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Examining the Bidirectional Relationship between Comorbid Depression and Type 2 Diabetes: A Managed Healthcare Perspective

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Original published work submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy.

Johannesburg, 2022

Declaration

I, Lovina Asha Corrien Naidoo, student number: 853697 declare that this Thesis is my own work and that I contributed adequately towards research findings published in the articles stated below which are included in my thesis.



……30 day of October, 2022

Lovina Asha Corrien Naidoo

Primary Supervisor



……2……day of …November….., 2022

Neil Buktow

Second Supervisor



……2……day of …November….., 2022

Elena Libhaber

Third Supervisor



……...2……day of …November….., 2022

Paula Barnard-Ashton

In memory of my late husband

Suren Naidoo

1963 -2011

And

My late mother

Hycinth Saldanha

1940 - 2021

Abstract

Introduction

Type 2 diabetes mellitus (T2DM) is common and has devastating outcomes for patients diagnosed with this disease. In Africa, the prevalence of T2DM is reaching epidemic proportions, especially in developing countries like Ghana, Nigeria and South Africa (SA). The financial burden of T2DM is seen in the public and private healthcare sectors in Africa. Major depressive disorder (MDD) frequently co-occurs as a discordant comorbidity with T2DM. MDD is an important component in the holistic management of T2DM care as the outcomes of both conditions are exacerbated by the presence of the other.

T2DM patients are at high risk for cardiovascular (CV) morbidity and mortality. The comorbidity of MDD among these individuals is associated with poor diabetes-related cardiovascular disease (CVD) outcomes such as myocardial infarction, stroke and cardiac failure, because MDD is a highly prevalent risk factor for CVD and T2DM alike. Little is known of the prevalence of MDD as a comorbidity of T2DM in SA or if MDD is a risk factor for the onset of T2DM. It is also unclear whether the treatment of depressive disorders in T2DM would improve glycaemic control. While the association between depression and T2DM in America and Europe is established, understanding the relationship between these two non-communicable diseases (NCDs) is lacking in SA.

The relationship between T2DM and associated co-morbidities, particularly MDD, is poorly acknowledged in chronic disease management practices in SA. The management of co-morbid conditions may influence managed healthcare costs and hospitalisation rates.

Aim and objectives

This thesis investigated the bidirectional relationship between T2DM and comorbid MDD within a South African privately managed healthcare organisation. The objectives of the study were to estimate the comorbidity incidence, resource utilisation (medicine, services and hospital), assess the cost between two T2DM management funding models, the influence of MDD on glycaemia, blood pressure and lipid control (ABC guidelines) and finally identify the depressive symptom and CV risk profiles of patients with T2DM with or without MDD and those with MDD alone.

Method

The thesis comprised four quantitative studies that analysed claims data from a privately funded healthcare insurer and electronic health records (EHR) from 2012 to 2019, and a cross-sectional survey from 2016 to 2019.

The methodology in the first study was a retrospective descriptive analysis of 902 adult patients with T2DM in 2014. Patients were identified with T2DM and their comorbidities and categorised as those with concordant comorbidities (CC), and those with discordant comorbidities (DC). Hospital admissions of patients with T2DM, with MDD (T2DM+MDD) versus those without MDD (T2DM-MDD), were further analysed.

The second study analysed the claims data of patients with T2DM and T2DM+MDD from 2012 to 2016. Annual healthcare costs were assessed between two funding models and categorised as in-hospital and out-of-hospital medicines and out-of-hospital services. Diabetes-related and other medicine-plus-services and hospitalisation costs between T2DM and T2DM+MDD were estimated.

In the third study, the cardiometabolic indices control of 1211 patients with T2DM+MDD, T2DM-MDD and MDD only were measured using their EHR for the year 2019. Claims for lipid-lowering therapy, hypoglycaemic agents, antihypertensives and antidepressant selective-serotonin-reuptake inhibitors (SSRIs) were assessed between the study groups. Frequencies of patients achieving target glycated haemoglobin (HbA1c), systolic blood pressure (SBP) and low-density-lipoprotein (LDL-C) were compared between groups. A stepwise multivariate logistic regression analysis was performed to identify predictors of HbA1c and LDL-C control of the study groups.

The fourth study conducted a cross-sectional survey of a random sample of members with T2DM+MDD, T2DM-MDD, MDD only, and a healthy control group between the years 2016 to 2019. The survey comprised a Patient Health Questionnaire-9 (PHQ-9) to assess possible depressive symptoms, and anthropometric measures (body mass index (BMI), family history of diabetes and/or heart disease, and smoking status as CV risk profiles).

Findings

The first study revealed a high incidence of CV concordant comorbidities (hypertension and hyperlipidaemia) in patients with T2DM+MDD, with MDD being the most prevalent discordant comorbidity of T2DM (17%). A higher percentage of patients with T2DM+MDD were admitted to hospital (42%, p=0.004) compared with those with T2DM-MDD (30%). The number of

overnight admissions was higher among the T2DM+MDD (76%, p=0.016) compared with T2DM-MDD (66%).

The second study focused on health care costs and the funding models associated with managed care. The direct medical costs of patients with T2DM and T2DM+MDD registered with a medical scheme over a 5-year period between two funding models were estimated and compared: a capitation risk-sharing model (CM) versus a traditional fee-for-service (FFS) model. Of the identified T2DM patients, 64% were enrolled in CM in 2012 and this rose to 81% by 2016. The implementation of CM resulted in a significantly higher cost to the scheme ($1,095) compared to FFS ($296) in 2016 (p<0.0001). Forty-six T2DM patients in this study incurred hospitalisation costs of ≥ $24,243 for T2DM-related or other hospital admissions (non T2DM-related). The healthcare expenditure consumed by patients with T2DM and T2DM+MDD on a capitation model of care for diabetes was high compared to patients on FFS. While the diabetes-related treatment and management were similar between patients with T2DM+MDD and T2DM-MDD, other medicine and services, expenditure was significantly higher in the T2DM+MDD group, for example T2DM+MDD patients had a median expenditure of $1,414 in 2016 compared to a median of $614 in T2DM-MDD patients (p<0.0001).

The third study assessed the HbA1c, SBP and LDL-C control target attainment (as per South African ABC guidelines) in patients with T2DM+MDD and T2DM-MDD and those with MDD alone. Only 13% of the patients in T2DM+MDD group and 7.1% in the T2DM-MDD group achieved ABC (HbA1c<7%, LDL-C<1.8mmol/l and SBP<140/90 mmHg) targets, despite hypoglycaemic, lipid-lowering therapy and antihypertensive claims, indicating a possible risk for CVD in T2DM+MDD and T2DM-MDD patients. A higher proportion of patients with T2DM+MDD (56%) achieved an HbA1c target of <7% compared to the T2DM-MDD group (45%, p<0.05). Multiple regression analysis showed that HbA1c control was independently associated (p<0.001) with older age, claims for statins and having a history of MDD, after adjusting for claims for antihypertensive therapy, metformin, newer hypoglycaemic agents, sex, and interaction factor of newer hypoglycaemic agents and metformin. Only 24% of patients in both the T2DM+MDD and T2DM-MDD groups reached the LDL-C target <1.8mmol/l. The predictors of LDL-C control between the T2DM+MDD and T2DM-MDD groups were older age (p<0.0001) and claiming statin therapy (p=0.001), after adjusting for antihypertensive therapy and metformin claims and sex.

The fourth study identified the depressive symptoms and CV risk factors (such as obesity, smoker status and family history of diabetes and heart disease) in individuals with T2DM+MDD, T2DM-MDD or MDD alone compared to a healthy control. The PHQ-9 scores revealed that patients in all four groups were within a range of mild to moderate-severe

depressive symptoms. The T2DM+MDD group had moderate-severe (PHQ-9≥10) depressive symptoms (58.8%) similar to the MDD group (54.2%, p=1.0) suggesting a poor response to antidepressants. Patients with T2DM-MDD had underlying unrecognized depressive symptoms: 20.5% had moderate-severe (PHQ-9≥10) depressive symptoms and 23.1% had mild (PHQ-9=5-9) depressive symptoms. Of concern was that 25% of the control (healthy) group recorded having moderate-severe (PHQ-9≥10) depressive symptoms and 21.4% of having mild depressive (PHQ-9=5-9) symptoms. The majority of the T2DM+MDD group was obese (76.5%) whereas 46.2% of the T2DM-MDD group were overweight. However, the control group, with no stated disease, were overweight (37.5%) or obese (30.4%). This study highlights the undetected MDD and high CV risk prevalent in this setting.

Conclusion

Within this South African private managed healthcare setting, comorbidities associated in patients with T2DM, i.e. MDD and CVD, are managed discretely. High-risk individuals with T2DM increase costs and resource utilisation within the private managed healthcare setting. In summary, the relevance of the research was to increase awareness of the consequences of comorbidity of T2DM and MDD and encourage routine screening for depression in T2DM patients, and glycaemic screening among patients with MDD. Managed care programmes should consider a patient-centric approach to assist patients in engaging with their T2DM and comorbidities more effectively by listening to their difficulties in terms of medication compliance, offering regular glycaemic and lipid blood tests and encouraging healthier diet through visits to dieticians or nurse educators.

Targeting primary healthcare as an intervention has the potential to reduce the hospitalisation burden by initially stabilizing patients with T2DM+MDD, providing cost-effective and appropriate medicine management (i.e. statins), improving attainment of ABC control targets and early screening for depression and non-invasive CV risk factors. Resource allocation for a coordinated care team that includes health professionals such as dieticians, endocrinologists, drug review utilisation (DUR) pharmacists, psychologists and nurse educators to treat patients with T2DM+MDD is indicated.

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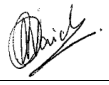
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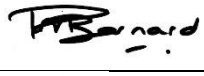
Agreement by co-authors

By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her thesis.

Paper 1: Naidoo L, Butkow N, Barnard-Ashton P, Libhaber E. Hospitalisation of Type 2 diabetes mellitus patients with and without major depressive disorder in a private managed healthcare organisation. Journal of Endocrinology, Metabolism and Diabetes in South Africa. 2019 Nov 1;24(3):70-6. **Student is the first author**. Status: Published

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2nd Author	Butkow N		02.11.2022
3rd Author	Barnard-Ashton P		02.11.2022
4th Author	Libhaber E		02.11.2022
Comments by primary supervisor: The candidate is the first author of the paper and contributed to all aspects of the conceptualisation, method, data collection, data analysis and writing of the paper. The authors 2-4 were supervisors of the study.			

Paper 2: Naidoo LA, Butkow N, Barnard-Ashton P, Miot J, Libhaber E. Is the Risk Really Shared? A Retrospective Analysis of Healthcare Costs of Patients with Type 2 Diabetes Mellitus on a Capitation Model. Value in Health Regional Issues. 2022 Mar 1;28:29-37. **Student is the first author**. Status: Published

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5th Author	Libhaber E		02.11.2022
Comments by primary supervisor: The candidate is the first author of the paper and contributed to all aspects of the conceptualisation, method, data collection, data analysis and writing of the paper. The authors 2,3 and 5 were supervisors of the study. Author 4 gave expert insights into the understanding of health economics in South Africa.			

Publications

Two peer-reviewed journal articles arose from this study and are presented in this thesis.

Peer-reviewed journal articles - Published

Paper 1: Naidoo L, Butkow N, Barnard-Ashton P, Libhaber E. Hospitalisation of Type 2 diabetes mellitus patients with and without major depressive disorder in a private managed healthcare organisation. *Journal of Endocrinology, Metabolism and Diabetes in South Africa*. 2019 Nov 1;24(3):70-6.

Paper 2: Naidoo LA, Butkow N, Barnard-Ashton P, Miot J, Libhaber E. Is the Risk Really Shared? A Retrospective Analysis of Healthcare Costs of Patients with Type 2 Diabetes Mellitus on a Capitation Model. *Value in Health Regional Issues*. 2022 Mar 1;28:29-37.

Conference and Academic Presentations

Conference Paper Presentations

Conference: The Pharmacology and Toxicology Congress at the University of Witwatersrand, Johannesburg (01 September 2015).

- Paper: Baseline characteristics of patients with Type 2 Diabetes and Depression in a South African Private Managed Healthcare environment

Conference: The Stroke & Hypertension congress, Johannesburg (19-21 August 2016)

- Paper: Comparison of costs and resource use between two health insurance models in type 2 diabetes patients with cardiovascular complications

Conference: Faculty of Health Sciences Research Day, at the University of Witwatersrand (01 September 2016)

- Paper: Care and resource utilisation of patients with type 2 diabetes mellitus in a privately managed health care organisation in South Africa

Conference Poster Presentations

Conference: The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) South Africa Chapter Conference, Protea Hotel Midrand (19-20 September 2016)

- Poster: Costs and resource utilisation associated with comorbid conditions of type 2 diabetes patients in a South African private managed healthcare organisation

Conference: The ISPOR 22nd Annual International meeting in Boston (22 to 25 May 2017)

- Poster: Costs and resource utilisation associated with comorbid conditions of type 2 diabetes patients in a South African private managed healthcare organisation

Conference: The World Clinical Pharmacology (WCP2018 KYOTO) 18th World Congress of Basic and Clinical pharmacology held in Japan (1-6 July 2018)

- Poster: Type 2 Diabetes Mellitus patients with comorbidities in a South African managed healthcare organization

Academic Presentations

Invited academic presentation: College of Pharmacy, Department of Sociobehavioral and Administrative Pharmacy, Nova Southeastern University, Florida USA (29 June 2022)

- Presentation: Costs and resource utilization associated with comorbid conditions in patients with type 2 diabetes mellitus in a South African private managed healthcare organization

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Contributions of Authors to the Study

The conceptualisation of the study, the research design and the research protocol, were primarily crafted by myself, under the guidance and mentoring of my supervisors. While the research implementation was conducted independently, my supervisors were available for consultation as needed.

Nomenclature

ABC	glycated haemoglobin, blood pressure, low-density-lipoprotein cholesterol
ADA	American Diabetes Association
AIDs	acquired immunodeficiency syndrome
ASCVD	atherosclerotic cardiovascular disease
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CC	concordant comorbidities
CDL	chronic disease list
CM	capitation risk-sharing model
CMS	Council of Medical Schemes
CV	cardiovascular risk
CVD	cardiovascular disease
DC	discordant comorbidities
DUR	drug utilisation review
EHR	electronic-health-records
EML	essential medicines list
FFS	fee-for-service
HbA1c	glycated haemoglobin
HIV	human immunodeficiency virus
ICD10	International Classification of Diseases and Related Health Problems,10th revision
IQR	interquartile range
LDL-C	low-density lipoprotein cholesterol
MCOs	managed care organisations
MDD	major depressive disorder
MDE	major depressive episode
NCDs	non-communicable diseases
NDRIs	norepinephrine-dopamine reuptake inhibitors
NHI	National Health Insurance
PHQ-9	Patient Health Questionnaire-9
REDCap	Research Electronic Data Capture
SA	South Africa
SBP	systolic blood pressure
SEMDSA	Society for Endocrinology, Metabolism and Diabetes of South Africa
SSRI	selective serotonin receptor inhibitor
STGs	standard treatment guidelines
T1DM	Type 1 Diabetes Mellitus

T2DM	Type 2 Diabetes Mellitus
T2DM-MDD	Type 2 Diabetes Mellitus without comorbid Major Depressive Disorder
T2DM+MDD	Type 2 Diabetes Mellitus with comorbid Major Depressive Disorder
UK	United Kingdom
USA	United States of America
USD	United States Dollar
ZAR	South African Rand

Chapter 1. Introduction

1.1. Background

Type 2 diabetes mellitus (T2DM) and major depressive disorder (MDD) are highly prevalent and often comorbid non-communicable diseases (NCDs). Globally, there are 537 million adults living with type 1 diabetes mellitus (T1DM) and T2DM,[1] and approximately 280 million people have MDD.[2] In 2021, 24 million people in Africa were diagnosed with T2DM, a prevalence that is predicted to increase by 129% by 2045 to 55 million people,[1] in a continent already encumbered with high rates of communicable diseases, such as human immunodeficiency virus (HIV) and tuberculosis.[3] The nature of T2DM can cause devastating personal suffering in terms of psychosocial behaviour (e.g. food cravings, a sense of hopelessness, family disruption) and financial stability (e.g. work absenteeism or loss of productivity).[4] On a health economic level for Sub-Saharan countries the burden of healthcare resource requirements increases as the incidence of T2DM rises.[5]

Major depressive disorder (MDD), a serious form of depression, has become one of the major public mental health problems worldwide and is a common comorbidity in patients with T2DM.[6] It is estimated that the prevalence and odds of MDD are significantly higher in adults with T2DM, twice that of the general population[7] (19.1% and 10.7%; odds ratio 1.73, 95% CI 1.38–2.16),[8] and higher in females (34%) than in males (23%).[9]

Comorbid MDD among individuals with T2DM (T2DM+MDD) is associated with poor diabetes-related cardiovascular disease (CVD) outcomes, such as myocardial infarction, stroke and heart failure, as MDD is a highly prevalent risk factor for CVD and T2DM.[10, 11] Findings of the INTERHEART study[11] showed that psychosocial factors i.e. depression and stress, accounted for 30% of the risk of myocardial infarction. MDD amplifies the risk of CVDs and mortality among patients with T2DM.[12] The presence of the additional diagnosis of MDD in patients with T2DM can adversely influence glycaemic control and outcomes for both diseases due to non-adherence to medications, blood glucose monitoring, having unhealthy dietary choices and low levels of physical activity.[13, 14] Combination of T2DM complications and MDD makes T2DM+MDD the worst pairing of NCDs compared to other chronic condition combinations (i.e. asthma or angina) in terms of quality of life and disability.[15] A systematic review conducted by Aga et al.[16] showed that some concordant comorbidities (CC) such as hypertension, and hyperlipidaemia having similar pathophysiological and care goals as T2DM might improve diabetes self-care. Whereas, T2DM-discordant comorbidities (DC) such as MDD may have a more detrimental effect on

self-care behaviours. T2DM+MDD poses a possibly devastating economic burden on an already overburdened health-care system in South Africa.[3, 17]

South Africa (SA) has a dual-tiered healthcare system administered by the Department of Health; comprising a private sector that covers 15% of the population,[18] and the balance of the population served by a public healthcare system.[19] In the public sector most patients access the health system at the primary level of health care, led by nurses with general physicians performing weekly sessions at the clinics.[20] Community health clinics have doctors working through-out the week.[21] Healthcare workers in this setting use the primary healthcare standard treatment guidelines (STGs) and essential medicines list (EML) as a guide for individual treatment algorithms in the management of T2DM, MDD and CVDs.[22] Diabetic patients collect their medications monthly at the clinics and have their blood glucose and blood pressure monitoring done four times a year.[20] This system appears fragmented with less time for patient education and preventative care practices by health care professionals.

In the private sector individuals enrol as members of a health insurance plan or medical aid scheme that has contracts with healthcare providers and medical facilities to provide quality healthcare at a reduced cost. Medical schemes in SA reimburse the treatment and management of a range of ailments defined as a set of 271 diagnoses and 26 Chronic Disease List (CDL) conditions. Insured patients receive benefits under the Prescribed Minimum Benefit-Diagnosis Treatment Pairs regulation as stipulated by the Council of Medical Schemes (CMS) in SA.[23]

South African healthcare systems characterize NCDs as discrete entities with minimal overlap, particularly with mental disorders associated with medical conditions such as T2DM and CVD. The context of this study is to examine the private sector-managed healthcare models of care for patients with T2DM plus comorbid MDD. Traditionally, the focus of managed healthcare models for T2DM is the prevention of hospitalisations due to hypoglycaemia or diabetic ketoacidosis.[24, 25] These models overlook other aspects of diabetes management such as CVD and mental illness. As many as 50% of patients with T2DM die of myocardial infarction,[26] whereas having associated comorbid MDD attributes to a 30% risk of acute myocardial infarction, ranking it third after dyslipidaemia and smoking.[11] Targeting CVD risk factors i.e. hypertension, dyslipidaemia and MDD have shown a reduction in rates of major cardiac events.[27-29]

Because of the prevalent nature of comorbid MDD and T2DM, the American Diabetes Association (ADA)[30] recommends routine depression screening for patients with diabetes (especially those with poor adherence), and patients who present with depression are

monitored over time for the development of diabetic symptoms and risk factors, including glucose dysregulation, diet, exercise, smoking, and medication adherence.[31]

The extent of the prevalence of MDD in patients with T2DM in SA or if MDD is a risk factor for the onset of T2DM in the South African adult population is not clear. It is also unclear whether the treatment of depressive disorders in T2DM would improve the outcomes of T2DM as seen in many general medical conditions.[32, 33] Studies reported by Lustman et al.[34, 35] and Brieler et al.[36] show that treating depressive disorders in T2DM is associated with improvements in glycaemic control, however, the evidence for benefits in glycaemic control are still controversial. A systematic review and meta-analysis conducted by Ismail et al.[37] showed depression to be weakly correlated to glycaemic control. A more recent study by Ismail et al.[38] found that in the initial two years of T2DM, the effect of depressive symptoms on glycaemic control was minimal. Among Ghanaians with T2DM with a high incidence of depression, no association of depression with their poor glycaemic control was reported.[39] Limitations of studies done so far include the sample size;[40] comparing T1DM and T2DM in the same sample;[41] the potential effects of antidepressants, for example nortriptyline on weight gain reported by Lustman et al[42]; different antidepressants used, i.e. bupropion due to its properties of reducing depression and weight simultaneously;[34] different assessment tools for depression used, for example the Hospital Anxiety and Depression Scale (HADS) was used in a study by Khuwaja et al. [43] and the patient health questionnaire-9 (PHQ-9) by Akpalu et al.[39]

While the association between depression and T2DM in the United States of America (USA) and Europe is established, the relationship between these two NCDs is lacking in SA.

1.1.1. Problem statement

Type 2 diabetes mellitus (T2DM) is of endemic proportions in SA and it increases the burden of disease on healthcare resources. More importantly, major macrovascular complications in T2DM, such as myocardial infarction are a leading cause of morbidity and mortality in patients with T2DM. T2DM concordant comorbidities (CC) such as CVD, the metabolic and renal disease's that share parts of the overall pathophysiologic profile and care management strategies, commonly co-occur with T2DM. Another well-recognised T2DM discordant comorbidity (differs in the treatment and care management with T2DM) such as MDD is shown to interfere with adherence to T2DM self-care and contributes to poorer diabetes control, more complications and higher healthcare utilisation. Within the South African managed care arena, the two diseases i.e. T2DM and MDD are seen as discrete, with T2DM as a cardiovascular (CV) risk equivalent and MDD as a mental health illness.

There is no accounting for the interaction between T2DM and MDD. Therefore, this research investigated the interaction between T2DM and comorbid MDD.

1.1.2. Aim of the research

The study investigated the bidirectional relationship between T2DM and comorbid MDD within a South African private managed healthcare organisation in terms of cost and resource (medicine, services and hospital) utilizations, and the influence of MDD on glycaemic, blood pressure and lipid control.

1.1.3. Objectives for each of the four studies

Study 1: Determine the prevalence of MDD co-morbidity in a T2DM population and assess diabetic and non-diabetic related events resulting in the hospitalization of patients with T2DM with MDD (T2DM+MDD) and T2DM without MDD (T2DM-MDD).

Study 2: 1. Estimate diabetic and non-diabetic related healthcare resources and costs consumed (in terms of hospitalization, medicine and services plus capitation fee) of patients with T2DM between two funding models: a CM versus a traditional FFS model.

2. Estimate diabetic and non-diabetic related healthcare resources and costs consumed by patients with T2DM+MDD between two funding models: a CM versus a traditional FFS model.

Study 3: 1. Determine the glycaemic and lipid control of patients with T2DM-MDD, T2DM+MDD and MDD.

2. To assess whether MDD, sex, lipid-lowering therapy, hypoglycaemic agents, antihypertensives and antidepressant-SSRI are independently associated with HbA1c and LDL-C control of patients with T2DM.

3. To assess the ABC (HbA1c <7%, SBP <140 mmHg and LDL-C <1.8mmol/l) targets achieved and the magnitude of ABC changes of patients with T2DM with and without MDD.

4. To evaluate the admissions for macrovascular complications among patients with T2DM+MDD, T2DM-MDD and MDD only.

Study 4: Compare the depressive symptoms and the CVD risk profiles (body mass index (BMI), depressive symptoms, smoker status and family history of diabetes or heart disease) within the T2DM+MDD, T2DM-MDD, MDD and a healthy control group.

1.2. Literature Review

1.2.1. The South African Health System Landscape

The health system in SA is described as a pluralistic system consisting of partly privatized and partly socialized health care.[44] The two-tier healthcare system in SA has a relatively large (85%) under-resourced public health sector,[19] with services ranging from free primary healthcare services to secondary and tertiary care offered at government state-owned hospitals. According to the 2019-2020 Council of Medical Schemes (CMS) annual report[45] the private sector, on the other hand, provides high-quality facilities for the insured minority (15%) or for those who can afford care out-of-pocket.

The private healthcare sector developed in response to the government concentrating on providing public healthcare services to those individuals of the populace who were unable to pay for healthcare services. However, in the last 2 decades service delivery and the standards of health facilities in the public sector have been deteriorating[46] leading to the demise of the public health sector and the rise of the private healthcare sector.

According to the 2012/2013 CMS report[47], and the general household survey (GHS) 2012[48], 16.6% of medical scheme beneficiaries and approximately 25.8% of non-medical scheme beneficiaries were served by the private healthcare sector (largely for primary healthcare services) at the end of 2012. Since 2012, the private healthcare sector has grown economically and is well established in providing excellent primary healthcare services to an estimated 38% (medical and non-medical scheme beneficiaries) of the South African population[47], made possible through skilled general practitioners, specialists and allied healthcare providers.[49] This sector plays a pivotal role in the healthcare economy of the country by creating employment, training and development programmes, investment prospects and healthcare scalability through innovation and productivity gains.[50]

The South African healthcare system is not without its challenges be it in the public or private sector. The burden of diseases borne by SA, with a population of 60,4 million, is seen as disproportionately high compared to other developing countries.[44] The combination of the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and tuberculosis epidemics, physical and mental health disorders, maternal, neonatal, and

child deaths together with unnatural causes account for the very high burden of morbidity and mortality in SA.[3] Results from a 14-year study (1997-2010) conducted by the burden of disease research unit at the South African Medical Research Council,[51] show that CVDs were among the leading categories of NCDs due to the high rates of hypertension[52] and obesity[53] among South Africans.

The increase in trends for specific diseases such as CVD and T2DM is driven by a change in economic shift and urbanisation associated with nutrition transition with more South Africans falling into the overweight and obese category. T2DM, due to its association with microvascular and macrovascular complications, continues to be a persistent public health problem in SA. The estimated direct medical costs attributed to 240,000 diagnosed, treated and controlled patients with T2DM in 2018 in the public sector was over ZAR 2.7 billion, with approximately 51% of the costs attributed to the management of T2DM and 49% to the cost of diabetic complications such as retinopathy, renal disease, amputation, stroke, coronary artery disease (CAD).[54]

As part of ongoing efforts in finding solutions to strengthen the health system in line with the principles of Universal Health Coverage, the National Department of Health launched nine commissions for discussion. Among the nine commissions, engagements with the private sector were professed to improve access, coverage and quality of health service, and empower the community with adequate and appropriate community-based care.[19] The private sector plays an important role in assisting the government to fulfil its mandate of providing quality healthcare services to all South Africans.

1.2.2. Private healthcare insurance in South Africa

Private medical schemes in SA are non-profit organisations that provide health insurance cover to their members.[55] Members belonging to a scheme contribute a fee and in return receive medical cover according to the rules of the scheme. Each medical scheme (health insurer) provides a minimum set of health benefits to its members and helps reimburse for their healthcare needs, such as doctor visits, nursing, surgery, dental work, medicine and hospital admissions. For the financial year 2019/2020, the South African CMS regulates 76 medical schemes, 19 administrators and 41 managed care organisations.[45] Being a member of a medical scheme means one has access to private medical care as opposed to relying on public health services.

Most medical schemes (e.g. Discovery Health (Pty) Ltd, Liberty Health Administration (Pty) Ltd) outsource their administration services to external companies that specialize in providing services such as day-to-day processing of claims, handling call-centre queries,

membership and payment issues, including managed-care services, whereas other schemes (e.g. Rand Water Medical Scheme, Medshield Medical Scheme) are self-administered.[45] Several managed care companies also exist offering specific types of services such as disease management programmes to medical scheme beneficiaries, whose purpose is to reduce costs and manage healthcare solutions.[45] Managed healthcare, in the context of this study will be explored further in the next section.

1.2.3. Managed healthcare

Managed healthcare is a management tool contracted by health insurance providers (medical schemes) to manage the provision of healthcare and is aimed at cost containment. The purpose of managed healthcare is to have better patient outcomes by focusing on illness prevention and care management of their scheme plan members. In the USA, different managed care systems are utilised, such as Health Maintenance Organization, Preferred Provider Organization and Point of Service, limiting a patient to the number of providers or choice of "within-network or out-of-network" provider care covered for the plan selected.[56]

Within the South African context, managed care organisations (MCOs) use a variety of strategies and management interventions to reduce costs, such as provider cost-sharing engagements, preferred provider arrangements, reimbursement mechanisms, and benefit designs for coverage and the level of benefits reimbursed. Managed care systems are individualised to suit patients' needs for physical or emotional illness, and vary significantly between MCOs.[18] Some managed care plans seek to improve the quality of health by emphasizing disease prevention and care management for diseases such as T2DM and CVDs., whereas others offer comprehensive care for an individual disease, e.g. cancer care in curative and palliative settings.[57]

Managed care was introduced in the South African healthcare market for the private sector in the 1990s using the American approach to healthcare delivery as a means to reduce costs. The managed healthcare method was incorporated into the Medical Schemes Act (MSA) in 2000[58] and defined as "*clinical and financial risk assessment and management of health care, with a view to facilitating appropriateness and cost effectiveness of relevant health services within the constraints of what is affordable, through the use of rules-based and clinical programmes*." (Regulation 15, page 13) [59]

To regulate the cost and utilisation of health services, different delivery models were developed to control costs and increase efficiency.[56] Managed care was one such model which was a medical delivery system offering various administrative and financial

arrangements to manage the quality and cost of medical services that individuals receive.[60] This led to the establishment of managed healthcare organisations contracted to medical schemes to provide healthcare services with higher levels of quality care at efficient costs to patients covered by the medical schemes in SA.[61]

The main features of managed healthcare delivery systems include integration of services among healthcare professionals, i.e. physicians, nurses, pharmacists and allied health professionals, cost-containment strategies such as a capitation model of care; network of preferred providers; and quality assurance mechanisms.[60] A common mode in the delivery of comprehensive care is through a pre-authorisation system, whereby the member and/or provider is directed to provider networks, utilisation review programmes, clinical guidelines, formularies, disease management programmes and risk-sharing arrangements.[50] This way, member benefits are moderated in cases where unauthorised services are accessed outside the managed healthcare system. The objective is to reduce healthcare costs, optimise scheme benefits and resource utilisation and to provide evidenced-based care management, thereby improving outcomes.[60]

These managed healthcare delivery systems for T2DM are endorsed by the CMS[18] and include drug utilisation review (DUR) pharmacists, T2DM and CVD nurse educators and chronic medicine management programmes that utilise evidence-based South African diabetes guidelines for medicine and disease management.[62] Some of the cost-effective tools employed to manage and monitor patients with T2DM are regular screening of glycated haemoglobin (HbA1c), blood pressure (BP) and lipid subfractions.

The main healthcare delivery payment systems utilised in the private schemes arena in SA are the traditional fee-for-service (FFS) payment model[63] and the capitation risk-sharing model (CM). In an FFS system, the provider is reimbursed for each service delivered. Conversely, in a CM payment system, a set negotiated fee is paid monthly in advance by the scheme to the managed healthcare organisations that are the coordinators who provide disease management programmes for members enrolled on CM.[18] Medical schemes incorporate CM models of care into their managed health delivery for the care of patients with T2DM to improve patient outcomes.[18,24]

1.2.4. Type 2 Diabetes Mellitus

Diabetes mellitus is a metabolic disorder that affects the blood glucose in the body, i.e. the body does not produce sufficient hormone insulin or the body is resistant to the insulin produced, and is characterised by chronic hyperglycaemia. Several pathogenic pathways are involved in the development of diabetes mellitus and include processes that impair or

destroy pancreatic beta-cell functions which result in insulin deficiency and abnormal insulin action (i.e. insulin resistance and insulin insensitivity).[62] The deficient action of insulin on the target liver, skeletal muscle and adipose tissues causes abnormalities in carbohydrate, protein and fat metabolism which also leads to diabetes mellitus.[62] Individuals are categorised as having or developing diabetes mellitus by clinical stages normoglycaemia, to intermediate hyperglycaemia (impaired fasting glucose, impaired glucose tolerance), and according to 'aetiology types' of diabetes, and other categories of hyperglycaemia (i.e. diabetes mellitus in pregnancy).[64] The aetiological types of diabetes mellitus are type 1, type 2 and gestational diabetes mellitus.[64,65]

Type 1 diabetes mellitus (T1DM) is immune-mediated and results from pancreatic beta-cell destruction which usually leads to absolute insulin deficiency, and occurs in 5%-10% of patients presenting with a form of diabetes mellitus.[62] Individuals with T1DM need daily insulin injections to keep their blood glucose levels within an appropriate range. Without insulin, they cannot survive. T2DM is the most common type (90% of patients presenting with diabetes mellitus),[1] and is a result of the progressive disorder of insulin action.[62] T2DM may develop and be present for a long time before diagnosis, and the onset of T2DM is most often difficult to determine. Therefore stringent measures for screening T2DM are strongly advocated, as almost 30-80%[62] of the population remain undiagnosed and are identified only after a complication of diabetes mellitus such as polyneuropathy, chronic kidney failure, retinopathy or a stroke has occurred.[1]

The causes of T2DM are strongly linked to overweight, abdominal obesity,[66] ethnicity, age and family history,[64] and of these risk factors, weight gain and obesity are modifiable.[1] The keystone of T2DM management is by promoting a healthy lifestyle and includes medical nutritional healthy diets, regular physical exercise, maintaining normal body weight and smoking cessation.[62] Should the lifestyle changes not be sufficient in controlling the blood glucose levels, then the recommendation from the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA)[62] and American Diabetes Association (ADA)[67] guidelines is the initiation of oral medication, usually metformin, as first-line medication. If metformin is still not adequate, then a range of non-insulin therapies (e.g. sulphonylureas, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 agonists and sodium glucose co-transporter 2 inhibitors) are available and can be used as combination therapy options.[62] Insulin therapy is also an add-on option if any non-insulin therapies fail to achieve blood glucose control.[62]

T2DM is a seriously debilitating condition and a well-established risk factor for CVD. In addition to hyperglycaemia over a prolonged period, individuals with T2DM are also predisposed to traditional risk factors such as hypertension, dyslipidaemia, abdominal

obesity or physical inactivity and therefore have an increased risk of CVD events compared to non-diabetic individuals.[68,69] Uncontrolled hyperglycaemia and variability in blood pressure (BP) in T2DM patients can lead to the development of adverse diabetic microvascular complications of the kidneys, eyes and peripheral nervous system, as reported by the United Kingdom Prospective Diabetes Study (UKPDS).[27] Therefore, beyond managing the control of blood glucose it is exceedingly important to manage BP and lipid levels frequently in individuals with T2DM.

Major diabetic vascular events related to fatal or non-fatal CVD events such as myocardial infarction, congestive cardiac failure, stroke, and angina have a strong bearing on the outcome of the disease, as these events require intense interventions, such as a percutaneous transluminal coronary angioplasty[70] or a coronary artery bypass surgery.[71] Coronary artery bypass grafts are extremely expensive and reported to be frequently performed and pose a significant drain of healthcare resources.[72] According to the Heart and Stroke Foundation, in SA approximately 8 400 coronary bypass operations are performed per year and most of them are done in the private sector.[73] Conclusive evidence exists in the secondary prevention of macro-and microvascular complications in patients with T2DM.[74,75] Interventions that reduce the risk of CVD events in patients with T2DM include improving their glucose, lipid and BP control[76] to achieve HbA1c <7.0%, BP <130/80mmHg, (140/90mmHg for low and middle-income countries including SA),[77] and LDL-C <1.8mmol/l, also referred to as ABC guideline targets for patients with T2DM[78, 79] - a strategy that is relatively simple and cost effective[80] compared to the costs associated in a procedure to remove a plaque from a blocked blood vessel or the implantation of stents in the coronary vessels.[81]

Targeting blood glucose alone in individuals with T2DM does not reflect the actual reduction in CVD events as was seen in the results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study[82] that showed a higher risk of CV and all-cause mortality in those on intensive glycaemic control having a higher risk for hypoglycaemia. Although insulin therapy has been reported to reduce glycated haemoglobin (HbA1c) aggressively, it is not as cost-effective due to the premium cost of insulin therapy compared to other hypoglycaemic agents.

T2DM continues to be a major public health issue affecting vast numbers of individuals in South Africa (SA). Globally the prevalence of T2DM is high, but it has reached endemic levels in SA driven by a societal, economical and nutritional transition over the past decade. This rapid rise is due to increasing urbanisation, lifestyles that are more sedentary, and greater consumption of unhealthy diets associated with obesity. The SA national prevalence

of adults (20-79 years old) with T2DM was 7% in 2015,[83] which increased to 12.7% in 2019.[84]

This poses a huge financial burden on the private healthcare system in SA in terms of treatment and management of T2DM and its complications.[54]

1.2.4.1. Medical management of T2DM within a private healthcare setting

Patients register on the scheme's chronic programme once the treating doctor states the patient's medical condition via a telephonic or written prescription to the medical scheme.[85] Patients are classified as having T2DM if they had any of the International Classification of Diseases and Related Health Problems, 10th revision (ICD10) diagnosis codes of E11.0 (Type 2 diabetes mellitus with hyperosmolarity) to E11.9 (Type 2 diabetes mellitus without complications) as stated by the practitioner, which is in accordance with the CMS Prescribed Minimum Benefits ICD-10 coded list.[23] In addition to the T2DM diagnosis code, any diagnostic glycaemic test defined by SEMDSA guidelines,[62] i.e. random plasma glucose is ≥11.1 mmol/L or fasting plasma glucose is ≥7.0 mmol/L or HbA1c is ≥6.5% is taken into account before a patient is registered as having T2DM by the scheme. Once the patient is registered on the chronic programme, the member will have access to benefits for their diabetic medications and medical management (consultations, services and procedures) for T2DM. The medical management of T2DM within the private healthcare setting is based on scheme protocols, rules and medicine formularies aligned with Prescribed Minimum Benefit-Diagnosis Treatment Pairs algorithms and CMS guidelines. Schemes include T2DM disease management programmes which involve a multidisciplinary team of doctors, diabetes nurse educators, dieticians, podiatrists and pharmacists at an allocated facility for review of the patient's diabetes management and treatment.[86] In this setting, T2DM is managed as a discrete condition; the focus is on the prevention of hospitalisations due to hypoglycaemia or diabetic ketoacidosis, and on glycaemic control to prevent long-term micro- and macrovascular complications of T2DM.[24] Comorbid conditions are seen as standalone and treated in isolation from T2DM.

1.2.4.2. Comorbidities in patients with T2DM

Patients with T2DM present with multiple comorbidities, with high frequencies of concordant comorbidities (CC), i.e. coronary artery and cerebrovascular diseases that share the same pathophysiology and management of T2DM;[87] and discordant comorbidities (DC) such as MDD, gout, cancer and rheumatoid arthritis managed discretely to T2DM, but may co-occur with T2DM.[88,89] A recent study conducted by Nowakowska et al.[90] in the United Kingdom reported that people living in the most deprived areas had more than one comorbidity

present at the time of diagnosis, with a high prevalence of depression, noted across both the deprived and affluent areas.

The presence of CC and DC in patients with T2DM has been reported to be associated with both better and worse diabetes care and self-management. Piette and Kerr's framework[91] of conditions concordant and discordant with diabetes care suggests that patients with CC will receive better diabetes care due to the provider's synergistic care that supports diabetes management with overlapping CV risk reduction goals i.e. blood pressure and lipid monitoring for T2DM, dyslipidaemia and hypertension, while patients with DC (dissimilar to diabetes management) may not receive the same care, as they may be less likely to be identified and included in diabetes care goals, due to provider distraction (for example, while ordering for glycaemic, lipid or kidney tests) and competition for time and resources. Discordance can be a deterrent when the task to manage T2DM is complex.[92]

The impact of CC and DC on ABC guideline target attainment in patients with T2DM has shown inconsistent outcomes. In considering CCs, Pentakota et al.[93] reported that having a CC only showed better lipid control, whereas Woodard et al.[94] found a higher likelihood of both glycaemic and lipid control. Similarly, DCs were found to be associated with both improved and poorer diabetes care, as reported by Magnan et al.[92], while Aung et al.[95] reports that the presence of DC influenced only one provider activity (BP examinations), having CC showed more adherence to T2DM guideline-recommended care. No association was found between comorbidity type and the overall Patient Assessment of Chronic Illness Care score.[95]

1.2.4.3. Depression as a risk factor for T2DM

Depression is a risk factor that is associated with a two to three-fold increased risk for obesity,[96, 97] T2DM[98] and CVD,[99] yet routine depression screening in patients with T2DM is not regularly performed at primary care clinics.[100] The course of depression in patients with T2DM is chronic and severe; even with successful treatment as many as 80% of patients who have T2DM with a depressive episode will experience depression relapse.[101]

Depression is a stronger predictor of T2DM than vice versa as evidenced by longitudinal studies conducted by Mezuk et al.[98] that showed depression associated with a 60% increased risk of developing T2DM and a 15% increased risk of developing depression in patients with T2DM compared to persons without T2DM. Golden et al.[102] reported a modest association of baseline depressive symptoms with incident T2DM that was to some extent attributed to poor health behaviours (i.e. high-calorie intake, being less physically active, are more likely to be smokers and alcohol users) that are typically associated with T2DM onset. Results from a meta-analysis conducted by Yu et al.[103] found that depressed people

have a 32% risk of developing T2DM. This is supported by the earlier report of a meta-analysis conducted by Knol et al.[104] where depressed adults have a 37% increased risk of developing T2DM.

Globally, the prevalence of T2DM and depression is increasing at a rapid rate, with more patients with T2DM presenting with comorbid depression at various levels of severity.[9] Depending on the severity of depressive symptoms, the increased risk of development of T2DM can amount to 30%. Depression is found to be associated with T2DM with hyperglycaemia,[105] with recurrent episodes of hypoglycaemia, glucose variability, non-compliance with treatment and diabetes-related complications.[106] These consequences suggest that the burden of having a chronic mood disorder such as MDD is associated with the development of T2DM and impaired or unstable glucose metabolism contributes to the co-occurrence of depressive symptoms in T2DM.[107,108]

Due to the prevalent nature of comorbid MDD and T2DM, patients who present with MDD should be monitored over time for the development of T2DM risk factors, including glucose dysregulation, poor diet, lack of exercise, smoking and poor medication adherence.[30] Targeted screening and monitoring of individuals with T2DM for depressive disorders can also assist in the detection of undiagnosed cases of MDD among patients with T2DM.[30] Primary healthcare screening protocols for these conditions can decrease the late entry of patients into the health systems thus managing the long-term complications of T2DM and MDD.

1.2.5. Major Depressive Disorder

Major depressive disorder (MDD), the most serious form of unipolar depressive disorder, is another important public health problem affecting a large number of individuals worldwide, with an overall prevalence being 8.7%.[109] The latest estimate of MDD among adults aged 18 or older in the USA to have had at least one major depressive episode was 8.4%.[110] In SA the lifetime prevalence of MDD is 9.7%.[111] According to the South African Stress and Health survey conducted between 2002 and 2004, females were 1.75 more likely to develop MDD than males.[112] Results of a longitudinal panel survey conducted from 2008 to 2012 of a nationally representative sample of households that assessed the spatial distribution of depression in SA showed substantial geographical clusters of depression around SA. The concentration of excessive clusters of patients with depression that overlapped with self-reported tuberculosis, poorer and less educated people living in traditional rural communities, was in the eastern part of SA.[113] Risk factors for depression include biochemical factors (low levels of serotonin, norepinephrine, dopamine), genetic (immediate family member with a mood disorder or depression), sleep disorders, serious illness

(cancer, stroke, diabetes, arthritis, heart disease, dementia, Parkinson's disease), social factors (abuse and violence), substance abuse, medications (sedatives, steroids) or major life events (death of a loved one, divorce, retirement).[114] MDD, also known as clinical depression, is characterised by single or recurrent major depressive episodes. The essential feature of a major depressive episode (MDE) is at least 2 weeks of depressed mood and daily presentation of any 5 of the following abnormal features: neurovegetative symptoms (e.g. weight loss, increase or decrease in appetite, insomnia or hypersomnia), psychomotor activity (e.g. fatigue or loss of energy and interests, agitation or retardation observed by others), cognition (feelings of unworthiness, hopelessness or inappropriate guilt, diminished ability to think or concentrate, indecisiveness), anxiety and suicidal ideation.[6]

The prognosis of MDD is lifelong. After the first MDE most patients will recover but are likely to present with recurrent major depressive episodes,[115] while some patients (approximately 30%) do not recover from the first episode and experience persistent mild depression with occurrences of major depressive episodes (double depression).[116,117] It is therefore critical to perform a thorough diagnostic evaluation to determine the presence of MDD and comorbid psychiatric or general medical conditions with regular monitoring of symptom severity.[118] Evidence-based clinical diagnostic tools and measurement-based diagnostic tools in the assessment of MDD, depression severity and presence of co-occurrence of other mood and general medical disorders are available as clinician-rated diagnostic instruments (such as the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition),[6] and for patients self-evaluation, a 9-item Patient Health Questionnaire (PHQ-9).[119]

With psychotherapy and or antidepressant treatment full remission is possible and can be defined as elimination of symptoms and depression scores of seven or less on the clinician-rated 17-item Hamilton Depression Rating Scale (HDRS-17).[120] The American Psychiatric Association (APA),[121] National Institute for Health and Clinical Excellence (NICE)[114] and the South African Society of Psychiatrists (SASOP) provide evidence-based treatment guidelines for psychiatric disorders.[118] For mild depression, psychotherapy or antidepressant monotherapy is advised, while for moderate and severe major depressive disorders, a combination of antidepressant therapy and psychotherapy is recommended as first-line treatment options.[118]

In terms of selecting the most appropriate choice of medication, the guidelines advise choosing drugs that are available, safe and tolerable, cost-effective and include patients' needs and preferences while deciding the appropriate therapy.[122] Evidenced based medicine has shown selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, or the norepinephrine-dopamine reuptake inhibitors,

and mirtazapine or trazodone as having superior tolerability and safety over the use of the tricyclic antidepressants and the monoamine oxidase inhibitors. Second-generation newer classes of antidepressants such as bupropion (a norepinephrine dopamine reuptake inhibitor) vortioxetine (a serotonergic antidepressant) or agomelatine (a melatonergic agonist) may also be used.[118]

More importantly, in patients with MDD with comorbid medical disorders, the choice of antidepressants requires careful consideration because of the potential for drug-drug or drug-disease interactions.[123] For instance in patients with cardiac disease, tricyclic antidepressants should be avoided,[124] while in patients with T2DM, stroke or epilepsy an SSRI is preferred.[125,126] In older adults and patients with CVD who do not respond to SSRI antidepressants, newer second-generation antidepressants can be offered as safe and effective alternatives to tricyclic antidepressants reported by Behlke et al.[127]

1.2.5.1. Medical management of MDD within a private healthcare setting

Patients register on the scheme's chronic programme once the treating doctor states the patient's medical condition of MDD with ICD10 codes F32.2 (MDD, single episode, severe without psychotic features) to F33.9 (MDD, recurrent, unspecified). Once the patient is registered onto the chronic programme, the member will have access to benefits for their antidepressant medications and psychotherapy management (consultations, services and procedures) for MDD. In addition, a minimum of 21 days of hospitalisation in a mental institution is reimbursed by the scheme for the acute phase of MDE or a severe episode of suicidality, psychosis, or level of functional impairment. This is per the PMB-CMS regulations.[23]

Members diagnosed with MDD enrol on an emotional wellness programme which involves a psychiatric nurse educator providing patients (telephonically) with emotional support, educational material on mood disorders, and referrals to psychiatrists and psychologists when required (i.e. should the member show signs and symptoms of suicidal ideations, thoughts of self-harm, struggling with mood issues, or declining functional assessment scores).

In this setting, MDD is managed discretely, with a focus on providing patients access to benefits and preventing readmissions. There is no holistic management of the comorbidities associated with MDD, such as T2DM or CVDs. These are seen as separate diseases and managed individually, despite the patient being registered on the chronic programme for MDD, T2DM and or CVDs.

1.2.5.2. Major Depressive Disorder as a risk factor for cardiovascular diseases and mortality

A bidirectional link between MDD and CAD has been established where CAD can cause MDD while depression is a risk factor for the development of CAD.[128] CAD is a heart condition brought about when the major blood vessels supplying the heart become damaged or diseased. Cholesterol plaques that build up in the coronary arteries together with the inflammation reduce blood flow and cause chest pains (angina) and shortness of breath. A complete blockage can cause a heart attack and is a leading cause of mortality and morbidity in patients with T2DM.[129] As many as 50% of patients with T2DM die of a heart attack,[26] and people with psychosocial stressors, especially MDD, have a 30% risk of acute myocardial infarction.[11]

The patient's overall medical health is negatively affected by MDD and can affect adherence to treatment regimens.[130] Active surveillance and treatment of MDD have shown better outcomes, especially in patients with CAD[131], besides the benefits of mood elevation. Effects of antidepressant medication with an SSRI have shown a 43% reduction in death or recurrent myocardial infarction as compared with the depressed patients not receiving an antidepressant.[29] Successful treatment of MDD can result in improvements in the patient's well-being as well as improved outcomes of their overall medical conditions.[132] Evidence from an Improving Mood-Promoting Access to Collaborative Treatment-IMPACT randomized controlled trial suggests that collaborative depression care lowered the excess risk of fatal or non-fatal CVD events by 48% among older depressed patients without baseline CVD.[133]

1.2.6. Relationship of T2DM and MDD

Although the comorbidity between T2DM and MDD is very common and the outcomes of each condition worsened by the other, the factors contributing to the relationship between these two NCDs have not yet been fully explored. According to Holt et al.[134] more research is needed to understand the factors contributing to individual differences in treatment response, the resistance to depression and metabolic disorders across the life span of the individual, the best care plans to be provided for individuals with T2DM and comorbid MDD in different healthcare settings. Currently, the relationship between T2DM and MDD is moderately explained by their shared pathophysiological and psychosocial behavioural mechanisms, the psychological and physical disease burden, poor diabetes outcomes and increased healthcare utilisation and healthcare costs; further elucidated in the sections below.

1.2.6.1. Pathophysiological relationship

There is substantial evidence showing inflammation as a critical mediator in the pathophysiology of depression.[135,136] Additionally, emerging evidence demonstrates shared mechanisms between MDD and T2DM and between MDD and CVD which are attributed predominantly to the immunometabolic pathways.[137,138,139,140] Elevated levels of pro-inflammatory cytokines have been demonstrated in patients with MDD and T2DM.[123] MDD has been attributed to alterations in the regulation of hormones through the hypothalamic-pituitary-adrenal axis activation often leading to high levels of pro-inflammatory cytokines and receptors.[141,142] Over some time, this alteration of hormone regulation can lead to somatic consequences such as elevated BP and blood glucose, abdominal obesity and dyslipidaemia. However, not all patients with MDD have elevated levels of pro-inflammatory cytokines, and not all patients with an inflammatory response experience alleviation from their depressive symptoms through anti-inflammatory agents as reported by Miller et al.[143] but they suggested that a subgroup of patients may develop depression due to inflammation.

1.2.6.2. Psychosocial behavioural mechanisms

Behavioural mechanisms such as inactive lifestyle, unhealthy dietary habits, ethnic risk factors and sleep disturbances shared between T2DM and MDD may be contributing factors in understanding the link between these two NCDs.[144] The risk of MDD among patients with T2DM is increased by a history of depression, diabetes symptoms, and having CV procedures.[145]

1.2.6.3. Healthcare utilisation and medical costs

Emerging studies have consistently shown increased healthcare utilisation and medical costs among individuals with T2DM and comorbid MDD than in individuals with T2DM alone.[146] Gilmer et al.[147] reported that depression was associated with a 50% increase in costs ($31,967 vs. $21,609; $p<0.05$) in patients with diabetes. Whereas Le et al.[148] found patients with T2DM and MDD on managed care plans in the USA had higher diabetes-related total medical costs ($19,298) than patients with T2DM alone ($4,819). Diabetes complications and MDD were strong predictors of health service costs reported by Simon et al.,[149] which were approximately 70% higher for individuals with MDD than for those without any depressive disorder ($5,361 over 6 months vs. $3,120, $p<.001$). MDD remained strongly associated with increased costs at all levels of diabetes severity.[149]

The trends in costs of depression in adults with diabetes in the USA from a Medical Expenditure Panel Survey for the years 2004-2011 showed that expenditures were $2,000-3,000 higher for unrecognised and asymptomatic depression than no depression, and $5,000 higher for symptomatic depression.[150] A follow-up study by Egede et al.[151]

highlighted the enormous cost savings possible through aggressive screening, diagnosis and treatment of depression from the survey responses.[151]

1.2.7. Association of comorbid MDD on the outcomes of T2DM

The association of mood disorders and general medical conditions has been well established, especially so in patients with T2DM who have CVD.[1, 152] As CVD is recognised as a major global health problem, the extent of mood disorders associated with CVD has received much attention. It is now established that the relationship between depression and CVD is a bidirectional one with depression being a CV risk factor; and CVD leading to an increased risk of depressive illnesses.[153] Studies show that improvement of depressive symptoms improves medication adherence in patients after an acute myocardial infarction.[154]

Treating depressive disorders in T2DM is associated with improvements in depressive symptoms [35,155,34,] but the evidence for a reduction in glycaemic control is still controversial. De Groot et al.[106] and Lustman et al.,[156] showed that patients with T2DM+MDD have higher HbA1c levels and increased prevalence of micro-and macrovascular complications compared to patients with T2DM-MDD. Yet a systematic review and meta-analysis of psychological interventions to improve glycaemic control in patients with T2DM by Ismail et al.,[37] reported depression to be weakly correlated with glycaemic status. Analysis of data in veterans with T2DM from a general hospital of psychiatry reported depression associated with persistently higher HbA1c levels over time and a significant longitudinal relationship between depression and glycaemic control.[157] The variation of glycaemic control across the studies may be attributed to the types of study designs; the veteran study investigated the effect of depressive symptoms on glycaemic control, whereas the systematic review was focused on the glycaemic control of people who received psychological therapies.

1.2.8. Bidirectional relationship of T2DM and MDD

Reports on the relationship between T2DM and MDD are now abundant. Longitudinal studies show the association between T2DM and MDD is bidirectional, with MDD increasing the risk of T2DM and consequently, T2DM increasing the risk of MDD.[98, 158] In addition, the manner of causation between these two NCDs may result in a relationship that is most likely to be bidirectional.[98] It is now commonly accepted that T2DM and MDD have bidirectional associations[159,160,161,107], although it is not known which condition typically develops first. The findings of Golden et al.[102] showed a modest association of depressive symptoms with incident T2DM and treated T2DM showed a positive association with improvement of depressive symptoms. Results of a meta-analysis of nine longitudinal studies suggest that

adults with depression or high-depressive symptoms have a 37% increased risk of developing T2DM compared with those who are not depressed or have low-depressive symptoms.[104]

It is also well established that the prevalence of MDD in patients with T2DM (17.6%) is approximately twice as high as for those without T2DM (9.8%), and higher in females with T2DM (24%) than in males (13%).[162] The bidirectional association of these severe NCDs contributes significantly to the excess morbidity and mutually adverse effects on long-term outcomes.[106] Individuals with T2DM+MDD or depressive symptoms tend to have impaired glycaemic control, increased rates of mortality, T2DM related complications and hospitalisations, poorer T2DM self-care and lower quality of life.[156]

MDD is often not acknowledged in depressive patients with a medical comorbidity. General physicians tend to investigate and treat general medical diseases, while depression is undetected or considered secondary. This was demonstrated in a population-based survey where only half of the patients with MDD were diagnosed and treated by a regular health care professional.[163] Chin et al.[164] showed that only 23.1% of depressive patients were diagnosed when consulting a primary care physician, patients with moderate depression being less likely to be diagnosed (17.8%) than those with moderately severe or severe depression (30.8% and 49.4%, respectively).

In this study, within the private healthcare setting, providers have the opportunity to identify high-risk individuals and improve the rate of early detection of T2DM and associated comorbidities i.e. hypertension, dyslipidaemia and MDD. Community based guidelines such as the SEMDA guidelines for the management of T2DM[62] focuses on affordable and inclusive interventions easily implemented and relatively straight forward to monitor with a simpler treatment and cost effective management**.** One such intervention includes six monthly blood glucose and lipid testing. Similarly, following SASOP guidelines[118] in terms of performing thorough assessments to determine the presence of MDD and comorbid general medical conditions, such as T2DM. From the scheme's perspective, implementing and encouraging members to actively perform PHQ-9 self-evaluation,[165] to identify undetected MDD in patients with T2DM, and measuring depressive symptom severity in patients with MDD. Ultimately, assisting patients with frequent check-ups, regular laboratory testing, measuring depressive symptoms, lifestyle management, and consistent adherence to medication, patients with T2DM+MDD can lead long and healthy lives.

1.3. Structure of the thesis

This research explored the relationship between T2DM and MDD in a South African private managed healthcare setting, in terms of economic burden (healthcare resource utilisation and medical costs) and clinical (Glycaemic and lipid control, and macrovascular complications) outcomes in patients with T2DM and comorbid MDD.

In order to gain better insight into possibilities for improved disease management of the two NCDs (T2DM+MDD) for better financial and health outcomes, a quantitative analysis of claims data over a 5-year period (2012-2016), and a structured survey of 15 questions (which included PHQ-9 and non-invasive CV risk anthropometric measurements) as a cross-sectional study was conducted from 2016 to 2019.

This research project utilised data of members of a private medical scheme between 2012 and 2019. The population sample selected was discrete for each study period. In 2014, the electronic-health-records (EHR) were more robust than the preceding years therefore, data in year 2014 was studied. In 2016, the scheme terminated the contract with the service provider utilising CM of care for diabetes management, hence the 5-year data analysed was until year 2016. The sample selected in year 2019 had more patients with available clinical data i.e. HbA1c, complete lipogram and BP readings.

Confidentiality was maintained throughout the analysis; the patients' unique scheme membership number and dependent code was used to align patient-level records. The University of the Witwatersrand Johannesburg, Faculty of Health Sciences Human Ethics Committee (M140326; M1911196) approved the study (Appendix A). Further approval was granted by the Principal Officer of the scheme for the scheme data to be used in the study and by the Human Resources Manager to gather data from the scheme administrative database for the research.

The sequence of the studies is shown in Figure 1.1 and the details of the methods are further elucidated in each respective study.

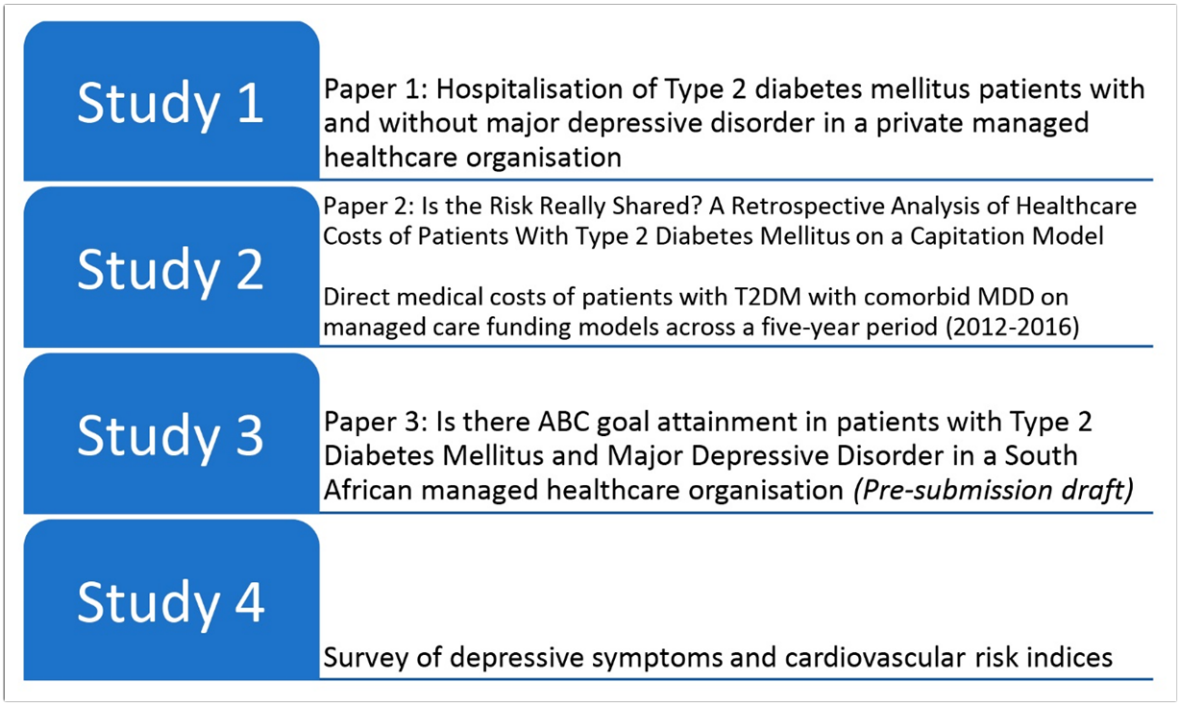


Figure 1.1 Sequence of studies within the thesis

Chapter 2. Study 1

2.1. Introduction to study 1

Study 1 is a published paper (paper 1). This paper describes the relationship between the type 2 diabetes mellitus (T2DM) and major depressive disorder (MDD) in terms of the prevalence of comorbidities, hospital resource utilisation for diabetes-related events (hypoglycaemia, micro-and macrovascular events) and other related events in this private managed care setting in 2014.

2.2. Contributions of the candidate to study 1

The candidate has made a substantial contribution to the preparation and submission of this study in terms of the intellectual content, i.e. the concept and design, acquisition of data, analysis and interpretation of data and drafting of the manuscript.

2.3. Paper 1: Hospitalisation of Type 2 diabetes mellitus patients with and without major depressive disorder in a private managed healthcare organisation

Naidoo L, Butkow N, Barnard-Ashton P, Libhaber E. Hospitalisation of Type 2 diabetes mellitus patients with and without major depressive disorder in a private managed healthcare organisation. *Journal of Endocrinology, Metabolism and Diabetes in South Africa*. 2019 Nov 1;24(3):70-6.

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ARTICLE

Hospitalisation of Type 2 diabetes mellitus patients with and without major depressive disorder in a private managed healthcare organisation

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Background: The relationship between Type 2 diabetes mellitus (T2DM) and associated co-morbidities, particularly major depressive disorder (MDD), is poorly acknowledged in chronic disease management practices in South Africa. Managed healthcare costs and hospitalisation rates may be influenced by the discrete management of co-morbid conditions. Therefore, the relationship between T2DM and MDD in terms of co-morbidity incidence and hospitalisation resource utilisation was investigated.
Method: This retrospective descriptive study analysed the data of 902 adult patients with T2DM from the health system database of a private managed healthcare organisation for 2014.
Results: The mean age was 57 ± 15 years and 85% of the identified T2DM patients had at least one recorded co-morbidity. Among this population 17% presented with MDD. A higher percentage of T2DM patients with MDD were admitted to hospital (42%, $p = 0.004$) compared with those without MDD (30%). The number of overnight admissions was higher among the T2DM with MDD (76%, $p = 0.016$) compared with T2DM without MDD (66%). The T2DM with MDD group (85%, $p = 0.018$) had greater non-diabetes related hospital events compared with the T2DM without MDD group (73%). The T2DM patients without MDD were more likely to be hospitalised for diabetes-related events (27%, $p = 0.018$) at significantly higher admission cost ($p = 0.001$).
Conclusion: Patients with T2DM and MDD present with more co-morbid conditions and had a higher number of hospitalisations than their non-MDD counterparts. However, the hospitalisation costs were significantly higher for diabetes-related admissions in the non-MDD group due to a higher number of macrovascular events. Healthcare organisations need to focus on an integrated approach in the management of chronic conditions with emphasis on active surveillance of T2DM patients, where MDD is identified and treated to lessen the risk of macrovascular complications.

Keywords: concordant and discordant co-morbidities, hospital utilisation, major depressive disorder (MDD), Type 2 diabetes mellitus (T2DM)

Introduction

Type 2 diabetes mellitus (T2DM) and major depressive disorder (MDD) are major public health problems affecting vast numbers of individuals worldwide. Based on the 2015 International Diabetes Federation (IDF) estimates for South Africa (SA), there were 2.3 million adults (aged 20–79 years) with diabetes; the national prevalence was 7.0% with a comparative world prevalence of 7.6%.[1] T2DM and its complications are a concerning source of mortality and a heightened healthcare burden in sub-Saharan Africa.[2] Many studies have discussed the healthcare utilisation and costs of T2DM patients with microvascular and macrovascular complications.[3] Developing and established economies such as Asia, Russia, Canada, the UK, Germany and Australia show that hospitalisation costs associated with major coronary artery disease (CAD), cerebrovascular disease and heart failure is significantly higher than hospitalisations for non-major cardiovascular outcomes.[4]

Co-morbidities frequently occur in patients with T2DM.[5] Approximately 80% of T2DM patients have at least one additional co-morbid condition creating further pressure on the patient and healthcare system.[6] Conditions that are co-morbid with T2DM such as coronary artery and cerebrovascular diseases are often referred to as concordant co-morbidities (CC), due to the similarity of pathogenesis and management. Discordant co-morbidities (DC) such as MDD, cancer and rheumatoid arthritis are considered discrete conditions to T2DM but may co-occur.[7] The 2009 prevalence data indicated that 9.7% of South Africans would have an MDD episode in their lifetime.[8] In the South African private managed healthcare arena the DC, such as patients with both T2DM and MDD, are managed individually through standardised protocols and guidelines per condition.[9,10]

Traditionally, the focus of managed healthcare models for T2DM is the prevention of hospitalisations due to hypoglycaemia or diabetic ketoacidosis.[11–13] These models overlook the other aspects in diabetes management such as cardiovascular disease (CVD), yet many studies have demonstrated the benefits of targeting CVD risk factors such as hypertension and hyperlipidaemia in T2DM patients.[14,15] As many as 50% of T2DM patients die of a CVD event such as CAD, which is a major macrovascular complication of T2DM.[16,17]

Few studies have focused on mood disorders in patients with T2DM, yet these patients are affected by MDD nearly twice as much as in the general population.[18] MDD has been identified as an independent risk factor for both the development of CAD and for worsening prognosis once CAD is established.[19] In an observational secondary analysis report of patients with CAD, the identification and treatment of MDD showed a 43% reduction of recurrent myocardial infarction.[20] Enhanced

depression care for patients with acute coronary syndrome and persistent depressive symptoms has shown promising reduction in the rates of major adverse cardiac events.[21] Therefore, we investigated the relationship between the stated diagnoses of T2DM and MDD, within a private managed healthcare setting, in terms of co-morbidity incidence and hospitalisation resource utilisation.

Method

Study design

The paper presents a retrospective descriptive study of the 2014 healthcare data of 902 adult T2DM patients in a private managed healthcare database of a Chartered Accountants (SA) Medical Aid Fund (CAMAF). Data were sourced from the iMed database, a commercially available administrative system that maintains membership data, claims processing and premiums of members of private medical aid organisations such as the patients with T2DM and/or MDD within CAMAF. The database included:

- patient-level demographics and periods of health plan enrolment;
- medicine management and prescription drug use;
- programme member registration;
- primary and non-primary International Classification of Diseases and Related Health Problems, 10th revision (ICD10) diagnosis codes;[22]
- detailed information regarding hospitalisations, diagnostic testing and therapeutic procedures;
- inpatient and outpatient physician and auxiliary services;
- cost data in the form of managed-care reimbursement rates for each service.

Confidentiality was maintained throughout the analysis; the patients' unique CAMAF membership number and dependent code were used to align patient records.

Setting

The data for this study was obtained at Sanlam Health, a private managed healthcare organisation. Sanlam Health is contracted out to private medical aid bodies such as CAMAF to deliver healthcare services. The study was approved by the University of the Witwatersrand Johannesburg, Faculty of Health Sciences Human Ethics Committee (M140326). Approval was also granted by the Principal Officer of CAMAF for the CAMAF data to be used in the study and by the Human Resources Manager of Sanlam Health to gather data from the iMed database for the research.

Patients

Patients were classified as having T2DM if they had any of the ICD10 diagnosis codes of E11.0 to E11.9 and E12.0 to E12.9 as stated by the practitioner and identified to be on insulin according to the Anatomical Therapeutic Chemical Classification of A10A ('Insulin and analogues'). Patients diagnosed with MDD were identified with ICD10 codes F32.2, F32.3, F32.8, F32.9, F33.1, F33.2, F33.3, F33.4, F33.8, and F33.9. The ICD10 codes utilised in this study were obtained from the Council of Medical Schemes Prescribed Minimum Benefit CMS PMB ICD-10 coded list 2013.[23]

Patients were included in the sample if they were registered on a medicine management programme for T2DM, MDD and other co-morbid conditions in 2014. The disease management programmes target registered patients' disease control in terms of medicines compliance, lifestyle changes and side effects on their medication. Advice is offered on the importance of doctor' visits, performing annual lipograms, blood pressure (BP) monitoring and smoking cessation.

Patients were grouped by their types of co-morbidities as outlined by Piette and Kerr[AQ1].[7] Clinically and economically relevant co-morbid conditions with T2DM were identified and categorised as CC and DC.[24] Initially, four mutually unique groups were created, i.e. T2DM patients without co-morbidities; T2DM patients with DC; T2DM patients with CC; and T2DM patients with CC and DC, to analyse the co-morbidity profile of the sample. Further analysis was performed on the patients with MDD (T2DM + MDD) versus without MDD (T2DM-MDD) due to the high prevalence of MDD in the sample.

Hospital admissions

Hospital admissions of the T2DM patients in 2014 were extracted from the hospital case management database. The primary diagnoses were identified by ICD10 code at the time of the hospital admission and were classified as hospital admissions for diabetes-related events (hypoglycaemia, micro- and macrovascular events) and for non-diabetes related events.[25] Hospitalisations were further categorised by same-day admissions or overnight admissions. Overnight admissions included episodes that required more than one overnight stay in hospital.

Statistical and data analysis

Data from the database were exported to a Microsoft Excel 2016 spreadsheet (Microsoft Corp, Redmond, WA, USA) and statistical analysis was performed with Statistica 13.3 (StatSoft Inc., Tulsa, OK, USA) and SAS 9.4 (SAS Institute, Cary, NC, USA). Continuous variables were presented as mean and SD or median and range and categorical variables as frequency and percentages. Comparisons of three independent groups were performed with analysis of variance (ANOVA). The Bonferroni post-hoc test was used for 2×2 comparisons. Categorical variables were compared with chi-square test or Fisher's exact test, as appropriate. Where multiple comparisons between groups were performed, the level of significance was adjusted using a Bonferroni correction, namely α/the number of comparisons. Hospitalisation costs were calculated as the total hospital admission costs in South African rand (ZAR) per annum and the average cost per overnight stay. Similarly, the costs for the diabetes versus non-diabetes related hospital admissions were individually calculated as the total and the average cost per annum. Average costs of hospital admissions were presented with the SD. A significance level was set at 0.05.

Results

Among the 46 000 registered beneficiaries (54.3% female) in the CAMAF database, 902 T2DM patients (2%) were identified. The co-morbidity profile of the T2DM patients is summarised in Table 1. The mean age of this cohort was 57 ± 15 years and predominantly male (57%). In total, 85% of the identified T2DM patients had at least one of the recorded co-morbidities. The T2DM patients who had both a CC and a DC (41%) were significantly older (63 ± 13.3; $p < 0.0001$) and had twice the rate of hospitalisations (44%) compared with the other groups ($p < 0.0001$).

Co-morbidities of the 902 T2DM patients within the healthcare organisation are shown in Figure 1. Patients may have one or more CC or DC, thus representing more than one condition

Table 1: Baseline characteristics of T2DM patients by types of co-morbidities in 2014

Characteristics	Total	T2DM patients without co-morbidities	T2DM patients with DC	T2DM patients with CC	T2DM patients with CC and DC	*p*-value
n (%)	902 (100)	136 (15)	33 (4)	363 (40)	370 (41)	
Age (years)	57 ± 14.7	44 ± 13.1	49 ± 11.2	56 ± 13.0	63 ± 13.3	< 0.0001
Male *n* (%)	518 (57)	82 (60)	14 (58)	233 (64)	189 (51)	0.0009
Female *n* (%)	384 (43)	54 (40)	19 (42)	130 (36)	181 (49)	
Number of patients on insulin *n* (%)	228 (25)	26 (19)	8 (24)	101 (28)	93 (25)	0.26
Number of patients hospitalised *n* (%)	289 (32)	28 (21)	8 (24)	89 (25)	164 (44)	< 0.0001

within the figures. Hypertension (64%) and hyperlipidaemia (63%) were the most prevalent CC, and MDD (17%) was the most prevalent DC.

T2DM patients with MDD (T2DM + MDD) and without MDD (T2DM-MDD)

Table 2 summarises the characteristics of the patients with T2DM + MDD and T2DM-MDD. In a predominantly male sample (Table 1), a significantly higher proportion of the female sample (Table 2) fell into the T2DM + MDD group ($p < 0.0001$). The T2DM + MDD group had a higher proportion of DC than those without MDD.

Hospital resource utilisation of T2DM + MDD and T2DM-MDD patients

The comparison of the hospital resource utilisation of the two groups is presented in Table 3. There were a greater number of T2DM + MDD patients admitted to hospital (42%) compared with the T2DM-MDD (30%) group ($p = 0.004$) and more patients were admitted overnight in the T2DM + MDD group (36%) compared with the T2DM-MDD group (21%), $p = 0.0001$. The overall admission rate was significantly higher in the T2DM + MDD group (82%; $p = 0.0001$; with 76% being an overnight admission, $p = 0.016$), compared with the T2DM-MDD group (56%) admissions (66% were overnight stays).

Hospital admissions for diabetes and non-diabetes related events in both groups

Table 4 compares the diabetes related admissions and costs between the T2DM + MDD and T2DM-MDD groups. Significantly more T2DM-MDD patients had diabetes related admissions (27%, $p = 0.018$) and significantly higher cost ($p = <0.001$). Figure 2 further shows that these admissions were for

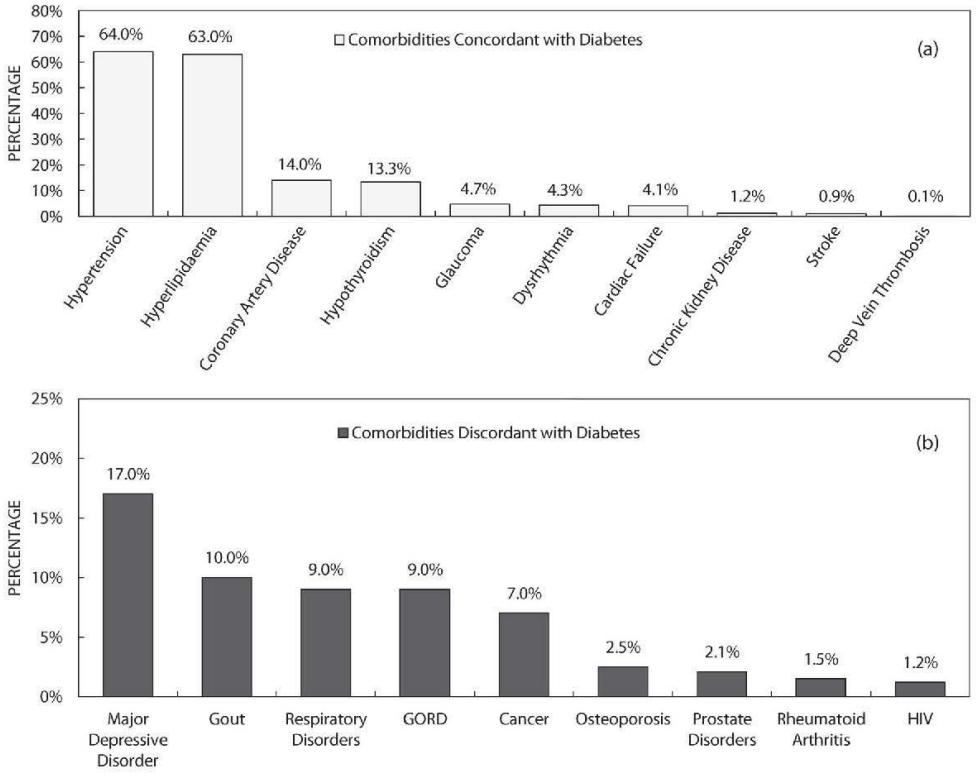


Figure 1: Percentage of T2DM patients with co-morbidities (a) concordant and (b) discordant with diabetes in the study.

Table 2: Characteristics of T2DM + MDD and T2DM-MDD patients in 2014

Characteristics	T2DM + MDD *n* = 153 (17%)	T2DM-MDD *n* = 749 (83%)	*p*-value
Age (years)	60 ± 14	58 ± 15	0.13
Female, *n* (%)	97 (63)	287 (38)	<0.0001
Number of patients on insulin, *n* (%)	42 (28)	186 (25)	0.43
Concordant co-morbidities (CC):			
Hypertension, *n* (%)	109 (71)	475 (63)	0.06
Hyperlipidaemia, *n* (%)	111 (73)	458 (61)	0.02
Hypothyroidism, n (%)	33 (22)	88 (12)	0.01
Coronary artery disease, *n* (%)	23 (15)	104 (14)	0.75
Cardiac failure, *n* (%)	4 (3)	14 (2)	0.44
Cardiomyopathy, *n* (%)	2 (1)	6 (1)	1.00
Dysrhythmia, *n* (%)	10 (7)	29 (4)	0.10
Stroke, *n* (%)	3 (2)	5 (1)	0.29
Chronic renal disease, *n* (%)	3 (2)	8 (1)	0.29
Glaucoma, *n* (%)	9 (6)	34 (5)	0.67
Deep vein thrombosis, *n* (%)	0 (0)	6 (1)	0.21
Discordant co-morbidities (DC):			
Cancer, *n* (%)	15 (10)	50 (7)	0.20
Asthma, *n* (%)	20 (13)	46 (6)	0.002
COPD, *n* (%)	7 (5)	12 (2)	0.031
Epilepsy, *n* (%)	8 (5)	7 (1)	0.0004
Gout, *n* (%)	14 (9)	78 (10)	0.71
GORD, *n* (%)	31 (20)	51 (7)	<0.0001
HIV, *n* (%)	2 (1)	9 (1)	1.00
Osteoarthritis *n* (%)	12 (8)	19 (3)	0.003
Rheumatoid arthritis, *n* (%)	4 (3)	10 (1)	0.049
Parkinson's disease, *n* (%)	5 (3)	4 (1)	0.049
Prostate disorders, *n* (%)	2 (1)	17 (2)	0.40
Osteoporosis, *n* (%)	8 (5)	15 (2)	0.031

COPD = chronic obstructive pulmonary disease; GORD = gastro-oesophageal reflux disorder; HIV = human immunodeficiency virus.

macrovascular complications 66% of the time, and microvascular complications in 34% of cases.

Table 5 indicates significantly higher non-diabetes related admissions for the T2DM + MDD group (85%) compared with the T2DM-MDD group (73%; $p = 0.018$) (Figure 3). The cost of non-diabetes related admissions was similar in the two groups.

Table 3: Hospital resource utilisation amongst T2DM + MDD and T2DM-MDD patients in 2014

Hospital resource utilisation	T2DM + MDD (*n* = 153) (17%)	T2DM-MDD (*n* = 749) (83%)	*p*-value
Total number of patients hospitalised, *n* (%)	64 (42)	225 (30)	0.004
Number of patients hospitalised overnight, *n* (%)	53 (36)	160 (21)	0.0001
Total number of hospital admissions, *n* (%)	126 (82)	417 (56)	<0.0001
Number of overnight hospital admissions, *n* (%)	96 (76)	277 (66)	0.016
Median length of stay, days (min, max)	4 (2, 50)	4 (2, 78)	0.67

Table 4: Costs of diabetes-related hospitalisations amongst T2DM + MDD and T2DM-MDD patients in 2014

Types of hospital admissions	T2DM + MDD (*n* = 153)	T2DM-MDD (*n* = 749)	*p*-value
Diabetes-related hospital admissions, *n* (%)	14/96 (15)	74/277 (27)	0.018
Total costs	R455 358	R4 746 683	–
Average cost per diabetes-related hospital admission	R32 526 ± R16 575	R64 144 ± R88 761	< 0.001

Discussion

This study reviewed the 2014 membership data of the CAMAF iMed database and extracted 902 member records of patients registered on the medicine management programme as having T2DM. The co-morbidity profiles were analysed in terms of CC and DC, yielding high rates of cardiovascular co-morbidity and a concerning 17% of the sample presenting with MDD, warranting further investigation into the relationship between these conditions. Factors such as other co-morbidities, hospital resource utilisation, diabetic versus non-diabetic complications and associated costs were investigated.

Despite the predominantly female population of the CAMAF membership, the sample comprised significantly more male T2DM patients (57%, $p = 0.0009$), but the female patients were more likely to have co-morbid MDD (63%, $p = < 0.0001$). It is well known that the incidence of T2DM is slightly higher in the male population[26] and the incidence of MDD is higher in the female T2DM population,[27] as reflected in our results.

In this study 85% of the T2DM patients had at least one additional recorded co-morbidity and were older than the group without co-morbidities. These results are similar in the findings of a cross-sectional analysis of 161 174 patients with T2DM using electronic health record (EHR) data supplied by United States providers in 2008–2012.[28] Hypertension (64%) and hyperlipidaemia (63%) were the most common CC and are specifically targeted within the CAMAF disease management programmes, which provides disease specific support and education to registered members. Despite being on a private managed care programme the number of T2DM patients treated for the above two major contributors to CVD was lower than the targets set by the 2017 Society for Endocrinology, Metabolism and Diabetes of SA (SEMDSA) guideline recommendations.[9] The guidelines advocate that dyslipidaemia and other CVD risk factors should be surveyed for and aggressively managed in every patient with T2DM. The treatment gap indicates that one in three T2DM patients within this managed care organisation may need antihypertensive or lipid-lowering intervention, as all T2DM patients should be considered at risk.[9] The prevalence rate of hypertension and hyperlipidaemia was also lower than those reported for hypertension (82%) and hyperlipidaemia (77%) in a study conducted by Iglay *et al.*[AQ2] from 2014 to 2015 using EHR of a cohort of 1 389 016 American adult T2DM patients.[29] This difference could be due to the higher prevalence of older, black and non-Hispanic patients among the US population.

The presence of DC is an additional burden on a diabetic patient, in terms of not only affordability to the healthcare resources, but also the understanding of the diseases and their management. The presence of DC has shown to be associated with diminished care, as the illnesses have unrelated pathogenesis and disparate

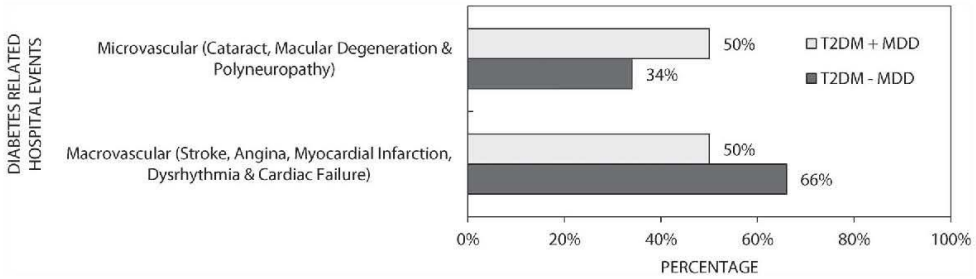


Figure 2: Diabetes-related hospital events in T2DM + MDD and T2DM-MDD.

Table 5: Costs of non-diabetes related hospitalisations amongst T2DM + MDD and T2DM-MDD patients in 2014

Types of hospital admissions	T2DM + MDD (n = 153)	T2DM-MDD (n = 749)	p-value
Non-diabetes related admissions, n (%)	82/96 (85)	203/277 (73)	0.018
Total costs	R4 150 932	R10 018 689	–
Average cost per non-diabetes related hospital admission	R50 621 ± R87 567	R49 353 ± R53 625	n.s.

n.s. = non-significant.

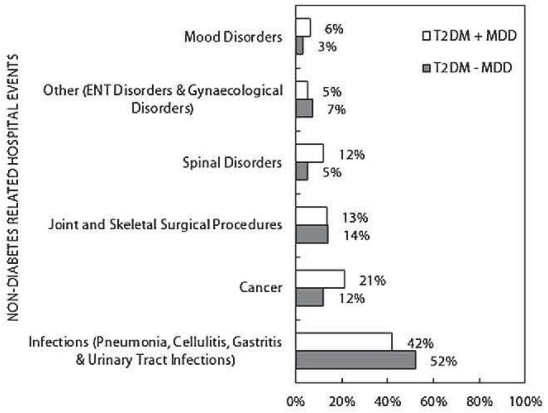


Figure 3: Non-diabetes related hospital events in T2DM + MDD and T2DM-MDD.

management plans to the T2DM management, unlike the similarity of care in CC.[24] In the National Health and Nutrition Examination Surveys (NHANES) conducted in the United States from 1988 to 2010, less than 50% of diabetic patients with multiple co-morbidities achieved glycaemic, BP and LDL cholesterol targets set by diabetes guidelines.[30]

The high incidence of MDD (17%) as a co-morbidity in this sample is consistent with international statistics. A meta-analysis of 51 331 people between 1980 and 2005 similarly showed that MDD was significantly higher in patients with T2DM compared with those without T2DM (17.6% vs. 9.8%).[27] Data of 16 180 T2DM patients presented by a health maintenance organisation (HMO) showed 17.9% incidence of MDD.[31] Depressive symptoms in individuals with diabetes have shown to be associated with poor glycaemic control and increased risk of micro- and macrovascular complications.[32,33]

Certain antidepressants i.e. paroxetine, mirtazapine and venlafaxine, have been shown to be associated with increased lipid levels and could possibly contribute to hyperlipidaemia in the group of patients treated for MDD.[34,35] The clinical parameters, i.e. lipid levels, BP and blood glucose, of the T2DM patients with and without MDD were not evaluated at this stage. Further studies will require evaluation of the clinical parameters of this cohort of T2DM patients. In this study, hyperlipidaemia was a generic classification on the system as a code and did not specify the type of hyperlipidaemia.

The presence of DC may draw resources away from other disease management and could compromise diabetes self-care in patients with pre-existing CC.[24] The T2DM + MDD group indicated higher rates of both CC and DC than their non-MDD counterparts. To support our findings Von Korff and colleagues have revealed that childhood adversity and depression occurring in adolescence to early adulthood were independent risk factors for development later of a range of medical disorders, including diabetes, CAD, asthma, osteoarthritis, epilepsy and hypertension.[36]

Conditions such as MDD, arthritis and asthma pose significant barriers to lifestyle changes and regimen adherence in patients with T2DM.[37] The prevalence of gastro-oesophageal reflux disorder (GORD) was significantly higher in patients with MDD in a cross-sectional study using the National Health Insurance Research Database in Taiwan during 2005; the study subjects included 4 790 patients with MDD and 728 749 people in the general population.[38] Likewise in our study, a significantly higher number of T2DM patients with MDD had co-morbid GORD compared with the group of T2DM without MDD.

A greater proportion of the T2DM + MDD patients (42%) were hospitalised compared with those without MDD (30%) during 2014. The increased rate of hospital admissions could be due to non-adherence to diabetic management, which leads to increased rates of diabetic complications such as ischaemic heart disease, peripheral vascular disease and admissions as reported in the Canadian study.[39] In our study, the diabetic patients who were being treated for MDD experienced more microvascular (polyneuropathy, macular degeneration) complications than those with diabetes alone. The presence of MDD might compromise diabetes care possibly because of over- or under-treatment, competing for time, attention or limited resources. This suggests the need for integrated care

coordination within the healthcare system to improve diabetes care among patients with MDD.

In addition, the results of this study also showed that in T2DM patients with MDD the rate of hospitalisation for non-diabetes related complications was much higher than for those without MDD. In a systematic review between the years 1995 and 2008 the studies focused mainly on outcomes, such as the changes in depressive symptoms and HbA1c.[40] Reduction of diabetes and non-diabetes related complications by active surveillance of diabetes and depression can improve and benefit this group of diabetic patients. Within CAMAF, DC are not looked at in the management of T2DM patients, as the focus is mainly targeting the CC, i.e. hypertension and hyperlipidaemia.

There was significantly higher hospitalisation cost for T2DM-MDD, though the LOS in hospital was similar between the T2DM + MDD and T2DM-MDD groups. The increased hospital costs could be attributed to the macrovascular complications of T2DM without MDD. Studies showed that hospitalisation costs associated with major CAD, stroke and heart failure are significantly higher than hospitalisations for non-major cardiovascular outcomes.[4]

In our group of T2DM + MDD, the patients were less likely to be hospitalised for macrovascular complications than those without MDD, which is contrary to what is stated in the literature where the presence of MDD in T2DM patients may compromise T2DM care. However, the T2DM-MDD were more likely to be hospitalised for macrovascular complications with significantly higher cost per admission. This suggests that the CAMAF medicine and the mental wellness programmes may be more effective in managing T2DM and MDD, and that the patients are more aware of their health status and were compliant with their treatment for T2DM and MDD. However, as we have very little information on the behaviour of the T2DM patients with and without MDD within CAMAF, future studies will be required to investigate the difference in outcomes of these groups of T2DM patients.

Patients registered for MDD on the chronic programme are treated for depressive symptoms with psychotherapy and antidepressants. This suggests that if the underlying MDD in T2DM patients is identified and treated, it would result in better T2DM outcomes, i.e. less hospitalisation for diabetic-related events or better diabetes management. The American Heart Association Science advisory committee, endorsed by the American Psychiatric Association, recommends that if the underlying MDD in CVD patients is identified and treated, the cardiovascular outcome is much improved.[41] Evidence exists for improved outcomes and lower financial burden by managing combined co-morbid conditions such as diabetes and hypertension; it was demonstrated in the UKPDS study[17] that tight BP control in patients with hypertension and T2DM reduced the risk of diabetes-related complications and deaths. Similarly, improved outcomes were demonstrated in a randomised control trial done on the integration management of T2DM and co-morbid MDD treatment to improve medication adherence at primary care level.[42] Due to the higher incidence of MDD in patients with T2DM (17%), more active surveillance of the T2DM patients for depressive symptoms is warranted for the early identification and treatment of MDD, possibly improving the CVD outcomes.

There is a need for additional research into the relationships between discordant co-morbid conditions such as MDD in T2DM patients to identify strategies to improve clinical outcomes. Further focus on the co-morbid status of other DC-related conditions would shed light on the pattern and clusters of multiple conditions that the T2DM patients are burdened with and associated poor patient outcomes. Healthcare organisations need to emphasise integrated multiple disease management in T2DM and MDD patients to lower the disease burden and improve outcomes.

Conclusion

Our results showed that in this cohort of 902 T2DM patients the incidence of MDD was 17%, a major discordant co-morbidity warranting deeper investigation into the relationship between T2DM and MDD.

Hospital resource utilisation of overnight admissions was higher among the patients with MDD compared with those without MDD. There was a greater number of admissions for non-diabetes related hospital events in the T2DM + MDD group compared with the T2DM-MDD group.

Active surveillance of T2DM patients is a recommendation for the future, where MDD is identified and treated to lessen the disease burden and reduce micro- and macrovascular complications. Future research needs to look at hospital and resource utilisation in T2DM patients with the added burden of MDD and to elucidate the healthcare needs of those patients.

A prospective study is being conducted on T2DM patients with and without MDD to identify factors associated with diabetes control such as blood glucose, BP and lipid profiles, and to compare the total healthcare costs.

Limitations

The administrative claims database has limitations regarding accuracy of diagnostic coding, billing practices and incomplete records. As the T2DM patients were from a private managed care organisation, their healthcare utilisation and costs might not represent those of uninsured patients or those managed in a public healthcare sector. The outcomes of this study are thus limited to the privately managed healthcare environment in South Africa.

The study was not statistically powered to perform a multivariate analysis to determine the contributions to number and cost admissions adjusting for individual co-morbidities.

Conflict of interest

The data for this paper were obtained from Sanlam Health, a managed healthcare organisation. There is no conflict of interest with the author obtaining the data from the workplace. Approval was granted unconditionally to utilise the data for research purposes only. No financial or non-financial interest was laid by the employer to perform the study.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Chapter 3. Study 2

3.1. Introduction to study 2

Study 2 comprises a published paper (paper 2) and an analysis of the influence of MDD on the costs for T2DM patients. Paper 2 (section 3.3) illustrates the estimated total direct healthcare costs of in-hospital and out-of-hospital medicine+services costs incurred by patients with type 2 diabetes mellitus T2DM enrolled on risk-sharing capitation model (CM) versus a traditional fee-for-service model (FFS) across 5 years (2012-2016).

Section 3.4 illustrates the estimated total direct healthcare costs of in-hospital and out-of-hospital diabetes-related medicine, diabetic supplies, diabetes-related treatment and management by service providers (including the capitation fee) costs incurred by patients with type 2 diabetes mellitus (T2DM) with major depressive disorder (MDD) enrolled on risk-sharing capitation model (CM) versus a traditional fee-for-service model (FFS) across 5 years (2012-2016).

3.2. Contribution of the candidate to study 2

The candidate has made a substantial contribution to the preparation and submission of this study in terms of the intellectual content, i.e. the concept and design, acquisition of data, analysis and interpretation of data and drafting of the manuscript.

3.3. Paper 2: Is the Risk Really Shared? A Retrospective Analysis of Healthcare Costs of Patients with Type 2 Diabetes Mellitus on a Capitation Model

Naidoo LA, Butkow N, Barnard-Ashton P, Miot J, Libhaber E. Is the Risk Really Shared? A Retrospective Analysis of Healthcare Costs of Patients with Type 2 Diabetes Mellitus on a Capitation Model. *Value in Health Regional Issues*. 2022 Mar 1;28:29-37

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Economic Evaluation

Is the Risk Really Shared? A Retrospective Analysis of Healthcare Costs of Patients With Type 2 Diabetes Mellitus on a Capitation Model

Lovina A. Naidoo, MPharm, Neil Butkow, PhD, Paula Barnard-Ashton, PhD, Jacqueline Miot, PhD, Elena Libhaber, PhD

ABSTRACT

Objectives: Private managed healthcare organizations in South Africa (SA) use a capitation model of care for patients within their healthcare delivery systems for the optimal management of type 2 diabetes mellitus (T2DM) to reduce healthcare costs. Few studies have categorized healthcare costs at a patient level to determine the actual healthcare costs incurred by private insurers for T2DM in SA. This study estimated the direct medical costs of patients with T2DM registered with a private health insurer over a 5-year period between 2 funding models: a capitated risk-sharing model (CM) versus a traditional fee-for-service (FFS) model.

Methods: This population-based cohort study used retrospective claims data of patients with T2DM from 2012 to 2016 of a private medical scheme in SA. Annual healthcare costs of T2DM were assessed.

Results: During the 5-year period, most of the identified patients with T2DM were enrolled in CM—534 (64%) of 828 in 2012, which rose to 789 (81%) of 971 in 2016. The median annual healthcare costs of the treatment and management of the patients with T2DM was significantly higher in CM ($2002 [interquartile range (IQR) 2106] in 2012 to $1095 [IQR 1042] in 2016) than FFS ($582 [IQR 772] to $296 [IQR 507]) ($P<0001$). A total of 46 patients with T2DM incurred hospitalization costs of ≥$24 243 for a T2DM or other event; 33 were enrolled on CM.

Conclusions: The patients with T2DM on CM accrue significantly higher annual healthcare costs than patients on FFS. The greatest portion of the overall T2DM healthcare costs was associated with high-cost hospitalization of T2DM complications.

Keywords: capitated risk-sharing model, healthcare cost, managed healthcare, type 2 diabetes mellitus.

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Introduction

Type 2 diabetes mellitus (T2DM) continues to be a relentless public health problem affecting a vast number of individuals worldwide. The latest South African estimate is that 12.7%[1] of adults (20-79 years old) have T2DM, which has increased from earlier reports of 7% in 2015.[2] Funding for T2DM treatment and management must compete with not only other noncommunicable diseases but also communicable diseases such as HIV/AIDS, tuberculosis, and other infectious diseases in sub-Saharan Africa.[3,4]

South Africa (SA) has a dual tiered healthcare system that is privately financed and covers 15% of the population[5] with an underfunded public sector that struggles to provide adequate healthcare for the 85% balance of the population.[6] Private medical schemes in SA are registered nonprofit organizations that guarantee payment for medical services to its members.[7] The government of SA has been explicit in its plans to roll out a more equitable National Health Insurance (NHI) scheme to provide universal health coverage for all South Africans.[8] A preliminary analysis using probabilistic modeling found that the capitation intervention model of T2DM care could be a cost-effective management strategy within the South African public sector for the NHI.[9] An in-depth understanding of how capitation models could affect or assist in the financing of the proposed universal health coverage is yet to be enumerated.

Comorbidities are common among T2DM individuals, compounding healthcare resource utilization and costs.[10] Patients with T2DM most commonly have cardiovascular comorbidities incurring significant financial burden[11] in addition to diabetic retinopathy and nephropathy costs. Medical schemes in SA use capitated risk-sharing models (CMs) of care for patients with T2DM within their healthcare delivery systems with the aim of reducing healthcare costs while improving patient outcomes.[12] In this model of care, insurers establish risk pools for each provider to act in the overall best interest of the patient. Providers that offer diabetes management programs (DMPs) contract with medical insurers and offer a minimum level of servicing for their enrolled patients with diabetes. The DMPs provide out-of-hospital diabetes-related services, which include medical care from various

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health specialists, including general practitioners, medical specialists and allied health professionals, pharmaceuticals, and medical consumables. The only in-hospital diabetic emergencies covered are restricted to diabetic ketoacidosis (DKA) and hypoglycemia crises by the DMPs.[13] In theory, overall risk should be shared between the DMP and the health insurer.

Payment to DMPs is made prospectively as a cost-containment strategy. Financial incentives for DMPs in a CM are to attract additional enrollees; nevertheless, this may lead to the selection of healthier enrollees and underprovision of services.[14] Conversely, in a fee-for-service (FFS) payment system, the provider or facility is reimbursed for each service provided, creating a strong incentive for increased (possible over) delivery of service to achieve a higher revenue.[15] Therefore, we aimed to estimate the healthcare costs in a cohort of patients with T2DM in a privately managed healthcare organization over a 5-year period between 2 funding models: a CM versus a traditional FFS model.

Methods

The study intended to estimate the complete medical costs including the capitation fee, T2DM and other treatment, management, and hospitalization costs to be able to compare the costs of the 2 models. The 2 models were compared with respect to total out-of-hospital costs and total in-hospital costs. This was a retrospective cross-sectional study of the administrative claims database of T2DM members of a South African private medical scheme. The scheme had an agreement with a service provider using a capitation and risk-sharing model for a DMP. Data were sourced from the iMed database, a commercially available administrative system that maintains membership data, claims processing, and contribution premiums of members of private medical schemes.

The iMed database included patient-level demographics and details of scheme member registration on CM and FFS. Records of medicines, diabetic supplies, treatment by providers, and hospitalization cases in conjunction with claims data were identified via the 10th revision of the International Classification of Diseases and Related Health Problems (ICD10) diagnosis codes.[16] The T2DM-related ICD10 codes used were E03 (other hypothyroidism) to E89 (postprocedural endocrine and metabolic complications and disorders), G45 (transient cerebral ischemic attacks and related syndromes) to G64 (other disorders of peripheral nervous system), H25 (age-related cataract) to H40 (glaucoma), I10 (essential hypertension) to I95 (hypotension), and N17 (acute kidney failure) to N19 (unspecified kidney failure). The remaining codes were classified as other, that is, not directly related to the T2DM codes.

Patients

Once the treating doctor has registered their condition with the medical scheme (via a telephonic or written prescription), members who received a diagnosis of T2DM register on the scheme's chronic program for funding of their diabetic medications and medical management (consultations and procedures) for T2DM. Effective from 2000, scheme members who received a diagnosis of T2DM were encouraged to enroll onto the DMP. The T2DM members who opted out of the DMP were managed within the medical scheme on a medicine management program via FFS. In FFS, the patients visited doctors, nurse educators, dietitians, podiatrist, and pharmacy of their own choosing for self-management of their diabetes. The FFSs for the diabetic services rendered to the patients with T2DM were reimbursed by the insurer on receipt of a claim from the respective service provider.

Patients with T2DM on the DMP visited a multidisciplinary team of doctors, diabetes nurse educators, dietitians, podiatrist, and pharmacy at an allocated facility for review of their diabetes management and treatment. The capitation fee covered the costs of the DMP service providers and diabetic oral and parenteral medications. The capitation fee was paid directly by the medical scheme, through the finance department, into the DMP bank account in advance for active members on CM. The DMP organization invoiced the capitation fee for the active members serviced in the previous month and refunded the insurer for patients who had resigned, were deceased, or opted out of the DMP and did not receive diabetic services. The insurer terminated the contract of DMP at the end of 2016 because of an increased number of member's requests to deregister from the CM, who preferred their own doctors to manage their diabetes, and the increase in the healthcare cost of the patients with T2DM on the CM.

Patients (>18 years old) were classified as having T2DM, if they had any of the ICD10 diagnosis codes of E11.0 (T2DM with hyperosmolarity) to E11.9 (T2DM without complications) as stated by the practitioner. These ICD10 codes were obtained from the Council of Medical Schemes Prescribed Minimum Benefit ICD10 coded list 2013.[17] In addition, the patients with T2DM who received a diagnosis of coronary artery disease, dysrhythmia, deep vein thrombosis, stroke, or valvular heart disease were further classified as having a thromboembolic comorbidity in this analysis.

Identified patients with T2DM were further stratified into 2 mutually exclusive funding models based on the program enrolment records, that is, patients with T2DM enrolled onto CM and patients with T2DM registered on FFS. In Figure 1, the movement of patients with T2DM in CM and FFS from 2012 to 2016 is depicted. Each year, patients with T2DM joining the scheme as new members were encouraged to enroll onto CM at the time of member registration. Existing scheme members registered on FFS when they received a diagnosis of T2DM were urged to enroll onto CM. Within this cohort, 105 patients with T2DM (new or existing members on the scheme) voluntarily moved between the 2 funding models between 2012 and 2016. Deceased or resigned patients were accounted for the full year, and their healthcare costs included until the date of their demise or resignation.

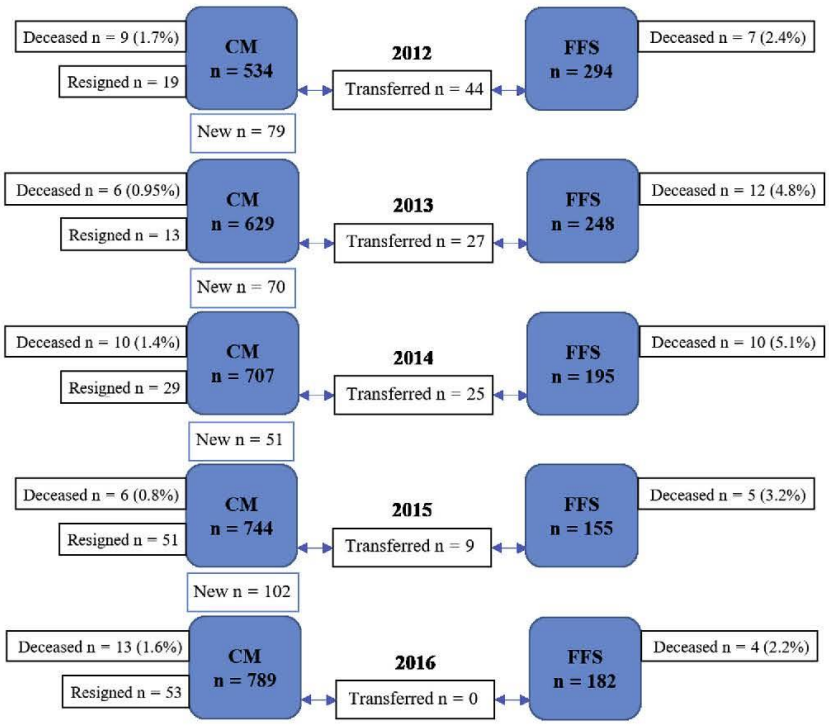
Ethical Considerations

Confidentiality was maintained throughout the analysis; the patients' unique scheme membership number and dependent code were used to align patient-level records. The study was approved by the University of the Witwatersrand, Johannesburg, Faculty of Health Sciences Human Ethics Committee (M140326). Approval was also granted by the Principal Officer of the scheme, for the scheme data to be used in the study and by the Human Resources Manager of the scheme administrator to gather data from the iMed database for the research. Approval was obtained from the chief executive officer of the CM for the transaction records of T2DM members enrolled on the DMP.

Categorization of Healthcare Costs

The healthcare costs were compared between FFS and CM and categorized as in-hospital and out-of-hospital medicines and out-of-hospital services (Fig. 2). In-hospital related costs included all in-hospital treatment, procedures, and emergencies for diabetes. Medicine fees included out-of-hospital diabetic and nondiabetic medicines. Services charged included all out-of-hospital physician visits, auxiliary services, laboratory, and radiology services for diabetes.

Figure 1. Movement of patients with T2DM within the CM and FFS per year.



CM indicates capitated risk-sharing model; FFS, fee-for-service; T2DM, type 2 diabetes mellitus.

Estimated Healthcare Costs

Healthcare costs were estimated based on member scheme plan options- and patient-paid amounts for medicines, services, and hospital claims on FFS and CM and were measured by category type across the 5 years using claims data and included (1) T2DM-related and other in-hospital costs defined as total per-patient-per-year (PPPY) cost related to all inpatient length of stay (LOS), treatment, procedures, surgical and medical appliances, and emergencies; (2) out-of-hospital medicine costs, defined as total PPPY cost related to all diabetic, nondiabetic chronic and acute, and over-the-counter medicines; (3) out-of-hospital services costs, defined as total PPPY cost related to out-of-hospital physician visits, auxiliary services, and laboratory and radiology services for diabetes and other events; and (4) capitation fee costs, defined as per-member-per-month enrolled on the CM, which for patients on oral treatment were $121, $99, $86, $64, and $65 and for patients on insulin or parenteral treatment were $287, $236, $205, $152, and $154 (2012-2016).

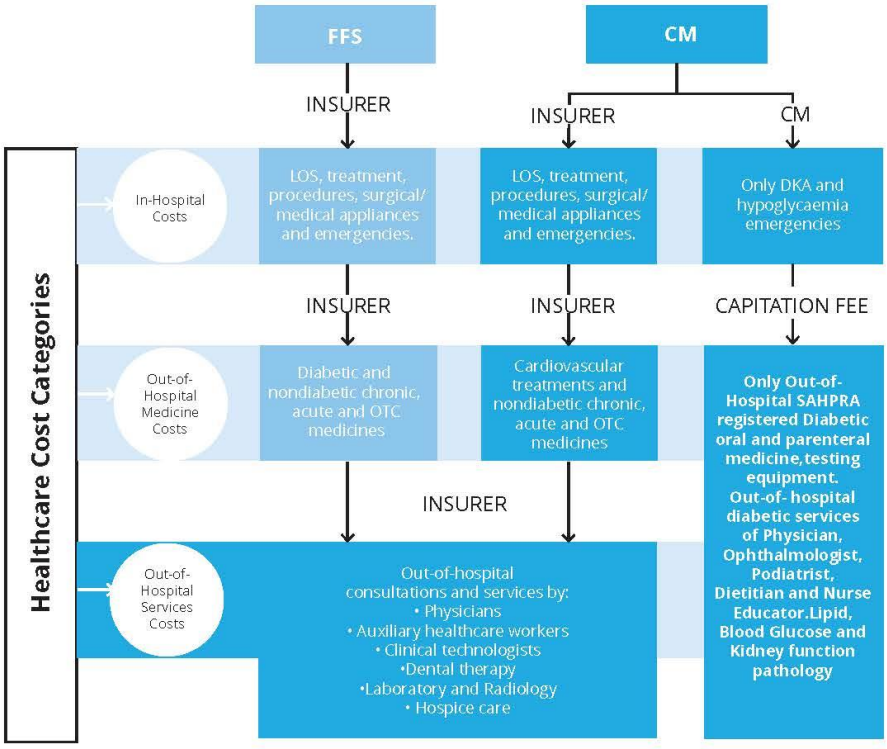
Given that the medicine and services fees covered by the insurer were categorized differently between FFS and CM, these costs were categorized as out-of-hospital expenditure and defined as out-of-hospital PPPY medicine + services + capitation fee per-member-per-month for the CM and PPPY medicine + services (diabetic and nondiabetic) for the FFS. The calculated costs represent total costs incurred by the insurer. Hospital claims for DKA and hypoglycemia admissions of patients with T2DM on the CM were invoiced by the medical scheme directly to the DMP. The DMP provider responsible for the patient's diabetes care would meet the full costs of the hospitalization for these patients.

Data collection on patient out-of-pocket expenses were not performed. There were no patient out-of-pocket costs incurred for patients enrolled on the CM. Nevertheless, patients with diabetes on the FFS who chose nonformulary medicines or, non-network physician and auxiliary services would incur out-of-pocket copayments. This analysis was undertaken from a provider perspective.

The medicine costs were adjusted to 2016 prices according to the ZAR value of the single exit price (SEP) as regulated each year by the South African National Department of Health.[18] The SEP adjusted price increases based on inflation were 2.1% in 2012, 5.8% in 2013, 5.82% in 2014, and 7.5% in 2015.[19] The SEP% increases each year were adjusted for all medicines authorized by the scheme and updated on the medicine management program by Medi-Kredit,[20] an independent technology company contracted to the scheme to process pharmacy claims.

Similarly, the costs of services were adjusted each year according to the ZAR value of the National Health Reference Price List (2012-2016) published by the South African National Department of Health[21] and implemented on the iMed systems. The average consumer price index SA[22] increases of 5.73% (2012), 5.78% (2013), 6.14% (2014), 4.51% (2015), and 6.59% (2016) were calculated into the cost of services. The hospital costs were paid at 100% of the negotiated rate by the scheme with the hospital groups for general wards and specialized units and updated each year onto the iMed healthcare payment systems. The average

Figure 2. Categorization of healthcare costs of patients with T2DM in CM versus FFS.



CM indicates capitated risk-sharing model; DKA, diabetic ketoacidosis; FFS, fee-for-service; LOS, length of stay; OTC, over the counter; SAHPRA, South African Health Products Regulatory Authority.

negotiated hospital rates of 7.1% (2012), 7.1% (2013), 6.9% (2014), 7.3% (2015), and 6.3% (2016) with the scheme[23] were used to inflate the hospital tariffs. Healthcare cost were converted for the period 2012 to 2016 to the US dollar (USD) value after adjusting for inflation in ZAR. The fluctuation in inflation rates report the true costs that the scheme paid for over the 5-year period where costs were escalated. Costs represented in USD were calculated according to the average exchange rate of 1 USD to the ZAR in December of that respective year[24]: 1 USD = 8.6 ZAR (2012), 1 USD = 10.4 ZAR (2013), 1 USD = 11.5 ZAR (2014), 1 USD = 15.0 ZAR (2015), and 1 USD = 13.9 ZAR (2016). The high-cost hospitalization amounts included in this study were determined at the 99.9th percentile of all hospitalization costs over the 5 years, which resulted in a value of ≥$24 243 per admission.

Statistical and Data Analysis

Data extracted from the database were exported to Microsoft Excel 2016, and statistical analysis was performed with Statistica 13.3 (StatSoft Inc, Tulsa, OK) and Statistical Analysis System 9.4. The total costs, the T2DM costs, and other costs for services, medicines, and hospitalizations were presented as median (interquartile range) costs per patient in USD per annum. The variables age, costs, and LOS of the 2 models were compared with a Mann-Whitney *U* test because the variables were not a normal distribution. For analysis purposes, patients in each year were treated independently, despite some remaining in each model through the 5 years (Fig. 1). Categorical variables such as sex, number of deceased patients, and number of claims for medicines, services, and hospitalizations of CM and FFS were summarized as frequencies and percentages and compared using chi-square or Fisher's exact tests. A significance level was set at 0.05.

Results

During the 5-year period (2012-2016), among the registered beneficiaries in the scheme database, a higher proportion of the identified patients with T2DM (64%-83%), represented in Table 1, were enrolled in CM at each year as opposed to FFS. The demographics for CM favored a younger male profile than the profile of FFS over the 5-year period, with a significant younger population in CM ($P<0001$) each year (Table 1). Patients with T2DM were older in FFS and had more thromboembolic comorbidities each year. The all-cause mortality rate of the patients with T2DM in CM (0.81%-1.4%) was lower than in FFS (3.2%-5.1%) between years 2013 to 2015. In the years 2012 and 2016, the mortality rates were similar in both models.

T2DM-Related and Other Medicine and Services Costs

The comparisons of the direct healthcare expenditure attributable to T2DM-related and other combined medicine and services PPPY between the 2 funding models across the 5-year period are presented in Table 2. The unit healthcare costs are represented as medians with the interquartile range difference between the

Table 1. Characteristics of patients with T2DM CM versus FFS.

Characteristics	CM, n (%)	FFS, n (%)	*P* value
2012	n = 534 (64%)	n = 294 (36%)	
Age (y)	55 ± 14	61 ± 15	<.0001
Male	322 (60)	156 (53)	.044
Thromboembolic comorbidity	89 (17)	67 (23)	.031
Deceased	9 (1.7)	7 (2.4)	.49
2013	n = 629 (72%)	n = 248 (28%)	
Age (y)	55 ± 14.2	62 ± 14.3	<.0001
Male	371 (59)	131 (53)	.11
Thromboembolic comorbidity	95 (15)	63 (25)	.0004
Deceased	6 (0.95)	12 (4.8)	<.001
2014	n = 707 (78%)	n = 195 (22%)	
Age (y)	55 ± 14.4	62 ± 14.6	<.0001
Male	417 (59)	101 (52)	.09
Thromboembolic comorbidity	107 (16)	51 (24)	.005
Deceased	10 (1.4)	10 (5.1)	.002
2015	n = 744 (83%)	n = 155 (17%)	
Age (y)	56 ± 14.4	68 ± 12.5	<.0001
Male	424 (57)	82 (53)	.37
Thromboembolic comorbidity	123 (17)	40 (26)	.031
Deceased	6 (0.81)	5 (3.2)	.013
2016	n = 789 (81%)	n = 182 (19%)	
Age (y)	56 ± 14.3	62 ± 14.2	<.0001
Male	442 (56)	100 (55)	.80
Thromboembolic comorbidity	132 (17)	42 (23)	.044
Deceased	13 (1.6)	4 (2.2)	.54

CM indicates capitated risk-sharing model; FFS, fee-for-service; T2DM, type 2 diabetes mellitus.

75th and the 25th percentile. T2DM-related medicine and services costs (includes the capitation fee) were significantly higher in CM than FFS $P<.0001$ across all years (Table 2). Other medicine and services costs incurred by the patient with T2DM were similar in both models. The total T2DM-related costs accrued over the 5-year period in CM was $6 277 453 compared with $816 321 incurred in FFS.

The cost of medicine and services claims for the members who crossed over between models were only included if they remained on a particular model for a consecutive period of longer than 6 months. The cost of members excluded over the 5-year period on CM amounted to $8757 (0.14%) and on FFS was $5216 (0.64%). These figures were not significant contributors to the overall costs.

T2DM-Related and Other Hospitalization Costs

The annual median T2DM-related hospital costs across the 5-year period represented in Table 3 showed no difference in the hospitalization costs between the 2 funding models, despite having T2DM members enrolled in a CM—a model contracted out as a cost-containment strategy aimed at achieving a reduction in-hospital costs. Additionally, the number of patients with T2DM

Table 2. Costs of T2DM-related and other combined medicine plus services PPPY in CM versus FFS.

T2DM-related medicine + services + capitation fee costs				Other medicine + services costs		
Year	CM	FFS	*P* value	CM	FFS	*P* value
	Median, $ (IQR)	Median, $ (IQR)		Median, $ (IQR)	Median, $ (IQR)	
2012	n = 534	n = 294		n = 534	n = 294	
	2002 (2106)	582 (772)	<.0001	1114 (1677)	1474 (2273)	.008
2013	n = 629	n = 248		n = 629	n = 248	
	1586 (1615)	487 (668)	<.0001	920 (1343)	1148 (1631)	.043
2014	n = 707	n = 195		n = 707	n = 195	
	1417 (1431)	333 (580)	<.0001	664 (1263)	778 (1603)	.14
2015	n = 744	n = 155		n = 744	n = 155	
	1065 (1064)	293 (458)	<.0001	660 (1012)	820 (1216)	.0061
2016	n = 789	n = 182		n = 789	n = 182	
	1095 (1042)	296 (507)	<.0001	690 (1100)	738 (1376)	.071

CM indicates capitated risk-sharing model; FFS, fee-for-service; IQR, interquartile range; PPPY, per-patient-per-year; T2DM, type 2 diabetes mellitus.

Table 3. Hospital admission costs PPPY in CM versus FFS.

Median hospital admission costs PPPY						
T2DM-related hospital admissions				Other hospital admissions		
Year	CM, n (%) Median, $ (IQR)	FFS, n (%) Median, $ (IQR)	*P* value	CM, n (%) Median, $ (IQR)	FFS, n (%) Median, $ (IQR)	*P* value
2012	n = 110/534 (21)	n = 45/294 (15)	.06	n = 193/534 (36)	n = 111/294 (38)	.65
	1634 (5456)	3032 (6167)	.30	2909 (7326)	3176 (6010)	.89
2013	n = 108/629 (17)	n = 36/248 (15)	.34	n = 201/629 (32)	n = 77/248 (31)	.79
	1905 (5368)	2290 (3600)	.81	2587 (5409)	2706 (9403)	.08
2014	n = 110/707 (16)	n = 32/195 (16)	.77	n = 219/707 (31)	n = 65/195 (33)	.53
	1816 (3828)	3182 (6078)	.53	2145 (3889)	2792 (7933)	.32
2015	n = 130/744 (17)	n = 28/155 (18)	.86	n = 238/744 (32)	n = 52/155 (34)	.71
	1111 (3459)	1139 (3594)	.64	1712 (3591)	2518 (6724)	.09
2016	n = 161/789 (20)	n = 26/182 (14)	.06	n = 311/789 (39)	n = 62/182 (34)	.18
	1544 (3341)	2627 (4457)	.06	2355 (4376)	1680 (4800)	.56

CM indicates capitated risk-sharing model; FFS, fee-for-service; IQR, interquartile range; PPPY, per-patient-per-year; T2DM, type 2 diabetes mellitus.

hospitalized each year for T2DM-related and other admissions was similar between the 2 models.

Table 4 depicts the very high-cost hospitalization cases of patients with T2DM (≥$24 423) within this cohort between 2012 and 2016. The LOS and proportion of costs covered by the scheme, CM, and the patient for each adverse outcome are shown in Table 4. Of the 46 patients with T2DM hospitalized for a very high-cost event, 33 were enrolled in CM. A total of 2 patients had repeated admissions for ketoacidosis and stroke and were fatal. Over the 5-year period, the DMP paid $26 912 (0.75%) for the DKA and hypoglycemia emergencies hospital costs of the total diabetes-related hospital admissions cost of $3 611 157.

Discussion

This study contributes to the understanding of the estimated direct medical costs of patients with T2DM within 2 funding models. Our findings showed that the financial burden of T2DM patient care on the insurer was substantial when the treatment and management costs related to the management of T2DM were compared between CM and FFS. Patients with T2DM enrolled on CM accrued a large proportion of the total costs annually, owing to the capitation fee. These costs were compounded by the very high in-hospital costs attributed to the complications of T2DM and other events, which were not covered by the DMP.

In this cohort, despite a predominantly female population of the overall scheme membership, the proportion of patients with T2DM within the funding models were mostly male (Table 1). It is well known that the incidence of T2DM is slightly higher in the male population.[25]

The demographics in the study showed a significantly younger population in CM across the 5-year period, possibly indicating a deliberate selection of younger patients thereby achieving better outcomes as complications increase with age. Older adults are more likely to develop other complications of T2DM, such as vision loss and kidney damage, besides the major cardiovascular and cerebrovascular events.[26] Theoretically, in this setting, one would expect a decrease in overall healthcare expenditure of the patients with T2DM and reduction in diabetic complications over the longer term, because of good compliance management on the DMP.

The findings of our previous study[10] showed that the patients with T2DM within this managed care organization had high rates of comorbidities and consumed significant healthcare resources. In 2013, the average overall direct healthcare expenditure for a T2DM patient in France was €6506 ($8652),[27] more expensive than our study possibly attributed to the larger cohort and higher prices of the newer antidiabetic drugs reimbursed during that year. In a Chinese multicenter prospective cohort study of 871 patients with T2DM in 2019, the mean annual total direct medical costs that included overall treatments, complications, and comorbidities were $1990 and the average costs per inpatient per admission were $2127.[28] These costs depicted were similar to our T2DM-related healthcare costs. The other costs in treating general conditions not directly related to T2DM were higher in our cohort, an additional comorbid illness burden to the patient and the scheme, which also reported in the US economic costs of diabetes for 2017.[29]

The analysis of CM in this study exposed several concerns, such as the following: it recruited an increased number of younger patients with T2DM and did not take the fiscal risk of the overall resource consuming treatment, management, and hospitalizations of the patients with T2DM, including the individual high-cost outliers that resulted in extended LOS and intense level of care in-hospital.

Patients with T2DM enrolled on CM did not have lower total healthcare utilization costs than patients enrolled on FFS. The capitation fee could then be thought of as an additional cost to the scheme with little to no financial benefit. This model does not align with the expected outcomes of a CM that would apportion risk to the DMP. The insurer was responsible for both the capitated fee and all the hospitalizations associated with CM, except for a $26 912 that was for the account of CM over the 5-year period constituting (0.75%) of the total hospitalizations. More patients with T2DM on CM ended up with high-cost adverse hospital outcomes (Table 4). Notably, in this study, the patients with T2DM in FFS were older and had more thromboembolic comorbidities each year and lesser cost than the patients with T2DM in CM.

Table 4. Highest cost proportions ≥$24 423 of T2DM and other hospitalizations CM versus FFS.

Adverse T2DM outcomes	Year	Model	LOS	Cost, $	Cost proportion, $		
					Scheme	CM	Patient
Acute renal failure	2012	CM	52	126 553	126 553	0	0
Acute renal failure	2015	CM	74	112 135	112 000	0	135
Fatal valve replacement	2012	CM	4	87 003	87 003	0	0
Ketoacidosis	2015	CM	32	66 845	65 687	1158	0
Valve replacement	2012	FFS	3	57 272	57 272	-	0
Fatal stroke	2015	FFS	35	52 855	52 855	-	0
CABG	2016	CM	9	50 743	50 743	0	0
Fatal ketoacidosis	2016	CM	39	50 504	50 504	0	0
CABG	2014	CM	15	46 059	46 059	0	0
CABG	2012	CM	8	45 196	45 196	0	0
CABG	2014	CM	10	43 941	43 941	0	0
Angioplasty	2015	CM	27	42 281	42 277	0	4
Angioplasty	2016	FFS	32	41 061	41 061	-	0
Unstable angina	2013	FFS	16	37 902	37 902	-	0
Atrial fibrillation	2012	CM	4	32 093	32 093	0	0
Stroke	2016	CM	46	31 522	31 522	0	0
ICD	2016	FFS	5	30 737	30 737	-	0
CABG	2014	CM	12	29 475	29 475	0	0
Fatal cardiac failure	2012	CM	8	28 400	28 400	0	0
CABG	2016	CM	9	28 157	28 157	0	0
Unstable angina	2012	CM	34	27 867	27 721	0	146
Acute renal failure	2013	CM	29	27 257	27 257	0	0
TAVI	2016	FFS	2	27 078	27 078	-	0
Chronic renal failure	2012	CM	10	26 538	26 538	0	0
Atrial fibrillation	2013	CM	2	25 262	25 262	0	0
Fatal atrial fibrillation	2014	CM	7	25 058	25 058	0	0
Other hospitalizations							
Fatal esophagitis	2016	CM	40	161 444	161 410	0	34
Fatal laparotomy	2015	CM	27	103 530	103 530	0	0
Laparotomy	2015	FFS	45	84 955	84 955	-	0
TSH	2016	CM	62	77 168	77 168	0	0
Hip fracture	2014	FFS	49	72 062	72 062	-	0
Laminectomy	2012	FFS	18	61 797	61 793	-	4
Fatal TSH	2012	CM	18	59 670	59 670	0	0
Oncology wound debridement	2012	CM	21	55 847	55 817	0	30
Hip replacement	2012	CM	17	39 557	39 557	0	0
Laminectomy	2013	FFS	12	37 787	37 405	-	382
Hip replacement complications	2012	CM	10	35 492	35 492	0	0
Cerebral meninges	2012	CM	16	33 973	33 973	0	0
Craniotomy	2014	CM	9	32 842	32 842	0	0
Fracture reduction	2016	CM	21	29 973	29 973	0	0
Spinal Fusion	2014	FFS	12	28 661	28 659	-	2
Multiple fractures	2014	CM	36	27 555	27 538	0	17
Spinal fusion	2013	FFS	7	27 074	27 074	-	0
Spinal fusion	2012	CM	7	26 118	26 106	0	12
Pneumonia	2012	CM	20	25 471	25 448	0	23
Laparotomy	2013	FFS	9	24 897	24 393	-	504

CABG indicates coronary artery bypass graft; CM, capitated risk-sharing model; FFS, fee-for-service; ICD, implantable cardioverter defibrillator; LOS, length of stay; T2DM, type 2 diabetes mellitus; TAVI, transcatheter aortic valve implantation; TSH, traumatic subdural haemorrhage.

Capitation fees with administrative costs were additional costs burdened on the insurer. Studies show that administrative costs account for a substantial part of healthcare expenditure, as seen in the United States where 62% of the healthcare expenditure was related to billing and insurance related expenditures.[30] Another study that examined the impact of the type of health

plan of Medicaid enrollees with T2DM found 14% more hospitalizations of patients on the capitated plan than those in FFS plans.[31]

The 46 severely ill patients hospitalized for T2DM-related high-cost events in our study accrued a total of $2 244 509 million; the greatest portion was reimbursed by the scheme and the balance of $1158 paid by the DMP. Acute renal failure and ketoacidosis were major cost drivers in addition to cardiovascular complications in this study. Similarly, the greatest mean hospitalization cost reported in a Taiwan study in 2012[32] was attributed to cardiovascular complications, for example, $10 411 for fatal ischemic heart disease. DKA that ended up with longer hospital stays and high costs was also reported in an inpatient audit conducted in the United Kingdom in 2012.[33,34] High-cost patients with T2DM accrued $52 000 more in total annual healthcare costs than the not high-cost patients with T2DM in the United States between 2005 and 2010.[35] In our study, the T2DM-related hospital unit median costs incurred in CM ranged from $1111 to $1905 during the 5-year period.

At present, in SA the proposed NHI system[36] will have to adapt the payment systems currently used in both the private and public sectors. Based on the results of this study, a benefit package could be established for diabetes as part of NHI, and CM improved with tighter management and a risk sharing for improved outcomes. A discrete choice analysis should be conducted to understanding what motivates providers, and the incentives could then be aligned with these.

Capitation is a widespread form of reimbursement system for medical care in countries such the United States (Medicare), United Kingdom's National Health Service, Israel's NHI law, and Sweden's healthcare system,[37-39] as well as Ghana's NHI scheme.[40] Similarly, FFS is equally popular in Organization for Economic Cooperation countries such as Belgium, Germany, Japan, Switzerland, and the United States, where most physicians are private and patients have the freedom to choose their physician.[41] From the perspective of the NHI and the resource constraints in SA, the present analysis demonstrates the influence of provider payment systems and limitations of a restricted CM in the management of T2DM.

Limitations

Several limitations must be considered in this study. First, a longitudinal study of the T2DM patient in this cohort was not feasible, because patients voluntarily transferred between the funding models. Our data could not differentiate the types of service or medicine items charged separately or precisely. Hence, the medicine and services costs were combined for both models. Micro costing was not feasible.

The insurer pays all the hospitalization costs incurred by the patients with T2DM on the scheme, directly to the hospital or clinic, with the agreed-upon negotiated tariffs among the hospital groups. This analysis did not risk adjust the healthcare costs or outcomes to account for the fact that there were older and sicker patients with T2DM in FFS. This study was restricted to direct medical costs from the insurer and CM's perspective; the indirect costs such as lost productivity and absenteeism were not addressed. The data set did not include patient-incurred costs, because the costs in this study were from the provider's perspective only. Further research would be necessary to assess costs incurred by the patient, because the different models may shift the costs to the patients, and this may adjust the perception of which model is more suitable for the patient.

Conclusions

The scheme incurred significant healthcare costs and resource utilization despite the patients with T2DM being on managed care models. FFS patients accrued significantly lower costs over the 5-year period of the study, despite CM being touted as a cost-containment strategy with expected better health outcomes. This study highlights that neither model is ideal and opens the possibility for a value-based care model structured according to a shared-savings and shared-risk model to lower diabetes-related adverse outcomes and improve cost management.

Article and Author Information

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3.4. Direct medical costs of patients with T2DM with comorbid MDD on managed care funding models across a five-year period (2012-2016)

3.4.1. Introduction

The financial burden of Type 2 Diabetes Mellitus (T2DM) is a matter of concern for many health systems worldwide. According to the International Diabetes Federation (IDF), South Africa (SA) is one of the leading five African countries for the prevalence of people with diabetes.[1] The latest South African estimate is that 12.7%[84] of adults (20-79 years) have T2DM, which has increased from earlier reports of 7% in 2015.[83] Rapid societal transitions creating increases in urbanisation and change in diet and lifestyle habits have contributed to the increase in obesity and to the T2DM epidemic in SA.[166] Furthermore, the prevalence of T2DM along with other non-communicable diseases (NCDs) is growing relentlessly,[167] and in the last decade, this issue has been exacerbated by the presence of other comorbidities, i.e. hypertension, dyslipidaemia, obesity, including mental disorders such as major depressive disorder (MDD).[168,9] Studies by Katon et al.[130,169,132] have shown the adverse health risk of comorbid depression in patients with diabetes. Among a large Medicare cohort of fee-for-service (FFS) beneficiaries with T2DM, comorbid MDD was associated with an increase in all-cause mortality over two years.[170]

MDD has been shown to adversely influence outcomes in patients with T2DM, in several ways such as functional impairment, increase in medical costs, poor adherence to diabetes self-management care in terms of medication compliance, glucose monitoring, physical activity and a healthy lifestyle, and increased risk of morbidity and mortality.[171,172] Lin et al. showed that comorbid MDD among people with T2DM links to a higher risk of advanced diabetic complications.[10]

In terms of economic burden, most healthcare resource utilisation and cost studies of T2DM and comorbid MDD have been reported from the United States of America (USA) and Europe. According to Ciechanowski et al.,[173] individuals with T2DM+MDD had twice the healthcare expenditure compared with those who did not have MDD. Another study found patients on managed care plans in the USA, with T2DM and MDD had higher diabetes-related total medical costs ($19,298) than patients with T2DM alone ($4,819).

In SA, funding for T2DM treatment and management must compete with not only other non-communicable diseases but also communicable diseases such as HIV/AIDS, tuberculosis and other infectious diseases in sub-Saharan Africa.[5,174] Findings from the previous study[175] showed that patients with T2DM on capitation-risk sharing model (CM) of care for patients with T2DM in the private sector was not cost-effective and consumed far more resources compared to patients on an FFS model. The greatest portion of the overall T2DM healthcare costs was associated with high-cost hospitalization for T2DM complications.

Comorbidities are common among T2DM individuals compounding healthcare resource utilisation and costs.[176] T2DM patients commonly have cardiovascular co-morbidities incurring a significant financial burden,[177] in addition to diabetic retinopathy and nephropathy costs. In SA, few studies have focused on mood disorders in patients with T2DM, yet MDD affects these patients twice as much as in the general population.[98] The high prevalence of MDD (17%) among patients with T2DM, previously reported within this private healthcare population sample, prompted a further investigation into the estimated direct medical healthcare costs of T2DM patients with MDD (T2DM+MDD) and without MDD (T2DM-MDD) between a CM vs a traditional FFS.

3.4.2. Methods

This research method followed the methods presented in paper 2 in terms of sample selection and stratification of patients with T2DM+MDD and T2DM-MDD across a 5-year period (2012 to 2016). (Figure 2 in Paper 2 above).

3.4.2.1. Patients

The sub-group of T2DM+MDD patients was identified with ICD10 codes F32.2 (MDD, single episode, severe without psychotic features) to F33.9 (MDD, recurrent, unspecified). These ICD10 codes were obtained from the Council of Medical Schemes Prescribed Minimum Benefit CMS PMB ICD-10 coded list 2013.[23]

3.4.2.2. Categorisation of Healthcare Costs

The healthcare costs were compared between CM and FFS and categorised as: In-Hospital, Out-of-Hospital Medicines and Out-of-Hospital Services (Figure 2 in Paper 2 above). In-Hospital related costs included all in-hospital treatment, procedures, and emergencies for diabetes. Medicine fees included out-of-hospital diabetic and non-diabetic medicines. Services charged,

included all out-of-hospital physician visits, auxiliary services, laboratory, and radiology services for diabetes.

3.4.2.3. Estimated Healthcare Costs

Healthcare expenditures of identified patients with T2DM with and without MDD were categorised as costs of T2DM-related and other combined medicine+services plus capitation fee, and diabetic-related and other hospital admission costs of patients with T2DM+MDD and T2DM-MDD accrued across the period 2012-2016.

3.4.3. Statistical and data analysis

Data extracted from the database was exported to Microsoft Excel 2016 and statistical analysis was performed with Statistica 13.3 (StatSoft Inc., Tulsa, OK) and SAS 9.4. The total costs, the T2DM and other costs for services, medicines and hospitalisations were presented as median (IQR) costs per patient in USD per annum. The variables age, costs, and length of stay of the two models were compared with a Mann-Whitney test, as the variables were not a normal distribution. For analysis purposes, patients in each year were treated independently, despite some remaining in each model through the 5 years (Figure 1, Paper 2). Categorical variables such as sex, number of deceased and number of claims for medicines, services, and hospitalisations of CM and FFS were summarized as frequencies and percentages and compared using Chi-square or Fisher-exact tests. A significance level was set at 0.05.

3.4.4. Results

During the five-year period (2012-2016), amongst the registered beneficiaries in the scheme database, the proportion of patients with T2DM+MDD in CM and FFS ranged from 15% to 23%. (Table 3.1). A higher proportion of females with T2DM and MDD (61% to 79%) in CM and FFS were observed. Demographics of the patients with T2DM+MDD portrayed an older group of individuals than those with T2DM-MDD. However, patients in the FFS were older than in CM, p=0.0001.

Table 3.1 Characteristics of patients with T2DM+MDD and T2DM-MDD in a CM vs FFS

Characteristics	T2DM+MDD CM n (%)	T2DM+MDD FFS n (%)	T2DM-MDD CM n (%)	T2DM-MDD FFS n (%)	Overall p-value
2012	**n=86/534 (16)**	**n=55/294 (19)**	**n=448/534 (84)**	**n=239/294 (81)**	

Age (years±SD)	59±13	62±13	55±14	60±15	<0.0001
Female	52/86 (61)	40/55 (73)	160/448 (36)	98/239 (41)	<0.0001
2013	**n=99/629 (16)**	**n=50/248 (20)**	**n=530/629 (84)**	**n=198/248 (80)**	
Age (years±SD)	55±14	61±14.1	55±14	62±14	<0.003
Female	64/99 (65)	35/50 (70)	197/530 (37)	82/248 (33)	<0.0001
2014	**n=109/707 (15)**	**n=44/195 (23)**	**n=598/707 (85)**	**n=151/195 (77)**	
Age (years±SD)	58±14	61±13	55±14	63±15	<0.0001
Female	74/109 (68)	32/44 (73)	225/598 (38)	62/151 (41)	<0.0001
2015	**n=113/744 (15)**	**n=33/155 (21)**	**n=631/744 (85)**	**n=122/155 (79**)	
Age (years±SD)	59±13	67±12.5	56±15	68±13	<0.0001
Female	69/113 (61)	26/33 (79)	251/631 (40)	47/122 (39)	<0.0001
2016	**n=123/789 (16)**	**n=40/182 (22)**	**n=666/789 (84)**	**n=142/182 (78)**	
Age (years±SD)	59±14	64±13	56±14	61±15	<0.0001
Female	76/123 (62)	31/40 (78)	271/666 (41)	51/142 (36)	<0.0001

CM indicates capitated risk-sharing model; FFS, Fee-for-service; MDD, Major Depressive Disorder; T2DM, Type 2 Diabetes Mellitus

3.4.4.1. T2DM related and other medicine and services costs

Table 3.2 shows the comparisons of direct healthcare costs attributable to T2DM related and other combined medicine and services PPPY between T2DM+MDD vs T2DM-MDD groups across the five-years.

T2DM related medicine and services costs (including the capitation fee) were similar between T2DM+MDD and T2DM-MDD groups across all years.

Conversely, other medicine+services costs accrued by the T2DM+MDD group were significantly higher by $2,125 [IQR (1,295-2,125)] in 2012 to $1,414 [IQR (739-2,293)] in 2016 than the T2DM group without MDD $1,057 [IQR (437-2,076)] to $614 [IQR (262-1,255)], p<0.0001 across all years.

Table 3.2 Costs of T2DM related and other combined medicine plus services PPPY in patients with T2DM+MDD vs T2DM-MDD

	T2DM related medicine+services+capitation fee costs			Other medicine+services costs		
Year	**T2DM+MDD**	**T2DM-MDD**	**p-value**	**T2DM+MDD**	**T2DM-MDD**	**p-value**
	Median (IQR 25^{th}-75^{th})	Median (IQR 25^{th}-75^{th})		Median (IQR 25^{th}-75^{th})	Median (IQR 25^{th}-75^{th})	
2012	**n=141**	**n=682**		**n=141**	**n=668**	
	$1,668 (761-2,814)	$1,559 (754-2,621)	0.539	$2,125 (1,295-2,125)	$1,057 (437-2,076)	<0.0001
2013	**n=148**	**n=718**		**n=148**	**n=709**	
	$1,458 (650-2,399)	$1,304 (734-2,165)	0.376	$1,743 (1,040-2,797)	$867 (374-1,667)	<0.0001
2014	**n=152**	**n=734**		**n=152**	**n=713**	
	$1,293 (624-2,457)	$1,259 (819-2,143)	0.772	$1,488 (657-2,755)	$630 (232-1,437)	<0.0001
2015	**n=144**	**n=743**		**n=146**	**n=733**	
	$956 (765-1,821)	$965 (720-1,821)	0.698	$1,246 (655-1,967)	$609 (237-1,144)	<0.0001
2016	**n=158**	**n=794**		**n=163**	**n=789**	
	$1,016 (774-1,647)	$994 (774-1,843)	0.793	$1,414 (739-2,293)	$614 (262-1,255)	<0.0001

IQR, Interquartile Range; PPPY, Per-Patient-Per-Year; MDD, Major Depressive Disorder; T2DM, Type 2 Diabetes Mellitus

3.4.4.2. T2DM related and other hospitalisation costs

The annual median T2DM-related hospital admission costs across the 5-year period represented in Table 3.3 showed no difference in the hospitalisation costs between the T2DM+MDD and T2DM-MDD groups, except in the year 2015.

Other hospital admissions costs were more in the T2DM+MDD group, observed in all years except in 2012 and 2014. However, in the year 2015 the hospital costs were significantly higher $p<0.001$, $3,829 [IQR (1,667-9,322)] compared to the T2DM-MDD group $1,477 [IQR (778-4,053)].

Table 3.3 Hospital admission costs PPPY with T2DM+MDD and T2DM-MDD

Median hospital admission costs PPPY						
	T2DM-related hospital admissions			**Other hospital admissions**		
	Median (IQR 25th-75th)			Median (IQR 25th-75th)		
Year	**T2DM+MDD n (%)**	**T2DM-MDD n (%)**	**p-value**	**T2DM+MDD n (%)**	**T2DM-MDD n (%)**	**p-value**
2012	n= 30/141 (21)	n= 125/687 (18)		n=74/141 (53)	n=230/687 (34)	
	$903 (326-3,229)	$2,083 (875-7,064)	0.112	$3,542 (1,270-12,757)	$2,828 (1,429-6,847)	0.189
2013	n=28/149 (19)	n=116/728 (16)		n=64/149 (43)	n=214/728 (29)	
	$2,901 (951-5,742)	$1,796 (551-5,552)	0.223	$4,018 (1,488-8,978)	$2,464 (891-6,270)	0.031
2014	n=27/152 (18)	n=115/749 (15)		n=69/152 (45)	n=215/749 (29)	
	$1,097 (301-4,707)	$2,085 (498-5,064)	0.311	$2,947 (1,078-6,589)	$2,124 (987-5,167)	0.281
2015	n=35/146 (24)	n=123/753 (16)		n=65/146 (45)	n=225/753 (30)	
	$489 (157-1,957)	$1,695 (359-4,572)	0.006	$3,829 (1,667-9,322)	$1,477 (778-4,053)	<0.001
2016	n=46/163 (28)	n=141/808 (17)		n=90/163 (55)	n=283/808 (35)	
	$1,781 (522-1,781)	$1,589 (556-4,336)	0.754	$3,331 (1,257-5,983)	$1,822 (893-5,291)	0.031

IQR, Interquartile Range; PPPY, Per-Patient-Per-Year; MDD, Major Depressive Disorder; T2DM, Type 2 Diabetes Mellitus

3.4.5. Discussion

The main findings show patients with T2DM+MDD accrued higher 'other' related costs within this setting compared to T2DM without MDD. This could be expected due to the additional treatment and management costs of MDD. In terms of their diabetes-related medicine+services (including capitation fee), there was no difference between the T2DM+MDD and T2DM-MDD groups, as patients with T2DM were managed on the DMP and incurred the same costs (Paper 2).

The findings of previous studies showed that patients with T2DM within this managed care organisation had high rates of comorbidities and consumed significant healthcare resources.[176] (Paper 1). A higher percentage of T2DM patients with MDD were admitted to hospital (42%) compared with those without MDD (30%) (Table 3, paper 1). The second study[175] (Paper 2) showed patients with T2DM on CM in this setting accrue significantly higher annual costs compared to patients on FFS.

Among these patients, the T2DM+MDD group accrued higher 'other' related treatment and management costs across the 5 years. Simon et al. have shown that MDD remained strongly associated with increased health service costs at all levels of diabetes severity.[149] The high cost of patients with T2DM+MDD could be attributed to the cost implications of treatment and management for MDD in patients with T2DM, as reported by Pouwer et al.[178]

The hospitalisation costs in general were similar among the patients in the T2DM+MDD vs T2DM-MDD groups and differed for the type of hospital admissions in the years 2013, 2015 and 2016.

The T2DM-related hospital unit median costs incurred among patients in the T2DM+MDD group in 2015 was significantly lower - $489 [IQR (157-1,957)] compared to $1,695 [IQR (359-4,572)]. However, the other related hospital admission costs was much more i.e. $3,829 [IQR (1,667-9,322)] vs $1,477 [IQR (778-4,053)] (T2DM+MDD vs T2DM-MDD). A possible explanation for the higher diabetes-related and other hospital costs among T2DM patients in 2015 could be due to the very high costs for acute renal failure, ketoacidosis, stroke, angioplasty, laparotomy, observed in the year 2015 (Table 4, in Paper 2).

A Medical Expenditure Panel Survey (2004–2011) conducted in the USA, estimated the average incremental costs of depressive disorder and T2DM was increased by $6,037 (CI 95% 5,243–6,830) per person per year in a pooled sample, after adjusting for sociodemographic factors, comorbidities and time trend covariates when compared to patients with none.[151] The substantial healthcare expenditure, defined as the sum of direct office-based medical, in and outpatient admissions, emergency room, pharmacy, home health and other medical care, was

higher compared to the diabetes-related medicine+services costs incurred in this study across the years i.e. $489 [IQR (157-1,957)] to $2,901 [IQR (951-5,742)]. This study had a smaller sample size of T2DM+MDD of 141 to 163 and did not include home health and emergency room costs. In- and out-patient admissions were analysed separately as hospitalisation costs but were a lot still less expensive than the USA study.

There are few study reports on direct or indirect healthcare costs of MDD and associated chronic conditions such as T2DM in the South African public or private sectors.[179]

In general, the highlights of the very high-cost findings of patients with T2DM in a private managed healthcare organisation as shown in Paper 2, are further exacerbated by associated MDD costs. Additionally, the diabetes-related cost due to macrovascular complications in this sample of patients with T2DM is high (Paper 1), and is increased with MDD. This translates to the fact that the CM model of care does not incorporate management of MDD when the outcomes worsen when NCDs overlap.

Within this managed care organisation, total healthcare costs associated with diabetes-related and other treatment, management and hospital admissions will tend to increase over the years, with the notably high incidence of T2DM+MDD, and a high hospital admission rate of this group in this setting. The variable with the greatest impact on healthcare expenditure was hospital admissions (Table 3.3) as seen in this study.

From the perspective of resource constraints in SA, the present analysis shows how important it is to holistically manage individuals with T2DM and comorbid MDD by identifying and managing them earlier to prevent hospitalisations.

3.4.6. Limitations

This study was restricted to direct medical costs from the medical health insurer's perspective; the indirect costs such as lost productivity and absenteeism were not addressed. Further research would be necessary to assess indirect costs incurred by the patient with T2DM and associated MDD.

3.4.7. Conclusion

The high medical healthcare expenditure incurred by the scheme despite the T2DM patients being on a CM of diabetes care shown in Paper 2, is further exacerbated by associated MDD costs. This makes the cost findings extremely beneficial to the healthcare industry in SA including an insight into the financial burden associated with MDD and T2DM.

Chapter 4. Study 3

4.1. Introduction to study 3

Study 3 is presented as a pre-submission manuscript. This study assessed the level of glycaemia, blood pressure and lipid control in patients with T2DM, with or without co-morbid MDD. The predictors of glycaemic and lipid control in these patients including the role of age, sex, statins, antihypertensive and antidepressant selective-serotonin-reuptake inhibitors (SSRIs) were exemplified.

4.2. Contributions of the candidate to study 3

The candidate has made a substantial contribution to the preparation and submission of this study in terms of the intellectual content, i.e. the concept and design, acquisition of data, analysis and interpretation of data and drafting of the manuscript.

4.3. Paper 3: Is there ABC goal attainment in patients with Type 2 Diabetes Mellitus and Major Depressive Disorder in a South African managed healthcare organisation

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This manuscript is in the final pre-submission draft below and will be submitted to the Cardiovascular Journal of Africa (CVJA)

Is there ABC goal attainment in patients with Type 2 Diabetes Mellitus and Major Depressive Disorder in a South African managed healthcare organisation?

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4.3.1. Abstract

Introduction: Type 2 diabetes mellitus (T2DM) and major depressive disorder (MDD) are highly prevalent diseases in South Africa (SA). Individuals with T2DM and comorbid MDD have the potential for greater adverse outcomes than those with T2DM alone. High blood glucose, uncontrolled systolic blood pressure (SBP) and elevated serum lipids in patients with T2DM result in a significant increase in the risk of cardiovascular disease (CVD) related morbidity and mortality. MDD is found to increase the risk of CVD in T2DM. The presence of MDD associated with worse glycaemic, BP and lipid control in patients with T2DM is unknown in the South African private managed healthcare setting.

Aim: The study investigated the glycaemic, blood pressure and lipid control and associated factors in patients with T2DM, with MDD (T2DM+MDD) and without MDD (T2DM-MDD) and control group of MDD patients.

Methods: Healthcare medical claims, electronic health records (EHR) and laboratory data of 1211 adult patients with T2DM and/or MDD from the database of a private managed healthcare organisation for 2019 were analysed. Cardiometabolic indices control was measured between T2DM+MDD, T2DM-MDD and MDD groups. Frequencies of patients achieving target glycated haemoglobin (HbA1c), SBP and low-density-lipoprotein (LDL-C), claiming lipid-lowering therapy, hypoglycaemic agents, antihypertensives and antidepressant selective-serotonin-reuptake inhibitor (SSRI) were compared between the study groups. In-hospital events of the study groups were assessed. A stepwise multivariate logistic regression analysis was performed to identify predictors of HbA1c and LDL-C control of the study groups.

Results: The median and interquartile range (IQR) of HbA1c [7.4% (6.0-8.2); 7.2% (6.2-8.5)] was significantly different ($p<0.05$) between the T2DM+MDD vs T2DM-MDD groups. However, the LDL-C [2.4mmol/l (1.8-3.1) vs 2.4mmol/l (1.8-3.1)] was similar among the T2DM groups. A higher proportion of patients with T2DM+MDD were achieving HbA1c<7% compared to the

T2DM-MDD group (56% vs 45%) p=0.05. Only 24% of patients reached LDL-C target <1.8mmol/l in the T2DM groups, with 13% and 7.1% of patients with T2DM+MDD and T2DM-MDD achieving HbA1c<7%, SBP≤140mmHg and LDL-C<1.8mmol/l (ABC) targets. Claiming patterns of antihypertensives were higher among patients with T2DM+MDD (79% vs 68%) p=0.001. However, lipid-lowering medications claimed were similar in the T2DM+MDD vs T2DM-MDD groups (78% vs 72%), and the MDD patients showed (36%; 35%) being on both. HbA1c control was significantly associated with T2DM patients who were older (p=0.002), claiming statin, p<0.0001 and having MDD p<0.0001. Similarly, older (p=0.0001) patients with T2DM, claiming statins (p=0.001) significantly affected LDL-C levels. The proportion of patients admitted due to macrovascular complications was higher among the T2DM+MDD group (22.8%) compared to T2DM-MDD (13.1%) and MDD group (9.9%) p=0.012.

Conclusion: Glycaemic and lipid targets of patients with T2DM+MDD and T2DM-MDD were unmet despite a high rate of claims for antidiabetic and dyslipidaemia therapies. Achievement of guideline targets of LDL-C was suboptimal in this setting, with a dismal 13% and 7.1% of patients with T2DM+MDD and T2DM-MDD achieving ABC targets. Older patients being treated for T2DM+MDD, showed better HbA1c and LDL-C control in this setting.

4.3.2. Introduction

Type 2 diabetes mellitus (T2DM) and major depressive disorder (MDD) are highly prevalent diseases in South Africa (SA)[1,111] with co-morbid MDD presenting in 17% of patients with T2DM in a privately managed healthcare organisation (reference paper 1). Naidoo et al.[176], in an analysis of the claims data, showed that significantly more (p=0.02) patients with T2DM and comorbid MDD (T2DM+MDD) (73%) experienced hyperlipidaemia than those with T2DM (61%) alone.

Type 2 diabetes mellitus (T2DM) is considered a cardiovascular (CV) risk equivalent.[180] Atherosclerosis and thromboembolic events are the most notable outcomes of T2DM.[181] The risk of cardiovascular disease (CVD) related events such as heart attacks, strokes and heart failure in patients with T2DM is increased two to fourfold compared with people who do not have diabetes.[182] The “ABC practice guidelines”[183] for atherosclerotic cardiovascular risk management indicate the evidence-based levels required to determine control of blood glucose, systolic blood pressure and serum lipid levels to reduce the risk of atherosclerotic cardiovascular events.[62,184,185] Poor ABC management in patients with T2DM results in a significant increase in the risk of CVD events and mortality.[186,187]

Trials have focused on reducing blood glucose levels to reduce the risk of microvascular complications.[187,188] However, macrovascular outcomes have a more negative impact on morbidity and mortality in T2DM. Intervention trials have allocated most of the resources to

lowering glycated haemoglobin (HbA1c) and tighter BP control,[27] but very little attention has been placed on lipid control. Altered serum circulating low-density-lipoprotein-cholesterol (LDL-C) and high-density lipoprotein (HDL) is directly correlated with higher thromboembolic events such as myocardial infarction [26] and stroke.[189]

The control of blood glucose is the fundamental objective in T2DM, with HbA1c being the best marker of glucose levels and microvascular (nephropathy, retinopathy and neuropathy) outcomes.[62] However, chronic hyperglycaemia is also an added risk factor for atherosclerosis in patients with T2DM. Atherosclerosis is often accelerated and severe in T2DM.[62] T2DM when presented with insulin resistance and hyperglycaemia over a prolonged period is a serious chronic condition. Complex manifestation of atherogenic dyslipidaemia[181] and significant alteration of circulating LDL-C, a major determinant of atherosclerotic CV risk predisposed to coronary artery disease (CAD), occurs in T2DM over time.[190] High BP is another vascular disease that affects people with T2DM during the course of their disease, putting them at a greater risk of developing target organ damage than non-diabetics.[76]

The interaction of T2DM and other non-communicable diseases (NCDs) increases the risk of comorbidities in T2DM.[191] One of the major comorbidities is MDD and it is found to heighten the risk of hospitalisation in T2DM.[176] The mutual causation between T2DM and MDD, where each illness becomes a risk factor for the other [102,98,] results in higher adverse atherosclerotic cardiovascular disease (ASCVD) outcomes.[192] These consequences may be attributed to inflammatory responses accompanying MDD that play a role in the progression of vascular complications among patients with T2DM[193]; alternatively due to non-adherence with medication.[130]

Depression related to long-term control of HbA1c, SBP and LDL-C in patients with T2DM has been well-studied in the United States of America. The findings by Heckbert et al.[194] report MDD was associated with slightly higher average HbA1c, and no difference in average SBP or LDL-C levels during follow-up in patients with T2DM whereas the study by Katon et al.[169] showed patients with T2DM and MDD, with or without evidence of heart disease, have a higher number of CVD risk factors. A recent study in Ghana conducted in a tertiary public healthcare facility reported no independent association of MDD with poor glycaemic control among the Ghanaians with T2DM+MDD.[39]

This study investigated the ABC guideline target attainment for ASCVD risk factors i.e. glycaemic control evidenced by HbA1c, BP control evidenced by SBP, and lipid control as evidenced by LDL-C. LDL-C was targeted because it is the best-predicted risk factor of CAD which can be reduced significantly but not completely with statin therapy.[28] There could be interactions of other residual pathogenic CV risk factors involved i.e. triglycerides, very-low-density and intermediate-density lipoproteins not explained by lowering LDL-C alone. In

patients with T2DM, reduction of LDL-C particularly with statin treatment reduces the risk for major CVD events.[190]

Within this organisation, there is a high incidence of T2DM with all the CV sequela in addition to having MDD overlapping as a most frequent discordant comorbidity.[176] The incidence of MDD in T2DM in developing countries such as Ghana (31.3%)[39] and India (38%)[195] has been found to be higher than in Brazil (18.6%)[40] and the USA (8.3%).[144] The disparity in prevalence rates between the different countries could be attributed to the difference in socio-cultural background and depression screening instruments used in the studies.[196,88]

In SA, the national prevalence of adults with T2DM is 12.7%[84] and with MDD is 9.7%.[111] However, the national co-prevalence of MDD in patients with T2DM is yet to be enumerated. It is clear that T2DM is a huge contributor to disease burden and the coincidence of MDD may have a negative effect on the outcomes of T2DM;[90] hence the focus is on cardiometabolic indices in individuals with T2DM+MDD.

Emerging evidence demonstrates shared mechanisms between non-communicable diseases i.e. MDD and T2DM and between MDD and ASCVD are attributed predominantly due to the immunometabolic pathways.[137,138,139,140] MDD has been attributed to alterations in the regulation of hormones often leading to high levels of pro-inflammatory cytokines and receptors[141,142] which over a length of time can lead to somatic consequences such as elevated BP and blood glucose, abdominal obesity and dyslipidaemia.[197] These are known traditional risk factors for T2DM, ASCVD and other related disorders.[198]

Statins (3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors) have been demonstrated to be effective in both primary and secondary prevention of ASCVD.[187] This effect is largely dependent on the extent to which LDL-C is lowered and not by the type of statin used.[28,187,75] Sadly, the main cause of death in MDD remains ASCVD,[199] where statins have proven therapeutic benefits.[200] Besides their lipid-lowering properties, large studies report that statin use was associated with a reduced risk of depression.[201] This intrinsic property of statins is beneficial in patients post-heart attack and in individuals experiencing excess inflammation due to physical diseases such as stroke that are highly co-morbid with MDD.[202] The combination of a selective serotonin reuptake inhibitor (SSRI) and a statin was associated with lower risks for psychiatric hospitalisations due to depression than with the use of either drug alone.[203] Lipophilic statins (simvastatin and atorvastatin) showed greater potential to decrease depressive symptoms than hydrophilic statins (rosuvastatin and pravastatin) as these statins can cross the blood-brain barrier.[204]

Given that lipid-lowering therapy, such as statins, in patients with a high risk of ASCVD reach evidence-based target LDL-C goals,[28] and SSRIs improve mood and offer better adherence to

medication,[155, 156] this study described the ABC guideline target attainment of individuals with T2DM with and without co-morbid MDD. These individuals are registered as patients in a managed healthcare organisation with access to antidiabetic agents, anti-hypertensive, lipid-lowering therapies and antidepressants.

4.3.2.1. Objectives

The study investigated the South African ABC (HbA1c<7%, SBP≤140mmHg and LDL-C<1.8mmol/l) guideline target attainment of patients with T2DM with a history of MDD (T2DM+MDD), without MDD (T2DM-MDD), and with MDD only. The factors (i.e. age, sex, statin claims, SSRIs, antihypertensive and hypoglycaemic agents claimed, and having MDD) associated with HbA1c and LDL-C control were assessed. Hospital admissions for macrovascular outcomes and depressive episodes of patients with T2DM+MDD and T2DM-MDD were assessed.

4.3.3. Methods

4.3.3.1. Study design and sample selection

This analysis used an integrated database of electronic health records (EHR), laboratory data, the medical, hospital and pharmacy administrative claims data of members with T2DM and MDD of a South African managed healthcare organisation in the year 2019. The EHR of study members registered with the medical scheme was linked to the administrative claims system which together provided membership, healthcare and claims processed data. The database included patient-level demographics and clinical characteristics (i.e. illnesses, hospital events, diagnosing and follow-up BP readings, HbA1c levels and lipogram reports). Medications claimed by study subjects were extracted from the administrative system claims database.

4.3.3.2. Patients

Patients 18 years and older were included in the study sample if they had a diagnosis code of T2DM and MDD registered for chronic benefits with the medical scheme. International Classification of Diseases and Related Health Problems, 10th revision (ICD10)[205] diagnoses codes E11.0 (T2DM with hyperosmolarity) to E11.9 (T2DM without complications) were used to classify patients having T2DM as stated by the practitioner. Patients diagnosed with MDD were identified with ICD10 codes F32.2 (MDD, single episode, severe without psychotic features) to F33.9 (MDD, recurrent, unspecified). These ICD10 codes were obtained from the Council of Medical Schemes Prescribed Minimum Benefit ICD10 coded list 2013.[23]

Sample selection inclusion criteria were patients with their latest HbA1c value recorded on the healthcare system in 2019. In addition, T2DM and MDD were also determined via pharmacy claims of either oral and/or injectable hypoglycaemic agents or insulin, and antidepressants

claimed sequentially over 6 months. Three groups of patients with T2DM+MDD, T2DM-MDD and a control MDD group (patients with MDD only) were selected to investigate their glycaemic, blood pressure and lipid profiles. Patients with no available clinical data i.e. HbA1c, SBP and LDL-C), and no claims of treatment modalities for T2DM and MDD were excluded from this study.

Of the 47 380 registered beneficiaries on the medical scheme in 2019, 879 adults with a registered diagnosis of T2DM and available HbA1c result who claimed hypoglycaemic agents for at least 6 months were identified. From these patients with T2DM, those registered with a diagnosis of MDD and claiming antidepressants were identified as T2DM+MDD (n=223). A second group with T2DM without a diagnosis of MDD nor claiming for antidepressants (T2DM-MDD) (n=656) was chosen. The third MDD control group (n=332) was selected from the beneficiaries that were registered as being diagnosed with MDD and claiming antidepressant usage without any history of T2DM.

4.3.3.3. Disease control measures

Glycaemic, BP and lipid level indices were defined and characterised with reference to the 2017 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines.[62] Study patients were grouped into individualised HbA1c targets according to risk: those with HbA1c control below 7% and those ≥7%; patients with lipid levels at target TC <4.5mmol/l; those below target LDL-C <1.8 mmol/l; those above target HDL-C >1.0 mmol/l men; >1.2 mmol/l women; those below triglyceride target level <1.7 mmol/l; and BP in patients with Systolic BP <140 mmHg and Diastolic BP <90 mmHg. The ABC goals of T2DM were defined by South African diabetes guidelines[62] as meeting HbA1c <7%, SBP <140 mmHg and DBP <90 mmHg, and LDL-C <1.8mmol/l - an abbreviation put together to bring awareness to the public by the American Diabetes Association and the American College of Cardiology.[183]

4.3.3.4. Hospitalisations

Using medical record review, the schemes hospitalisation management database, ICD10 diagnostic code and CPT-4 (current procedural terminology, 4th edition) procedure code data, physician-diagnosed documented major macrovascular hospitalisations were identified. Major macrovascular hospitalisations were identified as the presence of a diagnosis or an event of a CAD (i.e. unstable angina, angiogram, angina pectoris, atherosclerotic heart disease), congestive heart failure, atrial fibrillation, stroke, transient cerebral ischaemic attack, embolism and thrombosis of arteries or other specified veins, and peripheral vascular disease; or procedures such as coronary revascularization i.e. acute transmural myocardial infarction percutaneous procedures, coronary artery bypass, angioplasty-percutaneous-transluminal-coronary-angioplasty bare metal or balloon or drug-eluting, pacemaker insertion and cardioversion.

4.3.3.5. Classification of hypoglycaemic agents, lipid-lowering therapy and antidepressants claimed

Using the administrative medicines claims data that was categorised according to Anatomical Therapeutic Chemical (ATC) Classification,[206] individuals claiming hypoglycaemic agents were identified as using A10B (Blood glucose lowering drugs excluding insulins) i.e. older oral agents (metformin, glibenclamide, gliclazide, glimepiride, repaglinide, pioglitazone) newer agents (vildagliptin, dapagliflozin, liraglutide, empagliflozin, sitagliptin, exenatide, saxagliptin); and who were on insulin as A10A (Insulin and analogues).

Those on antihypertensive therapy were identified according to ATC C02 (Antihypertensives), C03 (Diuretics), C07 (Beta-blocking agents), C09 (Agents acting on the renin-angiotensin systems), C08 (Calcium channel blockers) and G04CA03 (Alpha adrenoreceptor antagonist). The choice of selecting antihypertensive medication is based mainly on the patient's glycaemic and lipid profiles. Although all classes of antihypertensive medications are efficient in reducing all cause and CV mortality, thiazides and beta-blockers disturb the lipid profile most markedly in many patients with diabetes. Alternative agents acting on the renin-angiotensin systems such as calcium channel blockers and alpha adrenoreceptor antagonists offer favourable metabolic profiles compared to thiazides and beta-blockers in diabetics.[207]

Patients claiming treatment for dyslipidaemia ATC C10 (lipid-modifying therapy i.e. statins (98% claim rate), fibrates, ezetimibe and bile acid sequestrants) were identified.

Patients claiming antidepressant ATC (N06A) were characterised according to those on SSRIs (i.e. Fluoxetine; Paroxetine; Sertraline; Citalopram; Escitalopram; Fluvoxamine) versus those not on SSRIs i.e. patients on Serotonin Norepinephrine Reuptake Inhibitors (Venlafaxine; Desvenlafaxine; Duloxetine), Noradrenergic and Specific Serotonergic Antidepressants (Mirtazapine; Mianserin), Serotonin Receptor Antagonists and Reuptake Inhibitors (Trazodone), Norepinephrine Dopamine Reuptake Inhibitor (Bupropion), Serotonergic Antidepressant (Vortioxetine) or Melatonergic Agonist (Agomelatine). The class of SSRI was characterised separately as data shows that in combination with a statin it had larger effects on depressive symptoms than either drug alone.[208]

4.3.3.6. Ethical Considerations

Confidentiality was maintained throughout the analysis by using the patients' unique scheme membership number and dependent code to align patient-level records. The University of the Witwatersrand Johannesburg, Faculty of Health Sciences Human Ethics Committee (M140326; M1911196), approved the study. Approval was granted by the Principal Officer of the scheme for the scheme data to be used in the study and by the Human Resources Manager to gather data from the scheme administrative database for the research.

4.3.4. Statistical and data analysis

Data extracted from the database were exported to Microsoft Excel 2016 and statistical analysis was performed with Statistica 13.3 (StatSoft Inc., Tulsa, OK) and SAS 9.4. BP was presented in mean(±SD) as data was normally distributed. HbA1c and lipid level records were not normally distributed and therefore displayed in median (IQR). Categorical variables such as sex, number of claims for medicines and disease control measures i.e. the HbA1c, BP and lipid level indices of patients were summarized as frequencies and percentages and compared using Chi-square or Fisher-exact tests. Multiple comparisons were analysed using Bonferroni Correction amongst the three groups; the level of significance was set at $p<0.0166$.

Stepwise multivariate logistic regression models were performed to determine factors predicting glycaemic (HbA1c) and lipid (LDL-C) control in the study groups of patients with T2DM and MDD only. Effects of demographic variables (age and sex), diagnoses of MDD, and treatment modalities (statins, selective-serotonin-reuptake inhibitors (SSRIs), combination of metformin with other regimens (insulin or new blood glucose lowering agents) and antihypertensives) were entered into two models. A sub-analysis of patients claiming different classes of antidepressants were compared between those on SSRIs with those not on SSRIs and equated them to their HbA1c targets attained. The significance level was set at $p<0.05$.

Discrete variables of patients claiming “Insulin only” 12/223 (5.4%) in the T2DM +MDD group and 15/656 (2.3%) were excluded from the multivariate regression analysis as very few were claiming for insulin only.

4.3.5. Results

Table 4.1 shows the characteristics of the patients within the T2DM+MDD (25%), T2DM-MDD compared to the Control (MDD) group. A higher proportion of females were among the T2DM+MDD and MDD groups (54%; 64%) $p<0.0001$ compared to the T2DM-MDD group (37%), and a significantly greater percentage of patients were older than 61±13 years (mean SD) in the T2DM+MDD group compared to the T2DM-MDD (57±14 years) and MDD (50±17 years) groups $p<0.0001$. The T2DM groups showed similar claiming patterns for lipid-lowering medications. However, a higher proportion of patients among the T2DM+MDD group vs T2DM-MDD group claimed antihypertensives (79% vs 68%) $p=0.001$; and 35%; 36% of the MDD patients claimed for both medications.

Table 4.1 Characteristics of patients with T2DM+MDD, T2DM-MDD, MDD control

Characteristics	T2DM+MDD n=223 (25%) n (%)	T2DM-MDD n=656 (75%) n (%)	p-value	MDD Control n=332 n (%)	p-value

Age (years) (mean±SD)	61±13	57±14	0.01	50±17	<0.0001
Female	121 (54)	245 (37)	<0.001	213/332 (64)	<0.0001
Therapy claimed					
Antihypertensives	177/223 (79)	447/656 (68)	0.001	121/332 (36)	<0.0001
Lipid-lowering therapy	173/223 (78)	471/656 (72)	0.092	117/332 (35)	<0.0001
Antidepressant therapy	223/223 (100)	-		262/332 (79)	<0.001
Selective serotonin reuptake inhibitors (SSRIs)	108/223 (48)	-		168/332 (51)	0.478

MDD, Major Depressive Disorder; T2DM, Type 2 Diabetes Mellitus

Table 4.2 depicts the CV indices of glycaemic, BP and lipid profiles of patients with T2DM+MDD, T2DM-MDD and MDD attaining targets. The LDL-C median (IQR) was similar among T2DM+MDD 2.4 mmol/l (1.8-3.1) and T2DM-MDD 2.4 mmol/l (1.8-3.1), but significantly lower when compared to MDD groups 3.0 mmol/l (2.4-3.8) p<0.001. The median (IQR) HbA1c in patients with T2DM+MDD was higher compared to the T2DM-MDD group [7.4% (6.0-8.2) vs 7.2% (6.2-8.5)] p<0.05. As expected, the patients with MDD showed significant differences in their median (IQR) HbA1c 5.4% (5.2-5.8) and were normoglycaemic compared to the T2DM groups p<0.001. Triglyceride levels were higher in T2DM irrespective of the presence of MDD. The SBP of patients among the T2DM+MDD, T2DM-MDD and MDD groups was similar and on target. The glycaemic and LDL-C control between the T2DM+MDD; T2DM-MDD groups were (56%; 45%) and (24%; 24%).

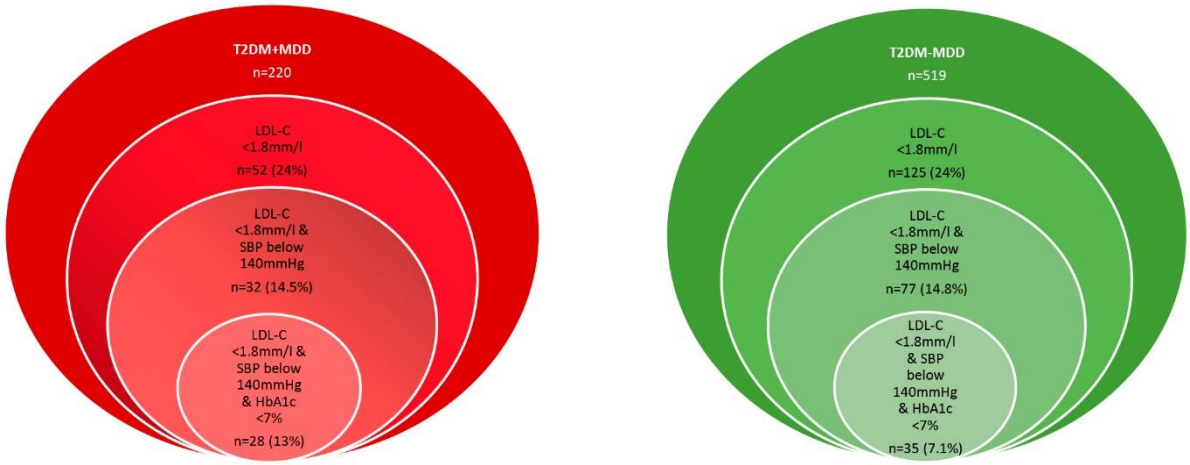
Table 4.2 Clinical profile of patients with T2DM+MDD, T2DM-MDD and MDD achieving targets

Clinical Characteristics	**T2DM+MDD**	**T2DM-MDD**	**MDD Control**
Patients with HbA1c%	**n=223**	**n=656**	**n=332**
HbA1c% Median (IQR)	7.4 (6.0–8.2)	7.2 (6.2-8.5)[#]	5.4 (5.2-5.8)**
HbA1c <7 n (%)	125/223 (56)[#]	295/656 (45)	-
HbA1c <7 Median (IQR)	6.1 (5.7-6.6)	6.2 (5.8-6.5)	-
Patients with TC mmol/l	**n=217**	**n=520**	**n=278**
TC Median (IQR)	4.4 (3.6-5.3)	4.3 (3.6-5.1)	5.1 (4.3-5.8)**
TC <4.5 n (%)	118/217 (54)	298/520 (57)	83/278 (30)**
Patients with LDL-C mmol/l	**n=220**	**n=519**	**n=268**
LDL-C Median (IQR)	2.4 (1.8-3.1)	2.4 (1.8-3.1)	3.0 (2.4-3.8)**
LDL-C <1.8 n (%)	52/220 (24)	125/519 (24)	-
LDL-C <1.8 Median (IQR)	1.4 (1.1-1.6)	1.5 (1.2-1.6)	-
Patients with HDL-C mmol/l	**n=215**	**n=507**	**n=139**
HDL-C Median (IQR)	1.1 (0.9-1.4)	1.1 (0.9-1.3)	1.3 (1.1-1.6)**

HDL-C ≥1 (male); ≥1.2 (female) n (%)	129/215 (60)	328/507 (65)	118/139 (85)**
Patients with Triglycerides mmol/l	**n=216**	**n=508**	**n=266**
Triglycerides Median (IQR)	1.70 (1.3-2.3)	1.7 (1.2-2.6)	1.3 (0.9-1.9)**
Triglycerides <1.7 n (%)	99/216 (46)	255/508 (50)	177/266 (67)**
Patients with BP mmHg readings	**n=181**	**n=451**	**n=107**
Systolic BP Mean±SD	132±17	134±17	135±17
Diastolic BP Mean±SD	79±12#	82±12	83±12
Systolic BP ≤140mm Hg n (%)	135/181 (75)	340/451 (75)	78/107 (73)

BP; Blood Pressure; HbA1c, glycated Haemoglobin; HDL, High-density Lipoprotein-Cholesterol; IQR, Interquartile Range; LDL-C, Low-density Lipoprotein-Cholesterol; MDD, Major Depressive Disorder; TC, Total Cholesterol; T2DM, Type 2 Diabetes Mellitus, *p<0.01 and **p<0.001 between the 3 groups; # p<0.05 between T2DM with and without MDD groups

Figure 4.1 shows 13% and 7.1% of patients with T2DM+MDD and T2DM-MDD achieved ABC (HbA1c<7%, SBP≤140mmHg and LDL-C<1.8mmol/l) targets.



HbA1c, glycated haemoglobin; LDL-C, Low-density Lipoprotein-Cholesterol; MDD, Major Depressive Disorder; T2DM, SBP, Systolic Blood Pressure; Type 2 Diabetes Mellitus

Figure 4.1 Percentage of patients with T2DM with and without MDD achieving ABC (HbA1c, SBP and LDL-C) goal

Logistic regression analysis was performed to identify predictors of HbA1c and LDL-C only as these were unmet targets in the study groups.

Table 4.3 depicts a stepwise multivariate logistic regression analysis that identified predictors of HbA1c control of the T2DM study groups, It was found to be significantly associated with older aged (p=0.002) patients, claims for statins and having diagnoses of MDD (p<0.0001).

Table 4.3 Stepwise multivariate logistic regression of HbA1c control in T2DM+MDD and T2DM-MDD groups

Variables	OR*	95% CI	p-value
Age	1.02	(1.01-1.04)	0.002

Statins claimed	2.09	(1.41-3.11)	<0.0001
Metformin claimed	0.51	(0.27-0.97)	0.04
Newer hypoglycaemic agents claimed	0.45	(0.21-0.99)	0.048
T2DM+MDD group	2.30	(1.47-3.61)	<0.0001

*Adjusted for claims for antihypertensive agents, sex and the interaction factor of newer hypoglycaemic agents and metformin

Table 4.4 depicts the stepwise multivariate logistic regression analysis that identified the predictors of LDL-C control of the T2DM+MDD vs T2DM-MDD groups. The significant contributing factors to LDL-C control between the two groups was being older (p<0.0001) and claiming statins (p=0.001).

Table 4.4 Stepwise multivariate logistic regression of LDL-C control in T2DM+MDD and T2DM-MDD groups

Variables	OR*	95% CI	p-value
Age	1.03	(1.01-1.04)	<0.0001
Statins claimed	2.51	(1.50-4.21)	0.001

*Adjusted for claims for antihypertensive agents, metformin and sex

4.3.5.1. Association of SSRI medication and HbA1c targets in patients with T2DM+MDD

Figure 4.2 displays the percentage of patients with T2DM+MDD on SSRIs reaching HbA1c of <7%. There was no statistically significant difference in the proportion of patients achieving HbA1c target regardless of the nature of their antidepressant therapy. After performing a multiple logistic regression in patients with T2DM+MDD it was found that SSRIs (p=0.19) and metformin (p=0.27) were not independently associated with HbA1c control when adjusting for age and sex.

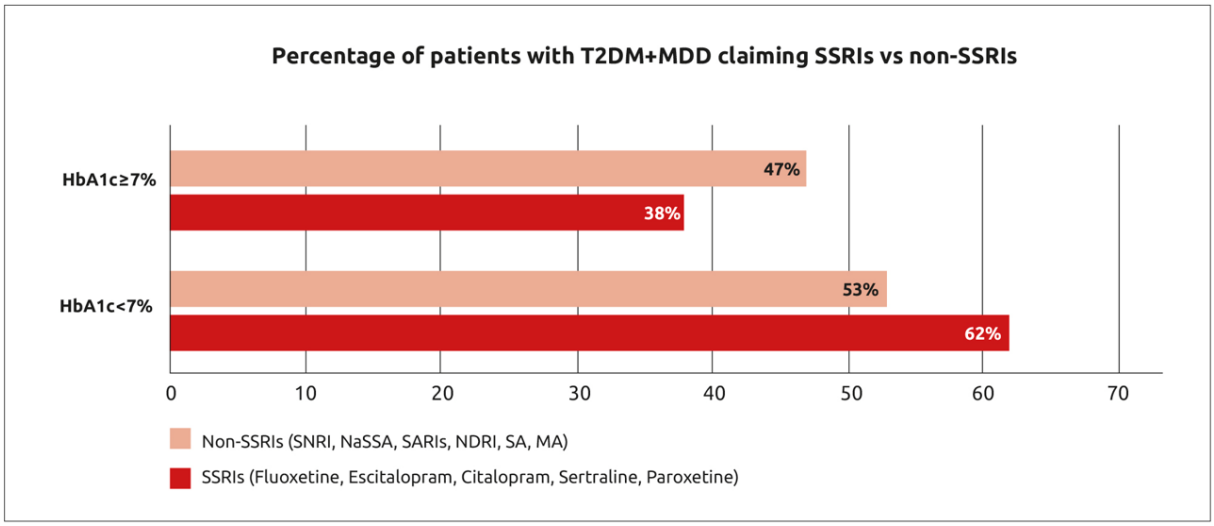


Figure 4.2 Percentage of patients with T2DM+MDD on antidepressants SSRIs vs non-SSRIs achieving HbA1c target

HbA1c, Glycated Haemoglobin; MDD, Major Depressive Disorder; MA, Melatonergic Agonist; NaSSA, NDRI, Norepinephrine Dopamine Reuptake Inhibitor; Noradrenergic and Specific Serotonergic Antidepressant; SSRIs, Selective Serotonin Reuptake

Inhibitors; SNRI, Serotonin Norepinephrine Reuptake Inhibitor; SARIs, Serotonin Receptor Antagonists and Reuptake Inhibitors; SA, Serotonergic antidepressant); T2DM, Type 2 Diabetes Mellitus

Table 4.5 shows the frequency of hospital admissions for macrovascular and depressive episodes among the T2DM+MDD, T2DM-MDD and MDD-only groups. There was a significant difference in the macrovascular hospitalization between the T2DM+MDD vs T2DM-MDD groups. A higher proportion of patients among the T2DM+MDD group compared to the T2DM-MDD and MDD-only groups were admitted for macrovascular events (23% vs 13.1%; 9.9%) p=0.012; with a significant number of macrovascular admissions among patients with T2DM+MDD (17.5%) compared to the T2DM-MDD (8.1%) and MDD group (8.6%) p=0.0006. Fewer patients with T2DM+MDD (3.3%) were admitted for depressive episodes compared to the patients from the MDD control group (15.5%) p=0.003.

Table 4.5 Hospitalisations of patients with T2DM+MDD, T2DM-MDD and MDD

Characteristics	T2DM+MDD n=223 n (%)	T2DM-MDD n=656 n (%)	MDD Control n=332 n (%)	P-value
Total number of hospital admissions	200/223 (89.7)	493/656 (75.2)	290/332 (87.3)	<0.0001
Total number of patients admitted	92/223 (41.3)	236/656 (36)	161/332 (48.5)	0.0007
Admissions per patient	200/92 (2.2)	493/236 (2.1)	290/161 (1.8)	
Patients admitted for macrovascular events	21/92 (22.8)	31/236 (13.1)	16/161 (9.9)	0.012
Total macrovascular admissions	35/200 (17.5)	40/493 (8.1)	25/290 (8.6)	0.0006
Patients admitted for Depressive episodes	3/92 (3.3)	-	25/161 (15.5)	0.003
Total Hospital Depressive episodes	3/200 (1.5)	-	29/290 (10.0)	0.0012

MDD, Major Depressive Disorder; T2DM, Type 2 Diabetes Mellitus

4.3.6. Discussion

While over seventy percent of patients in all three groups achieved the target Systolic BP of ≤140mmHg, the findings indicated inadequate glycaemic and lipid control among the T2DM patients managed in a private healthcare organisation, despite the high rate of claims for hypoglycaemic and lipid-lowering medications. Both study groups had a median target HbA1c closer to 7%, although the group with a diagnosis of co-morbid MDD had a higher HbA1c of 7.4% compared with the T2DM-MDD group. While Ismail et al. found that depression was weakly correlated with glycaemic status,[37] this study's findings are similar to studies which reported no association between poor glycaemic control and MDD.[39,209]

However, participants in this study had better rates of glycaemic control (HbA1c of <7%), T2DM+MDD (56%) and T2DM-MDD (45%), in comparison with the 22% seen across three public healthcare centres in rural Africa.[210] Coming from a privately managed health care environment that is well-resourced, the study population may be more aware of their diabetes

status and have access to newer hypoglycaemic agents and health-technology-assessment devices. In the public sector, service delivery is in the resource-constrained primary care centres. Masilela et al.[210] found African religious practices, weekly high fast-food consumption and younger (<55yrs) patients were some factors associated with poor glycaemic control. Unlike the public sector, the private healthcare sector allocates huge funds to treat and manage T2DM, including diabetes management programmes via a capitated risk-sharing model to improve patient outcomes and reduce healthcare costs.[175]

Of concern, only 24% of patients in the T2DM groups in this study achieved LDL-C control of <1.8mmol/l. In contrast, Boekholdt et al.[211] found that approximately 60% of patients were able to adequately lower their LDL-C levels on high-potency statin therapy, while the other 40% failed to reach LDL-C targets due to inter-individual variation of statin response and non-adherence. Dose-related adverse events, inadequate patient education, incorrect statin doses prescribed, and mood issues such as depression are some important factors as to why patients are non-compliant with their medications.[212,213]

The South African International Cholesterol Management Practice Study conducted by Blom et al.[214] reported that the low rates of LDL-C goal achievement among private health-insured participants were due to inadequate statin doses prescribed, use of low potency statins, and non-compliance. It also revealed that the physicians underestimated risk when utilising the risk score to assess CV risk, which results in a lack of intensifying statin lipid-lowering therapy. South African lipid guidelines are set to be updated to improve physicians' understanding of risk assessment and to promote adherence to guideline recommendations. This is in line with the American Heart Association guidelines which recommend utilising an appropriate statin dose for percentage reduction of LDL-C rather than treatment goals, as well as altering clinicians' behaviour concerning the treatment of hyperlipidaemia.[215]

Some patients may even require combination therapy with other classes of lipid-lowering therapies (e.g. ezetimibe, fibrates, bile acid sequestrants or niacin)[215] to sufficiently lower LDL-C. The magnitude of the change of LDL-C in the T2DM groups indicated a level of LDL-C that was 1.2 ±0.8mmol/l away from target levels. This clearly indicates that LDL-C targets remain a distinct reminder that a large proportion of the CV risk has not been adequately addressed within the confines of a managed care organisation.

Only 13% of patients with T2DM+MDD and 7.1% of patients with T2DM-MDD attained comprehensive glycaemic, SBP and LDL-C control. This is far less than global ABC targets (HbA1c, blood pressure, LDL-C) achieved in an Iranian population with T2DM (42%), reported by Larry et al.[216] Findings by Pinchevsky et al.[217] within a South African public tertiary hospital on a cohort of T2DM patients had results contrary to this study. The percentage of patients in the public sector reaching HbA1c, BP and lipid targets were 16.5%, 49.4% and 46.9%

compared to the T2DM+MDD; T2DM-MDD in private sector patients in this study with (56%;45%), (75%;75%) and (24%;24%) respectively.

Patients are referred to a tertiary hospital when their conditions have deteriorated, mostly with target organ damage as in the study by Pinchevsky.[217] In terms of poor glycaemic control among the cohort patients with T2DM attending the tertiary hospital sector, deterioration of HbA1c levels may be attributed to a decline in beta cell malfunctions, which is when glucose sensing is inadequate to stimulate insulin, resulting in persistently elevated hyperglycaemia seen in such a progressive disease.[218] Unlike the tertiary hospital setting study, this study looked at individuals largely managed at the primary healthcare level, where patients see a scheme plan option designated primary care provider (doctors, nurse practitioners or primary care specialists such as geriatricians and gynaecologists) for regular screenings, general check-ups and wellness visits. The type of primary care level provided, involves the initial diagnosis and standardised treatment protocol for better outcomes for the patient to avoid hospitalisation.

The LDL-C levels attained by patients in the tertiary hospital were much better and can be attributed to better compliance enforced by positive clinical inertia displayed by the clinical staff in the hospital setting.[217] The difference in BP attained between the private and public sectors may be attributed to the differences in methods and sample population (i.e. a more affluent sample in the private sector) in the studies. Factors affecting BP control were perhaps due to the increasing age, hyperglycaemia and its pathogenic effects on vascular function[219] and the use of angiotensin-converting enzyme inhibitors.

On the other hand, a meta-analysis of global achievements of guideline targets for people with T2DM from 20 countries including Europe, the USA and the rest of the world report a pooled target achievement rate of 42.8% (95% CI 38.1-47.5%) for glycaemic control, 29% (22.9-35.9%) for BP and 49.2% (39.0-59.4%) for LDL-C.[220] The result of the present study reflects a better glycaemic control (56%; 49%), BP control (75%; 75%), and worse LDL-C control (24%; 24%) among people with T2DM, with and without MDD respectively.

Results of the multivariate logistic regression analysis performed in this study suggest that distinct predictive patterns of glycaemic and lipid control exist for older adults and those claiming treatment. Findings also show a beneficial link between treatment modalities claimed (i.e. statins, metformin and newer hypoglycaemic agents) and HbA1c and LDL-C levels in older patients with T2DM and MDD. Medication claims appeared to be better in older age, because the elderly are more vigilant of their cardiometabolic indices, as these indices need to be stringently self-managed. The elderly are more aware of their trajectory of a healthier lifestyle and try to reduce their risks and better manage their glycaemic and lipid levels control. This finding is supported by Chiu et al.[221] where lifestyle significantly affected HbA1c levels in

middle-aged and older adults. Nichols et al.[222] and Chuang et al.[223] have suggested that younger age and early-onset T2DM are factors associated with worse glycaemic control

Patients with MDD in this managed care setting being treated showed better compliance and HbA1c control. Screening and treatment of depression in patients with CAD were found to improve the outcomes of CVD[131] alongside the benefits of mood elevation. Similarly, the recognition and monitoring of depression in T2DM are important because of their association with hyperglycaemia, diabetic complications and poor quality of life.[106]

Unlike hypoglycaemia, atherosclerotic disease is a disease with symptoms that develops gradually, and patients may be remiss in their statin therapy compliance. Patient-care in T2DM has an emphasis on blood glucose levels and hence, intake of hypoglycaemic agents to achieve the targeted glycaemic control may be enforced during their medical reviews. Additionally, over the past decade, health technology in T2DM and antidiabetic agents have received much attention, allowing diabetics a range of hypoglycaemic agents to lower blood glucose.[224,225,226,227] This may account for more patients reaching the glycaemic control target. However, this is not so for LDL-C targets where patients may not be aware of the detrimental effects of not complying with their lipid-lowering therapy and the choices of lipid-lowering therapy are limited. Educating members on the role of lipid-lowering therapy in preventing ASCVD is one of the crucial points that can be recommended in the arena of managed care disease management programmes.

Elevated serum levels of LDL-C are perhaps the biggest single contributor to atherosclerosis in CAD and thromboembolic stroke.[228,189] Reduction of LDL-C levels, usually with statins, confers protection, which is related to the absolute levels of serum LDL-C achieved in this therapy. Thus, a reduction in LDL-C by 1mmol/l usually confers a reduction of approximately 20% in CV risk.[21] Patients within this managed care need to be educated on the importance of compliance with lipid-lowering therapies in conjunction with their hypoglycaemic, BP and or antidepressant medications.

This study found higher macrovascular hospital admissions among patients with T2DM with comorbid MDD, compared with T2DM-MDD and control MDD groups. Association of depressive symptoms with increased risk of macrovascular complications has been reported in studies by Lin et al.[10] (in a cohort of 4,623), Scherrer et al.[229] (cohort of 12,679) and Ismail et al.[38] (cohort of 1,735).

Both hypo and hyperglycaemia have adverse outcomes and the maintenance of HbA1c below 7% reduces the risk of these adverse outcomes. However, aggressive lowering of HbA1c can result in CV complications and even death brought about by severe hypoglycaemia.[188]

Active surveillance of MDD in patients who have a primary high risk of CVD or a previous CVD event has shown an extremely high prevalence of depressive symptoms amongst patients with established CVD.[131] The aggressive treatment amelioration of these depressive symptoms has shown a reduction in CVD events by up to 43%.[29] Numerous intervention studies with statins have demonstrated a reduction of coronary events, all cardiovascular events and mortality by between 10% and 30% for every mmol/l reduction in LDL-C even if the baseline LDL-C level was at normal range[200] and in individuals with established CAD.[230,231,232]

In T2DM patients with comorbid MDD, certain antidepressants such as an SSRI (fluoxetine) and Norepinephrine Dopamine Reuptake Inhibitor (bupropion) have been associated with improvement in HbA1c control in patients with T2DM+MDD.[35,34] In the T2DM+MDD group in this study, 62% of those on SSRIs were at the HbA1c of <7% while 53% of those not on SSRIs achieved the same target, suggesting glycaemic control among patients with T2DM diagnosed and treated for MDD fared well with their diabetes. At this stage, since the true risk profile of the MDD group is not demonstrated, a future study will look at the risk profile of the patients with MDD and the depressive outcomes of the interaction of statins and SSRIs in this group.

This study explains the need for holistic management of T2DM and associated comorbidities i.e. MDD and CVD. Glycaemic and lipid targets attained as per guideline recommendations were suboptimal when treatment and management of NCDs are in silos as seen in this study. Responsibility is left solely to the patient. Bringing in more awareness on LDL-C control to patients with T2DM and MDD, and to their treating physicians and service providers, through collaborative care for patients with T2DM and comorbidities in this setting, is a gap that has to be addressed. Early intervention may be needed to assist younger individuals with T2DM and early onset T2DM with MDD, to achieve better glycaemic control.

4.3.7. Limitations

This study is not without limitations. Firstly, the duration of T2DM and MDD was not taken into account in this sample, which is a key feature in the risk stratification of individuals with diabetes for a CVD event or may infer causal effects of MDD. Secondly, the medication compliance of the patients was not recorded. Patients could have stopped lipid-lowering therapy due to statin-related common side effects such as myalgia and rhabdomyolysis. This is to be considered in future research. Lastly, data on other risk factors such as obesity, smoking and physical exercise, which contribute to the risk of a premature CVD event was not available, as very few members or practitioners forwarded this data to the healthcare organisation.

4.3.8. Conclusion

In a private managed healthcare setting in South Africa, this study shows overall poor ABC goal attainment, thus supporting the need for active surveillance for depressive symptoms in high-risk patients. The majority of patients with T2DM with and without MDD showed very poor achievement of the LDL-C target level recommended by the South African Heart Association (SA Heart) and Lipid and Atherosclerosis Society of Southern Africa (LASSA), which increases their risk of CV events, suggesting the possible need for medication adjustments for clinical effectiveness, and correct dose (i.e. switching medication to a different class or dose or combination therapy with other lipid-lowering agents in line with their target LDL-C level required as recommended by community-based guidelines). Older patients with T2DM+MDD being treated for them, showed better HbA1c and LDL-C control in this study, highlighting the need to assist younger adults who show poor adherence to medication recommendations to achieve ABC control.

Chapter 5. Study 4

5.1. Introduction to study 4

This study aimed to compare the depressive symptoms and the cardiovascular disease risk profiles (body mass index (BMI), smoker status and family history of diabetes or heart disease) within the T2DM+MDD, T2DM-MDD, MDD and a healthy control group.

5.2. Contributions of the candidate to study 4

The candidate has made a substantial contribution to the preparation and submission of this study in terms of the intellectual content, i.e. the concept and design, acquisition of data, analysis and interpretation of data and drafting of the manuscript.

5.3. Survey of depressive symptoms and cardiovascular risk indices

This chapter will be extended as a longitudinal study to further elucidate the bidirectional relationship between T2DM and MDD for future publication.

5.3.1. Introduction

Approximately, 88.5% of patients with type 2 diabetes mellitus (T2DM) have two or more comorbidities,[233] increasing the financial burden and health outcomes on the patient and health systems. In the private managed healthcare arena, non-communicable diseases (NCDs) such as T2DM and mental illnesses such as major depressive disorder (MDD) are seen as discrete endocrine and psychiatric disorders and are typically managed separately.

T2DM is viewed as a cardiovascular (CV) risk equivalent[234] as hyperglycaemia and insulin resistance increase oxidative stress leading to vascular inflammation, thrombosis and atherogenesis that result in coronary artery disease (CAD) and other cardiac complications.[235] Evidence suggests that MDD is a most pervasive mental health illness and a major risk factor for cardiovascular disease (CVD). Correll et al.[236] report individuals with severe mental illness (schizophrenia, MDD and bipolar disorder) have 53% higher odds of CVD than those without these conditions. While Inoue et al.[192] report a higher risk of non-fatal and fatal CVD events among individuals with T2DM and comorbid MDD (T2DM+MDD).

Screening to diagnose and treat patients with MDD in patients with CAD has shown better cardiac outcomes,[237] therefore routine depressive symptoms screening is American Heart Association (AHA) prevention committee and American Psychiatric Association (APA) guideline recommendation to identify patients who may require further assessment and treatment in patients with CAD.[238] Adverse cardiac outcomes in patients with T2DM and depressive symptoms, a very-high risk group in this private managed care setting, suggested the need to understand the bidirectional relationship between T2DM and MDD.

Tools such as a 9-question depression scale from the Patient Health Questionnaire (PHQ-9) that measures depressive symptoms are not actively performed within healthcare sectors in SA among patients with both T2DM and MDD. The PHQ-9 is a validated instrument frequently used in the United States of America (USA), in primary care clinics,[239] for all medical illnesses including patients with T2DM[240] and in-hospital patients admitted for cardiac conditions.[241] In SA, PHQ-9 is limited to more complex medical illnesses such as HIV/AIDs and is used more often in primary health care clinics,[242] and in mental health clinics.[243] It is not a common mental health-screening tool utilised within the private managed healthcare sectors.

Other forms of measuring non-invasive CV risk factors include anthropometric measurements such as height, weight, BMI and waist circumference; an immediate family medical history of diabetes and/or heart disease, and lifestyle risk factors (cigarette smoking; alcohol consumption). Within the medical scheme environment, these additional key non-invasive CV

risk factors are addressed after a CVD event, or when members enrol on discrete disease management programmes (i.e. diabetes mellitus or hypertension or hyperlipidaemia) and are not stringently utilised as screening tools to identify high-risk pre-diabetic members, or in the management of MDD and T2DM+MDD.

The principles of assessing and managing multiple major risk factors for CVD are critical in preventing macrovascular events such as stroke and myocardial infarction as endorsed by South African[244] and American guidelines.[245] Hypertension can seldom be managed in isolation from other related chronic diseases, as it often coexists as a cluster of symptoms with dyslipidaemia, obesity and glucose intolerance and a family history of early onset of CVD. South African guideline recommendations[244] have broadened the targets of management to include modifiable risk factors i.e. obesity, smoking, lipids as well as BP control.

5.3.2. Aim

A survey was conducted to determine possible undetected symptoms of depression and CV risk factors among patients with T2DM and/or MDD.

The objective of this phase of the research was to compare the PHQ-9 incidence of depressive symptoms and CVD risk profiles (Body mass index (BMI), smoker status and family history of heart disease and, or diabetes) within the T2DM+MDD, T2DM-MDD, MDD and a healthy control group.

5.3.3. Method

5.3.3.1. Sample selection

The 46 000 to 47 380 members of the medical scheme between 2016 and 2019 were the population for the study. The membership comprises accountants, lawyers, and employees of a telecommunication company and is predominantly female. The data consists of one hundred and thirty-six responses (69 males and 65 females, two undisclosed) from a random population sample of private medical scheme members, over 4 years. The goal was to collect survey responses from a random sample of beneficiaries of the medical scheme, i.e. 30 responses from each group of T2DM+MDD, T2DM-MDD, MDD only, and a healthy control group between the years 2016 to 2019. A sample size of n=29 per group was calculated based on a difference of 36% in PHQ>= 5 between T2DM+MDD vs T2DM-MDD groups (31.3% among Ghanaians with T2DM reported to have depression)[39] with an 80% power and a type I error of 5%.

5.3.3.2. Procedure

A standard letter explaining the purpose and benefits of the research was communicated to all members via email. This letter was sent each year to all scheme members.

Instructions to participants. Participants were told that the study was designed to investigate the relationship between diabetes and depression in the private healthcare sector in South Africa (SA), as the extent of the relationship is known in USA and Europe, and not known in SA. The benefits were to contribute to medical knowledge that may help other individuals that have MDD or T2DM.

Informed consent. Participants gave informed consent after they were advised of the confidentiality of any sensitive information, and that only unique membership numbers would be used in the analysis.

Assignment to conditions. Participants assigned themselves to levels of the independent variable and completed the questionnaire.

Follow through. Participating patients were contacted via email and phone as a follow-up. Research assistants i.e. in-house scheme pharmacy assistants, nurse case managers and customer care agents aided in the project by guiding the members telephonically, through the survey process.

5.3.3.3. Study design

This was a cross-sectional survey carried out from 2016 to 2019 conducted in a private healthcare setting. A structured questionnaire including a PHQ-9 was used to assess possible depressive symptoms, and compare anthropometric measures, family history of diabetes and or heart disease, and smoking status to assess CV risk profiles.

5.3.3.4. Data collection

Four groups of patients were identified in this study categorised into four groups: patients with T2DM and MDD (T2DM+MDD), patients with T2DM without MDD (T2DM-MDD), patients with MDD and a Control group of patients without any stated disease/s. A list of all active members was extracted from the scheme database and the study ‘informed consent’ and ‘survey link’ was sent to them. The consent from the members to participate in the study was obtained electronically.

PHQ-9[246] is used to screen and diagnose depression and has been validated in the sub-Saharan African population.[247,248,196] The PHQ-9 is a component of the Patient Health Questionnaire and includes nine short, simple questions that can be self-administered and

completed in 5 to 7 minutes. It helps healthcare professionals identify signs or symptoms of depression based on the scoring results of the PHQ-9 statements, and is a mandatory part of healthcare management in the USA for regular depression screening during primary care check-ups.[249] The components of the PHQ-9 test evaluate factors related to depression according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5),[6] and include low mood, anhedonia, feelings of hopelessness, sleep and appetite issues, a lack of energy, irritation, difficulty concentrating and suicidal ideation. Each question is presented as a statement and asked how often the feelings were experienced in the past 2 weeks. The PHQ-9 scores are assigned 0 to 3 points (0 - not at all, 1 - several days, 2 - more than half of the days, 3 - nearly every day) for the symptoms experienced.

A self-reporting structured survey was created in a secure platform: Research Electronic Data Capture (REDCap)[250] platform.[251] The survey questions included demographics, history of T2DM and MDD, and PHQ-9 assessment of specific symptoms over the past 2 weeks; non-invasive CV risk factors i.e. anthropometric measure such as height weight, BMI, waist circumference; smoker status, immediate family history of diabetes and or heart disease was linked to the survey.[252] The data was automated to download onto Excel, which was then captured and analysed. The REDCap survey questionnaire created is available in Appendix C. Data was collated for members who completed the form once during the years 2016 to 2019. Duplicate entries for those members who completed more than once were removed.

5.3.3.5. Ethical Considerations

Confidentiality was maintained throughout the analysis; the patients' unique scheme membership number and dependent code were used to align patient-level records. The University of the Witwatersrand Johannesburg, Faculty of Health Sciences Human Ethics Committee (M140326; M1911196) approved the study. Further approval was granted by the Principal Officer of the scheme for the scheme data to be used in the study and by the Human Resources Manager to gather data from the scheme administrative database for the research.

5.3.4. Statistical and Data Analysis

Data extracted from the database was exported to Microsoft Excel 2016 and statistical analysis was performed with Statistica 13.3 (StatSoft Inc., Tulsa, OK) and SAS 9.4. Categorical variables such as age, sex, BMI, PHQ-9, and CV risk factors, were summarized as frequencies and percentages and compared using Chi-square or Fisher-exact tests. A significance level was set at 0.05. Multiple comparisons were analysed using Bonferroni Correction amongst the four groups, the significance level was set at $p<0.0166$.

Patients were characterised into BMI categories (a BMI of 18.5 to 24.9 is within the normal range, a BMI between 25 and 29.9 is within the overweight range, and a BMI ≥30 falls within the obese range).[253] Patients' PHQ-9 scores were categorised according to symptoms experienced, i.e. <5 minimal symptoms not requiring antidepressants; 5-9 mild and ≥10 moderate to severe symptoms.[165]

5.3.5. Results

Table 5.1 displays the characteristics of individuals of the four groups; T2DM+MDD, T2DM-MDD, MDD and Control. The MDD group is younger (41.9±14.5) and has a greater proportion of females 69.6% (one undisclosed) and the T2DM-MDD are more male (64.1%).

The PHQ-9 scores revealed patients in all four groups presenting with a range of depressive symptoms (minimal, mild to moderate-severe). The T2DM+MDD group had moderate-severe (PHQ-9 ≥10) depressive symptoms (58.8%) similar to the MDD group (54.2%) (p=1.0). Whereas patients with T2DM-MDD had underlying unrecognized depressive symptoms, 20.5% had moderate-severe depressive symptoms, and 23.1% had mild (PHQ-9 =5-9) symptoms. Of concern, in the control (healthy group) 25% were recorded to have moderate-severe depressive symptoms, and 21.4% of having mild depressive symptoms.

The majority of the T2DM+MDD group is obese (76.5%) and the T2DM-MDD group are more overweight (46.2%) but only 23.2% of the Control group had a BMI within the normal range. The PHQ-9 between the T2DM+MDD group was significantly higher than the T2DM-MDD p=0.0105 (according to Bonferroni correction for 2x2 multiple comparisons (p<0.0166).

All groups T2DM+MDD (76.5%), T2DM-MDD (69.2%), MDD and Control (50%; 57.1%) have high rates of family history of diabetes and or heart disease.

Table 5.1 Characteristics and PHQ-9 scores of patients with and without T2DM and MDD 2016 to 2019

Characteristics	T2DM+MDD n=17 n (%)	T2DM-MDD n=39 n (%)	T2DM+MDD vs T2DM-MDD p-value	MDD n=24 n (%)	T2DM+MDD, T2DM-MDD vs MDD p-value	Control n=56 n (%)	T2DM+MDD vs T2DM-MDD vs MDD vs Control p-value
Age (mean±SD)	54.7 ±13.1	53.6 ±13.4	0.78	41.9 ±14.5	0.007	49.4 ±14.2	0.007
Sex male	8 (47.1%)	25 (64.1%)	0.233	7 (29.2%)	0.036	29 (51.8%)	0.081
PHQ9							
PHQ9 <5 PHQ9 5-9 PHQ9 ≥10	4 (23.5%) 3 (17.6%) 10 (58.8%)	22 (56.4%) 9 (23.1%) 8 (20.5%)	0.0156	4 (16.7%) 7 (29.2%) 13 (54.2%)	0.005	30 (53.6%) 12 (21.4%) 14 (25.0%)	0.004
BMI							
BMI <25 BMI 25-29.9 BMI ≥30 (Obese)	1 (5.9%) 3 (17.6%) 13 (76.5%)	6 (15.4%) 18 (46.2%) 13 (33.3%)	0.020*	7 (29.2%) 7 (29.2%) 9 (37.5%)	0.029*	13 (23.2%) 21 (37.5%) 17 (30.4%)	0.050
CV risk factors							
Smoker	2 (11.8%)	7 (17.9%)	0.707	5 (20.8%)	0.864	8 (14.3%)	0.857
Family history of heart disease /diabetes	13 (76.5%)	27 (69.2%)	0.754	12 (50.0%)	0.136	32 (57.1%)	0.203

*p-values not statistically significant as p-value needs to be <0.0166 per Bonferroni correction multiple comparisons

BMI, Body Mass Index; MDD, Major Depressive Disorder; T2DM, Type 2 Diabetes Mellitus; Patient Health Questionnaire (PHQ-9) score ranges from 0 (best) to 27 (worst); score 5-9 indicates mild depressive symptoms; score ≥10 indicates moderate to severe depressive symptoms; BMI of 18.5 to 25 is within the normal range, BMI between 25 and 30 is within overweight range, BMI ≥30 falls within the obese range

5.3.6. Discussion

The main findings of the survey showed individuals with T2DM with and without MDD, and the controls have moderate to severe depressive symptoms.

Amongst all four groups, the T2DM+MDD group (58.8%) had a PHQ-9 score of ≥10. The findings of high moderate-severe depressive symptoms among individuals in the T2DM+MDD group were congruent to a previous study by Binsaleh et al.[254] where 53% of individuals with T2DM taking antidepressants had moderate-severe depressive symptoms, suggesting that this group were not responding to pharmacological treatment and would probably require optimization of therapy. Patients in this group presented with significantly high BMI. It is known that weight gain is an adverse effect associated with certain antidepressants i.e. Selective-Serotonin-Reuptake Inhibitor, Serotonin Norepinephrine Reuptake Inhibitor and Serotonin Receptor Antagonists and Reuptake Inhibitors and can result in high BMI.[255] In the previous study 48% of the patients in this managed healthcare organisation were on SSRIs which may have an impact on their BMI. Healthcare providers (psychiatrists, physicians, diabetes nurse educators and dietitians) can assist patients with their treatment plans in adhering to Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guideline[62] recommended healthy diets, physical activity and choice of appropriate antidepressant[255,118] that suits the patient.

Patients with T2DM-MDD (43.6%) and individuals considered as healthy (46.4%) have a high rate of underlying unrecognized depressive symptoms. Depressive symptoms among patients with T2DM-MDD (20.5%) were high and similar to results reported where the prevalence rate was nearly twice as high in people with T2DM (19.1%, range 6.5-33% vs. 10.7%, range 3.8-19.4%) compared to those without T2DM.[7] In this study, members are in a highly stressed profession, which may be the reason for higher depressive symptoms.

Obesity or being overweight was noted among individuals in all the groups in this setting which shows the existing burden in SA and worldwide.[256,257] Clearly, diet and an unhealthy lifestyle is an issue, which is compromised with depressive symptoms, as one consumes more calories than the amount expended when the mood is low.[258,259]

Obesity adds to the burden as a comorbidity and a CVD risk factor, not only to the individual with T2DM and MDD concerned but also to the scheme in general. Decision policymakers need to update policies, protocols and resources to bridge the gap between depressive symptoms and clinical profiles (BMI, smoking status) among individuals with endocrine disorders and psychiatric disorders i.e. T2DM and MDD. Introduce the structured PHQ-9 plus anthropometric measures at event health check-ups.

Obesity is a high-risk T2DM[260] and of T2DM-MDD presented with undetected moderate-severe depressive symptoms, a longitudinal study of glycaemic levels within the cohort of controls and MDD groups will further elucidate the bidirectional relationship, of whether MDD predisposes the risk of developing T2DM. Poor glycaemic control, depressive symptoms and non-invasive CV risk factors add to the factors influencing the bidirectional relationship between T2DM and MDD since the influence of the aetiology of one disease in another disease is likely to have a bidirectional nature.[156,261]

Undetected depression in T2DM and undetected indicators of CV risk and T2DM in MDD patients can worsen their long-term mortality risks.[262] Therefore, early stringent screening and managing depressive symptoms and non-CV risk indices are paramount in this setting, to reduce the risk of non-fatal and fatal CVD events among patients with T2DM.

5.3.7. Limitations

Several limitations must be considered in this study. First, a longitudinal study was not feasible as most participants either resigned or died during the study period. Secondly, PHQ-9 scores were not consistently captured for all patients every six months due to operational challenges and low response rates (patients, doctors and nurses). Thirdly, some groups did not attain an adequate sample size according to the calculations. Lastly, data on abdominal measurements, alcohol consumption, behaviour and physical exercise and non-compliance with medication were not captured.

5.3.8. Conclusion

Important findings of the survey showed a greater proportion of females had T2DM with comorbid MDD. Of concern was that almost half of the sample those with T2DM-MDD and individuals considered as healthy had underlying unrecognized depressive symptoms. Moreover, all four groups were mostly overweight and obese.

5.3.9. Recommendations

Active surveillance of non-invasive CV risk factors in MDD patients, depressive symptoms, non-invasive body measurements and lifestyle surveys in patients with T2DM and individuals joining the scheme is critical. Making this mandatory every 6 months, during their regular check-ups with their physicians, to identify, treat and manage individuals with T2DM, MDD, or pre-diabetes and depressive/stress symptoms sooner.

Chapter 6. Conclusion

In South Africa (SA), not only has type 2 diabetes mellitus (T2DM) reached near endemic prevalence, the high incidence of concordant and discordant comorbidities severely complicates the health care management approach for these patients. In this privately managed healthcare organisation, major depressive disorder (MDD) was identified as the most frequent discordant comorbidity of T2DM. The added cardiovascular (CV) risk associated with both conditions raised concerns as to the impact of comorbidity on the burden of care and the possible bidirectional relationship between T2DM and MDD.

The presence of comorbidities is an additional burden on diabetic patients, and even more so on their management. The majority of the patients with T2DM (85%) presented with concordant and/or discordant comorbidities. Findings of this research highlight the nature of the possible bidirectional relationship between T2DM and MDD within a private healthcare setting in SA.

With T2DM considered a primary condition, the prevalence of MDD was 17% in T2DM patients in 2014. Females with T2DM were more likely to have comorbid MDD than males, as seen in 2014 when 63% of the T2DM+MDD patients were females and 61%-79% in 2012-2016. The prevalence of MDD in patients with T2DM had risen to 25% in this privately managed healthcare organisation by 2019. The gradual rise in the incidence of T2DM+MDD in this organisation is concerning, considering that this sample is a more affluent population with access to novel treatment and management of T2DM and MDD similar to the developed world.

Patients with T2DM+MDD and T2DM-MDD presented with a high incidence of hypertension (71%, 63%) and hyperlipidaemia (73%, 61%) in 2014 and 2019 patients with T2DM+MDD claimed more antihypertensives (79%) and lipid-lowering therapy (78%) than T2DM-MDD group (68%, 72%). Hypothyroidism (22%; 12%), and CAD (15%; 14%) were also prevalent in the T2DM+MDD and T2DM-MDD groups. Older T2DM patients presented with more thromboembolic comorbidities (i.e. coronary artery disease (CAD), dysrhythmia, deep vein thrombosis and stroke).

Healthcare resource utilisation and costs for patients with T2DM and those with T2DM+MDD were found to be substantial in this setting. Instead of the cost-containment expected of a capitation risk-sharing model (CM) for diabetes care, the healthcare expenditure consumed by patients with T2DM on CM was high compared with patients enrolled on a fee-for-service model (FFS), creating a financial burden to the medical scheme. The medical scheme was responsible for both the capitated fee and all the hospitalisations associated with CM, except for hypo- or hyperglycaemic admissions which amount to <1% ($1,158) over the 5-year study period. For instance, the costs associated with the hospitalisation of severely ill patients with

T2DM enrolled in the study, most of whom were enrolled on CM, amounted to $2.2 million and were on the account of the medical scheme.

Hospitalisation costs due to diabetes-related or other hospital admissions (non-diabetes related) in patients with T2DM and T2DM+MDD were expensive as seen in study 2. Patients with T2DM being treated for comorbid MDD were admitted to the hospital more often (42%) compared with the T2DM group without MDD (30%) in 2014 (study 1). A higher percentage of patients with T2DM+MDD was admitted to the hospital for other (non-diabetic related) events resulting in significantly higher costs in 2013, 2015 and 2016 than for the T2DM-MDD group (study 2). In 2019, a higher proportion of patients among the T2DM+MDD group compared with the T2DM-MDD and MDD only groups, were admitted for macrovascular events (23% vs 13.1%; 9.9%); with a significantly more macrovascular admissions among patients with T2DM+MDD (17.5%) compared with the T2DM-MDD (8.1%) and MDD group only (8.6%). Fewer patients with T2DM+MDD (3.3%) were admitted for depressive episodes compared to the patients from the MDD group (15.5%).

In general, high resource utilisation is seen, with the T2DM+MDD group having more hospital admissions. The very high-cost findings of patients with T2DM in a privately managed healthcare organisation are further exacerbated by associated MDD costs in patients with T2DM+MDD. Additionally, the diabetes-related cost due to macrovascular complications in this sample of patients with T2DM is high and is increased with MDD. This translates to the CM model of care not showing savings and being more expensive which worsens when NCDs overlap.

Regardless of the healthcare system funding models, privately insured patients observed in this research had access to novel hypoglycaemic agents, antihypertensives, lipid-lowering therapy and antidepressants, and were enrolled in disease management programmes for diabetes care and mood disorders. Yet attainment of South African guideline recommended ABC (glycated haemoglobin (HbA1c<7%), systolic blood pressure (BP≤140mmHg), LDL-C<1.8mmol/l) targets were suboptimal. Only 13% of patients in the T2DM+MDD group and 7.1% in the T2DM-MDD group achieved ABC targets.

Results from the survey of members with T2DM with and without MDD, those with MDD, and a healthy control group (with no chronic conditions) within this privately managed healthcare organisation revealed very high-risk individuals with moderate-severe depressive symptoms and CV risk factors. More than half of the T2DM+MDD group (58.8%) had a Patient Health Questionnaire-9 (PHQ-9) score of moderate to severe depression symptoms indicating that their MDD is not adequately managed. 76.5% of this group had body mass index (BMI) scores that considered them to be obese. More to the point, 20% of the T2DM-MDD had underlying undetected depressive symptoms that were moderate-severe. Of concern, all groups of

patients with T2DM with and without MDD, and individuals considered as healthy (Control group) had high CV risk profiles. This was observed in the survey where their BMI was within the obesity range and more than half of them had a strong family history of diabetes and/or heart disease.

Findings from this thesis showed vital information regarding members of this medical scheme. It is important that the scheme sees the accurate picture of their members' complete clinical profile i.e. medical and mental wellness in terms of prevalence, hospital admissions, resource utilisation and cost implications. This thesis found the management of T2DM and MDD as a single entity with a syndemic care approach. Patients need to be viewed as a one-person unit, as opposed to different disease units, by employing a holistic approach through identifying comorbidity profiles and treating the patient holistically.

6.1. Recommendations and way forward

This research project found important concerns that may have implications for health policy and planning, resource allocation, coordinated care and specific therapeutic and management guidelines for individuals with the comorbidities of T2DM+MDD. Most importantly, the first step is in recognising the bidirectionality of the two NCDs.

Further studies are required to assess the compliance of patients with their medications and to investigate the frequency of patients visiting their mental health professionals and nurse educators. More prospective studies are required to ascertain the extent of glycaemic control and depressive symptoms between T2DM and MDD. Future longitudinal research should be conducted to elucidate if, when and how often-depressive symptoms develop over time in T2DM, and if patients with MDD develop T2DM.

Identifying high-risk CVD individuals sooner and individuals with T2DM, depressive disorders, or pre-diabetes, will assist them with self-management of their comorbidities. It would prevent damage and long-term health issues caused by T2DM (i.e. blindness and gangrene amputations).

The findings of this research can benefit other private medical schemes in SA, including the public sector, with funding decisions, resource allocation and health plan benefits to identify high-risk patients with T2DM+MDD sooner and to treat them as a whole person rather than treating the individual disease, to prevent high-cost diabetic related and other hospitalisations.

Healthcare resource utilisation of T2DM+MDD and CVD at a managed healthcare and hospital level should be acknowledged for increased complications, burden and resource use when managed discretely. Ways to reduce this burden should be sought and implemented, i.e.

adapting healthcare payment systems for collaborative care of T2DM+MDD that include risk-sharing models with tighter management for improved outcomes.

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Appendices

Appendix A: Ethical Clearance Certificates | Human Research Ethics Committee (Medical)

Certificate No: M140326

R14/49 Ms Lovina Naidoo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140326

NAME: (Principal Investigator)	Ms Lovina Naidoo
DEPARTMENT:	Pharmacy and Pharmacology Sanlam Health Centre of Diabetes and Endocrinology Primary Health Care Clinics and GPs
PROJECT TITLE:	Examining the Bidirectional Relationship between Cormobid Depression and Type 2 Diabetes: A Managed Healthcare Perspective
DATE CONSIDERED:	28/03/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Neil Butkow and Elena Libhaber
APPROVED BY:	Professor Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	19/11/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

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 resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature

Date 8/12/2014

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Protocol Amendment of Informed Consent documents

Certificate No: M140326

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: PV Tobias Building 2nd Floor. Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za. Fax +27 (0)11-717-1265

11 December 2015

Ms Lovina Naidoo
Department of Pharmacy and Pharmacology

Sent by email to: Lovina.Naidoo@sanlamhealth.co.za

Dear Ms Naidoo

Re: **Protocol Ref no: M140326**
Protocol Title: Examining the Bidirectional Relationship between Cormobid Depression and Type 2 Diabetes: A Managed Healthcare Perspective
Principal Investigator: Ms Lovina Naidoo
Protocol Amendment – Informed Consent Documents

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has approved the amended informed consent documents for the abovementioned study, as detailed in your letter dated 31 May 2015.

Thank you for keeping us informed and updated,

Yours Sincerely,

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
11 DEC 2015
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

Ms Zanele Ndlovu
Administrative Officer
Human Research Ethics Committee (Medical)

Extension of data set

Certificate No: M140326

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

30 April 2018

Ms L Naidoo and Dr N Butkow
School of Therapeutic Medicine
Department of Pharmacy and Pharmacology
Medical School
University
Sent by e-mail to: Neil.Butkow@wits.ac.za and Lovina.Naidoo@sanlamhealth.co.za

Dear Ms Naidoo and Dr Butkow

Re: **Protocol Ref No:** M140326
Protocol Title: *Examining the bidirectional relationship between cormobid depression and Type 2 Diabetes: A managed healthcare perspective*
Principal Investigator: Ms L Naidoo

I refer to my recent e-mail exchange with Dr Butkow.

I confirm that the extension of the data set for the purposes of the study to the end of 2017 has been noted and approved.

Thank you for keeping us informed and updated.

Yours Sincerely

.....
Mr I Burns
For the Human Research Ethics Committee (Medical)

Research Office Secretariat:

Physical address: Phillip Tobias Building, 3rd Floor, Office 302, Corner York Road and Princess of Wales Terrace, Parktown, Johannesburg 2193.
Postal address: Private Bag 3, Wits 2050
Tel Nos. +27 (0)11-717-1234/2656/2700/1252
Office E-mail: HREC-Medical.ResearchOffice@wits.ac.za.
Website:http://www.wits.ac.za/research/about-our-research/ethics-and-research-integrity/

Extension of data set

Certificate No: M1911196

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2021/02/18

Ms L Naidoo
School of Therapeutic Sciences
Department of Pharmacy and Pharmacology
Medical School
University

Sent by e-mail to: Lovina.Naidoo@sanlamhealth.co.za

Dear Dr Butkow

Re: **Protocol Ref No:** M1911196
Protocol Title: *Examining the bidirectional relationship between comorbid depression and type 2 diabetes: A managed healthcare perspective*
Principal Investigator: Ms L Naidoo

Thank you for your letter of 2020/12/12 .

We have noted and approve of your proposal to recruit a cohort of diabetic/depressed and non-diabetic/depressed patients, who are members of the Chartered Accountants Medical Aid Fund, in collaboration with the health professionals at the Akeso Clinics.

Thank you for keeping us informed.

Yours Sincerely

J. Burns

.....

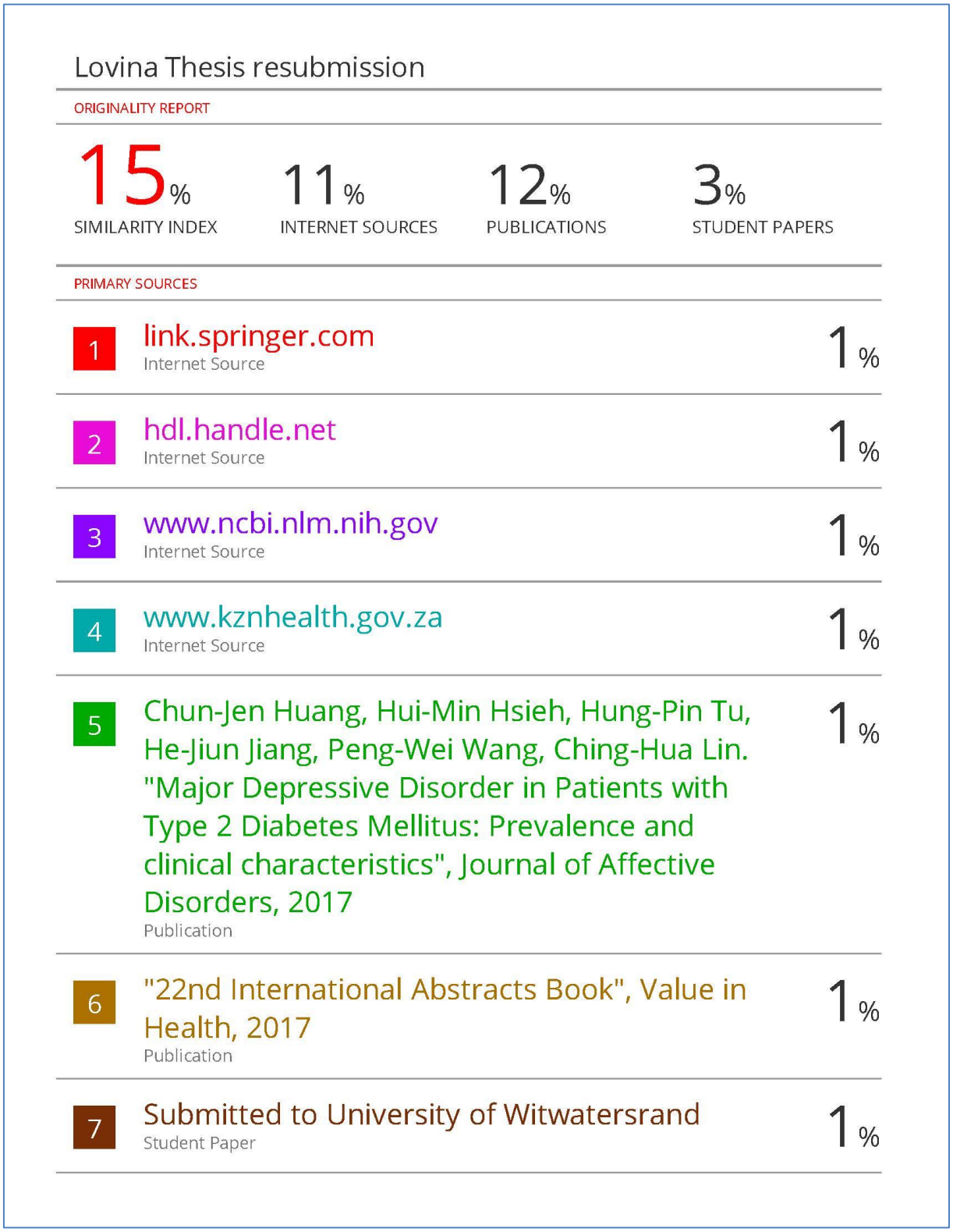
Mr I Burns
For the Human Research Ethics Committee (Medical)

CB Penny

.....

Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

Appendix B: Turn-It-In Report



Lovina Thesis resubmission

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24	Leonard E. Egede, Kinfe G. Bishu, Rebekah J. Walker, Clara E. Dismuke. "Impact of diagnosed depression on healthcare costs in adults with and without diabetes: United States, 2004–2011", Journal of Affective Disorders, 2016 Publication	<1 %
25	Fekadu Aga, Sandra B Dunbar, Tedla Kebede, Rebecca Gary. " The role of concordant and discordant comorbidities on performance of self-care behaviors in adults with type 2 diabetes: a systematic review ", Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 2019 Publication	<1 %
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39	Richard I.G. Holt, Mary de Groot, Irwin Lucki, Christine M. Hunter, Norman Sartorius, Sherita H. Golden. "NIDDK International Conference Report on Diabetes and Depression: Current Understanding and Future Directions", Diabetes Care, 2014 Publication	<1 %
40	Nicolau, Joana, Rosmeri Rivera, Carla Francés, Begoña Chacártegui, and Lluís Masmiquel. "Treatment of depression in type 2 diabetic patients: Effects on depressive symptoms, quality of life and metabolic control", Diabetes Research and Clinical Practice, 2013. Publication	<1 %

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Appendix C: The REDCap survey questionnaire

Examining the bidirectional relationship between depression and type 2 diabetes

I would like to invite you to participate in a research study, entitled: Examining the bidirectional relationship between comorbid depression and type 2 diabetes: A managed healthcare perspective.

Your participation in this study will contribute to medical knowledge that may help other individuals that have Depression or Type 2 Diabetes.

In anticipation.

Yours sincerely,

Lovina Naidoo

Before you agree to participate in the study, it is important that you read and understand the Information Leaflet and Informed Consent.

[Attachment: "Informed consent non-depressed group.docx.pdf"]

Informed consent non-diabetic group.

[Attachment: "Informed consent non-diabetic group.docx.pdf"]

If you decide to take part in this study, please sign using your finger (touch screen) or the mouse here.

_____

Please acknowledge that by completing this survey you are consenting to participate in this survey as described in the above introduction and the attached document. Do you consent to participate?	◯ Yes ◯ No

---

I hereby agree that I will have the following blood tests within the next four weeks: - Blood glucose - Cholesterol and Blood Pressure	◯ Yes ◯ No

---

Attached is the Lancet blood work up form for your convenience. You may include the name of your doctor on the top right corner of the form.

[Attachment: "CAMAF Diabetes Tests-Lancet Order Form.pdf"]

Demographic Information

Medical Aid Number	_____
Dependent Code	_____
Date:	_____
Age:	_____
Gender	◯ Male ◯ Female
Have you been diagnosed with Type 2 Diabetes?	◯ Yes ◯ No
When were you diagnosed?	_____
Have you been diagnosed with Depression?	◯ Yes ◯ No
When were you diagnosed?	_____
Is there a history in your immediate family of either diabetes or heart disease?	◯ Yes ◯ No
What is your height in centimetres (e.g. 172)	_____
What is your current weight?	_____
Your Body Mass Index is:	_____
What is your waist circumference in centimetres?	_____
Are you currently a smoker?	◯ Yes ◯ No

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

Over the last 2 weeks how often have you been bothered by any of the following problems? (Click the circle to indicate your answer)

1. Little interest or pleasure in doing things	◯ Not at all ◯ Several days ◯ More than half the days ◯ Nearly every day
2. Feeling down, depressed, or hopeless	◯ Not at all ◯ Several days ◯ More than half the days ◯ Nearly every day
3. Trouble falling or staying asleep, or sleeping too much	◯ Not at all ◯ Several days ◯ More than half the days ◯ Nearly every day
4. Feeling tired or having little energy	◯ Not at all ◯ Several days ◯ More than half the days ◯ Nearly every day
5. Poor appetite or overeating	◯ Not at all ◯ Several days ◯ More than half the days ◯ Nearly every day
6. Feeling bad about yourself -- or that you are a failure or have let yourself or your family down	◯ Not at all ◯ Several days ◯ More than half the days ◯ Nearly every day
7. Trouble concentrating on things, such as reading the newspaper or watching television	◯ Not at all ◯ Several days ◯ More than half the days ◯ Nearly every day
8. Moving or speaking so slowly that other people could have noticed? Or the opposite -- being so fidgety or restless that you have been moving around a lot more than usual	◯ Not at all ◯ Several days ◯ More than half the days ◯ Nearly every day
9. Thoughts that you would be better off dead or of hurting yourself in some way	◯ Not at all ◯ Several days ◯ More than half the days ◯ Nearly every day
If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	◯ Not difficult at all ◯ Somewhat difficult ◯ Very difficult ◯ Extremely difficult

Appendix D: Email from Journal of Endocrinology, Metabolism and Diabetes of South Africa (JEMDSA) manager granting copyright permission for Paper 1

From: Robyn Marais <robyn@jesser-point.co.za>
Sent: Thursday, 03 March 2022 06:51
To: Lovina Naidoo <lovina.n@hotmail.com>
Cc: 853697@students.wits.ac.za <853697@students.wits.ac.za>
Subject: RE: Request for Assistance - Copyright permission to reproduce JEMDSA article

Kind regards
Robyn Marais
Journal Manager
Medpharm Publications

Cell: 083 459 5580
Email: robyn@jesser-point.co.za

Medpharm Publications

From: Lovina Naidoo <lovina.n@hotmail.com>
Sent: Wednesday, 02 March 2022 21:53
To: Robyn Marais <robyn@jesser-point.co.za>
Cc: 853697@students.wits.ac.za
Subject: Request for Assistance - Copyright permission to reproduce JEMDSA article

Dear Robyn,
Trust this email finds you well.
Please could you assist me with the request below.
Thanks

To,

Prof Jeffrey Wing
The Editor-in-Chief
Journal of Endocrinology, Metabolism and Diabetes of South Africa
02/03/2022

Dear Prof Wing,

I am completing a doctoral thesis at University of the Witwatersrand, Johannesburg entitled "*Examining the Bidirectional Relationship between Comorbid Depression and Type 2 Diabetes: A Managed Healthcare Perspective.*" I would like copyright permission to reproduce the following article published in JEMDSA as a chapter in my Thesis.

Naidoo L, Butkow N, Barnard-Ashton P, Libhaber E. Hospitalisation of Type 2 diabetes mellitus patients with and without major depressive disorder in a private managed healthcare organisation. *Journal of Endocrinology, Metabolism and Diabetes of South Africa.* 2019;24(3):70-76.

Attached is the article referenced.

If this request meets with your approval, please sign this letter where indicated below and return it to me via email. Thank you very much.
Sincerely

Robyn Marais
Journal Manager: JEMDSA
PERMISSION GRANTED FOR THE USE REQUESTED ABOVE:
Date: 03/03/2022

Kind regards
Lovina Naidoo

Appendix E: Copyright permission from Value in Health Regional issues - Authorship form confirming retention of rights for Paper 2

Value IN HEALTH REGIONAL ISSUES

AUTHORSHIP FORM

MS Title/Number: Is the risk really shared? A retrospective analysis healthcare costs of Type 2 Diabetes Mellitus patients on a capitation model

By signing below, all authors acknowledge that they have read the Criteria for Authorship and the Copyright Transfer statements. In addition, your signature affirms that this work has not been previously published, is not subject to copyright or other rights except your own to be transferred to *Value in Health Regional Issues*/ISPOR—The Professional Society for Health Economics and Outcomes Research, and has not otherwise been submitted for publication, except under circumstances communicated to the Editors in writing at the time the work was first submitted. This form is available online at www.ispor.org and can be downloaded and distributed to authors electronically. Every author must complete this form, which should be uploaded with the rest of the manuscript files at the time of submission.

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Each author should meet the criteria for authorship as described in the International Committee of Medical Journal Editors (ICMJE).[*1] The ICMJE recommends that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The journal requires that each author indicate their specific contributions to the preparation of this manuscript by completing sections **A, B, C**, and **D**.

☑ **A.** I certify that:

- the manuscript submitted under my name represents valid, original work and has not been submitted elsewhere and will not be submitted for publication elsewhere while under consideration by *Value in Health Regional Issues*; and
- if requested, I will provide the data or will cooperate fully in obtaining and providing the data on which the manuscript is based for examination by the editors; and
- for papers with more than 1 author, I agree to allow the corresponding author to serve as the primary correspondent with the editorial office, to review the galley proofs, and to make decisions regarding release of information in the manuscript to the media, federal agencies, or both; or if I am the only author, I will be the corresponding author and agree to serve in the roles described above.

☑ **B.** I have given final approval of the submitted manuscript.

☑ **C.** I have participated sufficiently in the work to take public responsibility for it.

☑ **D.** I have made substantial contributions to the intellectual content of the paper as described below (check at least 3 below):

- ☑ Concept and design
- ☑ Acquisition of data
- ☑ Analysis and interpretation of data
- ☑ Drafting of the manuscript
- ☐ Critical revision of paper for important intellectual content
- ☐ Statistical analysis
- ☐ Provision of study materials or patients
- ☐ Obtaining funding
- ☑ Administrative, technical, or logistic support
- ☐ Supervision
- ☐ Other (specify): _____

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Reference

1. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. http://www.icmje.org/icmje.pdf. Accessed November 26, 2018.

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Author Information

Signature | Lovina Asha Naidoo (M.Pharm) | 25 November 2020
Full Name & Degree (please print) | Date

University of the Witwatersrand | 7 York Road | Johannesburg, South Africa | 2193
Institution | Street Address | City | State | Zip

853697@students.wits.ac.za | +27 (0) 836099246
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Acknowledgement (to be completed by the Corresponding Author only)
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