (Riza et al., 2014), its role in the advancement of latent TB to active TB determined by sputum tests such as Xpert/MTB/RIF used in this study is evident. It can be concluded from this study and those evaluated that diabetes disease increases the likelihood of developing TB

5.3 Association between Socio-demographic Factors and TB among Patients with DM

From the socio-demographic characteristics analyzed, this study showed that smoking (p-value = 0.025) was a statistically significant socio-demographic factor associated with an increased risk of developing tuberculosis infection if they also have diabetes.

The role of smoking in the development of tuberculosis is well established. A community-based cross-sectional TB prevalence survey in India's Madhya Pradesh state showed that tobacco smoking is significantly associated with pulmonary TB in that region (Rao et al., 2014).

Similarly, a systematic review of 34 studies on the association between tobacco smoking and tuberculosis came to the conclusion that both former and current smoking is associated with the risk of developing TB The review further noted that there is a strong dose-response relationship in terms of quantity and duration of smoking (Hassmiller, 2006). In the background of cigarette smoking as a risk factor for diabetes, as was found in an Ethiopian study by Glundlingh et al. (2022), it can be concluded that smoking is a significant factor in the occurrence of the two diseases. Therefore, when smoking and diabetes occur concurrently, the risk for TB is significantly increased. This relationship could be explained due to the pathogenesis of the disease as described by Silva et al. (2014).

There was a weak association between sex (p-value = 0.52) between DM and TB which was not statistically significant. However, among the GeneXpert positive 13 patients, they were almost equally distributed with seven male and six female patients.

A similar finding was also found in a study in Ethiopia where there were more males than females diagnosed with tuberculosis. However, that was not statistically significant (Amare et al., 2013).

Contrary findings on TB and sex relation were evidenced in a study done in Pakistan, which showed a higher number of male (78%) to female (22%) participants (Qayyum et al., 2004). Concurrently, Shimeles et al. (2019), in a study in Ethiopia, found out that even in the general population, males had an above average (55.8%) prevalence as opposed to less than average prevalence (44.2%) in females.

Age is a socio-demographic characteristic that has been studied and identified to have an association with TB and DM. From this study, however, age (p values = 0.699) was not statistically significant. The median age in this study was 57 (IQR 52, 66). It was noted in a study done in Ethiopia that they were more likely to develop TB infection if they also had diabetes.

The study noted that the majority of patients who developed TB were over 40 years (Amare et al., 2013). A similar finding was found in a study in South Africa, with a mean age of 55 years. The study found a p-value = 0.766, which was also not statistically significant. (Berkowitz et al., 2018). The possible reason for this could be due to compromised host immunity that increases susceptibility to tuberculosis with advancing age. From this study, patients with diabetes had a median age of 58 (IQR 50, 66).

Alcohol use (p-value = 0.534) in this study was not found to be associated with the development of tuberculosis among patients with diabetes. Similarly, a study in India showed that alcohol consumption was not associated with the risk of developing tuberculosis. (Rao et al., 2014)

A meta-analysis on alcohol consumption as a risk factor reported that alcohol consumption impairs the immune system, and this, in turn, increases the susceptibility to tuberculosis infection, as well as to reactivation of latent tuberculosis (Imtiaz et al., 2017). However, this has not been demonstrated in this study.

Among the comorbidities studied, having asthma showed some significant difference (p value=0.023). Although TB and asthma have different pathogenesis, endobronchial tuberculosis can mimic asthma symptoms. Although uncommon, the co-existence of asthma and tuberculosis can appear. (Nguyen-Ho et al., 2021). In a study in Sudan, the prevalence of asthma among patients with TB was found to be 5%. However, it was also noted that there was an increase in the number of asthmatic attacks before the development of TB (Bashir et al., 2016).

The association between TB in diabetic patients and asthma in this study can also be explained by the lack of a clear diagnosis of asthma among the respondents, as this was a self-reported diagnosis.

The findings of this study showed that the almost a fifth (15.6%) of the respondents were HIV positive. Out of these HIV positive cases 12 had presumptive TB and about a third of them (33.3%) had positive Xpert/MTB/RIF test. As compared to those who were HIV negative (n = 66), only about a fifth (13.6%) were found to have active TB disease. These findings correlate to those documented in Harries et al. (2011) evidencing that DM/HIV led to a 4.95 pooled odd ratio to the occurrence of TB.

Comorbidity with HIV (p-value = 0.130) among patients living with diabetes did not show a significant association with the development of TB in this study. However, studies in areas of high HIV/TB burden in South Africa showed a strong association between HIV/DM (p-value = <0.001) comorbidity and with development of TB (Berkowitz et al., 2018). Comparably to the South African study, a study in India by Kumpatla et al. also found a higher prevalence among patients with diabetes mellitus co-infected with HIV (Kumpatla et al., 2013). Although studies show a strong association between co-infection of HIV in diabetic patients increases the likelihood of developing TB, this was not the case in this study. This could be attributed to social desirability bias where those with HIV co-infection denied their HIV status.

This study did not show a statistically significant association between hypertension (p-value = 0.203) as a comorbidity with diabetes and an increased risk of developing TB A systematic review of the literature on the association between hypertension and tuberculosis found no evidence to support an association between TB and hypertension. However, these results should be interpreted with caution because of the lack of properly designed studies (Seegert et al., 2017).

In this study, COPD (p-value =0.071) was not found to be significantly associated with TB among patients with diabetes. COPD and TB have similar risk factors, such as smoking and dysregulation in the host immune system.

A population-based study by Inghammar et al. found a three-fold increase in the hazard ratio of developing TB, therefore, an increased risk of developing active TB compared to the general population (Inghammar et al., 2010). This was, however, not demonstrated in this study. This could be due to the reason that COPD diagnosis was based on the respondents reporting.

5.4 Strengths and Limitations of the Study

5.4.1 Strength of the Study

The study being a quantitative study utilising consecutive sampling technique to attain the desired sample size, this study can be generalised in the hospital setting.

5.4.2 Limitation of the Study

In evaluating for TB, GeneXpert alone may underestimate the prevalence of TB in the study population considering that there are other modalities for testing for TB including but not limited to microscopy using ZN staining technique, radiological diagnosis and sputum culture.

In this study, GeneXpert is a fully automated real-time semi-nested PCR assay endorsed as the most rapid test for diagnosis of pulmonary TB by WHO. It requires the production of sputum thus was not able to assess extrapulmonary tuberculosis and hence may have underestimated the prevalence of TB among patients with diabetes. Extrapulmonary tuberculosis (EPTB) represented 15% of the 6.3 million incident cases that were notified in 2016 by WHO. In Sub-Saharan Africa, North America and in Australia EPTB had exceeded 30% of all new and relapse tuberculosis cases in 2016 (Houda Ben et al., 2018)

In studying the prevalence of TB among diabetic patients it would have been important to measure the diabetic control of the diabetic patients which would disclose important information into the occurrence of TB Due to financial constraints, this study was not able to assess the diabetes control of the patients in this study.

CHAPTER SIX

6.0 CONCLUSSION AND RECOMMENDATION

6.1 Conclusion

The prevalence of TB among presumptive TB patients with DM was 16.7% (13, N=78) and the prevalence of GeneXpert positive TB among patients living with DM at Webuye County Hospital was 1.3% (13, N=975) which is higher than the WHO estimates of the burden of tuberculosis for Kenya for the year 2020 of 0.259%. However, this prevalence was comparatively lower than the prevalence of TB among patients with DM as compared to the WHO global estimate of the number of TB cases attributable to DM of 3.1%

This study found that male gender, smoking and asthma were factors associated with TB/DM co-morbidity. Other factors like age, sex, alcohol consumption, HIV infection, hypertension and COPD were not found to be significantly associated with TB/DM co-morbidity

6.2 Recommendation

With these findings, the study recommends that active case finding of TB among patients living with DM should be strengthened to reduce the risk of TB infection among patients living with DM

This study also recommends further studies on the prevalence of tuberculosis among patients with diabetes should be conducted.

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APPENDICES

Appendix 1: Informed Consent

ACTIVE CASE FINDING OF TUBERCULOSIS IN DIABETES PATIENTS ATTENDING DIABETIC CLINIC IN WEBUYE COUNTY HOSPITAL

Investigator: Dr Patrick K Rotich

What the study is about: You are being asked to take part in a research study. The purpose of this study is to assess the prevalence of TB and associated socio-demographic factors among patients with diabetes at Webuye County Hospital. You are being asked to take part since you have been enrolled at the diabetic outpatient clinic at Webuye County Hospital. Please read this form carefully (or it may be read to you) and ask any questions you may have before agreeing to take part in the study. You must be and adult above 18 years and have been enrolled to the diabetes clinic to take part in the study.

What we will ask you to do: If you agree to be in this study, we will conduct an interview with you. The interview will include questions about your age; level of education; cigarette and alcohol use; religion; residence; economic status and presence of other medical conditions. The interview will take about 10 minutes to complete. Participants who will present with signs and symptoms of TB will be asked to produce a sputum sample which will be taken for analysis (GeneXpert test) at the Hospital laboratory at no extra cost. The test results will be availed to the participant once they are ready. The procedure is risk free and does not involve drawing of blood. All findings of the test will be confidential and your participation will not be disclosed outside the research setting.

Risks and benefits: There is the risk that you may find some of the questions about Tuberculosis to be sensitive. Webuye County Hospital is a health facility offering tuberculosis diagnostic and treatment services and those with TB will be linked to the clinic for treatment and follow-up at no cost. This will inform the practice here so that the quality of services you get can be improved.

Compensation: There will be no compensation or cash benefits for participating in this study.

Your answers will be confidential. The records of this study will be kept private. In any sort of report we make public we will not include any information that will make it possible to identify you. Research records will be kept in a locked file; only the researchers will have access to the records.

Taking part is voluntary: Taking part in this study is completely voluntary. If you decline to take part in the study, it will not affect your current or future relationship with Webuye County Hospital. If you decide to take part, you are free to withdraw at any time.

If you have questions: The researcher conducting this study is Dr. Patrick Rotich. Please ask any questions you have now. If you have questions later, you may contact Dr. Patrick Rotich at pkbiomdo@gmail.com or at 0722231405. If you have any questions or concerns regarding your rights as a subject in this study, you may contact the Institutional Review and Ethics Committee (IREC) of Moi University at *IREC, Moi Teaching & Referral Hospital building, 2nd floor. Door No. 219, P.O. Box 3-30100, Eldoret, Kenya. Office line: 0787723677. Email: irec@mtrh.or.ke. Website: irec.or.ke*. You may also report your concerns or complaints anonymously through the above contacts for IREC. You will be given a copy of this form to keep for your records.

Statement of Consent: I have read the above information, or it has been read to me, and has received answers to any questions I asked. I consent voluntarily to participate as a participant in this research.

Your Name (printed) _____

Your Signature _____

Date _____

If unable to read and write

N.B.: A person able to read and write must sign as a witness (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are unable to read and write should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Appendix 2: Questionnaire

Date of Interview: ___/___/___

File No. :_____

Age: _____

Sex: Male [ ] Female [ ]

Section A: Other information from patient's file

Weight: _____Kg Height: _____cm BMI_____

Waist-to-Hip Ratio _____

SBP: _____ /DBP_____mmHg

HbA1c Results: _____% (Date done __/__/__)

Please tick in the box of the selected answer(s).

Section B: General and Demographic Questions

1. Marital status

   Single [ ] Married [ ] Divorced/separated [ ] Widowed [ ]

2. What is the highest level of education you have completed?

   No school [ ] Primary School [ ] Secondary school [ ]
   College [ ] University [ ]

3. Have you ever smoked a cigarette?

   Yes [ ] No [ ]

- If you answered ***Yes*** for the above question, please continue with the questions below

  a) On average how many cigarettes do you smoke per day

  Less than 5 [ ] 5-9 [ ] 10-14[ ] 15-24 [ ] more than 25[ ]

  b) How long have you smoked?

  Less than 1 year [ ] 1-2 years [ ] 2-5years [ ] 5-10 years [ ] More than 10 years [ ]

c) If you are an ex-smoker how long is it since you smoked a cigarette?

Less than 1 year [ ] 1-2 years [ ] 2-5 years [ ] 5-10 years [ ] More than 10 years [ ]

4. Do you consume alcohol?

Yes [ ] No [ ]

- If you answered ***Yes*** for the above question, please continue with the questions below

a) Which of the following do you drink?

Local brew (Busaa) [ ] Local brew (Changaa) [ ] Beer [ ]
Spirits [ ] Wine [ ]

b) How often do you drink?

Everyday [ ] 3-5 times a week [ ] once a week [ ] only on weekends [ ]

On special occasions [ ]

c) On a day when you have alcoholic drinks, how many drinks do you usually have?

1-2 [ ] 3-4 [ ] 5-6 [ ] 7-8 [ ] More than 8 [ ]

5. Do you have HIV/AIDS? Yes[ ] No[ ] Never been tested[ ]
6. Do you have Hypertension? Yes [ ] No [ ] Never been tested [ ]
7. Have you ever been told you have chronic obstructive pulmonary disease (COPD)? Yes [ ] No [ ] Never been tested [ ]
8. Have you ever been told you have Asthma? Yes [ ] No [ ] Never been tested [ ]
9. Have you ever been told you have heart disease? Yes [ ] No [ ]
   Never been tested [ ]

TB Screening Questions

1. Do you have a cough that has lasted more than 2 weeks?

   Yes [ ] No [ ]

   - If yes, for how long _____months and _____weeks
     Don't know [ ]

2. Have you ever coughed up blood in the last year?

   Yes [ ] No [ ]

   - If yes, how long ago did coughing up blood start: ___ months and _____weeks
     Don't know [ ]

3. Do you have fever that has lasted more than 3 weeks?

   Yes [ ] No [ ]

   - If yes for how long: _____month and _____weeks
     Don't know [ ]

4. Have you lost weight in the last year?

   Yes [ ] No [ ]

   - If yes, how long ago did weight loss start _____months and _____weeks
     Don't know [ ]

Additional TB questions

5. Do you have night sweats?

   Yes [ ] No [ ]

   - If yes, how long ago did night sweats start _____months and _____weeks

     Don't know [ ]

6. Do you get tired easily (fatigue)

   Yes [ ] No [ ]

   - If yes, how long ago did getting tired easily start _____months and _____weeks
     Don't know [ ]

7. Do you find you have breathlessness

Yes [ ] No [ ]

- If yes, how long ago did breathlessness start _____months and _____weeks

Don't know [ ]

8. Have you had chest pain

Yes [ ] No [ ]

- If yes, how long ago did chest pain start _____months and _____weeks

Don't know [ ]

If patient answers "No" to all questions do not collect sputum If suspect answered Yes to any question above, collect sputum

GeneXpert MTB/ RIF

Lab Serial Number

Spot Sputum

Collection Date ___/___/___

GeneXpert Results:

_____

Gene Xpert MTB/RIF Results Interpretation

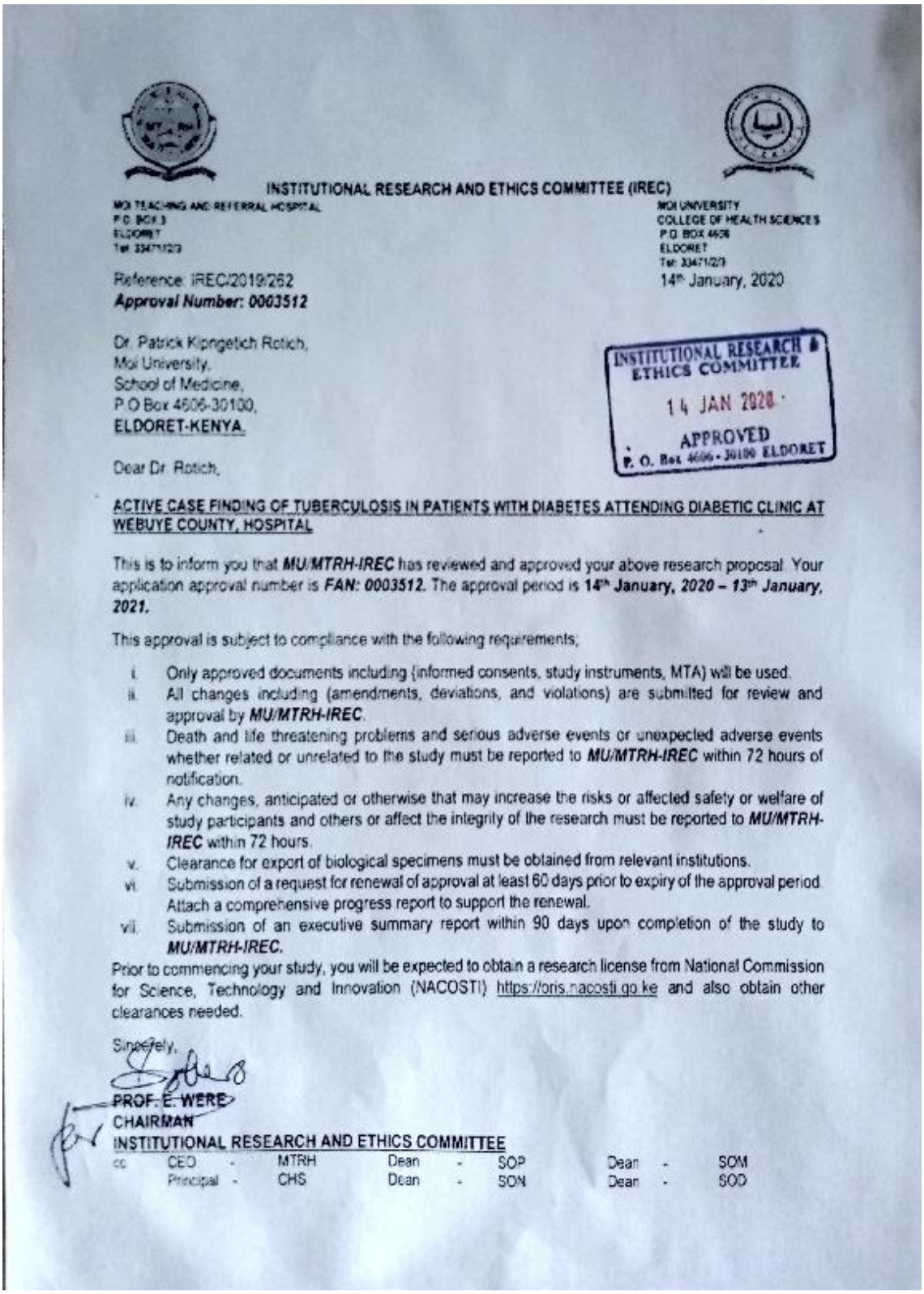
Negative	Reassess clinically for TB, consider Chest X-Ray
Positive	Diagnosis of TB: Begin anti-TB drugs
Other(circle one) Invalid / Error / No Result	Test inconclusive. Consult lab tech Consider collecting a new sample for Xpert evaluation

Chest X-ray: Normal /Suggestive

Date: __/__/__

Thank you very much for participating

Appendix 3: IREC Approval



INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2019/262
Approval Number: 0003512

14th January, 2020

Dr. Patrick Kipngetich Rotich,
Moi University,
School of Medicine,
P.O Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
14 JAN 2020
APPROVED
P. O. Box 4606 - 30100 ELDORET

Dear Dr. Rotich,

ACTIVE CASE FINDING OF TUBERCULOSIS IN PATIENTS WITH DIABETES ATTENDING DIABETIC CLINIC AT WEBUYE COUNTY, HOSPITAL

This is to inform you that ***MU/MTRH-IREC*** has reviewed and approved your above research proposal. Your application approval number is ***FAN: 0003512.*** The approval period is **14th January, *2020 – 13th January, 2021.***

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by ***MU/MTRH-IREC.***
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to ***MU/MTRH-IREC*** within 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to ***MU/MTRH-IREC*** within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to ***MU/MTRH-IREC.***

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://oris.nacosti.go.ke and also obtain other clearances needed.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix 4: Work Plan

WORK PLAN										
Year	2020			2021				2022		
month	10	11	12	1-3	3-6	6-9	9-12	1-3	3-6	6-9
Approval by IREC										
Sensitization of TB Clinic and Diabetic clinic staff										
Training of research assistants										
Pilot study										
Data Collection										
Data entry and analysis										
Manuscript for publication										
Defence										

Appendix 5: Estimated Budget

No	ITEMS	QUANTITY	COST per UNIT (Kshs)	TOTAL (Kshs)
	STATIONARY and EQUIPMENT			
1	Foolscap	2 reams	300	600
2	Printing papers	5 reams	450	2250
3	Ball points	2 packet	20	800
4	Pencils	5	20	100
5	Erasers	5 pieces	5	25
6	Note books	5	50	250
8	Pocket files	5	50	250
9	Staples	1 packet	200	200
	RESEARCH PROPOSAL DEVELOPMENT			
10	Printing of draft proposal	10 copies	500/copy	5000
11	Printing final proposal	7 copies	500/copy	3,500
12	Binding Research proposal	7 copies	200/copy	1,400
13	IREC FEE			2,000

	THESIS DEVELOPMENT			
14	Printing of draft thesis	10 copies	1000/copy	10,000
15	Binding thesis (hard cover)	7 copies	500/ copy	3,500
16	Photocopy schedule & consent	300pages	3/page	900
	FIELDWORK			
17	Research assistants training	2 people	20,000	20,000
	Research assistants' stipend	2 people	10000 * 2	20000
	Chest X-ray charges for those who cannot produce sputum	10	500*10	5000
	COMMUNICATION			
18	Phone, E-mail, and Internet searches	-	-	40,000
19	Consultancy (statistician)	-	-	30,000
20	Dissemination costs	-	-	20,000
	GRAND TOTAL			165,775

This Budget was funded by the principal investigator.