



PREVALENCE AND TREATMENT-RELATED OUTCOME OF HOSPITALIZED TYPE 2
DIABETES MELLITUS PATIENTS WITH COMORBIDITIES AT HELEN JOSEPH
ACADEMIC HOSPITAL IN JOHANNESBURG

By

Taoana Isaiah Makhabane

(1370887)

Research Report

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Supervisors: Dr Gary Gabriels

: Dr Sarentha Chetty

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DECLARATION

I, Taoana Isaiah Makhabane, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine- Pharmacotherapy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

A handwritten signature in black ink, appearing to read 'Taoana', written over a horizontal line.

28th Day of June 2023

ABSTRACT

BACKGROUND: Diabetic patients with comorbidities, have an increased risk of morbidity and mortality which leads to higher hospitalization and an overall increase in healthcare expenditure. Most of these patients, do not achieve the required glycaemic control (HbA1c <7%) even when they are on treatment.

Identification of comorbidities in T2DM patients will allow for more comprehensive care of these high-risk individuals. On admission to the hospital T2DM patients are often undertreated for their cardiovascular risk factors leading to higher hospitalization rates, and an overall increase in healthcare expenditure.

AIM: This study sought to investigate the control of modifiable risk factors in hospitalised T2DM patients, with and without comorbidities at Helen Joseph Academic Hospital.

METHOD: A retrospective chart review study which analysed 246 files of T2DM patients $\geq$ 18 years, admitted in 2019 at Helen Joseph Academic Hospital was conducted. Files were randomly selected from the files department at Helen Joseph Hospital. Data were summarized using descriptive statistics.

RESULTS: Two hundred and forty-six files of T2DM patients admitted in 2019, from Helen Joseph Academic Hospital with a mean (SD) age of 52 ± 13.4 years were investigated. In this cohort of patients, the comorbidity profile was found to be 73%, the majority of whom were female at 51%. Of the 73% of T2DM patients with comorbidities, 30% also presented with complications. The dominant concordant disease identified was hypertension, while the dominant discordant disease with the majority was HIV. The majority of T2DM patients (63%) were hospitalized, due to diabetes-related conditions with metformin being the most prescribed antidiabetic medication.

CONCLUSION: There is a high prevalence of comorbidity in T2DM patients who were hospitalized at Helen Joseph Hospital. The hospitalization reasons were found to be predominantly diabetic-related and required high care treatment. The HbA1c as a measure of glucose control over three months could not show any significant difference in patients with and without comorbidities. The BP was higher in T2DM patients with comorbidity than in those without. The majority of T2DM patients had diabetes related conditions as the reasons for their admission. Moreover, patients with comorbidities required high care and specialist services more often than those without.

Intensive screening of known concordant diseases like hypertension and cholesterol in T2DM patients on coming for their routine clinic visits could assist in early detection and prevention of worsening comorbidities and ultimately preventing unnecessary hospitalizations.

DEDICATION

I dedicate this research report to my daughter, Lebohang Makhabane. Your love and laughter kept pushing me even beyond my own limits.

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADA	AMERICAN Diabetes Association
ADDL	Amyloid Beta-Derived Diffusible Ligands
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
BMI	Body Mass Index
Bp	Blood Pressure
BSL 1	Blood Sugar Level on admission
BSL 2	Blood Sugar Level at discharge
CCF	Congestive Cardiac Failure
CHAT	Choline Acetyltransferase
CKD	Chronic Kidney Diseases
CKF	Chronic Kidney Failure
COPD	Chronic Obstructive Pulmonary Diseases
CRP	C - Reactive Proteins
CVDs	Cardio Vascular Diseases
DBP 1	Diastolic Blood Pressure on admission
DBP 2	Diastolic Blood Pressure at discharge
DISC1	Disrupted-in-Schizophrenia1
DM	Diabetes Mellitus

DNA	Deoxyribonucleic Acid
DVT	Deep Vein Thrombosis
FEV1	Forced Expiratory Volume
FVC	Forced Vital Capacity
HAART	Highly Active Antiretroviral Therapy
HbA1c	Glycated Haemoglobin
HCQ	Hydroxychloroquine
HCV	Hepatitis C Virus
HDL-C	High Density Lipoprotein - Cholesterol
HIV	Human Immuno-Deficiency Virus
HPAA	Hypothalamic–Pituitary-Adrenal-Axis
HREC	Human Research Ethics Committee
ICS	Inhaled Corticosteroids
ICU	Intensive Care Unit
IDE	Insulin-Degrading Enzyme
IGF-1	Insulin-Like Growth Factors
IL-6	Interleukin 6
IQR	Interquartile Range
LDL-C	Low Density Lipoprotein - Cholesterol
MDD	Major Depressive Disorder
MToP	Mammalian Target of Rapamycin

NO	Nitric Oxide
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
OGTT	Oral Glucose Tolerance Test
OS	Oxidative Stress
PEFR	Pulmonary Expiratory Flow Rate
PIs	Protease Inhibitors
PsA	Psoriatic Arthritis
PSMD9	Proteasome 26 Subunit, Non–ATPase 9
RA	Rheumatic Arthritis
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SARS–CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBP 1	Systolic Blood Pressure on admission
SBP 2	Systolic Blood Pressure at discharge
SCZ	Schizophrenia
SHBG	Sex Hormone-Binding Globulin
STGs	Standard Treatment Guidelines
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TAT	Trans-Activator of Transcription
TC	Total Cholesterol

TNF ALPHA	Tumour Necrosis Factor
UK	United Kingdom
USA	United States of America
VPR	Viral Protein R
WHO	World Health Organisation

CHAPTER ONE – INTRODUCTION

1.1 General Introduction

Diabetes mellitus (DM) is a metabolic chronic illness characterized by high random plasma glucose levels of ≥ 11.1 mmol/L or a fasting plasma glucose that is ≥ 7.0 mmol/L, (Sease & Shealy 2016). There are two types of DM (Type 1 and Type 2) (IDF 2023). Type 1 DM (T1DM), which is only responsible for 10% of all DM cases, is caused by the pancreas of the patient producing insufficient insulin. Type 2 DM (T2DM) which is responsible for 90% of all DM cases is characterised by insulin resistance and altered tissue sensitivity, resulting in some patients having normal insulin levels but manifesting with high blood glucose levels (International Diabetes Federation 2023).

Globally, it is estimated that 422 million people are currently living with T2DM according to the latest statistics in 2023 (World Health Organisation 2023). In South Africa, 4.2 million people are estimated to be living with diabetes as of December 2021 (International Diabetes Federation 2023).

Furthermore, it is projected that, by 2030, the number of cases worldwide will reach 570 million (WHO 2021). The main burden is in low and middle-income countries (WHO 2021). In South Africa, recent epidemiological prevalence data suggest that, of adults aged 20 – 79 years, 12.7% are living with T2DM (International Diabetes Federation 2023).

The best indicator of glycaemic control is the percentage of HbA1c taken over the last three months before a test is conducted (Sease & Shealy 2016). HbA1c levels higher than 7.5% are linked to an increased risk of microvascular complications (life-threatening diseases due to

uncontrolled diabetes) (Chiang *et al.*, 2020). This includes retinopathy, neuropathy, and nephropathy (Chiang *et al.*, 2020). The progression of these pathologies can be slowed by reducing blood glucose levels (Khadtare *et al.*, 2019).

Furthermore, it was estimated that 6.7 million people died from diabetes world-wide in 2021 and the majority of the deaths were due to cardiovascular complications (International Diabetes Federation 2023). Elevated cholesterol, high blood pressure and hyperglycaemia are modifiable risk factors, which impact both microvascular and macrovascular outcomes (Sease & Shealy, 2016; Ekoru *et al.*, 2019). Hypertension and hyperlipidaemia are both not adequately controlled in T2DM and are associated with an increased risk of cardiovascular morbidity and mortality (Meta-Cases *et al.*, 2019). Studies show that for T2DM there is a higher hospitalization rate for patients with comorbidities (presence of an additional one or more chronic diseases), than without comorbidities (Naidoo *et al.*, 2019). Common comorbidities associated with T2DM include cardiovascular diseases, arthritis, cancer, mental disorders, respiratory diseases and HIV (Chiang *et al.*, 2020). The comorbidities contribute to an increase in healthcare expenditure (Naidoo *et al.*, 2019).

1.2 Problem Statement

Recent South African studies by Naidoo *et al.* (2019) and Erzse *et al.* (2019), indicate that diabetic patients with comorbidities have prolonged hospital stays and increased healthcare costs compared to those without (Naidoo *et al.*, 2019; Erzse *et al.*, 2019).

It is thus possible that routine monitoring and management of the three critical cardiovascular modifiable risk factors: (i) elevated blood glucose, (ii) raised blood pressure, and (iii) high cholesterol in T2DM patients admitted to the hospital, for any health condition, may not be done to the same extent as T2DM patients at the community health facilities.

1.3 Significance of the study

The identification of comorbidities in T2DM patients will thus allow for more comprehensive care for these high-risk individuals. Furthermore, the extent to which cardiovascular risk factors are being monitored and controlled in hospitalized patients would indicate if the cardiovascular risk factors are receiving the required attention that they would normally secure in a community setting.

1.4 Research Question

Are T2DM patients with comorbidities, admitted at a public hospital, achieving the same control of their modifiable risk factors (elevated blood glucose, raised blood pressure and high cholesterol) as T2DM patients without comorbidities?

1.5 Aim

To investigate the control of modifiable risk factors in hospitalised T2DM patients, with and without comorbidities at Helen Joseph Academic Hospital.

1.6 Objectives

- To evaluate the prevalence of comorbidities in T2DM patients that have been hospitalised.
- To compare cardiac risk factors (blood glucose, blood pressure and cholesterol) in hospitalised T2DM patients with and without comorbidities.
- To compare the length of hospital stay, reasons for hospitalisations and levels of care received for patients with and without comorbidities.

- To assess adherence to the South African National Standard Treatment Guidelines in the treatment of T2DM patients and whether complications were present in patients with and without comorbidities.

1.7 Overview of the research report

Chapter one comprises of introduction, problem statement, significance of the study, research question, aim and objectives.

Chapter two comprises of the literature review which consists of introduction, and overview of how concordant and discordant chronic diseases affect the successful control of T2DM.

Chapter three comprises of the methodology which consists of study design and study site, study population, sample size calculation, study sample and sampling method, exclusion criteria, data collection, data management and analysis and ethics.

Chapter four comprises of the results. This includes an analysis of basic characteristics of study sample and their length of stay at the hospital in those with and without comorbidities, level of care in T2DM patients with and without comorbidities, whether the cardiovascular-risk factors identified were associated with comorbidities, prevalence of complications and comorbidities, reasons for admission and diabetic medications prescribed to patients in this study sample.

CHAPTER TWO - LITERATURE REVIEW

2.1 INTRODUCTION

Elderly diabetic patients more often than not, have one or more additional chronic conditions (Piette and Kerr, 2006; Meta-Cases *et al.*, 2019). It is important to treat these conditions effectively alongside their diabetes (Morley *et al.*, 2017). Poorly managed comorbidities could compromise the overall success of diabetes treatment (Morley *et al.*, 2017).

Furthermore, comorbidities in T2DM patients may hinder important medical services requirements such as screening, counselling and treatment due to exhaustive protocols involved in each condition (Piette and Kerr, 2006). It is important to manage diabetes well for optimal outcomes. Important aspects of diabetes management are patients' self-care and treatment adherence but some comorbid chronic conditions such as depression and dementia which affect mental health may cause patients to forget to take their medications (Morley *et al.*, 2017). Conditions such as arthritis and chronic low back pain affect a patient's mobility and dexterity and can make diabetes self-care challenging e.g. when needing to self-inject with insulin pens (Piette and Kerr, 2006; Chiang *et al.*, 2020).

Multiple comorbid conditions may also have an impact on the patient's self-care for diabetes since those conditions require additional time as well as multiple medications (Morley *et al.*, 2017; Aga *et al.*, 2019). Additionally, other clinically serious chronic comorbid diseases such as advanced lung cancer and advanced heart failure may compromise the management of diabetes as the treatment for these diseases may be intensive with the possibility of drug-drug and drug-disease interaction (Piette and Kerr, 2006)

These comorbid chronic conditions may affect patients who are unable to afford those additional costly treatments resulting in increased mortality. Therefore, a strengthened healthcare system

with adequate resources and proper management could assist (Piette and Kerr, 2006). In addition to cost, the presence of comorbidities is a major stumbling block in reaching desired therapeutic target goals in diabetes management which is a haemoglobin A1c (HbA1c) level of between 6.5% and 7% (Lang and Markovic, 2016). The added cost of treatment for patients with chronic illnesses uses a vast amount of the healthcare budget (Woodard *et al.*, 2011).

Specifically, in diabetic comorbidity, healthcare providers may intensively treat concordant diseases, such as high blood pressure and hyperlipidaemia which may help in reducing the spread of coronary heart diseases (Woodard *et al.*, 2011).

Additionally, medication adherence and frequent medical check-ups may play a mitigating role in the relationship between diabetic complications and improved patient care (Woodard *et al.*, 2011).

In a study conducted by Woodard *et al.* (2011) containing a cohort of 35,872 patients conducted in the United States of America, indicated that the appropriate recommended usage of primary and more complex specialized healthcare systems, results in a strengthened relationship between the patient and the healthcare worker. This in turn improves patient medication adherence and receipt of the accompanying health advice provided resulting in patients taking better care of themselves which plays a hugely positive role in the management of their diabetes (Woodard *et al.*, 2011). In elderly patients in particular, Vitry *et al.* (2010) in a retrospective cohort study on 20,134 Australian Veterans, maintained that holistic treatment of diabetes is lacking. He also outlined that a majority of chronic diseases are linked with slowing the progress of diabetes therapy due to factors such as frequent hospitalization (Vitry *et al.* 2010).

2.2 T2DM WITH CHRONIC COMORBIDITIES (CARDIOVASCULAR DISEASES, RESPIRATORY DISORDERS, HIV, ARTHRITIS, CANCER AND MENTAL HEALTH DISORDERS)

2.2.1 T2DM and Cardiovascular diseases

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality in T2DM patients (Tesfaye *et al.*, 2020). CVDs are more prevalent in T2DM because there is insufficient arterial blood circulation, poor cerebral hemodynamics and vascular derangements (Ruckert *et al.*, 2012). High mortality that is attributed to poorly controlled CVDs in T2DM patients results in microvascular illnesses (retinopathy, nephropathy and neuropathy) and macrovascular illnesses (coronary artery diseases and cerebrovascular accident), which results in poor prognosis, a burden to healthcare systems and untimely deaths in T2DM patients (Tesfaye *et al.*, 2012; Ruckert *et al.*, 2012).

T2DM complications combined with CVDs cause insulin resistance by forming atheroma plaque and causing hypertrophy leading to hyperglycaemia (Ruckert *et al.*, 2012). This makes it challenging for treatment to be optimized (Ruckert *et al.*, 2012).

In terms of treatment, suboptimal treatment of CVDs in T2DM patients leads to morbidity and mortality (Tesfaye *et al.*, 2020). Suboptimal treatment is not only attributed to poor medical management but also attributed to default on treatment by patients as well (Tesfaye *et al.*, 2020).

Furthermore, human factors such as inadequate health education, lack of patient self-motivation to implement lifestyle changes together with poor medication adherence due to polypharmacy, adverse drug events and forgetfulness contribute massively to uncontrollable CVDs in T2DM patients (Ruckert *et al.*, 2012).

Intensive management of CVDs in T2DM patients could help a great deal in improving the quality of life of T2DM patients with CVDs (Ruckert *et al.*, 2012; Ruckert *et al.*, 2015).

According to the American Diabetes Association, patients with diabetes and CVDs should have the following targets: blood pressure (BP) <140/90 mmHg and 1.15 – 1.4mmol/l, <2.6 mmol/l, <1.71 mmol/l for high-density lipoprotein cholesterol, low-level lipoprotein cholesterol and triglycerides respectively.

CVDs affect mostly elderly T2DM patients together with those who had lived with T2DM for ≥ 10 years (Ruckert *et al.*, 2015; Sharman and Bachmann. 2019). This happens particularly in patients that live in urban areas compared to those in rural areas (Colosia *et al.*, 2013). To achieve proper control of CVDs in T2DM patients, Sharman and Bachman (2019) in a study conducted in Kwazulu Natal, South Africa on 47,337 patients cohort, suggested that coordinated comorbid chronic illnesses management could be implemented within the healthcare system. T2DM+CVD patients should have full knowledge of their diseases as this is a crucial step in self-care (Sharman and Bachmann, 2019). Lifestyle changes and medication adherence is critical to successful treatment plans for such illnesses hence a need for strengthened health education (Colosia *et al.*, 2013; Sharman and Bachmann, 2019).

2.2.2 T2DM and Respiratory disorders

Patients living with T2DM have a higher chance of developing respiratory chronic illnesses such as asthma, lung injury, and chronic obstructive pulmonary disease (COPD) (Visca *et al.*, 2018; Khateeb *et al.*, 2019). George *et al.* (2018), in a qualitative study of 54,457 adults conducted in the USA, observed that the prevalence of respiratory disorders present in T2DM patients in the studies they conducted, from highest to lowest were: any respiratory diseases, followed by COPD, asthma and emphysema.

Men living with T2DM are at a higher risk than women living with T2DM of developing respiratory disorders (George *et al.*, 2018). Major risk factors for respiratory disorders in T2DM are smoking, lifestyle changes and high BMI (O'Byrne *et al.*, 2012; George *et al.*, 2018). The prevalence of respiratory diseases in T2DM patients, in particular, increases with increasing age and the severity of T2DM (O'Byrne *et al.*, 2012).

In T2DM patients who develop respiratory diseases due to obesity, the process happens via central fat deposition and prearrangement of genetics which then affects the lungs mechanically (Torres *et al.*, 2021). The associated link between obese patients with T2DM and asthma is that these patients are likely to have a low response to treatment, increased symptoms and poor quality of life in general (Forno 2017). However, diabetic patients can still be at risk of developing asthma regardless of obesity due to several other factors such as insulin resistance and metabolic syndrome (Forno, 2017).

In T2DM patients who had developed asthma, that asthma needs to be well controlled to avoid factors that may cause negative impact on the successful control of T2DM (Visca *et al.*, 2018). Sub-optimally controlled asthma requires greater usage of oral corticosteroids which elevates glucose levels and potentiates poorly controlled T2DM (Visca *et al.*, 2018). Insulin resistance in T2DM is associated with C-Reactive proteins (CRP), interleukin 6 (IL-6) and tumour necrosis factor (TNF alpha) which are also anti-inflammatory proteins released in COPD (Khateeb *et al.*, 2019; Torres *et al.*, 2021). In COPD, inhaled corticosteroids (ICS) are essential medications used in the management of COPD, especially for those patients with recurrent exacerbating COPD. Inhaled corticosteroids can increase glycated haemoglobin in T2DM (O'Byrne *et al.*, 2012; Torres *et al.*, 2021).

Uncontrolled T2DM leads to the development of diabetes complications, which then damage the large network of capillaries found in the lungs, thereby contributing to respiratory disorders (George *et al.*, 2018).

The respiratory disorder occurs when the parasympathetic branchiomotor tone is decreased, and the diameter of the basal airway is increased (Visca *et al.*, 2018). This causes bronchoconstriction, which then impairs autonomic ventilation control (Visca *et al.*, 2018).

Moreover, diabetes itself causes malfunction of the lungs by causing biochemical changes in the lungs' connective tissue (collagen and elastin components) (George *et al.*, 2018). This causes microangiopathy that occurs as a result of the glycosylation of proteins non-enzymatically due to hyperglycemia (Visca *et al.*, 2018). Microangiopathy leads to thickening of the walls of the alveolar in the basement making it hard for carbon monoxide to be released (Ehrlich *et al.*, 2010; Zineldin *et al.*, 2014; George *et al.*, 2018; Visca *et al.*, 2018).

Also, found particularly in diabetic patients, elevated blood glucose levels can cause pulmonary impairment leading to histopathologic lesions (Visca *et al.*, 2018). In patients living with T2DM, studies conducted by Zineldin *et al.* 2014, Forno *et al.* (2015) and George *et al.* (2018) show that lung functions such as forced vital capacity (FVC) and forced expiratory volume (FEV1) are decreased. This decrease potentiates the severity of respiratory diseases that therefore warrants the intensive use of corticosteroids (George *et al.*, 2018; Khateeb *et al.*, 2019). The use of corticosteroids in turn cause hyperglycaemia in diabetic patients, which decreases the immune system response in a patient whose immunity is already compromised (George *et al.*, 2018; Khateeb *et al.*, 2019).

Furthermore, when hyperglycaemia in T2DM is not well-controlled, increased protein turnover leads to a change in the metabolism of L arginine (Forno *et al.*, 2015). The lack of enough L arginine limits nitric oxide (NO) generation and availability (Gabriels, 2022).

NO plays several crucial physiological and pathophysiological functions in the human body (Gabriels, 2022). Among others, NO protects lung epithelial tissues from damage and in the absence of NO, airway exchange in the lungs is affected (Forno *et al.*, 2015). Therefore, insulin resistance which causes diabetes thus has a direct effect on asthma pathogenesis (Forno *et al.*, 2015).

2.2.3 T2DM and HIV

Some patients living with human immunodeficiency virus (HIV), and on highly active antiretroviral therapy (HAART), have been shown to have abnormal blood glucose levels (Ryan, 2010). The development of T2DM in HIV-infected patients has been associated with the use of HAART (Paik and Kotler, 2011; Khoza *et al.*, 2018). Abnormally elevated glucose levels lead to the development of T2DM in HIV co-infected patients leading to the development of conditions such as lipodystrophy, impaired carbohydrate metabolism, hypercholesteremia, hypertriglyceridemia and lactic acidosis. (Khoza *et al.*, 2018). These conditions are all risk factors for T2DM (Ryan, 2010).

Hence, T2DM prevalence escalates with the introduction of antiretroviral therapy (ART) in HIV-infected patients (Duncan *et al.*, 2018; Bam *et al.*, 2020). This occurs due to the development of glucose intolerance, which then causes hyperinsulinemia that leads to an abnormal fat distribution (Paik and Kotler, 2011). The abnormal fat distribution is a risk factor for T2DM (Paik and Kotler, 2011).

HAART treatment may also cause hyperinsulinemia (Bam *et al.*, 2020). Hyperinsulinemia develops about a year after patients have been initiated on a HAART regimen containing drugs such as nucleoside reverse transcriptase inhibitors (NRTIs) e.g. zidovudine and protease inhibitors (PIs) such as ritonavir (Paik and Kotler 2011; Karamchard *et al.*, 2016).

PIs cause insulin resistance precipitating the development of T2DM (Bam *et al.*, 2020). In addition, NRTIs like abacavir cause fat distribution leading to insulin resistance and the risk of developing T2DM (Ryan 2010; Paik et al 2011). Abnormal fat distribution contributes to a large extent to the development of abnormal fasting glucose levels, obesity and insulin resistance which are risk factors for T2DM (Visnegarwal *et al*, 2005; Ryan 2010).

The Hepatitis C virus (HCV) is the main cause of morbidity and mortality in HIV-infected patients (Visnegarwal *et al.*, 2005; Doyle *et al.*, 2016). This is because HCV is also associated with insulin resistance (Doyle *et al.*, 2016), and hence increases the prevalence of T2DM in HIV/HCV co-infected patients (Visnegarwal *et al.*, 2005).

HCV in addition to causing insulin resistance causes dyslipidaemia. The synergistic contribution of HIV and HCV to T2DM risk factors has been established to have an increased incidence of T2DM in patients with HIV+HCV than those with HIV alone (Paik and Kotler, 2011; Doyle *et al.*, 2016).

Inflammatory markers such as CRP, TNF and IL-6 which are known to be associated with insulin resistance are also highly prevalent in HIV-infected patients, especially in those who are not well-controlled (Rubin *et al*, 2020).

Commencement of HAART in HIV-infected patients leads to organ and immune system recovery which in turn causes insulin resistance due to an inflammatory response (Paik and Kotler, 2011). The work of Paik and Kotler, (2011) indicates that certain HIV accessory proteins such as *Trans-Activator of Transcription* (Tat) and *viral protein R* (Vpr) may inhibit the transcriptional activity of insulin thereby encouraging insulin resistance development.

NRTIs especially thymidine analogues in addition to inhibiting HIV reverse transcriptase, also inhibit DNA polymerase gamma which helps in mitochondrial replication, causing a dysfunctional mitochondrion associated with HIV (Paik and Kotler, 2011; Bam *et al.*, 2020).

Early diagnosis of DM in HIV-positive patients is important (American Diabetes Association, 2021). The American Diabetes Association (ADA) suggests that diagnosis of T2DM in HIV-infected patients, who are on ART, should be by oral glucose tolerance test (OGTT) not by the use of haemoglobin A1C (American Diabetes Association, 2021).

The basis for using OGTT is that ART has been shown to elevate the HbA1c percentage and can overestimate the actual level of glycaemia (American Diabetes Association, 2021). Furthermore, ADA also advises that the management of T2DM in HIV-infected patients should be by encouraging non-pharmacological management such as lifestyle modification through regular exercise and having a healthy diet (American Diabetes Association, 2021).

One of the major stumbling blocks in achieving desired treatment goals in HIV/diabetic co-infected patients as stated by Pillay, (2020) is that of defaulting treatment. Reasons for defaulters are forgetfulness, discrimination and the socioeconomic status of such patients (Pillay, 2020). Furthermore, a major consideration that encourages treatment default relates to poor healthcare systems that cause long patient waiting times, overcrowding and fear of being scolded (Pillay, 2020).

T2DM patients living with HIV are at higher risk of hospitalization and mortality due to the development of complications emanating from untreated diseases (T2DM + HIV) (Palacios *et al.*, 2006).

Patients who are treated with ART develop T2DM, irrespective of family history of having T2DM (Khoza *et al.*, 2018). Insulin resistance is the first step that indicates a T2DM development in

HIV-infected patients on ART, due to weight gain which impairs glucose metabolism (Paik and Kotler, 2011).

Whilst the introduction of HAART to HIV-infected patients has played a major role in reducing morbidity and mortality, there is a risk of the development of T2DM associated with the use of ARV drugs (Duncan *et al.*, 2018; Bam *et al.*, 2020). This requires that healthcare providers regularly assess patients for T2DM, and initiate treatment when required. This would avoid the development of complications, frequent hospitalizations and increased mortality (Bam *et al.*, 2020).

The pharmaco-therapeutic approach in T2DM+HIV patients should be done with caution to avoid drug-drug interactions (Kalra *et al.*, 2011). In particular whilst metformin is the drug of choice in managing T2DM, this drug interacts with NRTIs like stavudine and zidovudine by potentiating fat deposition, insulin resistance and lactic acidosis (Kalra *et al.*, 2011).

The symptoms of lactic acidosis, which include fatigue, weight loss, nausea, stomach pain, dyspnoea, and arrhythmia, should be explained to HIV patients taking metformin (Schambelan *et al.*, 2002). Patients should be advised to immediately report these symptoms to healthcare workers (Schambelan *et al.*, 2002). The research by Feigenbaum and Longstaff, 2010 explains that insulin is much more tolerable in people living with HIV as insulin has fewer drug interactions with ARVs, and is thus recommended for use, as the drug of first choice in T2DM+HIV (Feigenbaum and Longstaff, 2010).

2.2.4 T2DM and Arthritis

Arthritic diseases like Psoriatic arthritis (PsA) and Rheumatic arthritis (RA) have a high prevalence of T2DM in patients (Dal Bello *et al.*, 2020; Solomon *et al.*, 2010). This is due to factors such as severe pain, inflammation, inflexibility of the joints, and lack of physical activity (Tian *et al.*, 2021).

More women than men living with PsA and RA have T2DM. The reason for this is unknown (Dal Bello *et al.*, 2020; Dreier *et al.*, 2013). In both sexes (men and women), the prevalence of T2DM in patients with PsA and RA increases with an increase in age (40-60 years) and duration of arthritis (>5-10years) (Su *et al.*, 2013; Dal Bello *et al.*, 2020; Dreier *et al.*, 2013).

The pathophysiological view of T2DM in PsA and RA patients is attributed to inflammation of the skin and joints (Dubrenil *et al.*, 2014; Dal Bello *et al.*, 2020). Inflammation increases the levels of inflammatory factors such as TNF- α and IL-6 which then cause insulin resistance, dyslipidaemia and later development of T2DM (Dubrenil *et al.*, 2014).

Glucocorticoids are an integral part of arthritis treatment (Korman. 2020). Moreover, most PsA and RA patients are treated with glucocorticoids, such as prednisolone during their pre-diabetic phase (Dal Bello *et al.*, 2020). Glucocorticoids promote gluconeogenesis while on the other hand, antagonising insulin actions thereby causing hyperglycaemia (Dal Bello *et al.*, 2020).

Glucose regulatory hormones like omentin and adiponectin which normally sensitize insulin, are reduced in PsA patients leading to higher blood glucose than normal (fasting blood glucose >7.8mmol/L) (Dal Bello *et al.*, 2020).

In T2DM + arthritis patients, cardiovascular diseases are the leading cause of morbidity and mortality due to the complexity of treatment of this type of comorbidity (Baghadi, 2020; Su *et al.*, 2013). Inflammation in PsA and RA is related to insulin resistance, dyslipidemia and possibly

hypertension which then promote poor prognosis of arthritic patients living with T2DM (Solomon *et al.*, 2010). Of equal importance, T2DM is exacerbated by risk factors such as obesity and lifestyle practices (smoking, alcohol use and unhealthy diets) in arthritic patients (Baghadi, 2020).

Obesity is the most prevalent in RA patients and has been singled out as the most metabolic condition causing T2DM (Dubrenil *et al.*, 2014). Body Mass Index (BMI) and obesity were found to be higher in PsA than in RA patients (Dubrenil *et al.*, 2014). This in part explains the higher prevalence of T2DM in patients with PsA than in RA (Dubrenil *et al.*, 2014).

Anti- TNF- α drugs such as infliximab and anti-IL-6 drugs such as sarilumab are used in the treatment of arthritis (Dal Bello *et al.*, 2020; Chen *et al.*, 2017). These drugs can provide a balance between treatment and insulin resistance (Dal Bello *et al.*, 2020; Chen *et al.*, 2017). The use of methotrexate for the treatment of arthritis decreases the chances of developing T2DM in patients with arthritis and improves prognosis in those patients with arthritis + T2DM (Chen *et al.*, 2018; Baghadi, 2020).

This was confirmed by unchanged glucose profiles after six months of treatment with leflunomide in in-vivo done in China and America (Chen *et al.*, 2018). The researcher however cautions that lower doses of methotrexate should be used as it has the potential of causing liver diseases in T2DM patients (Chen *et al.*, 2018). The risk-benefit use of methotrexate in controlling arthritis in T2DM is that it also has a cardio-protective effect (Baghadi, 2020).

An alternative approach to arthritis treatment is to use leflunomide, which is a pyrimidine synthesis inhibitor used in PsA and RA (Chen *et al.*, 2017; Chen *et al.*, 2018). Leflunomide has been found to control hyperglycemia and increase insulin sensitivity (Chen *et al.*, 2017; Chen *et al.*, 2018). Furthermore, hydroxychloroquine (HCQ) in PsA and RA patients with T2DM increases insulin tolerability and decreases the incidences of hyperglycemia (Dessein *et al.*,

2003). HCQ is also beneficial in patients with dyslipidemia which is a prevalent chronic disease in T2DM patients (Chen *et al.*, 2017).

2.2.5 T2DM and Cancer

Several studies have discovered that there is a significant prevalence of cancer in T2DM patients (Zhu *et al.*, 2013; Ma *et al.*, 2018; Wang *et al.*, 2020). The most common types of cancers found in T2DM patients are rectal, colon, pancreas, bladder, kidneys and liver cancer (Zhu *et al.*, 2013; Ma *et al.*, 2018; Wang *et al.*, 2020). In most cases, the risk of developing cancer in T2DM patients increases with age and the duration of T2DM (Pan *et al.*, 2020).

There is a direct link between T2DM and cancer pathogenesis (Sciacca *et al.*, 2013). Insulin has been linked as the major promoter of cancer (Pan *et al.*, 2020). T2DM is known for insulin resistance, and eventually hyperinsulinemia (Fang *et al.*, 2013; Lee *et al.*, 2020). This occurs as a result of insulin receptors being expressed by most cancer cells hence hyperinsulinemia activates carcinogenesis (Fang *et al.*, 2013; Lee *et al.*, 2020).

Insulin levels lower the concentration of insulin-like growth factors (IGF-1) receptors and eventually elevate the concentration of bioactive IGF-1 (Fang *et al.*, 2013; Zhu *et al.*, 2013). IGF-1 has a mitogenic and anti-apoptotic characteristics and could function as an activator for increased pre-neoplastic and neoplastic cells (Fang *et al.*, 2013; Maskarinec *et al.*, 2019; Lee *et al.*, 2020). Glucose metabolism could lead to tumour initiation (Zhao and Ren, 2016).

Tumour initiation and progression are also associated with oxidative stress provoked by altered glucose metabolism and chronic inflammatory promoters' conditions (Zhao and Ren, 2016). For instance, inflammatory promoters like IL-6 stimulate nuclear factor-KB and elevate cyclin D1, developing tumour initiation and progression at the end (Wang *et al.*, 2020).

TNF- α is known as a vital mediator of anti-tumour immune responses (Wang *et al.*, 2020). However, chronic exposure to TNF- α can stimulate a series of signalling pathways such as nuclear factor-KB, Jun kinases, and mitogen-activated kinases (Wang *et al.*, 2020). These signalling pathways inhibit controlled cell division, consequently speeding up cancer cell growth and metastasis in the end (Wang *et al.*, 2020).

Uncontrolled sex hormones (oestrogens and androgens) levels can also encourage the development of cancer (Calip *et al.*, 2015). Sex hormone-binding globulin (SHBG) and albumin can bind to floating sex hormones to control their concentration and bioavailability (Calip *et al.*, 2015; Wang *et al.*, 2020). Nonetheless, hyperglycaemia and insulin decrease the amount of free SHBG thereby affecting glucose homeostasis (Calip *et al.*, 2015; Wang *et al.*, 2020).

Consequently, elevated sex hormone levels increase the chance of prostate, breast, and endometrial cancers (Calip *et al.*, 2015; Wang *et al.*, 2020).

A high level of glucose as is the case in poorly controlled T2DM provides a favourable environment for cancer cells to thrive and grow (Wang *et al.*, 2020). Hyperglycaemia also speeds up the dysfunction of mitochondria and the development of free radicals together with other reactive molecules like reactive oxygen species (ROS) (Wang *et al.*, 2020). The presence of free radicals and ROS lead to the generation of advanced glycation end products which activates the protein kinase C isomer that then stimulates genetic mutation and metastasizes the tumour (Wang *et al.*, 2020).

Furthermore, hyperglycaemia in T2DM may interfere with ascorbic acid's effects on intracellular metabolism (Ma *et al.*, 2018). This effect decreases ascorbic acid's efficacy in the immune system and controls the number of reactive oxygen species which then potentiate the development of cancer and growth in T2DM patients (Ma *et al.*, 2018).

The risk of cancer in T2DM is further brought about by a group of metabolic risk factors and other factors, such as insulin resistance, some glucose-lowering drugs, hormonal dysregulation, hyperglycaemia, dyslipidaemia and inflammation which changes the renin-angiotensin system leading to carcinogens (Yang and Wang, 2019; Pan *et al.*, 2020).

In addition, diabetes and cancer share common behavioural risk factors such as poor diet, lack of exercise leading to obesity ($\geq 30\text{kg/m}^2$), cigarette smoking and excessive use of alcohol (Maskarinec *et al.*, 2019; Lee *et al.*, 2020).

T2DM is, specifically, linked to breast cancer in two ways: (i) due to the direct influence of high concentrations of insulin on breast tissue and (ii) as a consequence of the influence of insulin on increasing sex steroids because of prevention of SHBG, high IGF-1 concentration release and disturbance of adipokines (Calip *et al.*, 2015). Hence worldwide, results show a higher morbidity and mortality in T2DM + cancer, than in those patients with T2DM or cancer alone (Zhao and Ren, 2016).

As an example, where there is synergistic activity of both oestrogen and IGF-1, this may result in increased breast cancer cell multiplication and consequently leads to high mortality in patients living with T2DM (Luo *et al.*, 2015; Lee *et al.*, 2020).

For patients with T2DM + Cancer, the work of Srokowski *et al.*, (2009) provides reasons why a high mortality rate is observed in this group. Srokowski *et al.*, (2009) indicate that cancer patients with T2DM are managed less robustly with chemotherapy and radiotherapy, and hence have a poor prognosis compared, to those with either of these conditions alone. Furthermore, patients with comorbid cancer and T2DM usually have poor tolerance to cancer therapy as well as high infection rate and intraoperative-related mortality (Srokowski *et al.*, 2009).

Those patients having a low immune system due to T2DM may further be compromised by accelerated cancerous cell growth (Tao *et al.*, 2020).

T2DM and cancer comorbidity also leads to high complications (Stein *et al.*, 2010; Luo *et al.*, 2014). To further illustrate the complication in this specific comorbidity, complications in T2DM + colorectal cancer include stomatitis, infection, leukopenia, high postoperative hepatic decompensation, myocardial infarction and anastomotic complications on top of the normal complications of T2DM alone (Stein *et al.*, 2010; Luo *et al.*, 2014). These complications lead to poor prognosis, higher hospitalization, and ultimately death (Stein *et al.*, 2010; Luo *et al.*, 2014).

Unlike sulphonylureas and insulin, which increase plasma insulin, metformin is the preferred drug for controlling T2DM in the case of comorbid cancer (Zhu *et al.*, 2013). Metformin stimulates adenosine monophosphate-activated protein kinase (AMPK) which then halts various tumour-generating metabolic pathways such as releasing anticancer activities through the suppression of mammalian target of rapamycin (MTorP) pathway that is crucial in interrupting cancer cell multiplication and growth (Calip *et al.*, 2015; Lee *et al.*, 2020). Baur *et al.*, (2011) claim that metformin has anti-inflammatory and antioxidant characteristics which are important in lowering the risks of cancer development in T2DM patients.

Thus, T2DM patients with a concurrent comorbidity of cancer generally have a poor quality of life due to the burden and aggressiveness of these conditions (Bowker *et al.*, 2006). A clear knowledge of the link between T2DM and cancer together with their related comorbidities and complications may have crucial guidance for the treatment and suppression of these chronic conditions (Bowker *et al.*, 2006).

Hence, the belief that treatment and suppression plans ultimately have an improved positive benefit on health-related quality of life in patients living with these conditions concurrently (Bowker *et al.*, 2006).

2.2.6 T2DM and Mental Health Disorders

Patients with schizophrenia (SCZ) have increased incidences of prediabetes risk factors such as unhealthy dietary practices, lack of physical exercise, obesity, high levels of fasting blood glucose and insulin resistance consequently predisposing them to develop T2DM (Mamakou *et al.*, 2018).

Additionally, genetic risk factors such as transcription factor 7- like 2 (TCF7L2) together with proteasome 26 subunit, non-ATPase 9 (PSMD9) and environmental risk factors such as prenatal famine independently influence morbidity and mortality in T2DM and SCZ patients (Postolache *et al.*, 2019).

Specifically, a gene disrupted-in-schizophrenia1 (Disc1) which causes mental illnesses also interferes with beta cell function in the pancreas, leading to low beta cell multiplication which then influences abnormal cell growth and indirectly causes hyperglycaemia leading to T2DM (Jurczyk *et al.*, 2016).

Adherence to T2DM+SCZ medications is vital in achieving set pharmacotherapy goals in T2DM+SCZ patients (Kreyenbuhl *et al.*, 2010). Several patients fail in adherence due to the intensity of the disease state, polypharmacy, and often severe adverse effects leading to higher chances of hospitalization, and poor prognosis (Kreyenbuhl *et al.*, 2010; Mamakou *et al.*, 2018).

SCZ itself is a limiting factor and often has negative effects on several aspects including the patients' ability to function well, the patients' quality of life and daily self-care requirements such as exercising, confusing medication frequency and identity (Kreyenbuhl *et al.*, 2010). This leads to an overall high percentage of treatment non-adherences in these patients (Kreyenbuhl *et al.*, 2010).

For major depressive disorder (MDD), the prevalence is estimated to be around 20-25% and in patients with T2DM, this is almost doubled, compared to individuals who only have MDD (Wu *et al.*, 2020). Various pathways are associated with MDD, which if tempered lead to T2DM development (Postolache *et al.*, 2019). As an example, hypothalamic–pituitary-adrenal-axis (HPAA) and erotogenic systems have a vital role in both MDD and T2DM as these two conditions are both linked to HPAA impairment, causing weight gain, insulin resistance and hypocortisolaemia (Wu *et al.*, 2019).

MDD also leads to insomnia thereby disturbing the circadian rhythm which then also causes insulin resistance due to weight gain (Nechita *et al.*, 2015). High levels of inflammatory markers and cytokines, increase T2DM risk (Hajebrahimi *et al.*, 2016). Normal gut flora and a healthy diet, contribute significantly to T2DM and MDD. This is because if they are tempered, they affect immune stimulation and inflammatory reaction, which are implicated in the pathophysiology of metabolic disorders and depression (Slyepchenko *et al.*, 2017).

Comorbidity of T2DM and MDD exceptionally weaken the quality of life, and is linked with morbidity and mortality due to less adherence, increased complications, disability (unable to take medications on their own), and lower production capabilities (Reus *et al.*, 2017).

Genetic crossing in T2DM and MDD has been shown (Kavanagh *et al.*, 2015). As an example, the 12q24 locus is associated with T2DM and MDD as well as dyslipidaemia, obesity, stroke and early signs of retinopathy while a gene like a protease 26 subunit non-ATPase 9 (PSMD9) also causes MDD (Postolache *et al.*, 2019). This perspective is provided with evidence of more complications and mortality rates associated with patients living with T2DM + MDD (Pan *et al.*, 2011; Deschenes *et al.*, 2017; Wu *et al.*, 2020).

Complications are due to mismanagement of the diseases and poor adherence to treatment and unhealthy lifestyle practices in T2DM+MDD patients (Domingo *et al.*, 2015; Deschenes *et al.*,

2018). Hence T2DM patients should be regularly screened for MDD, as the detection of the condition early on, would help in proper management, thereby improving the prognosis and quality of patients' lives (Lankarai and Assari, 2015; Deschenes *et al.*, 2018).

There are many factors linking T2DM to epilepsy (Shlobin and Sander, 2020). One example is obesity, which is highly linked with epilepsy, and is also a known risk element for T2DM (Tedruss *et al.*, 2018). In obese individuals, there is a high release of glycerol, hormones, pro-inflammatory cytokines and non-esterified fatty acids (Shlobi and Sander, 2020). The consequence of these elements is to lessen the reaction of tissues to insulin, leading to T2DM development (Guilhereme *et al.*, 2008).

Anti-seizure medications have also been shown to contribute to T2DM development (Shlobi and Sander, 2020). Valproic acid, which is an enzyme inhibitor in the management of epilepsy, is linked with weight gain, obesity and hyperinsulinemia and ultimately T2DM (Shlobi and Sander *et al.*, 2020). Epilepsy causes mitochondrial dysfunction (Shlobi and Sander *et al.*, 2020). Dysfunctional mitochondria are associated with obesity, impairment of beta cells in the pancreas and insulin resistance leading to the development of T2DM (Lu *et al.*, 2018; Shlobin and Sander, 2020).

In a large population study conducted in the Netherlands, UK, Korea, Sweden and the USA for Alzheimer's disease (AD), the authors conclude that there is a significant number of T2DM patients with Alzheimer's disease (Meng *et al.*, 2020). T2DM and AD share the same pathophysiological factors (Silzer and Philips, 2018). There are various explanations for the shared pathophysiology between T2DM and AD (Silzer and Philips, 2018). This is due to mitochondria causing glucose-stimulated insulin production from the beta cells of the pancreas (Meng *et al.*, 2020). T2DM and obesity produce high levels of harmful lipids thereby damaging

the mitochondria due to the increased release of calcium from the endoplasmic reticulum (Cárdenas-Pérez and Camacho, 2016).

Mitochondrial dysfunction leads to the production of high levels of reactive oxygen or nitrogen species (ROS/RNS) (Carvalho *et al.*, 2015; Zilliox *et al.*, 2016). Normal ROS/RNS levels in the human body have an important contribution to increasing insulin sensitivity in the periphery, however, an impairment in the ROS/RNS levels leads to oxidative stress (OS) in the brain which is involved in the pathology of T2DM and AD (Butterfield *et al.*, 2014; Silzer and Philips, 2018).

OS interfere with the blood-brain barrier leading to vascular leakage, neuronal inflammation and damage to the neurons in the brain and less sensitivity to insulin hence the development of T2DM and AD (Mittal and Katare, 2016; Chen *et al.*, 2019). Hyperglycaemia also leads to damage to brain insulin receptors leading to deprivation of energy to brain cells increasing the risk for AD (Chen *et al.*, 2019).

Another mechanism involves choline acetyltransferase (ChAT) which is stimulated by insulin and IGF-1 receptors (Monte *et al.*, 2006). Insulin and IGF-1 resistance which is common in T2DM leads to low levels of ChAT resulting in brain plasticity and diminished cognition (Monte *et al.*, 2006). Additionally, insulin resistance in T2DM leads to increased inflammatory markers levels such as IL-6, C-reactive protein and 1-antichymotrypsin resulting in impaired immune response and hence the development of AD (Mushtaq *et al.*, 2015).

Moreover, advanced glycated end products (AGEs) levels are increased in T2DM patients causing increased levels of amyloid beta plaques and neurofibrillary tangles which interfere with memory, and other cognitive functions, hence the development of AD (Takeuchi and Yamagishi, 2008). Amyloid beta is involved in normal neural growth and repair (Miguel-Yanes *et al.*, 2018). However, in T2DM there is hyperglycaemia and increased ApoE4 genes which increase plasma lipids consequently increasing amyloid plaques on the surface of the brain that combines with

tau protein to form neurofibrillary tangles that affect the normal functioning of the memory and cognitive capabilities leading to AD (Mittal and Katare, 2016; Tang *et al.*, 2019).

Furthermore, the insulin-degrading enzyme (IDE) helps in the clearance of amyloid beta plaques, from the brain (Craft *et al.*, 2004), however, IDE has a higher affinity to insulin than beta plaques causing the accumulation of amyloid beta plaques (Craft *et al.*, 2004). Amyloid beta-derived diffusible ligands (ADDL) influence the lack of insulin resistance in the brain (Felice *et al.*, 2008). This causes memory loss by obstructing the mechanisms involved in the formation of memory as they change the insulin receptors' shape thus causing insulin inhibition which is sometimes referred to as brain diabetes (Felice *et al.*, 2008).

2.3 COMPLICATIONS OF UNCONTROLLED T2DM

Diabetic microvascular complications include retinopathy, neuropathy and nephropathy (Ekoru *et al.*, 2019). Diabetic macrovascular complications are hypertension, hyperlipidaemia and stroke (Ekoru *et al.*, 2019; Chisholm-Burns *et al.*, (2016).

Retinopathy is a microvascular complication that damages the peripheral retina and macula in T2DM patients, consequently, the patient may have visual impairment as well as blindness (Cade, (2008)).

Hyperglycaemia due to poor diabetic control leads to severe smooth muscle contraction of the retina thereupon, causing vitreous haemorrhage and retinal detachment (Cole and Florez, 2020). Vision is lost due to retinal vessel leakage and resulting in macula oedema (Cade, 2008; Lotfy *et al.*, 2015).

Diabetic neuropathy is the damage of nerves due to uncontrolled blood glucose levels which often causes foot damage, consequently leading to amputation if not detected and managed early (Cole and Florez, 2020). One of the major microvascular complications in T2DM patients

is nephropathy, manifesting as microalbuminuria or macro albuminuria, which is damage to kidney vessels affected by hyperglycaemia thereby causing chronic kidney diseases (CKD) (Zhuang *et al.*, 2020). Zhuang *et al.* (2020) maintain that suboptimal management of CKD gives rise to complete damage of the kidneys in T2DM, which demands that patients undergo dialysis; a process that is costly and has a poor prognosis in these patients.

CHAPTER THREE - METHODOLOGY

3.1 Study design and study site:

This was a quantitative study based on a retrospective record review. The study was conducted at Helen Joseph Academic Hospital, where inpatient records were reviewed. Helen Joseph Academic Hospital is one of the largest tertiary academic Hospitals in Johannesburg, Gauteng Province, South Africa. The hospital has a 636 bed capacity and provides tertiary services and specialized clinics services such as oncology, HIV, breast, pain and endocrinology clinics.

3.2 Study population:

T2DM patients, aged 18 years or older, that were admitted to Helen Joseph Academic Hospital from 1st January 2019 to 31st December 2019 were included in the study. The year 2019 was chosen as patients admitted in 2020/21, could have been affected by SARS-CoV-2 (Coetzee *et al.* 2020), which could be a potential confounder in this study.

3.3 Sample size calculation:

The sample size was calculated using the formula: $n = \frac{Z^2 P(1-P)}{d^2}$

Where n = sample size, Z = standard normal variate at 5% error at a 95% confidence interval. P values were regarded as statistically significant when they are less than 0.05 therefore 1.96 is utilized in the formula (Charan & Biswas 2013). P = anticipated prevalence from previous similar studies of which an average prevalence of 20% was calculated from a study by Naidoo *et al* (2019) which found the prevalence of 20% of T2DM patients having comorbidities. (Pourhoseingholi *et al.* 2013).

Therefore, $n = \frac{1.96^2 \times 0.20 \times (1-0.20)}{(0.05)^2} = 246$ files evaluated.

3.4 Study sample and sampling method:

Two hundred and forty-six (246) patients' records were included. Patients' files were identified from the in-patient records department, using systematic sampling. Starting with the first identified patient in 2019; every second file was selected thereafter. In the case where the required data was not recorded in the patient file, that file was excluded and the next sequential file was selected until the total number of required files was attained.

3.5 Exclusion criteria:

The study excluded pregnant women (gestational diabetes) together with data on patients readmitted in 2019, (i.e., only records for the first admission in 2019 was included).

3.6 Data collection:

The data from each patient record was transcribed onto the data collection form as presented in Appendix A.

This form consisted of two sections. Section 1 (demographics and characteristics). Demographics include: age, sex, weight, height, length of hospital stay, BMI and waist circumference. Characteristics include: a reason for admission, level of care (ICU, high care, specialist care, normal care (general), previous hospitalization and the number of admissions, and hospitalization outcome (discharged, death, referral).

Section 2 consisted of clinical indicators, diabetic management history, diabetic complications, and comorbidities. Clinical indicators include: fasting/random blood glucose (mmol/l), blood pressure (mmHg), HbA1c (%), total cholesterol (mg/dl), triglycerides (mg/dl), high-density lipoprotein (HDL-C) (mg/dl), low-density lipoprotein (LDL-C) (mg/dl). Diabetic management history variables include: the date of first diagnosis for T2DM, prescribed T2DM medication used up to 6 months before hospitalization, prescribed T2DM medication on admission,

prescribed T2DM medication used in hospital, prescribed T2DM medication on discharge, prescribed medication for all other conditions, except T2DM and history of cardiovascular procedures (stenting and coronary artery bypass grafting (CABG)).

Diabetic complications such as retinopathy, nephropathy, neuropathy, gastroparesis, and amputations (peripheral vascular disease) were included. The following comorbidities were included: hypertension, hyperlipidaemia, coronary artery disease, hypothyroidism, glaucoma, dysrhythmia, cardiac failure, chronic kidney failure disease, stroke, and deep vein thrombosis, asthma, chronic obstructive pulmonary diseases (COPD), HIV, cancer, major depressive disorder (MDD), schizophrenia, bipolar, anxiety, epilepsy, Parkinson's disease, Alzheimer's diseases, rheumatoid arthritis and other arthropathies.

3.7 Data management and analysis:

Data was collected, transcribed into an Excel version 2019 spreadsheet and analysed with Statistica version 14.0. Data is presented as follows: Continuous variables are presented as means and standard deviations (SD), and categorical variables are presented as frequencies and percentages. To compare variables between two groups (T2DM with comorbidities and T2DM without comorbidities) the *t*-test was used where data was normally distributed and the Mann-Whitney U test was used where data was not normally distributed.

To measure objectives, comparing co-morbidities (and their prevalence) in T2DM patients that have been hospitalised, percentages of comorbidities were analysed together with the percentage of each comorbidity present. To compare cardiac risk factors (blood glucose, blood pressure and cholesterol) in hospitalised T2DM patients with and without comorbidities, the *p* values of each of the risk factors were used to establish any statistical significance concerning T2DM patients with and without comorbidities. To compare the length of hospital stay, the mean and standard deviation were used and compared in T2DM patients with and without comorbidities. Reasons for hospitalisations were measured using the percentage of whether the

disease that led to admission was related to diabetes or not while levels of care received for patients with and without comorbidities were measured using percentages of patients cared under different levels (ICU, high care, specialist care and normal care).

To assess adherence to the South African National Standard Treatment Guidelines 2019 in the treatment of T2DM patients, diabetes medications prescribed were assessed to see if they were prescribed in line with the guideline.

3.8 Ethics

The study involved access to patients' files from Helen Joseph Academic Hospital. An ethical clearance certificate with reference number M210814 (Appendix C) was obtained from the human research ethics committee (HREC) (University of Witwatersrand). Permission to carry out the study was obtained from the CEO of the hospital. Patients' confidentiality was protected by the exclusion of any identifiable characteristics and the allocation of a participant study number to each data collection form (Protection of Personal Information Act no.4. 2013 s. 19 of South Africa). No identifiable information was therefore included in the research report. The raw data will be destroyed within a reasonable time (up to 5 years) following data analysis and completion of this research report, unless otherwise required by law for it to be retained (Protection of Personal Information Act no.4. 2013 s. 14).

CHAPTER FOUR - RESULTS

4. Results

Two hundred and forty-six (246) T2DM patients with a mean (SD) age of 52 ± 13.4 were identified. The majority (126, 51%) were females. The mean ($\pm$ SD) of blood sugar levels, blood pressure glycated haemoglobin and cholesterol levels on admission and discharge respectively are summarized.

Fifty-four (54, 22%) patients had a history of previous hospitalization, whilst (192, 78%) were hospitalized for the first time. One hundred and forty-three (143, 58%) of T2DM patients, had no complications compared to (103, 42%) of T2DM patients who presented with complications. A hundred and seventy-nine (179, 73%) of the T2DM patients had comorbidities, whereas (67, 27%) of the T2DM patients had no comorbidities. All patients in this study cohort were discharged and no file was assessed to ascertain whether any patient(s) had died in the hospital. No patient was referred out.

Table 1: T2DM patients' basic characteristics (continuous variables)

Variable	Basic patients characteristics		
	Number of patients	Mean $\pm$ SD	P value
age	246	52 ± 13.4	<0.0001
length of stay	246	5 ± 4.3	<0.0001
BSL1	246	18 ± 7.5	<0.0001
BSL2	245	9 ± 2.1	<0.0001
SBP1	246	138 ± 22.1	0.0106
DBP1	246	82 ± 15.7	<0.0001
SBP2	242	126 ± 14.4	<0.0001

Variable	Basic patients characteristics		
	Number of patients	Mean $\pm$ SD	P value
DBP2	242	75 $\pm$ 10.8	0.0712
HbA1c	65	12 $\pm$ 3.5	0.0884
TC	19	3 $\pm$ 1.7	0.1159
HDL-C	16	1 $\pm$ 0.8	<0.0001
LDL-C	19	2 $\pm$ 1.1	0.2186

BSL 1&2 = Blood sugar level on admission and discharge respectively.

SBP 1&2 = Systolic Blood Pressure on admission and discharge respectively.

DBP 1&2 = Diastolic Blood Pressure on admission and discharge respectively.

4.1 Reasons for admission

Figure 1 shows reasons for admission indicating that the majority was related to diabetes while 91 (37%) being unrelated to diabetes.

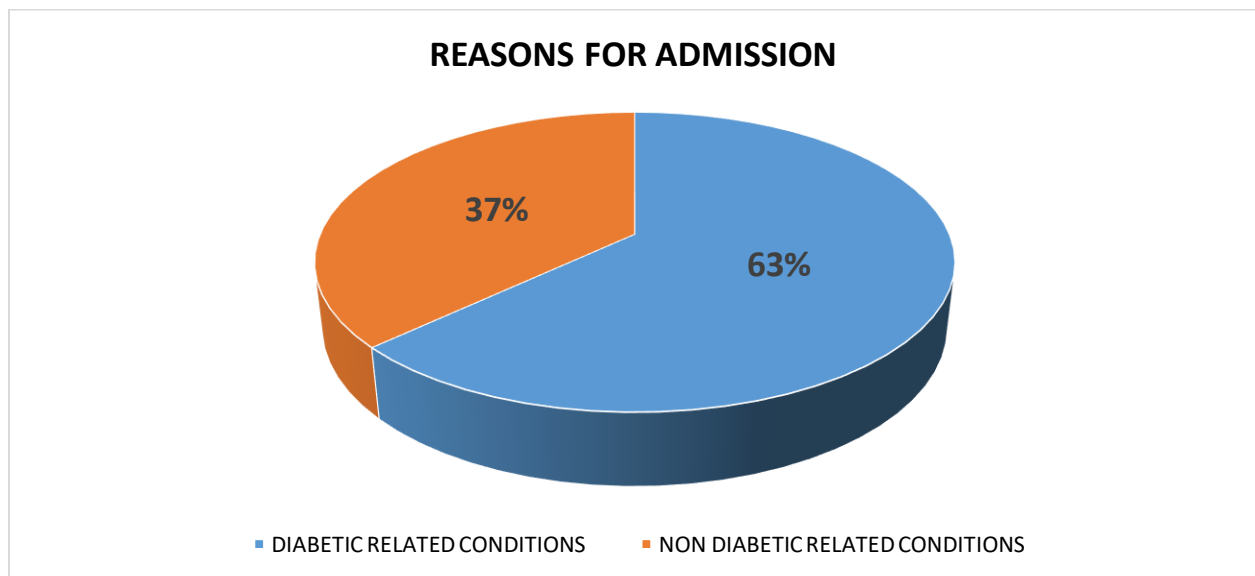


Figure 1: Percentages of diseases that let to T2DM patients being hospitalized.

4.2 Level of care T2DM patients with and without comorbidities received whilst in hospital.

Table 2 shows the level of care those T2DM patients with and without comorbidities received whilst in hospital.

Table 2: Comparison of level of care that T2DM patients with and without comorbidities received whilst in hospital.

Level of Care	Comorbidity Present		No Comorbidity	
	Total number of patients(n)	Percentage (%)	Total number of patients(n)	Percentage (%)
ICU	1	0.6	0	0
High Care	128	71.5	25	37.3
Specialist Care	20	11.2	3	4.5
Normal Care	30	16.8	39	58.2
Total	179	100	67	100

4.3 Length of hospital stay of patients with and without comorbidities

Patients with comorbidities stayed longer in the hospital with a mean (SD) hospital stay of 6.0 ± 4.7 compared to 3.6 ± 2.0 of the patients without comorbidities. Eighty-four of these patients (84, 34%) were male and (95, 39%) were female.

4.4 Association of cardiovascular risks factors to comorbidities.

Table 3 summarizes the association of cardiovascular risk factors to comorbidities. Blood sugar levels both on admission and discharge had no relationship with comorbidities, whereas blood pressure (BP) of patients with comorbidities was higher both on admission and discharge with a *P value* less than 0.05, compared to that of patients without comorbidities.

Table 3: Association of cardiovascular risks factors to comorbidities

	No comorbidity	Comorbidity present	
	Mean $\pm$ SD	Mean $\pm$ SD	<i>P value</i>
BSL1	17.6 $\pm$ 4.6	17.4 $\pm$ 8.3	0.368266
BSL2	9.1 $\pm$ 2.6	9.0 $\pm$ 1.9	0.689567
SBP1	131.1 $\pm$ 17.7	141.1 $\pm$ 23.0	0.001422 *
DBP1	79.7 $\pm$ 13.0	82.7 $\pm$ 16.5	≤ 0.0001 *
SBP2	119.7 $\pm$ 10.1	127.8 $\pm$ 15.1	0.000079 *
DBP2	72.5 $\pm$ 8.9	75.3 $\pm$ 11.3	0.065050
HbA1c	11.4 $\pm$ 3.5	12.58 $\pm$ 4.2	0.208614

BSL 1&2 = Blood sugar level on admission and discharge respectively.

SBP 1&2 = Systolic Blood Pressure on admission and discharge respectively.

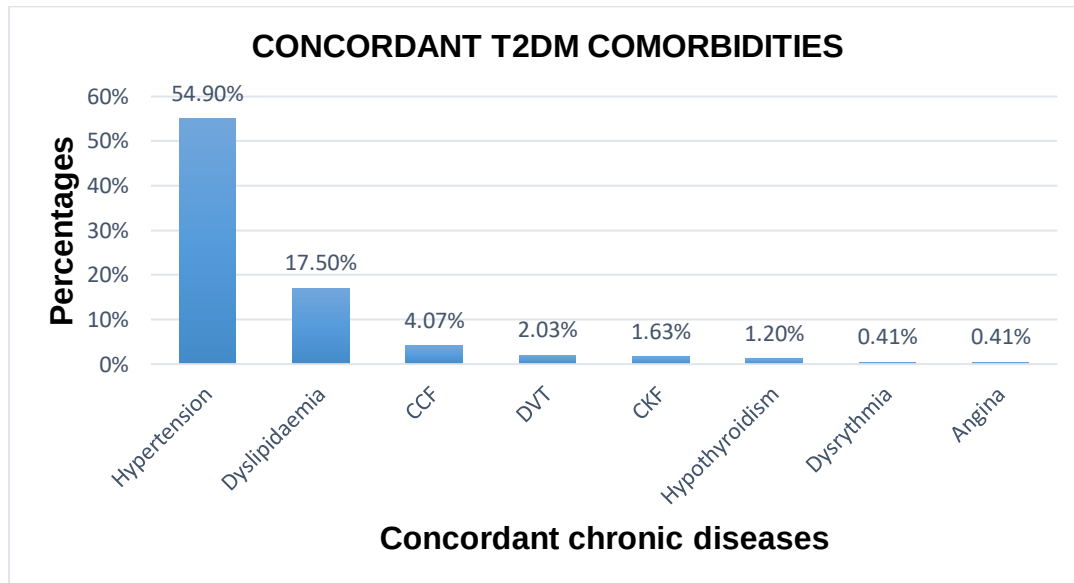
DBP 1&2 = Diastolic Blood Pressure on admission and discharge respectively.

HbA1c = glycated hemoglobin

* Statistically significant results.

4.5 Comorbidity profile of T2DM

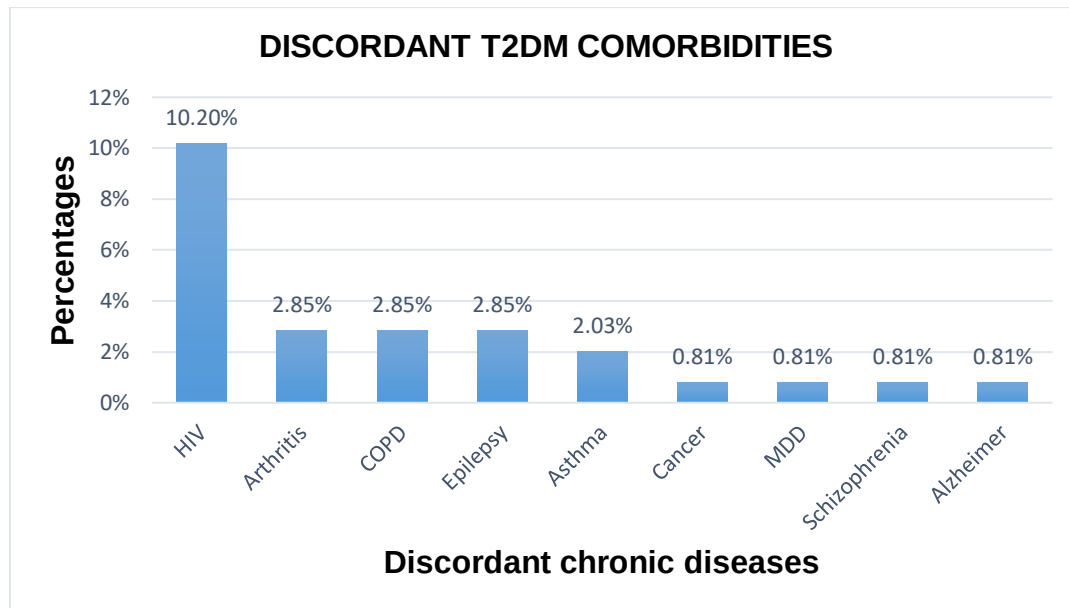
For concordant diseases, the most prevalent disease is hypertension at (135, 54.90%) followed by dyslipidemia at (43, 17.50%). Dysrhythmia and angina are the least prevalent both at (1, 0.41%) as summarized in Figure 2 below.



CCF: congestive cardiac failure. DVT: deep vein thrombosis. CKF: chronic kidney failure.

Figure 2: Concordant diseases present in T2DM patients.

For discordant diseases, the most prevalent disease is HIV (25, 10.20%) followed by arthritis, COPD and epilepsy (7, 2.85%) then asthma (5, 2.03%). The least prevalent diseases were cancer, MDD, schizophrenia and Alzheimers disease (2, 0.81%) as summarized in Figure 3 below.



HIV: human Immune deficiency virus. **COPD:** chronic obstructive pulmonary diseases. **MDD:** major depressive disorder.

Figure 3: Discordant diseases present in T2DM patients.

4.6 Complications present in T2DM patients

Seventy four T2DM patients (74, 30%) had both complications and comorbidities whilst (29, 12%) had comorbidities without any complications.

Figure 4 below shows complications identified in this patient cohort. Diabetic ketoacidosis (DKA) (57, 23.20%) was the most prevalent followed by neuropathy (23, 9.35%) and amputation being the least prevalent with (5, 2.03%).

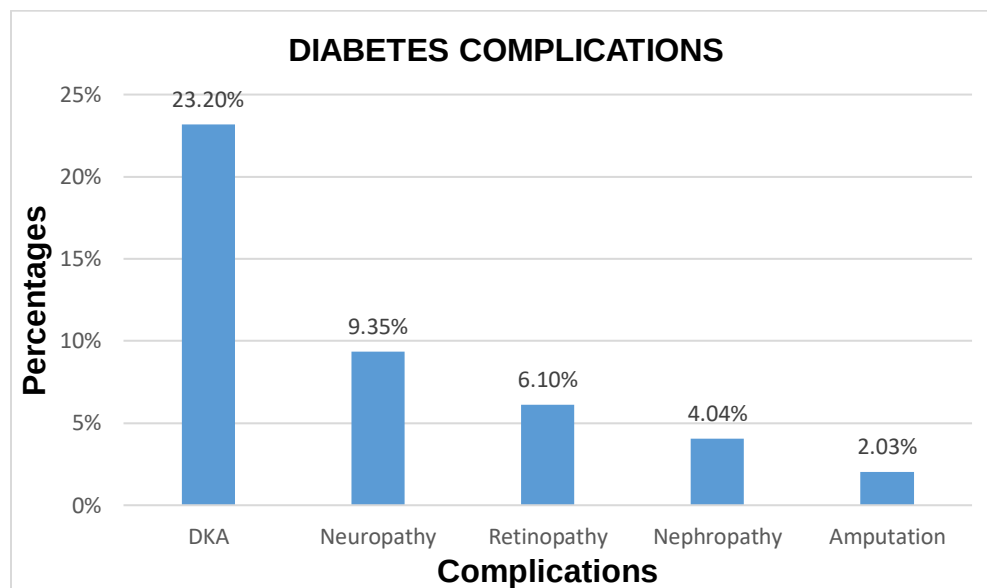


Figure 4: T2DM complications identified in hospitalized patients.

4.7 Adherence to South African standard treatment guidelines of diabetic medications prescribed for T2DM patients.

Figure 5 shows the medications that were prescribed to the T2DM patients with metformin being the most prescribed having been used by (155, 63.00%). There were only (17, 6.91%) on glimepiride. For patients on injectables, actraphane accounted for about (96, 39.02%) of the cases, followed by protaphane (30, 12.20%) and then actrapid (23, 9.34%).

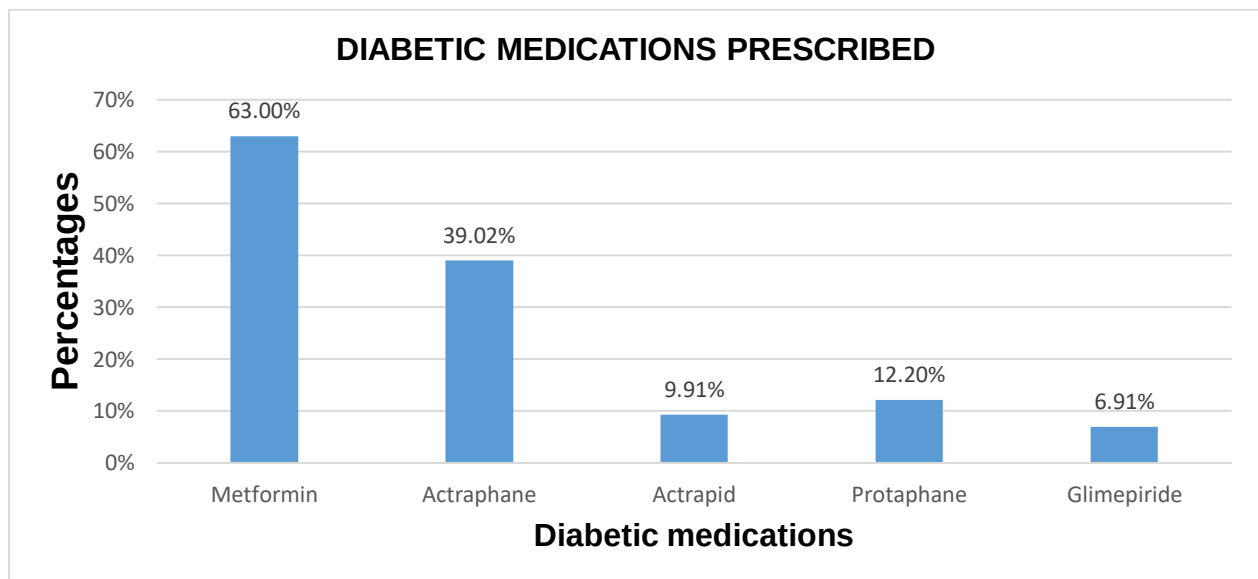


Figure 5: Diabetic medications prescribed to T2DM patients.

CHAPTER FIVE: DISCUSSION

T2DM is known to be associated with a reduced quality of life due to a high prevalence of comorbidities and complications (Pati *et al.*, 2020). This study is important as it assesses the influence of different T2DM patients' characteristics and comorbidities on successful glycaemic control of T2DM patients hospitalized at Helen Joseph Hospital in 2019.

The analysis of the comorbidity profile was done according to concordant comorbidities; diseases that have similar pathophysiology as diabetes (hypertension, dyslipidaemia, congestive heart failure, deep vein thrombosis, chronic kidney failure, hypothyroidism, dysrhythmia and angina) and discordant comorbidities; diseases that are not directly related to diabetes (HIV, arthritis, chronic obstructive pulmonary disease, epilepsy, asthma, cancer, major depressive disorder, schizophrenia and Alzheimer disease) classification. Factors such as level of care, length of hospital stay, hospitalization outcome, complication profile, the reason for admission and the diabetic medication prescribed were also investigated and analyzed.

This study revealed that almost three quarters of T2DM patients had one or more chronic diseases. The most common comorbidity was hypertension which was similar to the study carried out by Naidoo *et al.* (2019) in a retrospective descriptive study of 902 patients conducted in private health sector in South Africa. The majority of these patients were females. This is a similar finding to the work carried out by Adriaanse *et al.* (2016). Adriaanse conducted a cross-sectional study on 1676 T2DM patients in the Netherlands, where he found 79% had one or more chronic diseases. In general, there was a high prevalence of comorbidities in T2DM patients that were hospitalized.

Almost three quarters of the patients with comorbidities required a high level of care whilst in the hospital. T2DM patients with comorbidities also had a prolonged stay in the hospital generally with a mean (SD) of 6.0 ± 4.7 compared to those without comorbidities with a mean (SD) stay of

3.6 ± 2.0. These findings also agree with Struijs *et al.* (2006), where a retrospective database analysis of a sample size of 7499 conducted in the Netherlands, revealed a mean(SD) hospital stay of 9.5(9.1) days for T2DM patients with comorbidities compared to the mean (SD) of 6.7(10.6) days in T2DM patients without comorbidities. T2DM patients with comorbidities require high care in hospital and generally spend more days in hospital than those without comorbidities.

Erzse *et al.* (2019) explain some economic challenges with diabetes management in South Africa. In their findings, they claim that diabetes as a lifelong disease, demands frequent care and monitoring which requires a significant amount of the healthcare budget but the amount received may be inadequate in South African public health facilities due to other prevalent diseases including HIV/AIDS and Tuberculosis (Erzse *et al.* 2019).

Lower budgets results in suboptimal treatment for diabetic patients leading to an increase in the prevalence of complications such as blindness, amputations and kidney failures which becomes even more expensive to manage (Erzse *et al.*, 2019). Studies conducted by Ariza *et al.* (2010), in the United States of America evaluating economic challenges in treating diabetes, have shown that diabetic patients with comorbidities incur more costs than patients with T2DM. These are costs linked to every level of healthcare but hospitalization accounts for the bulk of the costs (Ariza *et al.*, 2010).

In this study, just under a quarter of T2DM patients had multiple admissions at Helen Joseph Hospital before 2019. Among the T2DM patients with comorbidities, almost a third had complications which were predominantly diabetic ketoacidosis (23.20%) (Figure 1). This could be due to poor adherence to medication or the presence of competing chronic illnesses causing difficulty in administering medication (Cade, 2008; Piette and Kerr, 2006).

In our study, hypertension was observed in more than half of the T2DM patients assessed followed by dyslipidemia. This is similar to the work of Mutyambizi *et al.* (2017) and Pati *et al.* (2020), studies that were conducted in South Africa and India respectively, which both established hypertension as the dominant concordant disease among T2DM patients at 68.5%. The possible contributing factor to this as discussed by Piette and Kerr (2006), is due to the lack of intensive screening on each T2DM review visit, as healthcare providers often find it too exhausting and time-consuming (Vitry *et al.* 2010). This study, however, could not establish the reason for hypertension dominance in this patient cohort.

Patients with T2DM have the highest prevalence of cardiovascular diseases (CVDs) (Tesfaye *et al.*, 2020; Ruckert *et al.*, 2015). A study by Mutyambizi *et al.* (2017) a cross-sectional household survey of 25,532 participants from the South African 2012 national health and nutrition statistics, showed that in T2DM patients, hypertension was a common condition in most patients, followed by stroke, heart disease and then dyslipidaemias (Mutyambizi *et al.* 2017).

For discordant diseases, this study found HIV as the leading disease followed by arthritis, COPD and epilepsy. The estimated overall HIV prevalence rate is approximately 13.7% among the South African population. The total number of people living with HIV (PLWHIV) is estimated to be approximately 8.2 million in 2021. For adults aged 15–49 years, an estimated 19.5% of the population is HIV positive (Statistics South Africa, 2021). The high rate of HIV in South Africa could be the possible reason why there is a high prevalence of HIV in T2DM patients in this study.

Many patients in this study who have T2DM are elderly with a mean (SD) age of 52 ± 13.4 . Arthritis was found to be the most prevalent disease in older people in a study conducted by Dal Bello *et al.* (2020) in Italy, this could be the possible reason why arthritis was more prevalent in this study. Furthermore, a majority of T2DM were found to have been admitted due to diabetic-

related conditions such as hyperglycemia among others. The work of Naidoo *et al.* (2019) in a retrospective descriptive study of 902 patients conducted in South Africa also had similar findings, with 66% of T2DM admitted due to diabetes-related events. As a result, diabetes related conditions were regarded as the main reason why T2DM patients were admitted at the hospital.

An analysis of prescribed medications showed that the T2DM patients in this study were predominantly treated with metformin. The current South African treatment guideline, (2019 update), recommends the use of metformin tablets as the first-line treatment in patients diagnosed with T2DM if there are no contraindications or allergies. Metformin is a well-accepted, efficacious antidiabetic drug with side effects that are minimal, compared to other anti-diabetic drugs (Pillay, 2020). Metformin is recommended because it also promotes weight loss among people living with T2DM (Pati *et al.*, 2020). This shows that there was compliance with national guidelines.

The study could not establish any statistically significant association between comorbidities and BSL on both occasions (admission and discharge) with a *P value* of 0.368266 and 0.682567 respectively which are both greater than 0.05. In this study, the T2DM patients did not reach the HbA1c target of $6.5\% \leq x \leq 7\%$ as stipulated in the South African treatment guideline, (2019 update). Failure to reach the HbA1c target could be the possible reason why the majority of T2DM (63%) were admitted due to diabetic related diseases. There was no significant relationship of HbA1c in patients with and without comorbidities with a *P value* of 0.208614. The study therefore, showed no difference in cardiac risk factors of T2DM patients with and without comorbidities. Meta-Cases *et al.* (2019), in a cross-sectional study of 373,185 participants conducted in Catalonia, Spain, pointed out that the presence of comorbid chronic conditions may affect the therapeutic targets of diabetes thereby leading to increased emergency and

unnecessary recurring hospital admissions. Readmissions become more expensive for diabetic patients with comorbid chronic conditions than those without comorbidities (Erzse *et al.*, 2019).

CHAPTER SIX

6.1 Conclusion

The study showed that in this cohort of T2DM patients, the prevalence of one or more comorbidities was 73%. The main concordant disease was hypertension and the main discordant disease was HIV. T2DM patients with comorbidities generally stayed longer in the hospital in comparison to those without comorbidities. Metformin was the most widely used antidiabetic medication. This demonstrates adherence to the latest South African STGs. The study found that there was no statistically significant association between comorbidity and BSL even though clinically comorbid T2DM patients had higher mean values of BSL. HbA1c as the measure of glucose control over three months could not show any significant difference in patients with and without comorbidities. BP was higher in T2DM patients with comorbidity than in those without. The majority of T2DM patients had diabetes related conditions as the reasons for their admission. Moreover, patients with comorbidities required high care and specialist services more than those without, comorbidities.

6.2 Limitations

Files of patients who passed away could not be assessed as the files could not be located. Some of the patients' parameters like cholesterol, BMI, and waist circumference were not routinely done, therefore, could not be evaluated. The study was conducted in one public hospital around Gauteng and may not give a true reflection of the whole province and or the country. Some of the files selected could not be found on the shelves due to filing challenges which could contribute to selection bias.

6.3 Recommendations

A cholesterol test, BMI, measurement, and waist circumference measurement should form part of the routine pre-admission screening for T2DM patients. This will help in detecting dangerous body fats like HDL-C which often complicates successful control of T2DM. The study found very few patients had their cholesterol levels measured both on admission and discharge. T2DM patients should be referred for testing of HbA1c which gives the best indication of the glucose level in the body, especially for T2DM patients who have been on diabetes treatment for over three consecutive months. Healthcare workers should be encouraged to integrate a comorbidities service specifically for T2DM patients, to encourage good medication and lifestyle adherence and reduce recurring hospitalizations.

Further studies with a larger sample size including more Gauteng tertiary hospitals could be explored in future to establish the percentage prevalence of T2DM comorbidities on a larger scale, and also determine if there is an association between comorbidities and blood sugar level of T2DM.

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APPENDICES

APPENDIX A: DATA COLLECTING FORM

Study Participant Number:	
Date of admission:	
Date of discharge:	
1. DEMOGRAPHICS AND PARAMETERS:	
Sex	☐ MALE ☐ FEMALE
Age at admission	[]
Weight(kg)	[]
Height (m)	[]
Length of stay in hospital until time of outcome: [] Reason for admission: _____ Hospitalized here before? ☐ yes, ☐ no , if yes how many times? [] Hospitalization Outcome: discharged ☐ died ☐ referred ☐ Level of care: ICU ☐ High Care ☐ Specialist Care ☐ Normal Care (General) ☐ BMI (Kg/m2) on admission ☐ on discharge ☐ if recorded otherwise to be calculated Waist circumference (cm) on admission ☐ and discharge ☐ if available	
2. CLINICAL INDICATORS:	
Fasting/Random blood glucose (mmol/l)	[] on admission/first reading [] date [] on discharge/last reading [] date
Blood pressure(mmHg)	[] on admission/first reading [] date [] on discharge/last reading []

		date
	HbA1c (%)	[] date:
	Total Cholesterol (mmol/l)	[] date:
	Triglycerides (mmol/l)	[] date:
	High Density Lipoprotein (HDL-C) (mmol/l)	[] date:
	Low Density Lipoprotein (LDL-C) (mmol/l)	[] date:
	Waist circumference (cm)	[]
3. DIABETIC MANAGEMENT HISTORY:		
	Date of the first diagnosis	[]
	Prescribed T2DM medication used up to 6 months prior to hospitalization	Start date, name of medication, dosage - - - - -
	Prescribed T2DM medication on admission	Start date, name of medication, dosage - - - - -
	Prescribed T2DM medication used in hospital	Start date, name of medication, dosage - -

		- -
	Prescribed medication for all other conditions, excluding T2DM, used before hospitalization (6 months)	Start date, name of medication, dosage - - - - -
	Prescribed medication for all other conditions, except T2DM, on admission	Start date, name of medication, dosage - - - -
	Prescribed medication for all other conditions, except T2DM, used in hospital	Start date, name of medication, dosage - - - - -
	Prescribed medication for all other conditions, except T2DM, on discharge	Start date, name of medication, dosage - - -

		-
	History of cardiovascular procedures	☐ stenting ☐ CABBAG
4. DIABETIC COMPLICATIONS:		
	Complication/s present:	☐ retinopathy, diagnosis date: ☐ ☐ nephropathy, diagnosis date: ☐ ☐ neuropathy, diagnosis date: ☐ ☐ amputations (peripheral vascular disease) - date ☐ other + date
5. CORMOBIDITIES:		
	Concordant comorbidities present	☐ hypertension, diagnosis date: ☐ hyperlipidemias diagnosis date: ☐ angina ,diagnosis date: ☐ coronary artery disease, diagnosis date: ☐ hypothyroidism, diagnosis date: ☐ glaucoma, diagnosis date: ☐ dysrhythmia, diagnosis date: ☐ cardiac failure, diagnosis date: ☐ chronic kidney failure disease, diagnosis date: ☐ stroke, diagnosis date: ☐ deep vein thrombosis. diagnosis date: ☐ other + date

Discordant comorbidities present	☐ Asthma diagnosis date: ☐ Chronic obstructive pulmonary diseases (COPD), diagnosis date: ☐ HIV, diagnosis date: ☐ Cancer, diagnosis date: ☐ Major depressive disorder (MDD), diagnosis date: ☐ Schizophrenia, diagnosis date: ☐ Bipolar, diagnosis date: ☐ Anxiety, diagnosis date: ☐ Epilepsy, diagnosis date: ☐ Alzheimer, diagnosis date: ☐ Rheumatoid Arthritis, diagnosis date: ☐ other arthropathies
Any additional comments:	

APPENDIX B: TITTLE APPROVAL LETTER

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG



Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

08 November 2022
Person No: 1370887
PAG

Mr TI Makhabane
kubake
P.O. BOX 623
MOHALESHOEK
LESOTHO
800
Lesotho

Dear Mr Taoana Makhabane

Master of Science in Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Prevalence and treatment-related outcome of hospitalized type 2 diabetes mellitus patients with comorbidities at Helen Joseph Academic Hospital in Johannesburg* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

A handwritten signature in black ink, appearing to read 'S. Benn'.

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences



APPENDIX C: ETHICAL CLEARANCE



R49 Mr TI Makhabane

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE NO. M210814

NAME:
(Principal Investigator)

Mr TI Makhabane

DEPARTMENT:

School of Therapeutic Sciences
Department of Pharmacy and Pharmacology
Medical School
University

PROJECT TITLE:

*Prevalence and treatment-related outcome of
hospitalized type 2 diabetes mellitus patients with
comorbidities at Helen Joseph Academic Hospital in
Johannesburg*

DATE CONSIDERED:

2021/08/27

DECISION:

Approved unconditionally

CONDITIONS:

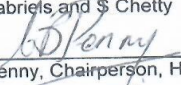
NOTE:

If contact information regarding student study participants is required,
please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>

SUPERVISOR:

Drs G Gabriels and S Chetty

APPROVED BY:


Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL:

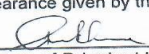
2022/10/24

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report.** When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **August** and therefore reports and re-certification will be due in the month of **August** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).


Signature of Principal Investigator

25/10/2022
Date

APPENDIX D: HELEN JOSEPH HOSPITAL APPROVAL LETTER



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Gauteng Department of Health
Helen Joseph Hospital
Enquiries: Dr. M. Mukansi
Research Committee: Chairperson
Tel : (011) 489-0306/1087
Fax : (011) 489 1038
E mail: Murimisi.mukansi@wits.ac.za

29 April 2021

To whom it may concern

Subject: HELEN JOSEPH HOSPITAL RESEARCH COMMITTEE APPLICATION

PROTOCOL TITLE: Prevalence and treatment-related outcome of hospitalized type 2 diabetes mellitus patients with comorbidities at Helen Joseph academic hospital in Johannesburg.

Protocol Ref No: Taoana Isalaha Makhabane

Ethics Clearance: Pending

Principal Investigator: Taoana Isalaha Makhabane

Department: Helen Joseph Hospital

Committee Recommendations

The Committee is giving you Conditional access while awaiting the final ethical clearance certificate from the University of Witwatersrand HREC.

It is the duty of the researcher to collect the data to the relevant department after the Research Committee approved the study.

Dr. M. Mukansi
Chairperson of HJH Ethic and Research Committee

APPENDIX E: INTERNAL MEDICINE DEPARTMENT APPROVAL LETTER

Department of Internal Medicine

Helen Joseph Hospital, Private Bag X47, Perth Road Auckland Park 2006

03 September 2021



Dear Professor Penny / Dr Mukansi

I grant permission for Taoana Isaiaha Makhabane to conduct a research project entitled

'Prevalence and treatment-related outcome of hospitalized T2DM patients with comorbidities at Helen Joseph Academic Hospital in Johannesburg

The approval is subject to all the conditions set out by the Wits Human Research Ethics Committee (Medical) and the necessary approval by the CEO of HJH.

Sincerely and Kind Regards

A handwritten signature in black ink, appearing to read "Dr. Bayat".

Dr Bayat
Head of Department: Internal Medicine
Head of Division: Endocrinology, Diabetes and Metabolism
Helen Joseph Hospital
zaheer.bayat@wits.ac.za

DEPARTMENT OF MEDICINE
HELEN JOSEPH HOSPITAL
PRIVATE BAG X47
AUCKLAND PARK 2006
TEL: +27 11 489-0866/8
FAX: +27 11 489-0717