A COMPARISON OF DIABETES CARE OF PATIENTS ATTENDING CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL AND HOUGHTON CENTRE FOR DIABETES & ENDOCRINOLOGY

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DECLARATION

I Yacob Pinchevsky declare that this Thesis is my own, unaided work. It is being submitted for the Degree of Philosophiae Doctor at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

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(Signature of candidate)

_____day of_____20_____in_____

DEDICATION

This thesis work is dedicated to my wife (Tarryn Shung), who has been a constant source of support and encouragement during the challenges of this thesis. I am truly thankful for having you in my life. This work is also dedicated to my parents, Moshe & Rina Pinchevsky, who have always loved me unconditionally and whose good examples have taught me to work hard for the things that I aspire to achieve. Finally, this thesis is also dedicated to my two late grandfathers, Boris Grin and Yaakov Pinchevsky both of which suffered from Type 2 Diabetes Mellitus and its complications.

PRESENTATIONS ARISING FROM THIS STUDY

1. School of Therapeutic Sciences Biennial Research Day, held on 12 September 2017 at the Faculty of health Sciences, University of the Witwatersrand, Johannesburg, South Africa. Title of oral presentation: “A Comparison Of Diabetes Care Of Patients Attending Charlotte Maxeke Johannesburg Academic Hospital And Houghton Centre For Diabetes & Endocrinology.”

PUBLICATIONS PUBLISHED BY THE CANDIDATE DURING THE COURSE OF THE DEGREE

1. Pinchevsky Y, Rothberg A, Butkow N, Chirwa T, Distiller L, Raal F. Quality of Care Delivered To Type 2 Diabetes Mellitus Patients in Public and Private Sector Facilities in Johannesburg, South Africa. International journal of general medicine. 2018; (11) 383 – 390.

2. Pinchevsky Y, Butkow N, Chirwa T, Raal F. Treatment Gaps Found in the Management of Type 2 Diabetes at a Community Health Centre in Johannesburg, South Africa. Journal of Diabetes Research. 2017; 2017:9536025.

3. Pinchevsky Y, Shukla VJ, Butkow N, Chirwa T, Raal F. Multi-ethnic differences in HbA1c, blood pressure, and low-density-lipid cholesterol control among South Africans living with type 2 diabetes after a 4-year follow-up. International Journal of General Medicine. 2016; (9) 419 – 426.

4. Pinchevsky Y, Butkow N, Raal FJ, Chirwa T. Glycaemic, blood pressure and cholesterol control in 25,629 diabetics: a literature review. South African Journal of Diabetes & Vascular Disease. 2015; 2(12) 68 – 71.

5. Pinchevsky Y, Butkow N, Raal FJ, Chirwa T. Glycaemic, blood pressure and cholesterol control in 25,629 diabetics: a literature review. Cardiovascular Journal of Africa. 2015; 26(4):188-92.

6. Pinchevsky Y, Shukla V, Butkow N, Raal FJ & Chirwa T. The achievement of glycaemic, blood pressure and LDL cholesterol targets in patients with type 2 diabetes attending a South African tertiary hospital outpatient clinic. Journal of Endocrinology, Metabolism and Diabetes of South Africa. 2015; 20(2): 81-86.

ABSTRACT

Introduction: With the realities of resource constraints existing in South Africa's public sector and evidence of disparities in healthcare between populations, the study sought to compare aspects of quality of diabetes care and Health Related Quality Of Life (HRQoL) in patients with Type 2 Diabetes Mellitus (T2DM) receiving care within two specialised settings, one in the public sector (Charlotte Maxeke Johannesburg Academic Hospital - CMJAH) and the other in the private sector (Centre for Diabetes and Endocrinology - CDE). Particular emphasis was placed on complication rates at the two sites.

Methods: Quantitative data were collected between June and October 2016 from existing patients at each setting. Data collected included patient demographics, potential barriers to accessing care, medical history, laboratory results, pharmacological treatment, and diabetes-related clinical, biochemical and HRQoL outcomes. With outcome measurements being the priority, methodology incorporated the Donabedian Model in which 'structure' of the health systems, access to care and processes of care are key to determining outcomes.

Results: Two-hundred ninety T2DM patients were enrolled. Analysis revealed that CDE patients were predominantly Caucasian with higher socioeconomic indicators ($p<0.01$) and education levels ($p<0.0001$), and experienced fewer access barriers to clinical services/care ($p<0.0001$). They also had more-frequent consultations with dieticians ($p<0.0001$), podiatrists ($p<0.0001$) and biokineticists ($p<0.0001$) compared to patients attending the CMJAH. Multivariate analysis of the complete sample showed that outcomes were related to factors other than the setting in which care was provided. Some outcomes were related to demographic factors e.g. higher risk of macrovascular disease in Caucasian and Asian patients, while others were related to difficulties in accessing care, patients' education, and/or T2DM duration and disease severity. In the important area of complications, which ultimately determine the course of T2DM, rates of micro- and macrovascular disease were similar between the sites, as were HRQoL scores and sub-scores as measured by the EQ-5D-5L assessment tool. However, site-related data suggest that a) identification of early microvascular complications may vary between the sites, and b) while care at CMJAH may be equivalent in terms of the outcomes of interest, the clinic is treating a smaller number of patients than would be ideal in terms of the public sector burden of T2DM.

Conclusions: Despite differences in patient demographics and resources, the HRQoL and T2DM-related complications were found to be similar across the two settings. Attention should be directed towards identification of modifiable factors that would be of benefit to patients at the two sites and possibly beyond.

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ACCORD	-	Action to Control Cardiovascular Risk in Diabetes
ACE	-	Angiotensin Converting Enzyme
ADA	-	American Diabetes Association
ADVANCE	-	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AGEs	-	Advanced Glycation End-Products
ARB	-	Angiotensin Receptor Blockers
BTT	-	Benefit-Based Tailored Treatment
BMI	-	Body Mass Index
BP	-	Blood Pressure
CARDS	-	Collaborative Atorvastatin Diabetes Study
CCB	-	Calcium Channel Blockers
CDE	-	Centre for Diabetes and Endocrinology
CHC	-	Community Health Centre
CMJAH	-	Charlotte Maxeke Johannesburg Academic Hospital
CMS	-	Council for Medical Schemes
CRF	-	Case Report Form
CVD	-	Cardiovascular Disease
D-39	-	Diabetes-39
DBP	-	Diastolic Blood Pressure
DCCT	-	Diabetes Control and Complications Trial
DKA	-	Diabetic Ketoacidosis
DM	-	Diabetes Mellitus
DSMB	-	Data and Safety Monitoring Board
EDL	-	Essential Drug List
EQ-5D	-	EuroQol-5 Dimension
FPG	-	Fasting Plasma Glucose
GDP	-	Gross Domestic Product
HbA1c	-	Glycated Haemoglobin
HDL-C	-	High Density Lipoprotein Cholesterol
HPA	-	Hypothalamo–Pituitary–Adrenal
HREC	-	Human Research Ethics Committee
HRQoL	-	Health-Related Quality Of Life
HQA	-	Health Quality Assessment
ICER	-	Incremental Cost-Effectiveness Ratio
IDF	-	International Diabetes Federation
Kg	-	Kilogram

LADA	**-**	Latent Autoimmune Diabetes in Adults
LDL-C	**-**	Low Density Lipoprotein Cholesterol
LMICS	**-**	Low- and Middle-Income Countries
MAUI	**-**	Multi-Attribute Utility Instrument
Mg	**-**	Milligrams
MS	**-**	Metabolic Syndrome
NDOH	**-**	National Department of Health
NGSP	**-**	National Glycohaemoglobin Standardization Program
NHI	**-**	National Health Insurance
NHIA	**-**	National Health Insurance Agency
NICE	**-**	National Institute for Clinical Excellence
NIDS	**-**	National Income Dynamic Study
NS	**-**	Non-significant
OGTT	**-**	Oral Glucose Tolerance Test
OR	**-**	Odds Ratio
SBP	**-**	Systolic Blood Pressure
SANHANES	**-**	South African National Health And Nutrition Examination Survey
SEMDSA	**-**	Society for Endocrinology, Metabolism, and Diabetes of South Africa
SF-20	**-**	Short Form Health Survey
Statin	**-**	HMG CoA Reductase Inhibitor / 3-Hydroxy-3-Methyl Glutaryl Coenzyme A Reductase Inhibitor
TC	**-**	Total Cholesterol
TG	**-**	Triglyceride
T1DM	**-**	Type 1 Diabetes Mellitus
T2DM	**-**	Type 2 Diabetes Mellitus
TIA	**-**	Transient Ischaemic Attack
TTT	**-**	Treat-To-Target
UK	**-**	United Kingdom
UKPDS	**-**	United Kingdom Prospective Diabetes Study
US	**-**	United States of America
WHO	**-**	World Health Organization

1. INTRODUCTION (Part A)

1.1 Diabetes In The 21st Century

1.1.1 Global Rates of Diabetes Mellitus

The number and prevalence of people with Diabetes Mellitus (DM) are rapidly rising. Diabetes is a chronic progressive condition which results in significant morbidity, premature death and economic burden to any healthcare system. Globally, as many as 5.0 million people aged between 20 and 79 years perished from diabetes-related mortality in 2015, which is equivalent to one person every six seconds.[1] This makes DM more lethal than the combined number of deaths from HIV/AIDS (1.5 million), tuberculosis (1.5 million), and malaria (0.6 million), with almost half (46.6%) of the deaths aged <60 years.[1] According to the International Diabetes Federation (IDF), globally, there were 415 million people or 8.8% of the world's population living with diabetes in 2015, with 80% originating from low- and middle-income countries (LMICs).[1,2] Overall, it is estimated that 642 million will have the disease across the world by 2040.[1]

1.1.2 Classification of Diabetes Mellitus

Diabetes mellitus is a disorder characterised by glycaemic disturbances as a result of defects in insulin secretion, insulin action or both.[3] Poor insulin action leads to abnormalities of carbohydrate, fat and protein metabolism in target tissues.[4] Approximately 5-10% of patients with diabetes have Type 1 Diabetes Mellitus (T1DM) which occurs through the destruction of pancreatic beta-cells.[5] Patients with T1DM are typically younger and absolutely insulin deficient, and therefore require exogenous insulin.[6] Many patients with T1DM are highly susceptible to diabetic ketoacidosis (DKA), diabetic coma and/or even death.[7] Aetiology has been postulated to be immune-mediated.[8] Latent Autoimmune Diabetes in Adults (LADA) is, as the name suggests, T1DM which occurs later in life.[8]

The majority of patients with DM (90-95%) develop Type 2 diabetes mellitus (T2DM).[5] This type of DM arises through the gradual loss of insulin secretion which may be partly related to obesity, pancreatic beta-cell function decline and eventual hyperglycaemia.[9] Patients with T2DM develop insulin resistance, which ranges from a relative deficiency to a complete insulin secretory defect.[5] The aetiology of T2DM is most likely associated with the interaction between genes and the environment.[10] A study by Pierce et al[11] demonstrated that a family history of T2DM increases the chances of developing this disease 2 – 4 fold. Similarly, there is a 40% lifetime risk of

developing T2DM when at least one parent has the condition.[12] When both parents have T2DM the risk is increased to 70%. Environmental or epigenetic causes of T2DM are evident in the absence of concordance in monozygotic twins.[13] Type 2 Diabetes Mellitus is considered a 'disease of lifestyle', hence frequently found in individuals with raised Body Mass Index (BMI), blood pressure and other cardiovascular risk factors. Therefore, management of T2DM includes changes in the diet and exercise routine, various forms of pharmacotherapy including combinations of antihyperglycaemic agents (oral and often insulin), antihypertensives, lipid-lowering and sometimes anti-platelet therapy.[3]

1.1.3 Diabesity[14]

Globally, more than 600 million people are clinically obese.[15] In the United States (US) alone, more than 1 in 3 adults and 17% of the youth were obese between 2011 - 2014.[16] One study suggests that the obesity pandemic has gone as far as reaching two-thirds of adults living in the United States.[17] Due to a worldwide increase in high calorie diets, sedentary lifestyles and urbanization, obesity has now become an established risk factor for T2DM and/or metabolic syndrome (MS).[18] Hence, the obesity prevalence is being paralleled by similar increases in the number of patients with T2DM or MS.[19] Often found in tandem in patients, raised BMI has been shown to be the strongest risk factor for the development of DM. Obesity is defined using cut points of BMI which measures the relationship between weight and height and is not age or gender dependent.[20] On the other hand, total body fat varies by age, gender and ethnicity. Hu et al[21] reported in an analyses of two cohorts that for every two extra years of a person being overweight there was a 9% increased risk of developing T2DM. In obese patients the risk increased to 14% for patients exposed for the same duration. In addition to increased DM risk, obesity has been established as an independent risk factor for cardiovascular disease through its indirect influence on multiple comorbidities such as hyperlipidaemia, hypertension, insulin resistance, endothelial dysfunction and inflammation.[22] Certain minority ethnic groups seem to be at a higher risk of developing obesity and DM, whilst children/adolescents share equal risk as their adult counterparts.[23] In children it has been reported that as many as 41.3% spend more than 3 hours a day engaged in video games or watching television, which was independently associated with weight gain.[24,25] Rising trends in abdominal obesity in children and adolescents between 1988-1994 and 1999-2004 were as high as 65.4% (from 10.5% to 17.4%) for boys and 69.4% (from 10.5% to 17.8%) for girls.[26] In adolescents, T2DM arises from pathways which are similar to those proposed in adults.[27] These range from insulin resistance to failure of pancreatic α-cells, β-cells, incretin production, kidney glucose filtration and lipolysis.[27] Likewise,

complications and comorbidities develop in a similar fashion in adolescents as with adults with T2DM. However, adolescents with T2DM present with a disease that rapidly progresses, has treatment challenges, and both micro- and macrovascular complications develop at a rapid pace.[28] To treat hyperglycaemia in adolescents with T2DM, lifestyle modification together with biguanides (metformin) and/or insulin have been recommended.[29] For those who require additional long-term glycaemic improvements and weight loss, early bariatric surgery has a place, although not yet established as a mainstream option due to limited data.[30,31]

1.1.4 Undiagnosed Diabetes Mellitus

Globally, as many as 175 million people are estimated to be undiagnosed and living with DM.[32] This figure ranges from as many as 24.1% to 75.1% of all diabetes cases across different regions, with 83.8% originating from LMICs.[32] The Pacific Island populations have been shown to have the highest prevalence of undiagnosed DM.[32] Underperforming healthcare systems and poor awareness among the general population/healthcare professionals have been suggested as reasons why so many patients remain undiagnosed. Other reasons include few or even an absence of symptoms which are commonly associated with the condition. The initial protracted and asymptomatic period of T2DM may last several years before a diagnosis of T2DM is finally made, which directly contributes to complications that arise.[3] The following symptoms are characteristic of DM: thirst, polyuria, polydipsia, blurred vision, unexplained weight loss and polyphagia. The most devastating clinical manifestations are diabetic ketoacidosis (DKA) and a non-ketotic hyperosmolar state, both of which in the absence of treatment, result in lethargy, stupor, diabetic coma and/or death. According to Motala, DM was detected in 36% fewer patients (2.5% vs. 3.9% of the cohort) when only the fasting plasma glucose test was performed rather than an oral glucose tolerance test (OGTT).[33] Hence, fewer patients with impaired glucose tolerance (pre-diabetes) would have been diagnosed. Plantinga et al[34] showed that in the US as many as 41.7% of individuals with previously undiagnosed DM presented with chronic renal disease. In China, diabetic retinopathy was found to be >30% among undiagnosed individuals with DM.[35] With undiagnosed DM carrying a similar risk of mortality as diagnosed DM, and a 1.5- to 3.0-fold increased risk of mortality compared to non-diabetic individuals, there is clearly a major need for higher-quality screening.[36,37]

1.1.5 Diabetes Duration

Previous data have indicated that there are independent associations between age, age at diagnosis, diabetes duration and the risk of macrovascular events and/or death, whilst only diabetes duration is independently associated with the risk of microvascular complications.[38] Macrovascular complications may arise across all age groups (albeit more commonly in older DM patients). Hence younger patients with DM are more likely to develop microvascular complications earlier. One study proved that the development of retinopathy in patients with T1DM will occur after continuous exposure to hyperglycaemia.[39] However, the same study also showed the distinction between duration of exposure (at a certain threshold) and intensity of the hyperglycaemia, with the former risk factor having a greater effect on microvascular complications. Similarly, it has been demonstrated that retinopathy in patients with DM was more correlated with the duration of DM than with the age of onset of the disease.[40] Therefore, earlier and more intensive control is needed in DM, particularly in overweight patients in order to minimize the risk of complications.

1.1.6 Complications Associated with Diabetes Mellitus

The T2DM condition is associated with a multitude of complications such as cardiovascular disease (CVD) and diabetic retinopathy, neuropathy and nephropathy.[41] Rates of complications have been shown to be high in people with previously-undiagnosed DM compared to non-diabetic patients. As many as 25% of patients with T2DM present with retinopathy at diagnosis. Mbanya et al[42] showed that diabetic retinopathy complications are seen in 15–55% of DM patients, with a large percentage of these patients having proliferative retinopathy and/or macular oedema. Whilst 32–57% of DM patients develop renal complications (microalbuminuria or macroalbuminuria) within 5–10 years of their diabetes duration, half of the patients on maintenance haemodialysis also have a positive diagnosis for DM.[42,43,44] In an article on the cardiovascular complications of DM in sub-Saharan Africa, the authors discuss the increasing prevalence of major and emerging cardiovascular risk factors and their role in the growing burden of cardiovascular disease.[45] Diabetes in all its forms is one of the main cardiovascular risk factors. Close to 15% of patients with stroke have diabetes, approximately 30% of patients treated in cardiovascular intensive care units have diabetes, and 2 of every 3 diabetic patients will die as a result of cardiovascular complications.[45] Overall, patients with T2DM have mortality rates approximately twice those of non-diabetics of equivalent age. Clinical trials targeting modifiable risk factors have shown efficacy and reduction in complications associated with DM, thus, many of the challenges associated with DM are modifiable and offer the potential for improvement.[41]

1.1.7 Ethnicity/Culture

Evidence suggests that lifestyle habits and health behaviours are directly linked to risk factors and prevalence of DM.[46] While classical risk factors such as raised blood pressure, dyslipidaemia, smoking and obesity contribute towards the development of DM, there are considerable disparities in the susceptibilities of certain ethnic groups. For example, in a group of 3193 men and 561 women aged 40-69 years studied in the United Kingdom (UK), in comparison with the Caucasians the Asian group not only had a higher prevalence of DM (19% vs 4%) but also higher blood pressures, higher fasting and post-glucose serum insulin concentrations, higher plasma triglyceride, and lower HDL cholesterol concentrations.[47] In the same study, mean waist-hip girth ratios and trunk skinfolds were higher in the Asian group.[47] Similarly, angiography studies have shown that in comparison with Caucasians, Asians in the UK were more likely to have triple vessel disease, several lesions on angiography and non-discrete lesions.[48] More worrying is the fact that Asians generally have smaller total coronary vessel diameters compared with Caucasians, which may increase technical difficulties and affect therapeutic coronary interventions.[49] Statistical data from the US suggest that African American adults are at least 50% more likely to have DM than their Caucasian counterparts.[50] Whilst no clear reasons were provided, contributing factors such as modern lifestyle factors (which promote obesity), socioeconomic and direct genetic propensity or gene-environmental interactions were all postulated.[50] In a large, prospective cohort analysis of more than two million adult members of a Kaiser Permanente Northern California integrated healthcare delivery system, in which all participants had uniform access to healthcare, the DM prevalence and incidence rates in the combined Asian and Pacific Islanders group were greater than Caucasians, but lower than Latinos or African Americans.[51] Strikingly, the Pacific Islanders group had more than three times the incidence of DM relative to Caucasians, and a 75% increased DM incidence compared with African Americans and Latinos.[51] If the analysis were to consider minority Asian subgroups, then the previous study's conclusions may have differed, given the fact that the larger subgroups (Chinese and Filipinos) most likely influenced the Asian group's overall standing.[52] Consequently, treatment of diabetes should not only be multifactorial, but also tailored to the cultural backgrounds of the patient. Cooper-Patrick et al[53] have shown that when patients and physicians share a similar ethnic background, better outcomes are observed. Hence, differences across ethnic diversities require different strategies in understanding and improving the health outcomes among distinct and perhaps higher-risk ethnic groups.

1.1.8 The Aging Process

As many as 10.9 million US adults aged ≥65 years have been diagnosed with DM.[54] The incidence rates tend to increase with age until approximately 65 years, after which both the incidence and prevalence rates seem to remain stable.[54] Diabetes mellitus in older adults who are diagnosed after the age of 65 years is known as 'incident DM', which differs from long-standing DM where onset occurs in middle age or earlier.[55] The regular anatomical and physiological changes associated with the aging process are in fact hastened with DM, resulting in a reduction in life expectancy.[56,57] In fact, it has been shown that adults aged 55 to 64 years who had DM experienced a life expectancy reduction of up to 8 years.[58,59] The continued exposure to hyperglycemia induces oxidative stress, which further results in systematic endothelial dysfunction and vascular complications. Several molecular mechanisms have been proposed to explain the hyperglycemia-induced tissue damage found in patients with DM, one of which includes formation of advanced glycation end-products (AGEs) which are responsible for the pathogenesis of diabetic complications such as retinopathy, nephropathy, neuropathy and cardiomyopathy.[60]

1.1.9 Gender differences

There is growing evidence that T2DM and its complications are related to gender differences. These differences occur as a result of hormonal variations, sociocultural behaviours, environmental changes (diet, lifestyle, stress, attitudes) and gene-environment interactions.[61] For instance, men are more likely to be diagnosed with T2DM at an earlier age and with a lower BMI, whilst obesity, a strong risk factor of T2DM, is more commonly found in women upon diagnosis.[62] Thus, females who attain a higher BMI tend to develop DM faster than men. Although women without DM generally have less risk of cardiovascular events than men, a change in glucose metabolism appears to reverse this phenomenon.[63] This may be due to the fact that females have increased capacity for adipocyte enlargement which could lead to fat deposition abnormalities.[64] Furthermore, endocrine changes caused by the onset of menopause in women, lowers oestrogen production, leading to changes such as an increase in proinflammatory abdominal adipose tissue. As a result, the oestrogen-derived cardioprotection normally active in women is lost over time, increasing the cardiovascular risk.[65] In a pooled analysis of 900 000 individuals across 64 cohorts and 28 000 coronary events, DM accounted for a three-fold increase in the risk of incident heart disease in women, whereas men had a two-fold increase in risk.[66] Therefore, one cannot ignore the pronounced effects of sex hormones which regulate the body's metabolism, vasculature, and inflammation.

1.1.10 Education

Education affects the ability to make lifestyle decisions and/or self-manage a disease such as diabetes.[67] Individuals with lower education levels have been shown to have higher rates of sedentary lifestyle, obesity, and alcohol consumption, all of which are recognized risk factors for the development or worsening of diabetes.[67] Similarly, populations with lower literacy levels have been linked to a lower likelihood of using general preventive measures, which may lead to higher morbidity and mortality rates.[68] Conversely, well-educated groups have been shown to be more capable of navigating or following complicated self-care regimens as used in the treatment of conditions such as HIV/AIDS and DM, thereby resulting in better health outcomes.[69] Other studies have also found that education is linked to faster adoption of new medical technologies.[70] One such study showed that in patients with DM the level of general education was significantly associated with referral.[71] The authors concluded that their better-educated patients with DM were better advocates for their own health, and more likely to be referred earlier in the course of their condition. Therefore differences in education contribute to health disparities.

1.1.11 Marital Status

Data have shown that there are health-augmenting outcomes associated with positive personal relationships, especially with marriage.[72] In comparison with unmarried people, marriage offers a continued, long-lasting supportive environment which may promote physical and mental health.[73] Higher rates of cardiovascular disease and premature mortality have been shown in individuals who have never been married vs. those who have had their marriage ended through either death or divorce.[74] One study found that after a 22-year follow-up, a significantly increased risk of T2DM was found among unmarried men.[75] Interestingly, in an analysis of 379 men and women aged ≥70 years, diabetes was found to be less prevalent among married vs. unmarried, widowed or divorced individuals,[76] and Martin et al[77] found that there was a higher prevalence of DM among the widowed in comparison with married subjects. The theories which support the above include the ‘protective’ aspect of marriage which is lost when the significant other has left or died, leading to loneliness, depression, risky health habits, poorer physical and cognitive function, poor self-rated health and increased risk of institutionalization.[73,78,79]

1.1.12 Employment Status

The onset of T2DM usually occurs during the working life of individuals, with peak incidence in the fourth decade of life.[80] Employment-related stressors such as shift work and work stress may trigger the development of T2DM through overactivation of the hypothalamo–pituitary–adrenal (HPA) axis and cortisol production.[81,82,83] However, there is also evidence that individuals who lose their job are at greater risk of developing chronic diseases.[84] The rate of cardiovascular mortality is doubled in those who are unemployed in comparison with employed people, particularly in the first year of unemployment. [85,86] Unemployment may elevate lifestyle risk factors such as low nutrient diets, lack of exercise, increased smoking and alcohol abuse.[87] Other inappropriate health behaviours could arise from changes in social relationships and psychological disorders which follow financial difficulties.[88]

1.1.13 Economic Impact of Diabetes Mellitus

In terms of the economic impact of DM, in the US Hogan et al[89] documented that the medical expenditures associated with the disease in 2002 were estimated to be 132 billion US dollars. Ten years later (2012), the estimated costs were almost double ($245 billion), of which $176 billion was attributed to direct medical costs and $69 billion for lost productivity costs.[90] Complications and comorbidities associated with DM are responsible for the highest costs of diabetes management. For instance, Li et al[91] demonstrated that females with a duration of DM ≥15 years, positive smoking history and several micro- and macrovascular complications attracted up to 50% more costs than those without the complications. In the same study, the most costly complication was end-stage renal disease treated with dialysis or transplantation, which was also approximately 3 to 5 times the cost of treating early-stage renal complications (microalbuminuria).[91] Zhuo and colleagues estimated that 48%–64% of the lifetime medical costs were attributable to DM-related complications, with 57% spent on macrovascular disease (stroke and coronary heart disease).[92] In addition, men diagnosed with T2DM when aged ≥65 years spent approximately 64% of their costs on the treatment of diabetes-related complications, whilst those diagnosed between 25–44 years spent ≤50%.[92] Diabetes is a cost burden to any economy, but in particular LMICs which is where 80% of the world's DM population originate.[1] In well-resourced high-income countries the economic burden lies with governments, whereas in LMICs, individuals with DM and their families often bear the brunt of high costs associated with insulin and other essential treatments.[1] The impact of DM includes work disabilities, early retirement, loss of income/savings, lost work hours, absenteeism and presenteeism, most of which have negative effects on employment chances or work performance.[93] A study by Travis Minor found that the employment probability of patients with T2DM is negatively impacted across both genders, and

in addition, T2DM males are estimated to earn less than their healthier non-diabetic counterparts.[94] Specifically, T2DM males have a 'wage penalty' of about 52% after having lived with the disease for over 20 years.[94] There is substantial expenditure associated with DM, its related complications as well as loss of productivity at work. Thus, it is necessary to pay closer attention to the control of risk factors and the disease itself through diabetes prevention and management programs, as well as to further prevent or reduce costly complications associated with the DM.

1.2 Diabetes Mellitus in sub-Saharan Africa

1.2.1 Epidemiology: Africa

Africa was once considered "one of the social environments that is kindest to the human cardiovascular system".[95] Tribes of Africa (e.g Xhosa and San Bushmen) lived in the desert as hunter-gatherers where diets consisted of game and/or wild vegetation, long distances were walked and blood pressures remained unaffected by the aging process.[96,97] Yet today, rapid urbanization and modern stress has resulted in diseases of lifestyle such as T2DM increasing both in prevalence and incidence faster than in high-income economies.[98] In fact, sub-Saharan African countries have seen more than a 500% increase in the number of people with DM since 1980 - more than five times the increase in Europe over the same period.[99] Hence, the IDF has estimated that the largest increases of the DM disease are expected to occur in developing regions of the world where as many as 77% of the world's diabetics are already living.[1] In 2015 an estimated 14.2 million diabetic adults aged 20-79 years lived in the Africa Region, translating to a prevalence rate of 3.2% (range 2.1-6.7%), two-thirds of which were undiagnosed.[1] A majority (58.8%) of patients with DM live in cities, although the population in the region is predominantly rural (61.3%).[1] Rural Uganda reportedly has 0.6% of its population living with DM, whilst urban Kenya has 12.2%.[100,101] Perhaps Uganda's prevalence was underestimated due to paucity of data, the use of low sensitivity screening methods and/or non-standardised diagnostic criteria.[102] According to Seedat, urbanized Africans have a higher prevalence of non-communicable disease in comparison with their rural counterparts, due to biosocial factors such as higher incidence of obesity, anxiety-driven insomnia, cigarette smoking, alcohol intake and lack of traditional diets or recreational activities.[103] Other African countries such as Cameroon, Ghana, Guinea and Nigeria have prevalence rates of 5.3-10%.[104,105,106,107] The highest prevalence of diabetes in the Africa Region is on the island of Réunion (15.4%), followed by Seychelles (12.1%) and Gabon (10.7%).[2] Some of Africa's most populous countries have the highest numbers of people with DM, with more

than half of all people with diabetes in the region living in just four of these countries: Nigeria (3.9 million people with DM), South Africa (2.6 million), Ethiopia (1.9 million), and Tanzania (1.7 million).[2] The data on the epidemiology of diabetes in Africa indicate that projected numbers will still rise by 48% (from a mean of 3.2% to 4.9%) by 2025.[108] Hence Sub-Saharan Africa's increasing prevalence of DM is a public health concern which requires that effective interventions be implemented in order to prevent the disease itself as well as the morbidity and mortality associated with this condition.

1.2.2 Epidemiology: South Africa

South Africa's healthcare system is faced with a quadruple burden of perinatal and maternal conditions, injury-related disorders, communicable and non-communicable diseases.[109,110,111] While dealing with its unprecedented HIV/AIDS epidemic, South Africa is also in the midst of a health transition that is characterised by a rise in non-communicable diseases.[112] In studies conducted between the 1960s and the early 1980s, the prevalence of T2DM was found to be <1% in South Africa.[113] By 2015, it was estimated that 7.0% of South Africans or 2.3 million adults (aged 20-79 years) had DM.[1] Of the 2.3 million people with diabetes, it was estimated that 66.7% were undiagnosed.[1] In the South African National Health And Nutrition Examination 2014 Survey (SANHANES), 25 532 people from 6305 households were interviewed and clinically examined.[114] In participants aged >45 years, 16-25% were estimated to have DM, whilst 11-20% had 'sub-diabetes' with abnormal HbA1c.[114] Only 5% indicated that they had DM.[114] Counterintuitively, a higher prevalence of DM (11.9%) was detected in those living in rural settings, which was slightly higher than for those living in urban settings (11.3%).[114] In the South African medical aid environment, which covers almost 9 million people, approximately 3.8% were registered as having T2DM in 2015.[115]

1.2.3 Obesity in South Africa

As with other countries, unhealthy lifestyle choices are a problem in South Africans, who will no doubt also experience increases in obesity rates and associated diseases (i.e. cardiovascular disease, hypertension, T2DM, stroke, osteoarthritis and certain cancers).[116] Already in 2002 the South African Demographic and Health Survey revealed that 56.6% of women and 29.2% of men were overweight.[117] Subsequently, the SANHANES 2014 survey of more than 25 000 people demonstrated that 40% of South African adult women were obese, whilst two-thirds were overweight, obese or severely obese.[114] With childhood obesity being recognised as a strong predictor of adult obesity, almost 25% and 16% of young girls and boys were also found to be

overweight or obese.[114] Furthermore, a study conducted in a Western Cape population reported obesity in ≥50% of its cohort, whilst those within a DM subgroup had an even higher obesity prevalence (≥80%).[118] Quite perversely, perhaps one of the contributors to obesity in South Africa's Black African population is the HIV/AIDS epidemic. Here the postulate is that because weight loss and wasting are commonly associated with advanced AIDS, the cultural perception of a bulkier body size (representing good health) leads to purposive weight gain.[119,120] Fortunately, as evidence draws us closer to reality, the misperceptions are being corrected, allowing one to address the current obesity epidemic, and to recognize and manage the comorbidities of obesity, such as T2DM.[121]

1.2.4 Undiagnosed Diabetes Mellitus

No country has diagnosed every person with DM.[1] According to the IDF, as many as two-thirds of all people with DM remain undiagnosed and Africa is most likely the continent with the highest proportion of undiagnosed individuals (Table 1.1).[1] Due to the asymptomatic nature of early and even intermediate T2DM, several years may pass without any diagnosis before complications begin to manifest.[1] Consequently, many patients present with complications at the time of diagnosis of DM.[1] According to an epidemiological study of 2479 subjects conducted by Omar et al[133] in South Africa's city of Durban, 244 patients or 9.8% were found to have DM. However, only 183/244 of patients had prior knowledge of their diabetes status before the study, which meant that an additional 61 patients or 25% of those diagnosed in the study were previously undiagnosed. Similarly, Levitt et al[131] found as many as 23/46 patients or 50% of their study participants in Cape Town with DM were undiagnosed before the start of the study. Both of the latter studies show rates of undiagnosed DM that are below many cited figures for Africa, possibly reflective of the urban nature of their study populations.

Table 1.1 Proportion and number of people (20-79 years) living with diabetes who are undiagnosed, 2015[1]

IDF region	Proportion undiagnosed (%)	Number of undiagnosed people with diabetes (millions)
Africa	66.7	9.5
Europe	39.3	23.5
Middle East and North Africa	40.6	14.4
North America and Caribbean	29.9	13.3
South and Central America	39.0	11.5
South-East Asia	52.1	40.8
Western Pacific	52.1	79.8
World	46.5	192.8

1.2.5 Diabetes Duration

It has been established that in terms of the development of diabetes-related complications, the duration of DM exposure rather than the age of onset of the disease is what matters.[40] For example, in a longitudinal study at Johannesburg's major public sector academic hospital, patients with T2DM were studied over a 4-year period. Although both blood pressure and LDL-C levels improved, HbA1c worsened over the study duration. This resulted in a 41.4% and 40.0% increase in both coronary artery disease and stroke, respectively. Retinopathy, neuropathy and nephropathy rates increased by 53.8, 61.9 and 60.0% over the study period.[122]

1.2.6 Control/Complications Associated with Risk Factors In South African Diabetics

According to Statistics South Africa, in 2012 DM was the fifth leading cause of death in South Africa.[123] Rather than being limited to control of glycaemia alone, the management of T2DM includes identification and management of other modifiable risk factors.[124] Webb et al[125] in 2015 studied the intensity of screenings, disease control and the extent of complications within a DM population receiving primary care from the Tshwane District Hospital which is located north of Johannesburg in the Gauteng Province. The total cohort (n=599) was comprised of subjects with a mean age of 58 years; 68% were female and 80.5% were overweight (BMI ≥25 kg/m^2). Close to one-third met both HbA1c (27%) and LDL-C (33%) treatment targets, and two-thirds achieved systolic blood pressure targets. Retinopathy was detected in 29%, 11% had neuropathy and 7.4% had nephropathy. Macrovascular disease was detected in up to 17% of patients. The study investigators concluded that the screening and diabetes care available to patients at a primary care level was sub-optimal and vast numbers of poorly-controlled diabetic patients require earlier

detection of risk factors, especially those at high risk of diabetes related-complications. In a 2009 audit at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), retrospective data were obtained from a total of 666 patients with T2DM defined according to the SEMDSA definition for diabetes, or based on patients receiving oral/injectable diabetes treatment.[126] In the study cohort, 6.3% had retinopathy, 7.1% neuropathy and 11.1% had documented nephropathy. Macrovascular disease (cardiovascular disease or stroke) was present in 15.5%. In a retrospective database analysis conducted by Pillay et al[127] the clinical characteristics, diabetes control and complications were examined in 653 diabetics attending the Edendale Regional Hospital which is located in the city of Pietermaritzburg, KwaZulu-Natal province. The study commenced in October 2012 and lasted 12 months. The cohort was comprised of 77.0% females and 83.4% of the study participants had T2DM. At least 6.4%, 45.2% and 20% had evidence of retinopathy, neuropathy and overt nephropathy, respectively. Patients with T2DM had higher rates of obesity (using BMI as an indicator) than T1DM (62.02% vs. 39.81%). Levitt et al[128] performed an audit of three of the largest ambulatory primary care diabetes clinics around Cape Town. The aim was to determine the prevalence of diabetes complications, and level of glycaemic and blood pressure control in a random sample of 243 individuals with DM. Of the total cohort, the mean age was 56 years and 61.7% were females. The minority (39%) were employed, and all individuals were of Black African descent. One-fifth had a normal HbA1c (20%), whilst in those who were receiving antihypertensive pharmacotherapy, 38.5% had normal blood pressure (systolic <140mmHg and diastolic blood pressure<90mm Hg). The above figures from around South Africa indicate that across the range of primary to tertiary level (public sector) facilities, diabetes control is difficult and T2DM complications exist at fairly high rates.

1.2.7 Ethnicity

According to the SANHANES study, Black Africans and Caucasians had similar prevalence rates (>8%), whilst Mixed-Ancestry (13.4%) and Asian/Indians had the highest (30%).[114] In a series of other studies, prevalence rates ranged from 3-28% across the ethnic groups of South Africa (Table 1.2). In addition, approximately 115 000 new cases of DM are expected every year.[129] In terms of risks according to ethnicity, several South African population-based studies have reported differences in diabetes related outcomes.[130] Ethnic groups differ in their risk of developing morbidity and mortality associated with T2DM, which may suggest that aggressive action in respect of modifiable risk factors may be warranted, particularly in high-risk ethnic groups.[130]

Table 1.2 Prevalence of type 2 diabetes in different South African ethnicity groups

Population	Region (n)	Prevalence (%)	Age range (years)	Reference
African	Cape Town, urban (729)	8.0	30 +	([131])
	QwaQwa, rural (853)	4.8	25 +	([132])
	Mangaung, urban (758)	6.0		
	Durban, urban (479)	5.3	15 +	([133])
Mixed- Ancestry	Cape Town, urban (200)	28.7	65 +	([134])
	Cape Town, peri-urban (974)	10.8	15 - 86	([135])
European	Durban, urban (396)	3.0	15 - 69	([136])
Indian	Durban, urban (2479)	13	15 +	([137])

1.2.8 The Aging Process

Sub-Saharan Africa faces many challenges relating to the development of T2DM.[1] One such challenge relates to food insecurity which affects the availability of nutrients delivered to the mother before, and to the foetus during the pregnancy. This has been shown to increase the risk of adult chronic diseases in affected offspring.[138] However, whilst inadequate nutrition and unhealthy lifestyle choices such as smoking and drinking during pregnancy may theoretically be modified, aging, an established risk factor of DM, cannot. South Africa has an aging population, with the proportion of this population group projected to increase.[139] In fact, South Africa has the highest proportion of older people in Africa.[139] According to Statistics South Africa, the life expectancy at birth for 2017 is estimated to be 61.2 years for males and 66.7 years for females.[140] The higher prevalence of DM among younger adults in LMICs will also drive T2DM increases as those people age, countries develop, and life expectancy increases.[141] In a systematic review by Werfalli et al[142] across 41 studies providing 49 separate data contributions involving over 16000 individuals, it was found that in people >55 years living in Sub-Saharan Africa there was an overall DM prevalence of 13.7%. Thus, in addition to its inherent diabetes risk factors, the number of people at risk of developing T2DM is expected to increase in South Africa, particularly as the country reverses the pattern of premature death related to HIV/AIDS.

1.2.9 Gender differences

There is mounting evidence of clinically important gender differences in T2DM.[143] Although males develop T2DM at a lower age and body mass index, obesity, the most prominent risk factor, is more commonly found in women upon diagnosis.[143] Diabetes-attributable mortality is 1.7 times higher in women compared to men.[1] In the US Framingham heart study cohort, the lifetime risk of experiencing a cardiovascular event in obese individuals with DM was 78.8 and 86.9% in women and men, respectively.[144] Sadly, given the high rates of obesity and DM, South Africans are heading down the same path if current trajectories do not change.[114] In a study by Goedecke et al[145] both insulin sensitivity and secretion were compared in black South African males and females with normoglycaemia. It was found that women had lower insulin sensitivity than their male counterparts, but increased insulin release in order to maintain normoglycaemia. The findings could not be fully explained by higher BMI and prevalence of obesity in females vs. males (82% vs. 30%), but rather, the association between BMI and insulin sensitivity was stronger in men than women.[145] Notably, these findings were in contrast to studies in largely European populations, in which it was shown that adult men are more insulin resistant compared to women.[146]

1.2.10 Education

Population groups with lower education levels may be more vulnerable and at increased risk of developing chronic diseases such as T2DM.[67] In addition, an inverse relationship has been found for education and diabetes-related mortality.[147,148] However, some studies in Africa present a different picture in terms of the mitigating effects of education.[149] Data collected from an urban township in South Africa's Cape Town found that a higher socioeconomic status (defined by educational attainment and income) was positively and significantly related to obesity in women, but the same was not true in men.[149] The authors of the study explained that the women who were more likely to become obese had different perceptions of 'ideal' body shapes in comparison to men, and in those households where women generated the income (through work and government subsidised child grants) they had status as 'decision-makers', allowing them to channel more spending towards food.[149] In a separate study conducted in the Eastern Cape (South Africa), higher levels of education were found to be a determinant of obesity in individuals who adopted Western dietary habits over their less-educated peers.[150] The above findings correlate with Martorell et al[151] who found higher obesity levels among urbanised and higher educated women across Africa, but contrasted with results from the US where women with higher levels of education showed the lowest levels of obesity. This phenomenon has been described

as the ‘reversal hypothesis’, identified when overweight or obesity is associated with individuals from lower socioeconomic status in high-income countries vs. individuals with high socioeconomic status in low-income/LMICs.[152] According to Levitt, given the strong relationship between level of education and obesity, subjects with higher socioeconomic status and living in countries with lower gross national product are more likely to be obese.[120] This disturbing trend of a direct relationship between education and obesity/disease in Africa is counter to that observed in developed countries, possibly also reflective of traditional, cultural or historical diets. For example, most South Africans have a history of maize-based diets and less access to high quality protein.[153] Ideally, improved education and socioeconomic advancement would alter this situation, but this does not appear to be the case at this time. This phenomenon has been described as ‘nutrition transition’.[154]

1.2.11 Marital Status

Many health-enhancing properties of personal relationships, and particularly marriage, have been documented.[72] In a South African study which assessed psychosocial stress and its effect on metabolic control in patients with DM, it was found that being married was associated with a lower odds ratio of being extremely stressed.[155] Studies have shown that psychosocial stress and stressful life events lead to an activation of the HPA axis resulting in high cortisol levels which antagonise the actions of insulin, thereby increasing the risk of T2DM onset.[81] Negative life events were examined in a similar study consisting of 25–74-year-old residents living in the predominantly black African areas of Langa, Guguletu, Crossroads, Nyanga and Khayelitsha in Cape Town. The study revealed that death of a parent, child or spouse, and/or separation caused by marital difficulties was significantly associated with the risk of diabetes in both men and women.[118] Another local study demonstrated that amongst other factors, being unmarried was positively associated with obesity, therefore increasing the risk for the development of DM.[150] Hence, more attention to the social arrangements in patient’s lives may assist healthcare providers’ ability to implement timely preventive or intervention strategies.[75]

1.2.12 Employment Status

Unemployment has been shown to be a common stressor for work seekers and a major impediment to attaining good health.[156] In addition, there is significant evidence to show that poverty is associated with shorter life span and increased mortality, particularly cardiovascular mortality.[71] South Africa's unemployment rate of 27.7% in the second quarter of 2017 was unchanged from the previous period's 13-year high.[157] Adeniyi et al[150] found unemployment to be

positively associated with obesity. Similarly, using South Africa's National Income Dynamic Study (NIDS) data which is a nationally-representative household survey, it was found that obesity had a negative effect on employment. In a European study, it was found that a negative relationship exists between BMI and earnings.[158] Thus, the health consequences of unemployment may be a predictor of specific disease risk, but it is debatable whether obesity impacts on 'employability' or unemployment results in dynamics that lead to obesity.[150]

1.2.13 Economic Impact of Diabetes Mellitus

Diabetes imposes massive direct and indirect economic costs to any healthcare system.[1] Sub-Saharan Africa's total health expenditure for DM is expected to rise by approximately 50% between 2010 and 2030.[159] The 2017 Lancet Commission on Diabetes in Sub-Saharan Africa has estimated that in 2015 the total cost of DM in Sub-Saharan Africa was close to $20 billion or 1.2% of the cumulative gross domestic product (GDP).[160] Diabetes-related costs such as drugs, hospital stays and complications accounted for approximately $11 billion (55.6%) of the costs, of which, more than half were likely to be patient out-of-pocket payments.[160] Due to the majority (76.4%) of diabetes-related mortality occurring in people <60 years, devastating economic consequences follow when the working age population is impacted the most.[161,162] South Africa's DM-related costs are projected to be between 1.1 – 2 billion USD by 2030.[163] In a study based on a best-practice model, Volmink et al[164] performed an analysis to determine the potential cost-effectiveness of adapting a private sector diabetes management programme to the South African public sector. The probabilistic modelling showed the intervention to be cost-effective, with an incremental cost-effectiveness ratio (ICER) of ZAR 8 356 (USD 1018) per life year gained. Hence piloting the service within the public sector was recommended as an initial step, as this would provide data for more accurate economic evaluation.[164] In a resource-poor environment, in addition to DM exhausting whatever family resources are available, the loss of breadwinners could drive many families into further poverty.[165] Due to the nature of DM, treatment is long-term, and treatment associated with diabetes complications becomes unaffordable for most within the public sector. Insulin and other drugs are not only unaffordable for many of the poor, but often not obtainable on a continuous basis due to supply issues.[102] Hence, the growing cost burden of diabetes represents a major public health challenge, with LMICs having to carry a substantial amount of the burden. Given the resource constraints existing in South Africa, cost-effective strategies are needed in order to alleviate the major morbidities and mortalities associated with DM.

1.2.14 Conclusion

With the worldwide increase in high calorie diets, sedentary lifestyles and urbanization, the prevalence of DM is rapidly mushrooming out of control, particularly in LMICs such as South Africa. Yet, many individuals remain undiagnosed. Obesity has become established as one of the strongest risk factors for the development of DM and there appears to be a worrying trend that education and relative affluence are driving obesity rates rather than the reverse. There are multiple debilitating complications, some of which, (e.g. retinopathy) are correlated with the duration, rather than the time of onset of DM. In addition to the classical risk factors, gender and ethnic differences make particular groups more susceptible to the onset of DM or DM-related complications. Education, urban-living, employment and marital status contribute towards diabetes-related outcomes. There is substantial expenditure associated with DM, particularly diabetes-related complications. Lastly, the high prevalence of DM and its complications in South Africans call for a multi-facetted strategy before the prospect of even further rises becomes a reality.

2. INTRODUCTION (Part B)

2.1 Introduction: Quality of Care

As the rates of DM continue to rise, so too do concerns around the abilities of a healthcare system to deliver quality healthcare. As discussed in Chapter 1, DM-related morbidity and mortality are impacted by genetic and environmental elements, but other contributing factors may include inequalities in the delivery of healthcare. To remain productive members of society, patients with DM require adequate self-management behaviours as well as multidisciplinary treatment in order to maintain normoglycaemia and prevent complications associated with DM. Hence, the chronic nature of DM makes this disease particularly reliant on a functioning healthcare system, and a lack thereof could result in poor health outcomes.

The concept of the 'iron triangle' identifies that a healthcare system is comprised of three elements of care: access, quality, and cost.[166] Any change in one or two elements induces change/s in one or two of the others. Such change may be positive or negative. If a healthcare system were to provide services at lower levels of funding, then this would likely result in reductions in access and/or quality. Increasing access could increase costs and/or reduce quality. A real life example of this is South Africa's public sector which is generally underfunded and is poorly accessible to large numbers of the population. Consequently, the abovementioned healthcare system has been criticized as being "of dismal quality" due to the infrastructure being run-down and dysfunctional.[167] Much of the public sector's increased spending has gone towards HIV/AIDS medication, with relatively little spent on the maintenance and/or development of public hospitals.[167] On the other hand, South Africa's private healthcare sector is comprised of a system whereby 'a select few' are able to afford and easily access supposedly higher quality care, at higher cost.[167] The key question is whether improved access to and funding of care actually result in better quality. In this regard the 'law of diminishing returns' comes into play. This is a principle of economics which states that once one variable is increased and other factor inputs are held fixed, eventually a threshold is reached and any further input will yield progressively smaller increases in output.[168] This law may be applied to clinical medicine. For example, due to the advancements in the field of modern surgery, the prostheses used in hip arthroplasty have become so flawless that any further improvements would require even greater investment but only modest clinical results.[169] "However, the profession and industry will not stand still…the law of diminishing returns applies. As the product becomes more successful, an exponentially greater investment is required to achieve further improvement."[169] In the field of diabetes care, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, intensive glucose lowering in

high-risk patients with T2DM resulted in increased mortality.[170] This is another example of the law of diminishing returns.

In order to 'balance' the cost, quality access triangle, a single-payer system of healthcare has been proposed for South Africa.[171] This has the potential to bring the private and public sectors together to build a system that suits everyone's needs and provides quality care to all.[167] The envisaged system is known as National Health Insurance (NHI) and is to be administered by an NHI Agency (NHIA). The single-payer system would receive its revenue from payroll taxes, employer contributions and government contributions (where the unemployed cannot contribute), which would be used to obtain and provide cost-effective healthcare services and products to all South Africans. According to the NHI plans proposed by the National Department of Health (NDOH) and supported by Government, the currently existing private sector would only exist as a partner to the NHI, whereby 'top-up' cover or benefits would be available to those able to afford services beyond those available through the NHI.

Having discussed cost, quality and access in the context of healthcare, there is the question of how one actually determines quality. In order to define what quality of a healthcare system is, the Donabedian Model (conceptualized by Professor Avedis Donabedian in the early 1980s) describes a system which again uses three elements of care: structure, process and outcome.[172] Although each component has its particular relevance in the measure of quality of care of a healthcare system, it is the interaction between these elements that is of importance.[172] Donabedian stated that "good structure increases the likelihood of good process, and good process increases the likelihood of good outcome".[172] The structures of healthcare within the Donabedian Model are the physical and organizational features of healthcare settings such as facilities, equipment and personnel but also includes the patients.[172] In this regard the following elements would also be relevant: disease and health status of the patients within the health system under review, and how easy it is for such patients to enter the system. The processes rely on the ability of the structure to provide the resources and mechanisms needed to carry out patient care activities.[172] The final element of quality includes the patient- and health outcomes associated with medical care, which reflect the effects of care on the health status of patients/populations, and is comprised of: clinical outcomes, perceived quality of life and functional status, patient satisfaction with the care received, and costs.

Therefore in this chapter, the quality of diabetes care will be described in terms of the Donabedian Model (Access, Process & Outcomes) in both global and local settings.

2.2 Global: Access, Process & Outcomes

2.2.1 Access and Outcomes: Diabetes Care of Immigrants/Migrants/Refugees

Lack of healthcare access among immigrants has far-reaching consequences. For example, in the US, immigrants of Hispanic origin represent 15.5% of the total US population and have diabetes prevalence rates as high as 12.8% vs. the US overall prevalence of 9.3%.[173,174] Immigrants undergo acculturation and may take on a range of poor lifestyle habits such as eating high calorie foods, engaging in low physical activity and smoking, which could put them at high risk for the development of obesity and/or DM. Many Hispanic immigrants are poor, have low education levels and are uninsured. At least 51% are 'on welfare', which makes accessing healthcare difficult, and perhaps unattainable for most.[175] Similar findings exist for immigrant South Asians (Pakistanis, Indians, and Bangladeshis) in England, where language affected providers' ability to recognize disease or communicate interventions.[176] Hence, access barriers experienced by migrant groups have major public health implications, leaving such individuals worse-off despite the need to access healthcare as much, if not more than the citizens of a particular country.

2.2.2 Access and Outcomes: Transportation and Travel Times

Patients without access to transportation to their healthcare facilities are exposed to a host of poor health outcomes. Provider appointments may be missed, cut-short and/or rescheduled, or patients may run out of medication and care may be compromised.[177] Particularly with chronic diseases such as DM there is a need for regular provider visits, medication supply and modification of outdated, ineffective treatment plans. As many as 67% of health-related appointments may be missed due to transportation problems.[178,179] Arcury and colleagues found that when members of a rural Appalachian cohort had family or friends with a driver's license and car there was an increase in healthcare utilization.[180] Conversely, Rask et al[181] found that patients who had no access to private transportation had a higher likelihood of delaying care. Other barriers included an inability to rapidly access care due to remoteness of residence, no interstate transportation systems or public transportation, and finally, the cost of transportation.[182] In addition, prolonged travel time is an obstacle to management of disease. For instance, two studies found that patients with T2DM who lived closer to their healthcare providers tended to have better glycaemic control than those who lived further away.[183,184] Conversely, it has also been found that the further the driving distance for individuals with DM, the lower the likelihood of being an insulin

user.[183] A reason cited for the latter was that providers worried about the detrimental risk of hypoglycaemia in patients who live in remote areas and may not have access to emergency care if required. In summary, patients who cannot travel or those who travel for long times/distances may experience access barriers to healthcare, which impedes optimal management.

2.2.3 Access and Outcomes: Uninsured Diabetics

Preventive medical care is particularly important for patients with DM who require frequent check-ups to monitor glycaemic control, diabetes-related complications, and disease progression.[185] Better outcomes through larger reductions in HbA1C have been documented in patients with DM who had more frequent healthcare visits.[186] Hence, for uninsured and underinsured populations with DM, the quality of care which healthcare systems normally deliver may be compromised. Nelson et al[187] found that in comparison with insured diabetics, those who are uninsured monitor daily blood glucose less frequently and have fewer annual dilated eye exams, foot examinations, and HbA1c tests. Data from the 2009 National Health Interview Survey showed that due to the cost implications, uninsured diabetics were six times more likely to forgo necessary medical care in comparison with those who were continuously insured.[188] Along similar lines, not having a standard site for care and/or substituting an emergency department for the site which should be regularly utilized for healthcare, were associated more with uninsured patients with diabetes than with those who were insured (47.5% vs. 7.7% and 7.1% vs. 1.1%; $p<0.001$).[189]

2.2.4 Access and Outcomes: Other Barriers

Research suggests that in comparison with wealthier people, those who come from a lower socioeconomic background experience a lower level of medical care, leading to higher rates of morbidity and mortality.[190] Kerner et al[191] reported that poorer patients were found to have negative experiences when dealing with the healthcare system. In the latter study, patients described healthcare staff as “cold, unfriendly and insensitive to their particular cultural needs”.[191] Hence it is often the case that as the demand for healthcare increases, so do barriers for poor populations. Another challenge which arises is taking time off from work. In a study by Ahmed and colleagues, 31% of the study population reported that it was “very hard” to be absent from work when a medical emergency arose.[192] In addition, diabetics with children were even more likely to report this as a barrier to obtaining healthcare.[192] In the US, a group of American Indians was found to be 1.6 times more likely to report work/family responsibilities as a barrier to care, and similarly, financial worries were a commonly-cited barrier.[193] Long waiting times and short

doctor consultations may also be barriers to obtaining healthcare services. One study reported that as many as 61% of the respondents waited for as long as 90-180 minutes in the clinic (entry to exit). [194] In addition, in terms of the consultation time, 36.1% (35/96) of respondents spent <5 minutes with the doctor, whilst only 19.6% (19/96) spent >10 minutes.[194] The mean consultation time with the doctor was 7±4 minutes.[194] Perhaps this was a reflection of the large number of patients, with few healthcare workers available.[194]

2.2.5 Process and Outcomes

Diabetes Mellitus is the leading cause of blindness, non-traumatic lower extremity amputations and renal failure, whilst also raising the risk for cardiovascular disease.[195] Preventive care is achieved through regular monitoring of HbA1c, blood pressure, lipids, microalbuminuria and through performing ophthalmic and foot care examinations, all of which may reduce the occurrence and progression of diabetes-related complications.[196] Hence, evidence-based guidelines e.g. those of the American Diabetes Association (ADA) recommend that individuals with DM receive 2-4 annual medical visits which include: two annual HbA1C tests and one annual lipid test, a retinal examination, a microalbuminuria test and an annual comprehensive foot evaluation.[197] Blood pressure and anthropometric measurements (e.g. BMI and waist/height ratio) should also be conducted at every routine visit.[197] Yet, countless patients with DM still do not receive recommended services despite the benefits associated with preventive care.[198] Fewer medical visits result in 'lost opportunities' for the implementation of critical diabetes-related preventive care.[199] Additionally, although annual HbA1c testing rates as a DM-quality measure may appear to have little, if any, direct relationship to better cardiovascular outcomes, it has been found that more-consistent testing over time is associated with improved cardiovascular outcomes.[200] Many studies report sub-optimal rates of preventative tests performed. In an Indian study, which set out to assess diabetes care processes, it was reported that in 406 patients with DM the following were performed over a 1 year period: only 7.4% received dilated eye examinations, 15.1% had their feet examined and 29.1% had an electrocardiogram performed.[201] These outcomes were despite testing rates of 51.7%, 88.4%, and 28.1% of ≥1 for HbA1c, BP, and lipids respectively. Non-physicians can also assist with various aspects of diabetes care such as sending patient reminders for tests, or relaying of important dietary information and physical activity advice to patients.[201] In the US, involvement of nurse practitioners in diabetes care resulted in more guideline enforcement, which yielded better HbA1c outcomes in patients.[202] Possibly supporting the argument that regular consultations and monitoring will reduce the need for multiple ad hoc visits for control or complication-related problems, is a multi-country study by

Assaad-Khalil et al[203] in which 1082 physicians were surveyed on barriers to diabetes care. It was found that 32% of patients visited their physician up to 5 times/year whilst 34% visited 6–10 times/year and 20% 11–15 times/year.

The United Kingdom Prospective Diabetes Study (UKPDS) was one of the most pivotal diabetes studies ever conducted.[204,205,206] The study enrolled 5102 newly diagnosed T2DM patients across 23 collaborating United Kingdom centres between 1977 and 1991. Each patient contributed at least one decade worth of data towards the study. This allowed the investigators to study how intensive use of pharmacotherapy would translate into clinical benefit, how reductions in blood glucose levels could potentially lower micro- and macrovascular complications, and how certain drug classes such as the sulfonylureas, biguanides or insulin would have particular benefits. Similarly, ACE inhibitors and β-blockers were studied in hypertensive patients with T2DM in order to measure optimal blood pressure levels as well as determine therapeutic benefits. Results from the study proved that microvascular complications were reduced by 25% through the intensive use of glucose lowering treatment (whereby patients achieved a mean HbA1c of 7.0%) in comparison with the regular doses (mean HbA1c 7.9%). Likewise, for every 1% reduction in HbA1c, a 35% and 25% decrease in the risk of microvascular complications and diabetes-related deaths were achieved in study patients. Reduction in complications were not linked to specific glycaemic thresholds. A 16% decrease (borderline not statistically significant; p=0.052) in macrovascular endpoints was observed for combined fatal or nonfatal myocardial infarction and sudden death. Lowering of blood pressure to mean levels of 144/82 mmHg was shown to reduce strokes, diabetes-related deaths, heart failure and retinopathy.

In the Steno-2 study, 160 patients with T2DM and microalbuminuria were recruited at the Steno Diabetes Center in 1993.[207] The aim of the study was to determine the rate of cardiovascular events after patients with T2DM were challenged to treatment of their risk factors against multiple predefined targets. One hundred and sixty patients were randomized to either the conventional group or the intensified multifactorial treatment group. The intense arm employed both behavioural and pharmacological approaches in order to treat cardiovascular risk factors associated with T2DM. At the end of follow up, thirty-eight intensive-therapy patients vs. fifty-five conventional-therapy patients died. The median time to first cardiovascular event was 8.1 years longer in the intensive group (p=0.001). The study investigators found that after 21.2 years of follow-up or 7.8 years of intensified, multifactorial, target-driven treatment of risk factors associated with patients having T2DM and microalbuminuria, a median of 7.9 years of life were gained by the study patients.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study aimed to determine how predefined intensive glucose (to targets of HbA1c <6.5%) and blood pressure control impacted major micro- and macrovascular composite end points vs. standard-control.[208] A total of 11 140 patients with T2DM were enrolled across 215 centres in Asia, Australia, Europe, and North America. The microvascular end points were composites of new onset or progressive retinopathy or nephropathy, whilst macrovascular end points were composites of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Of the total group, 2125 patients experienced either a major micro- or macrovascular event; 18.1% in the intensive-control group vs. 20.0% in the standard-control group (p=0.01). Individually, the intensive-control group had a significant reduction in the incidence of major microvascular events vs. the standard-control group (p=0.01), however, no differences were found across major macrovascular events between the groups (p=0.32). Nephropathy rates were clearly reduced through intensive glucose control (2.9%, vs. 4.1% with standard control; p<0.001). Systolic blood pressure was reduced by 5.6mmHg in the intensive group (perindopril and indapamide) in comparison with the control group, which resulted in a 9% relative risk reduction for the combined composite micro- and macrovascular end point.

The results of the UKPDS, the ADVANCE study confirmed that an intensive strategy in patients with T2DM achieved beneficial and safe mean HbA1C levels of 6.5% without increased risk of mortality. Against this background, the ACCORD study set out to assess the outcomes associated with intensive lowering of glucose (to targets below HbA1c <6%), systolic blood pressure (<120 mm Hg) and blood lipids (reduce both LDL-C and triglycerides, but raise HDL-C) compared to the standard arm (guideline recommended targets).[170] There were 10 251 participants with an average of 10 years of T2DM enrolled in 77 clinical centres across the United States and Canada. Study participants had at least two risk factors such as smoking, obesity or history of vascular disease in order to meet study criteria. All participants were randomized to either an intensive study arm or the standard treatment arm. The medications used for the management of risk factors in study participants were all previously FDA-approved drugs, with the choice of drugs based on the doctor's medical judgment and common use in the community for the general treatment of diabetes. The study results in terms of the glucose lowering arm were unexpected as there were 257 deaths in the intensive arm and 203 deaths in the standard group. Hence, the study Data and Safety Monitoring Board (DSMB) stopped the glucose arm prematurely as it was found that there was an increased risk between the two groups which outweighed the potential benefits of the intensive treatment strategy on nonfatal events. Therefore, the study's

investigators recommended that as per guidelines, people with T2DM should aim for an A1C level of 7%. The blood pressure arm of the study did not show any reduction in the rates of composite outcomes of fatal and nonfatal major cardiovascular events for patients being treated in the intense arm (target systolic blood pressure of <120 mm Hg), as compared with those in the standard arm (<140 mm Hg). The lipid arm showed that statins were beneficial in lowering cardiovascular risk, whereas the fibrates appeared to only show efficacy in a specific population of patients (i.e., those with significant hypertriglyceridemia and low HDL-C). Hence, stringent targets but not beyond the recommendations of HbA1c (<7%) and systolic blood pressure (<140 mmHg) were found to be the most appropriate levels for the treatment of risk factors in patients with T2DM.

As previously discussed, patients with T2DM have a substantially increased risk of cardiovascular disease. Thus, in the Collaborative Atorvastatin Diabetes Study (CARDS), patients with T2DM and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension but without previous cardiovascular disease or high LDL-C levels, were assessed for first major cardiovascular event or stroke whilst either using a statin (atorvastatin) or placebo.[209] A total of 2838 patients, across 132 centres in the UK and Ireland were randomized to placebo or atorvastatin 10 mg daily. After a mean duration of almost 4 years, the primary end point (first occurrence of any of the following: acute coronary heart disease events, coronary revascularisation, or stroke) occurred in 127 patients vs. 83 statin treated patients (p=0.001). The trial was concluded 2 years earlier than anticipated as there was 37% reduction in at least one major cardiovascular event or equivalent, 36% reduction in acute coronary heart disease, 31% reduction in coronary revascularisations, 48% stroke reduction and death reduction of death by 27%. Hence, it was found that high risk patients with T2DM and at least 1 additional risk factor can have significant reductions in risk of cardiovascular events or stroke events upon statin usage, even when initial LDL is already ≤ 3mmol/l.

The above studies confirm that strict attention to the processes of care does have an impact on outcomes. However, there appear to be limits beyond which the benefits may be lost and there are diminished returns for additional input and investment.

2.2.6 Outcomes: Quality Of Life in Diabetes

Diabetes is a chronic disease with long-term consequences.[195] Many patients with DM, with or without complications, experience changes in lifestyle and reduced health-related quality of life

(HRQoL). Studies have shown that patients with DM have a reduced HRQoL in comparison with non-diabetics in the same age group, with the former group having an even greater decline in HRQoL as disease advances and/or complications develop.[210,211] Hence, the measurement of HRQoL has become an important component of care. The World Health Organization (WHO) defines HRQoL as a "state of complete physical, mental, and social well-being, not merely the absence of disease".[212] As a tool previously utilized in studies of populations with DM, the EQ-5D (EuroQol-5 Dimension) is a multi-attribute utility instrument (MAUI) which assesses health problems on five levels and five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[213,214] The EQ-5D has also been widely used in economic evaluations by the National Institute for Clinical Excellence (NICE) in the UK, and the Healthcare Insurance Board in the Netherlands.[215] In the ADVANCE study in which 978 Australian patients with T2DM completed the EQ-5D questionnaire, it was shown that patients with major diabetes-related events such as stroke or myocardial infarction had a lower HRQoL.[213] Similar findings were shown in the UKPDS 37 study where complications of the disease affected HRQoL. However, it could not be determined whether frequent hypoglycaemic episodes affected HRQoL.[216] In a US study it was found that body weight had an inverse relationship with HRQoL in patients with T2DM.[217] Hence, DM and its associated complications, especially macrovascular disease, have been shown to reduce HRQoL in patients, and it should be a consideration to assess HRQoL before implementing diabetes interventions so that one is able to establish a baseline and then monitor change and rate-of-change over time.

2.3 South Africa: Access, Process and Outcomes

2.3.1 Access and Outcomes: Diabetes Care of Immigrants/Migrants/Refugees

Challenges in accessing healthcare services not only affect South Africans, but also immigrants and refugees living in South Africa.[218] In fact, immigrants living in South Africa may face additional barriers as they are often disregarded and may be subjected to abuse by members of the general public e.g. work-related discrimination, xenophobic violence when businesses are foreign-owned, and financial disincentives e.g. having to pay more for education and/or healthcare.[219] One study showed that hospital security guards in a public hospital were turning non-South Africans away and/or placing them in longer waiting lines in order to deny care or directly exclude foreign individuals from receiving healthcare.[220] Such abuse of immigrants has been characterized as 'medical xenophobia'.[220] South Africa has 11 official languages and up to 80% of healthcare consultations may involve language 'mismatches' between patient and providers of care.[221] Many

South African citizens and residents do not communicate well in English, which often leads to incorrect diagnoses, poor treatment adherence or inability to follow medical instructions, any/all of which may compromise the quality of patient care.[222] Hence language or medical xenophobic barriers, combined with the high-risk chronic nature of DM, make immigrants, migrants and refugees living in South Africa particularly vulnerable to poor health outcomes.

2.3.2 Access and Outcomes: Transportation and Travel Times

Transportation is a fundamental requirement for patients requiring healthcare. In a study which set out to assess the barriers to utilization of maternal healthcare services across three diverse geographic regions in South Africa (Western Cape, Eastern Cape and Kwa-Zulu Natal) it was found that transportation and distance from care were the most frequently-reported access barriers, particularly in rural areas.[223] Similar findings were reported in a multi-country study (Sudan, Namibia, Malawi and South Africa) in which lack of transportation or its associated costs were found to be the main barriers to accessing healthcare services.[224] According to the General Household Survey (GHS), most South Africans who fall ill or are injured would seek help at their nearest public healthcare facility.[225] However, due to the long waiting periods and overcrowding associated with many of the facilities in South Africa, almost one-fifth (18.9%) of patients reported that travelling to a healthcare facility beyond their normal catchment area was the only way to ensure they would access the healthcare services needed.[225] McLaren and colleagues found that the lowest income quintiles of South Africans were more likely to live further away from their nearest health facility.[226] Thus distance to healthcare facility, transportation and its associated costs all have a definite impact upon a diabetic patient's ability to access healthcare.

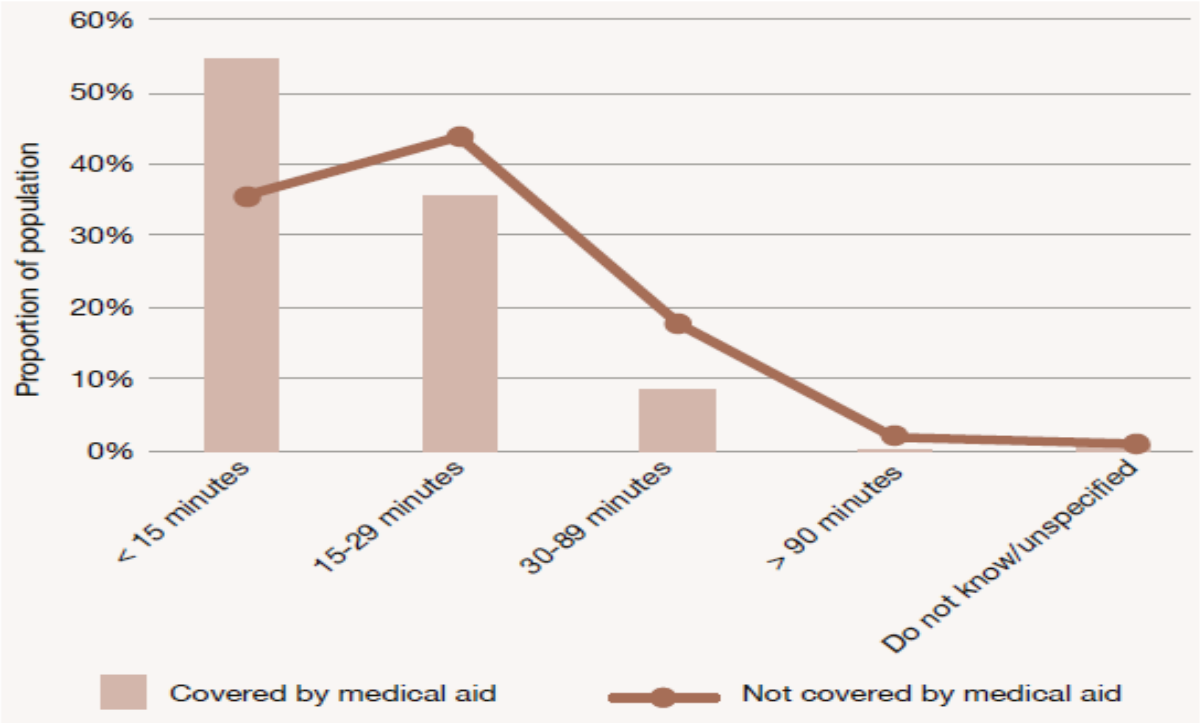
2.3.3 Access and Outcomes: Uninsured Diabetics

People with DM are in need of routine care in order to prevent serious diabetes-related complications.[185] In fact, more frequent healthcare visits in patients with DM may lead to better outcomes.[186] Uninsured populations with DM tend to have fewer consultations than are needed for general, eye and foot care.[185] Hence lack of health insurance could result in major barriers to healthcare access, potentially leading to adverse consequences in patients with DM.[188,189] South Africa has an estimated population of 55.5 million, of which only 17% have private health insurance and access to private healthcare facilities.[140] Hence the majority of South Africans receive their healthcare from the public sector's healthcare facilities. In comparison with South Africa's private healthcare sector, most of the clinics and hospitals within the public sector are in a state of disarray, with infrastructure run-down and dysfunctional. Additionally, more barriers to access are experienced by patients in the public sector (Figure 2.1).[227] This may be related to the fact that many of the facilities are underfunded, poorly managed and neglected.[228] According to the Lancet Commission on Diabetes in Sub-Saharan Africa, South Africa's public sector and other Sub-Saharan Africa health systems have "inadequacies at all levels" through "inadequate availability of simple equipment for diagnosis and monitoring, a lack of sufficiently knowledgeable health-care providers, insufficient availability of treatments, a dearth of locally appropriate guidelines, and few disease registries."[160]

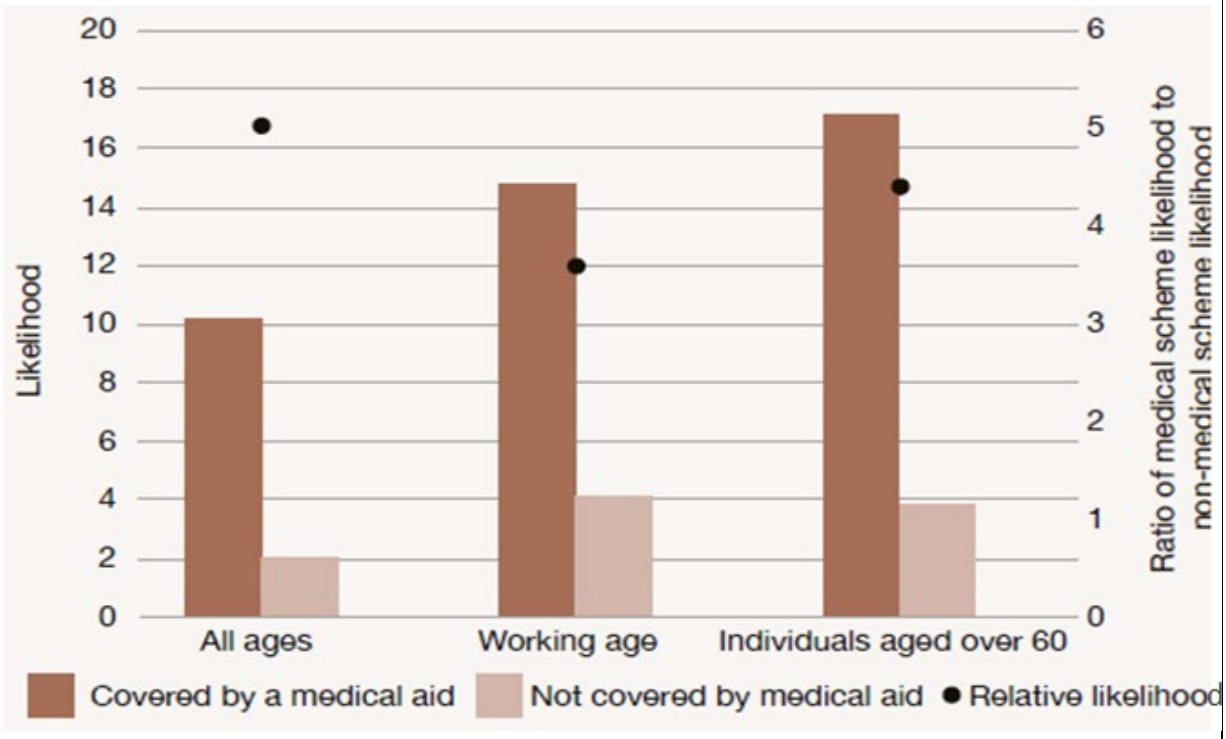
Figure 2.1 Comparison of Access Barriers across the Public and Private Healthcare

Sectors in South Africa[227]

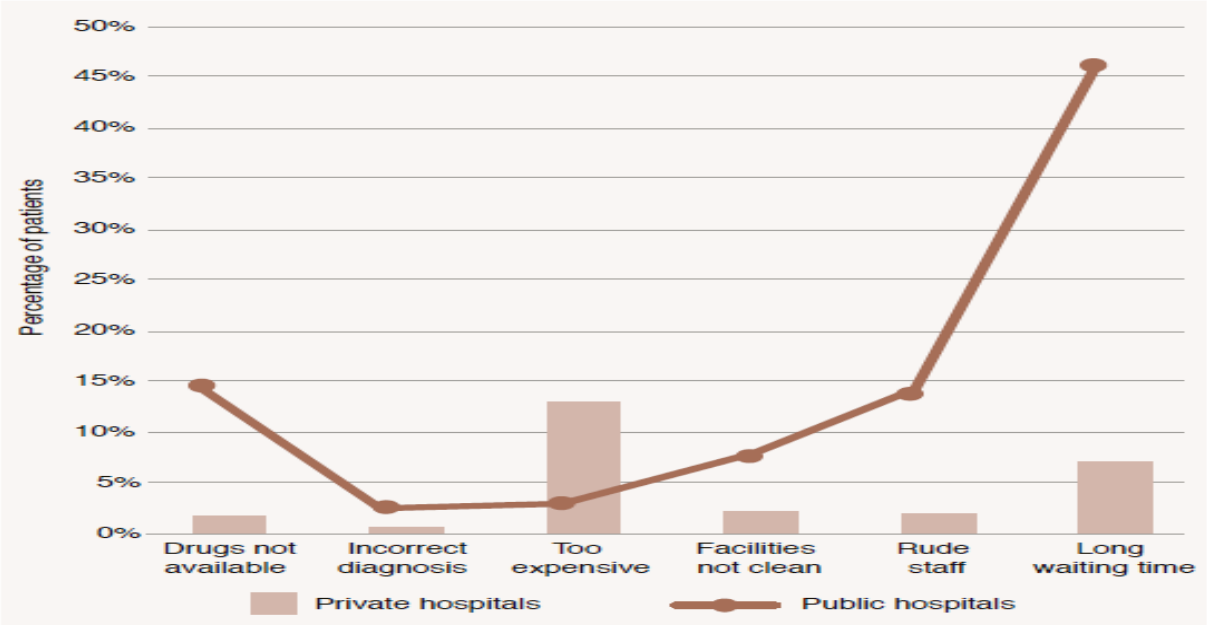
Travel time to a health facility for those with and without medical scheme coverage in South Africa, 2015



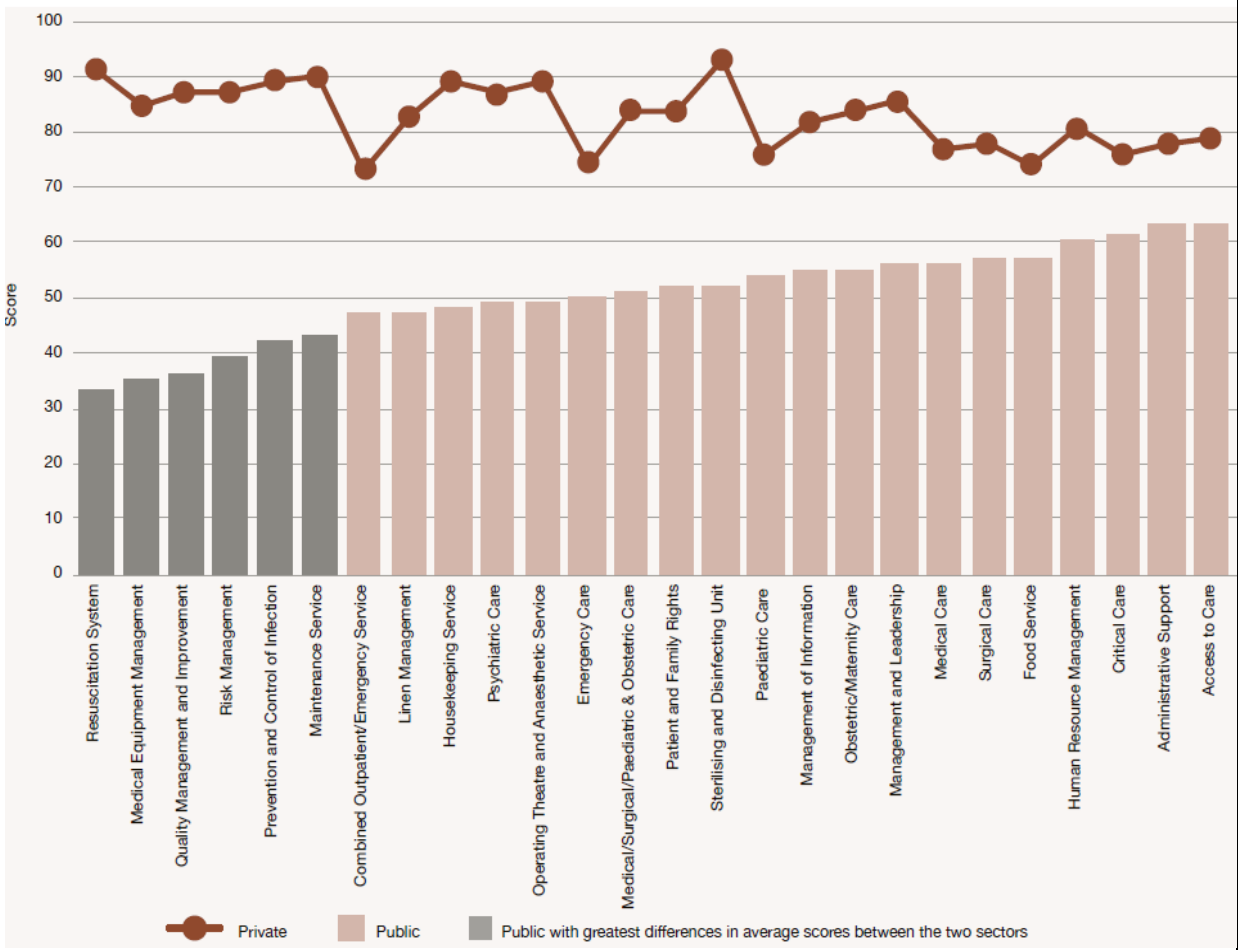
Likelihood of accessing a hospital for those with and without medical scheme coverage in South Africa, 2010–2013



Problems experienced by patients at public and private hospitals in South Africa, 2009–2010



Comparison of average service element scores for the public and private health sectors in South Africa, 2001–2014



Consequently, as many as 25.3% of uninsured households which should be accessing public sector services pay out-of-pocket for private sector healthcare services such as doctor consultations and/or hospital care.[229] Some individuals can afford to use a combination of both healthcare systems. According to Tlebere et al[223] it was found that women seeking maternal health services in South Africa appeared to initially present to a healthcare setting within the public sector, but if this did not resolve their health-related complaint then a private doctor, traditional healer, or both would be consulted.

This may be compounded by the fact that the private sector absorbs 70% of skilled healthcare professionals.[228] Landau and May, in their editorial titled "Diabetes care in South Africa: A tale of two sectors", compare the resource differences available to people attending the public and private sectors, and explain how the latter group is undoubtedly more acquainted with the latest of technologies, whilst the former have little to no access to the simplest of treatments.[230] In the same editorial the authors hypothesize that the 'where' of diabetes care has a powerful influence on patient outcomes.[230] People with DM are a high-risk population which requires frequent routine medical care. In the case of South Africans who are uninsured and have DM, access barriers to quality healthcare may be experienced in comparison to those with insurance, impacting negatively on their health and outcomes.

2.3.4 South African Process of Care and Outcomes

Diabetes Mellitus is a complex and chronic condition which requires lifelong management and interaction with a healthcare system. Failure to control risk factors through preventive care may lead to a host of diabetes-related complications. According to the IDF, an estimated 63 061 South Africans died from diabetes-related complications in 2012.[231] Preventive techniques include regular medical visits and simple processes such as periodic testing for HbA1c, blood pressure, lipids, microalbuminuria, and retinal/foot examinations. Yet, most patients do not receive optimal diabetes care. In a study across multiple countries including South Africa, it was shown that the fewest medical visits occurred in the United Arab Emirates and South Africa, in which 65% and 87% of patients with DM visited their healthcare providers ≤5 times each year.[203] In the same study, 76% of patients had HbA1c measurements performed, 45% had lipid parameters and 31% had microalbuminuria testing, whilst only 8% were tested for a combination of other tests including renal or hepatic function tests, urinalysis, eye examinations, thyroid function tests and electrocardiogram.[203] In an urban Johannesburg-based community health centre (CHC) study of 519 patients with T2DM, it was found that <60% of patients had their lipids tested, whilst only

68.8% had valid HbA1c measurements.[232] Perhaps monitoring and assessments are not always performed due to insufficient provider knowledge or dissemination of the DM guidelines, although in a previous study it was shown that guidelines were followed by 55% of South African practitioners compared with 4–7% of physicians in other countries.[112,203] Healthcare resource or budget constraints may also hinder testing or investigations. In a study conducted across 18 CHCs in Cape Town's public sector, it was reported that routine tests such as HbA1c were curbed from use in diabetes patients as they "would consume the centres' entire allocation for biochemical investigations".[233] Perhaps practitioners in Sub-Saharan Africa feel that the currently available tests and the target levels or cut-off points used to define DM may not be appropriate for non-Western populations.[160] On the other hand, even in settings where resources appear to be more abundant and patients generally have access to more screenings, routine testing is not always performed. The report from the Health Quality Assessment (HQA) organisation and the 2016 Annual Report of the South African Council for Medical Schemes (CMS) demonstrate that many private sector patients with DM who are enrolled in 'Disease Management Programmes' do not receive routine testing as per guideline recommendations (Table 2.1 and Table 2.2).[234,115] Patients with DM require frequent medical visits and examinations for preventive care, yet levels of routine checks remain sub-optimal, placing patients at increased risk of developing complications and/or poor clinical outcomes.

Table 2.1 Patients with diabetes mellitus accessing screening, treatment and services within the Private Sector Medical Schemes Environment (Only Medical Schemes Contracted to HQA)[234]

Description of Service	Patients Receiving Service (%)
HbA1c coverage for Diabetic patients (%)	51.6
Cholesterol related tests coverage for Diabetic patients (%)	47.3
Monitoring Nephropathy for Diabetic patients (%)	56.3
Ophthalmologist/optometrist coverage for Diabetic patients (%)	26.0
Podiatrist cover (%)	1.7
Statin coverage (%)	42.3

Table 2.2 Patients accessing Screening, Treatment and Services within the Private Sector Medical Schemes Environment (All Medical Schemes Registered under the CMS)[115]

Description of Service	Patients Receiving Service (%)
≥2 HbA1c testing in Diabetic patients (%)	25
Chronic medicine for Diabetic patients (%)	50
≥1 Creatinine testing in Diabetic patients (%)	47

2.3.5 South African Outcomes: Quality of Life in Diabetes

Diabetes is a complex disease associated with high morbidity and mortality.[109] As a consequence of unsatisfactory control, whether medical or even psychological, considerable long-term complications may arise which significantly impair or negatively affect a patient's quality of life. Increased risk of other chronic conditions and the effects of polypharmacy make DM consistently associated with a reduced HRQoL.[235] Hence, the prevention of progression of disease and complications in patients with DM has the potential to improve a patient's HRQoL. Additionally, measurement of HRQoL allows healthcare professionals to assess the impact of disease and implement intervention strategies targeted at risk factors commonly associated with DM.[210,211] Alongside conventional biomarkers in DM such as HbA1c, HRQoL has become an established marker of health outcomes.[236,237] In a descriptive study of 200 patients attending a major public sector hospital in Johannesburg, South Africa, HRQoL was measured using the Diabetes-39 (D-39) questionnaire and showed that raised HbA1c, concomitant hypertension and dyslipidemia all individually reduced a patient's HRQoL.[238] Similarly, in a South-African black urban population with T2DM (n=281), using multiple analyses of covariance which were controlled for gender, BMI, hypertension, arthritis and asthma, the 20-Item Short Form Health Survey (SF-20) tool was used across multiple health items (physical functioning, role functioning, social functioning, mental health, general health perception and pain) to ascertain the effects of blood glucose control on HRQoL.[239] It was found that satisfactory blood glucose control (defined as <10.0 mmol/l) was found to be associated with better physical functioning and mental health than patients with poor control.[239] Given the fact that fear of hypoglycaemia affects HRQoL, and hypertension and/or dyslipidemia are frequent bedfellows of DM, the above results mirror findings from other countries. The scarcity of HRQoL data available in South Africa does not detract from the fact that patients with DM are at high risk of developing complications which will affect their HRQoL. Hence, the combination of clinical parameters and HRQoL should be evaluated in order to achieve improved outcomes in patients with DM.

3. STUDY DETAILS

3.1 INTRODUCTION

In theory, the basic management of DM and its associated risk factors is regarded as being 'relatively simple' and low-cost.[160] However, diabetes-related complications require highly-skilled providers and high-cost specialised equipment.[160] Hence the prevention of DM-related complications is essential. Yet, many healthcare systems around the world are incapable of providing basic services, treatment and advice needed for patients with DM.[240] Consequently, countless patients with DM receive suboptimal diabetes care and face adverse health outcomes. In the 2017 Lancet Commission on Diabetes in Sub-Saharan Africa, diabetes care was found to be largely confined to hospital-based settings, which meant that many patients were not able to access basic services and follow-up care for reasons ranging from resource limitations in the facilities, to long travel distances for patients.[160] It was proposed that unless the effective prevention of complications is carried out through task-shifting of care i.e. from hospital experts to community health workers/non-clinical providers in the primary care system, compromised quality management of DM would likely follow.[160] In addition, the Commission investigated whether there would be value in modifying care plans from the usual 'targeted' approach (e.g. to a defined HbA1c target) to one that combines various risk factors and aims to reduce overall risk.[241] Being a LMIC, South Africa faces the spectrum of challenges identified in the Commission's report. Hence one of the objectives of the much publicised NHI plan for South Africa is to re-engineer primary healthcare facilities in order to improve timely access, promote health and prevent disease-related complications.[171] Under the NHI, only the more-complex patients would be managed at central hospitals. These academic hospitals would be under the control of the NDOH and would form the platform for the training of health workers and conducting research. The quality of healthcare in the public sector would need to be carefully and continuously evaluated, given the concerns raised in the past e.g. increased patient loads, high burden of disease, staff attitudes, waiting times, cleanliness, drug stock-outs, staff and patient safety, etc.[171] The private sector would also play a role within the NHI environment, although specifics are yet to be defined. However, in the interim, the private sector continues to provide services at a significantly higher cost in comparison with the public sector, and it is assumed that the quality and outcomes are commensurately better.

3.1.1 AIMS

This study set out to measure and compare the quality of diabetes care associated with T2DM management of patients attending a specialised public (Charlotte Maxeke Johannesburg Academic Hospital - CMJAH) or private (Centre for Diabetes and Endocrinology - CDE) healthcare facility within urban Johannesburg.

3.1.2 OBJECTIVES

The objectives of this study were to determine:

1. The demographics of patients with T2DM attending either the public or private sector facility.

2. The perceived barriers to access of diabetes-related healthcare in patients with T2DM attending either the public or private sector facility.

3. The processes of care associated with diabetes management that is provided to patients with T2DM attending either the public or private sector facility, using guideline-derived, evidence-based care processes.

4. The outcomes, including clinical outcomes and HRQoL attained by patients with T2DM attending the public or private sector facility, using guideline derived, evidence-based targets, and to explore how objectives 1-3 impact on these outcomes. Particular emphasis was placed on T2DM-related complications resulting from micro- and macrovascular disease, because these are ultimately key determinants of morbidity and mortality.

3.1.3 HYPOTHESIS

The quality of diabetes care in patients with T2DM attending CMJAH is inferior to that offered to patients attending the private sector's CDE.

3.2 RESEARCH DESIGN AND METHODS

This study was a retrospective, cross-sectional, quantitative audit and analysis which set out to measure and compare the quality of diabetes care associated with T2DM management of patients attending either a specialised public (CMJAH) or private (CDE) healthcare facility within urban Johannesburg. The major objectives of the study were to evaluate the demographics, the perceived barriers to access of diabetes-related healthcare, the processes of care associated with diabetes management and the clinical outcomes and HRQoL attained by patients with T2DM attending either the public or private sector facility.

3.2.1 Study Sites

The two sites chosen for this study were the CMJAH and CDE which, as per the objectives of this study, were representative of the public and private sectors, respectively. The sites are close to one other (2.48 km, Figure 3.1) within adjacent and affluent suburbs of Johannesburg, but show differences in resource availability (Table 3.1). Both the CMJAH and CDE offer diabetes management by specialist and sub-specialist physicians (i.e. endocrinologists) who utilize evidence-based guidelines as their framework in the management of patients with T2DM.

Figure 3.1 Distance between Charlotte Maxeke Johannesburg Academic Hospital vs. Centre for Diabetes and Endocrinology - Google Map©

3.2.1.1 Charlotte Maxeke Johannesburg Academic Hospital

Built in 1978 and officially opened in 1979, the CMJAH is a 1088 bed level 3 Provincial academic hospital offering in- and outpatient services to patients requiring medical, surgical, paediatric, obstetric and gynaecological, and psychiatric care. Through its association with the University of the Witwatersrand, the CMJAH is an academic hospital with facilities which cater for patient care, teaching, research, training of medical (general/specialist) and allied under- and postgraduate medical students. Being one of four central hospitals within the Gauteng Province, the CMJAH offers specialised care to the local community and especially to those in need of tertiary level care. Although considered a level 3 hospital, the CMJAH offers services at all levels of healthcare, i.e. primary, secondary, tertiary and quaternary. Outpatients with diabetes are treated at the CMJAH's Diabetes Clinic which operates only on Mondays and Thursdays, whilst other chronic conditions e.g. bone (osteoporosis), renal, thyroid and hypertension problems are treated on other weekdays. It is assumed that the majority of outpatients attending the CMJAH's Diabetes Clinic are cases which could not be comprehensively managed at local primary/secondary level facilities. Patients with diabetes who have severe disease-related complications or who have not adequately responded to treatment are usually referred to CMJAH by means of a detailed referral letter from their primary healthcare provider (non-specialist doctor or nurse). Patients receiving diabetes care at the CMJAH are managed for their risk factors using guideline-derived clinical protocols: hyperglycaemia (Appendix A), blood pressure (Appendix B) and cholesterol (Appendix C). In addition, as with all public sector facilities in South Africa, medications prescribed to patients at the CMJAH are based on the Essential Drug List (EDL) (Appendix D) and purchased via the State tender system which acquires medication at substantially lower cost than in the profit-driven private sector.

Figure 3.2 The Charlotte Maxeke Johannesburg Academic Hospital

3.2.1.2 Houghton Centre for Diabetes and Endocrinology

The CDE came into existence in 1994 as the first dedicated Diabetes Centre of Excellence in South Africa. Created by Endocrinologists, the idea behind the CDE was to offer specialised care through a multi-disciplinary programme and team which also included diabetes nurse educators, podiatrists, dieticians and biokineticists. Over time, private healthcare insurers began funding the CDE programme, which then became available to patients with private insurance (medical aid) throughout the country's 'franchised' network of collaborating accredited CDE centres. However, in this thesis the focus is on the CDE in Houghton, which is considered the 'head-office' of CDE as well as the centre with the most advanced and comprehensive facilities. The majority of patients attending the CDE are assumed to be patients who have been referred to the centre for specialist care. 'Down-referral' or 'back-referral' of patients may not always happen within the private sector. As such, many patients continue to be managed by Endocrinologists at Houghton CDE. For the purposes of this study, the CDE represents the most advanced and specialised facility available to patients with diabetes within the private sector, and therefore allows for comparison with the public sector's specialised clinic at the CMJAH (Table 3.1). It must also be stated that each study site follows slightly different clinical protocols and drug formularies. Patients at the CDE generally have access to a wider selection of treatments than are available to patients within the public sector, but this in turn may depend on the formulary determined by the patient's private medical scheme which might have independent 'disease management programmes' for diabetes-related complications such as hypertension, hyperlipidaemia, coronary artery and/or renal disease (Appendix E).[242]

Figure 3.3 Houghton Centre for Diabetes and Endocrinology

Table 3.1 Characteristics of the patients, providers and facilities at the Charlotte Maxeke Johannesburg Academic Hospital and Centre for Diabetes and Endocrinology

Clinic Characteristics	CMJAH	CDE
Patients		
Reminders to attend clinics	No	Yes
Regular communication on disease management	No	Yes
Diabetic camps/meetings	No	Yes
Additional case management if disease complicated	Yes	Yes
Providers		
Clinics per week	2 days/week	5 days/week
Annual doctor consultations	±200/week	±400/week
Staff by discipline at the clinic	2 Endocrinologists 2 Generalist Physicians 4 Medical Officers* 4 Nurse Educators 2 Dieticians 2 Podiatrists	6 Endocrinologists 2 Generalist Physicians 6 Nurse Educators 3 Dieticians 2 Podiatrists 5 Biokineticists 1 Clinical Psychologist
Continuing Medical Education offered to Staff	Doctors only	Doctors, Nurse Educators, Dieticians, Podiatrists
Facilities		
Structured referral system of patients	No	Yes
Incentives for staff to achieve certain targets	No	No
Electronic patient management system	No	Yes
Management care maps / protocols / guidelines	Yes	Yes
Checklists of tests, visits, examinations e.g. biochemical, eyes, feet etc	Yes	Yes
Formulary for management of diabetes	Yes (EDL)**	Individualised***
Formulary for management of hypertension	Yes (EDL)**	Individualised***
Formulary for management of hyperlipidaemia	Yes (EDL)**	Individualised***
24-hour emergency line	No	Yes
Outcome Assessments		
Glycaemic control	Yes	Yes
Blood pressure	Yes	Yes
Lipids	Yes	Yes
Microvascular complications	Yes	Yes
Macrovascular complications	Yes	Yes
Patient satisfaction surveys i.e. quality of care and quality of life	No	Yes

*Medical Officer refers to a Medical Practitioner completing mandatory community service; **EDL = Essential Drug List developed by the National Dept. of Health for use in the Public Sector; *** The CDE is not limited by any formulary and therefore follows "individualized best practice" although subject to the patient's private insurance cover (medical aid formulary).

3.3 STUDY POPULATION

3.3.1 Study Participants

Only patients ≥18 years of age with a documented diagnosis of T2DM treated at either the CMJAH/CDE for ≥1 year were included in the study. For the purposes of this study, T2DM was defined as per the 2012 Society of Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines that applied at the time of the study (Table 3.2).

Table 3.2 The Society of Endocrinology, Metabolism and Diabetes of South Africa (2012) Criteria for the Diagnosis of Diabetes[3]

Diagnostic test	Diabetes
Fasting plasma glucose (FPG)[1]	≥7.0 mmol/l
Two-hour plasma glucose (2-h PG) during oral glucose tolerance test (OGTT)[2]	≥11.1 mmol/l
Glycated haemoglobin A1c (HbA1c)[3]	≥6.5%
Random plasma glucose (RPG)[4]	≥11.1 mmol/l if classic symptoms of diabetes or hyperglycaemic crisis is present

1: "Fasting" is defined as no caloric intake for at least eight hours.

2: The test should be performed as described by World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in 250 ml water ingested over five minutes.

3: Provided that the test method meets stringent quality assurance criteria, that the assay is standardised according to criteria aligned with the international reference values [National Glycohemoglobin Standardization Program (NGSP) -certified and standardised to the Diabetes Control and Complications Trial (DCCT) assay], and that there are no conditions present which preclude its accurate measurement

4: "Random" (casual) is defined as any time of day, without regard to time of last meal. The classic symptoms of hyperglycaemia include polyuria, polydipsia and weight loss. "Hyperglycaemic crisis" refers to diabetic ketoacidosis or hyperosmolar nonketotic hyperglycaemia.

3.3.2 Exclusion Criteria

- Patients with any other form of diabetes.
- Women who were pregnant or breast feeding.

3.3.3 Sample Size

The measurement most commonly utilized in the outcome studies of patients who have T2DM is HbA1c. Therefore, the percentages of patients achieving HbA1c targets (<7%) from two published studies relevant to the population/s under review were utilized to calculate the sample size needed (50% for CDE and 25% for CMJAH).[126,243] The confidence level selected was 95%, with a significance level of 5% and power of 80%. Although the total sample size needed for the study was 188 patients (94 per site), a decision was taken to enrol ±50% more i.e. ±150 patients from each site in order to accommodate for drop-outs and missing data, and to enhance accuracy and validity of the results.

3.4 DATA COLLECTION

3.4.1 General Structure

Data collection at the two sites commenced once the necessary approvals were in place. Firstly, ethical clearance was obtained from the University's Human Research Ethics Committee (Appendix F). This was followed by a protocol submission to the University Research Office outlining the design of the study (Appendix G). Finally, a study site letter was presented to each study site's Director/CEO for approval (Appendix H).

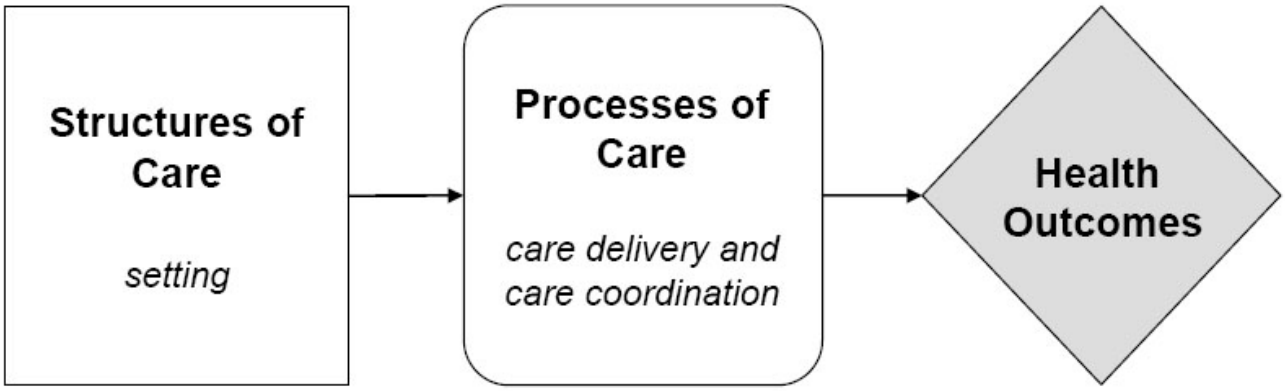
Data collection was conducted by quantitative means during the months of June to October 2016. Existing patients attending either CMJAH or CDE were enrolled. Data were collected through an interview process as shown in Appendix I. Additionally, medical information was collected retrospectively (the most recent information available) from each participant's clinical record using a case report form (CRF), (Appendix J). Some overlap of information was intentionally captured from the interview and the clinical records (Appendices I & J). This was done in order to cross-

check, match specific patient information, and ensure data consistency across the two methods used (interview and record review). For optimal accuracy and where possible, results from laboratory print-outs which were found within patient clinical records were captured into the CRFs. When laboratory print-outs were not available, the values or measurements from clinical notes in the patient records were captured into the CRFs. If data discrepancies existed, the participant was telephonically contacted in order to confirm the detail in question. The data from both the questionnaire and CRF (Appendices I & J) were transferred to a secure electronic database at the University of the Witwatersrand for safekeeping and analysis.

3.4.2 Donabedian framework

In order to evaluate differences in quality of care between the two sites, Donabedian's framework was adapted for the needs of this study. As discussed in Chapter 2 and according to the Donabedian framework, the quality of care of a health system is defined as the relationship between its structure, processes and outcomes. To study the structure, processes and outcomes of the site/patient, a patient questionnaire was developed (Appendix I). In addition, a validated quality of life tool was utilized in order to assess a primary outcome of the study – Health Related Quality of Life (Appendix I).

Figure 3.4 The Donabedian Conceptual Model of Relationships between Structures, Processes and Health Outcomes



3.4.2.1 Donabedian Structure Assessment

Essentially the quality of care within a health system will not only depend on where and how care is delivered, but also to whom it is delivered and how easily beneficiaries are able to access the care. As such, the first element of the study aimed to determine the characteristics of the populations at the two study sites, and their perceptions of barriers in the way of care for their diabetes. The information captured for each participant included the following:

- Demographics (age, gender, ethnicity)
- Anthropometrics (weight, height, waist circumference)
- Education level
- Marital status
- Employment status
- Medical aid status
- Duration of diabetes
- Medical history

In terms of the barriers which may have obstructed access to the necessary diabetes care from either the CMJAH or CDE, participants were asked if they were South African citizens/residents, were enrolled as members of a medical scheme (i.e. were covered by private medical insurance), the form of transportation (public/private) used, and the time it normally took to travel to the CMJAH/CDE. Purchasing of additional diabetes-related treatment (e.g. medication) or services (laboratory tests, consultations and consumables such as glucometers, glucose test strips) outside of the participant's regular clinic (CMJAH/CDE) was also assessed. Further barriers such as personal, work or financial constraints, or access to services/staff at CMJAH/CDE were adapted from the literature in order to assess patients attending the two sites (Appendix I).[244,245,246,247,248]

3.4.2.2 Donabedian Processes of Care

The second element in determining the quality of each healthcare system required an assessment of the processes of care at the two sites. The processes of care for this study were derived from guidelines - CDE's 'Minimum Care Guidelines' which were in fact based on the International Diabetes Federation (IDF) guidelines as well as the SEMDSA 2012 Diabetes Guidelines.[1,3] These guidelines were also used as a means to benchmark performance across the study sites. The

specific process measures which were captured included:

- The frequency of consultations each patient had received from healthcare professionals (doctors, nurses, dieticians, podiatrists, ophthalmologists, optometrists, biokineticists) for a period of 12 months.
- The frequency of specific laboratory tests (HbA1c, lipid profile, renal function, full blood count) performed for each patient for a period of 12 months. For the purposes of this study, a renal function test will be counted as any of the following: microalbuminuria, GFR, creatinine, albumin:creatinine ratio.
- The medications prescribed: treatment for glycaemic control (oral and insulin), antihypertensive agents (ARBs, ACE-Inhibitors, CCBs, diuretics, β-blockers), lipid-lowering agents ('statins'), thyroid and antiplatelet drugs.

3.4.2.3 Donabedian Outcomes

The final element of the Donabedian quality of care assessments entailed a review of each participant's clinical and biochemical outcomes (using clinical records) as well as assessing health related quality of life (HRQoL). The HRQoL was assessed using a validated questionnaire known as the EQ-5D-5L (Appendix I). The EQ stands for EuroQoL (developers of the questionnaire), whilst 5-D and 5-L refers to the 5 dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression) and 5 levels (no problems, slight problems, moderate problems, severe problems and extreme problems) of the tool, respectively. Results are calculated using the EQ-5D-5L tool which utilizes one of a number of validated country-specific datasets. Only the following countries had a validated dataset available at the time of the study: Denmark, France, Germany, Japan, Netherlands, Spain, Thailand, UK, US and Zimbabwe. For countries which did not have a validated dataset available, as in the case of South Africa, the developers of EuroQoL in consultation with the researcher advised that the default UK dataset be used when calculating the outcomes from the data collected (Appendix K). As such it should be noted that permission from the EuroQoL group was obtained prior to the EQ-5D-5L tool being utilized for this study (Appendix L). Given that the participants in this study were derived from clinics in the more-affluent Johannesburg Metropolitan region, the UK dataset appeared to be appropriate for subjects who were likely to be literate and with whom communication would not be a problem.

3.4.3 Clinical Outcomes

The fact that the two settings for this study are referral centres immediately suggests that a more-complicated category of patient would be managed at these sites. It was therefore expected that some of the patients being treated at the study sites would present with diabetes-related complications. Hence, for the purposes of the study, participants receiving antihypertensive treatment were classified as hypertensive. Microvascular disease included any of the following conditions: retinopathy (including blindness), neuropathy (including amputation) and nephropathy (including chronic kidney disease, chronic renal disease and chronic renal failure). Macrovascular disease consisted of cardiovascular and/or cerebrovascular disease or equivalent: angina, myocardial infarction, ischaemic heart disease, coronary artery disease, peripheral vascular disease, stroke, transient ischaemic attack, and also cardiovascular related procedures (stent, coronary artery bypass grafts).

In this element of the study, control of HbA1c and blood pressure were also recorded in the process of determining outcomes and the presence of vascular disease (both micro- and macrovascular) was assessed. Using forms shown in Appendix I and J, the following data were captured from participants within each setting:

- The occurrence of microvascular complications such as retinopathy, neuropathy and nephropathy as defined above.
- The occurrence of macrovascular complications such as pre-existing cardiovascular disease, cardiovascular intervention(s) and cerebrovascular disease as defined above.
- The latest blood pressure measurements (systolic and diastolic).
- The latest laboratory measurements (HbA1c, total cholesterol (TC), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C) and triglycerides (TG)).
- The occurrence of any other diabetes-related complications, procedures or hospitalisations.

Laboratory measurements were obtained from the clinical records, however, it was beyond the scope of this thesis to confirm whether the correct techniques were employed in order to obtain the above measurements. Rather, it was assumed that the best practices in phlebotomy were followed by nurses or laboratory staff when drawing blood in study participants in order to minimize the risk of contamination or erroneous laboratory test results. Similarly, standardized techniques and use of the correct brachial cuff size were assumed to have been followed by the

nurses or doctors who measured blood pressure in study participants (using appropriate guidelines).[249] Finally, compliance with overnight fasting was also assumed to have occurred in participants who had their blood drawn for laboratory testing of HbA1c, lipids etc.

Efforts were made to capture all of each participant's data. In the event of missing data, datasets were analysed for each site to assess whether missingness was inherent to a particular group or subgroup or was missing completely at random. Using appropriate statistical tests, factors with missing data were compared (in terms of differences between those with the missing data vs. those without missing data). If the p-value was found to be not statistically significant ($p>0.05$), then the missing data was assumed to be missing completely at random. Appendix P provides detail of frequency of missing data for key variables.

The attainment of diabetes treatment goals for critical modifiable risk factors such as HbA1c and blood pressure using national guidelines (SEMDSA 2012 - the latest guidelines at the time of this study) were compared in each setting (CMJAH vs. CDE). Achievement of targets was determined by applying the following targets to the data collected from clinic records:

- Systolic Blood Pressure (SBP) <140 mmHg
- Diastolic Blood Pressure (DBP) <80 mmHg
- HbA1c <7%
- TC <4.5 mmol/l
- LDL-C <2.5 mmol/l
- HDL-C >1.0 mmol/l (men), HDL-C >1.2 mmol/l (women)
- TG <1.7 mmol/l

3.5 STUDY CONDUCT

Participants were consecutively chosen from the list of scheduled appointments provided by the administration office at the two study sites. Patients were approached in the waiting area and provided with an overview of the study using a patient information sheet (Appendix M). If the patient was willing to participate, a voluntary consent form was signed (Appendix N). The consent obtained from the study participants provided the necessary permission for both the interview process and for access to clinical records. Once participants were enrolled, an interview was conducted. To ensure privacy and confidentiality, the interview took place in a private area within the clinic/hospital. This was followed by data collection of medical information using the

participant's clinical record. All study participants enrolled into the study had physical clinical records which included all medical history (including notes from doctors/other healthcare professionals), the pharmacological treatment prescribed and laboratory-issued reports. Only the latest data were captured from the clinical records and no clinical records were removed from the study sites by the clinic staff, study participant or researcher. The participant's clinical records were stored in filing cabinets which were maintained by each clinic's administration staff who would assist the researcher in obtaining the records during the data collection period. All interviews and data collection were carried out by the researcher without the assistance of staff at the two sites or research assistants as per Table 3.3.

3.5.1 Data Sources for Results:

Table 3.3 Data sources of specific inputs needed to determine the differences of study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	Data Source: Appendix I	Data Source: Appendix J	Data Source: Appendix I & J
Age, Gender, Duration of Diabetes			X
Weight		X	
Ethnicity			X
Education	X		
Marital, Employment Status	X		
South African Citizenship	X		
Transportation, Travel Times	X		
Medical Insurance	X		
Patient-reported Access Barriers	X		
Annual Healthcare Professional Visits			X
Annual Tests Performed			X
Medications		X	
Complications			X
Blood Pressure, Glycated Haemoglobin		X	
Cholesterol (TC, LDL-C, HDL-C, TG)		X	
Health Related Quality of Life	X		

3.6 STATISTICAL TESTS AND DATA ANALYSIS

Following the 5-month data collection period, descriptive analysis was carried out for age, duration of diabetes, weight and height of participants at each study site. The percentage distribution of gender, race, education, marital status and employment status was determined and compared for the two study sites. Complications (microvascular and macrovascular) in participants were

reported by means of frequency tabulations. Frequency tables of patient usage of chronic medication for the treatment of hyperglycaemia, hypertension and lipids as well as those receiving antiplatelet treatment were also produced. The percentage of patients reaching SEMDSA treatment goals for various clinical parameters was calculated. Where appropriate, the student t-tests (continuous data) or chi-square test (categorical data) were used to investigate associations between variables of interest and outcome measures. Means were expressed as mean ± SD. Tests were two-tailed and a significance level of 5% was used for the analysis. Non-parametric data were expressed as median and range, and were compared by means of the Mann-Whitney U test. Of particular importance in the study was the identification of outcome differences that were related to patient characteristics within each site, and exploration of these in relation to processes of care within the sites. The final step of analysis involved multivariate logistic regression analysis, first through exploration of associations using univariate analysis for defined outcomes, followed by entry of significant independent variables into a multiple logistic model that would identify which factor/s were significantly associated with the outcomes of particular interest, specifically HRQoL and the complications of micro- and macrovascular disease. Data were entered and managed using Microsoft Office Excel 2010 (Microsoft, Redmond, WA, USA), whilst statistical analysis was conducted by means of STATISTICA version 13.2 (TIBCO Software Inc., Palo Alto, CA, USA).

3.7 ETHICAL CONSIDERATIONS

As described in 3.3.1 above, ethical clearance was applied for and obtained from the University's Human Research Ethics Committee (certificate clearance: M150140), and permission to perform the study was obtained from each study site (Appendix F). Once approval was received, the collection of data was commenced.

4. RESULTS

4.1 Demographics

4.1.1 Age, Gender, Duration of Diabetes and Weight

The study population consisted of a sample of 290 adults ≥18 years with T2DM. There were 144 patients enrolled from the CMJAH diabetes clinic and 146 from the Houghton CDE. Data were collected by means of interview and clinical records from each patient between July and November 2016. The CMJAH group was younger than the CDE group (58.6 ± 10.9 vs. 63.2 ± 12.2 years; p<0.001). Ages of the CMJAH group ranged from 28 - 84 years vs. CDE's 29 – 92 years. Females made up two-thirds of the CMJAH group vs. less than half of the CDE group (66.0% vs. 46.6%; p<0.001). The mean duration of self-reported diabetes was similar across settings (CMJAH 12.4 ± 8.3 vs. CDE 11.6 ± 7.6 years; p=0.41). Weights were similar across the settings; Body Mass Index could not be assessed because height was not recorded for many patients, but predominantly at CMJAH. Please refer to Appendix P for missing data.

Table 4.1 Demographic differences between study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values
Age (years)	58.6 ± 10.9	63.2 ± 12.2	p<0.001
Females, n (%)	95 (66.0)	68 (46.6)	p<0.001
Duration of Diabetes (years)	11.0 (1-47)	10.0 (1-48)	NS
Weight (kg)	88.7 ± 21.1	89.6 ± 21.8	NS

4.1.2 Ethnicity

As historically categorised in South Africa, there were four ethnic groups represented in the study: Black African, Caucasian, Indian/Asian and Mixed-Ancestry. The largest group at CMJAH was Black African (63.9%) whilst at the CDE, Caucasians made up the majority (63.0%). Mixed-Ancestry patients were least represented at both CMJAH (6.3%) and CDE (4.1%).

Overall percentages of T2DM participants by ethnicity were Black African 38.3%; Caucasian 37.6%; Indian/Asian 19.0%; Mixed-Ancestry 5.2%, while within the two study sites the ethnic distributions give some indication of the populations served by the public and private sectors respectively (see Chapter 1).

Table 4.2 Ethnic differences between study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values (pairs)	p-values (group)
Black African, n (%)	92 (63.9)	19 (13.0)	p<0.0001	p<0.0001
Caucasian, n (%)	17 (11.8)	92 (63.0)	p<0.0001	
Indian/Asian, n (%)	26 (18.1)	29 (19.9)	NS	
Mixed-Ancestry, n (%)	9 (6.3)	6 (4.1)	NS	

4.1.3 Education

The self-reported highest level of education at CMJAH and CDE are shown in Table 4.3. Significantly more patients attending the CMJAH reported secondary education as their highest level vs. CDE (59.9% vs. 38.6%; p<0.001), while more CDE patients reported a tertiary education vs. CMJAH patients (57.9% vs. 11.3%; p<0.001).

Table 4.3 Highest education level of study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values (pairs)	p-values (group)
None, n (%)	12 (8.5)	3 (2.1)	p<0.05	p<0.0001
Primary, n (%)	29 (20.4)	2 (1.4)	p<0.0001	
Secondary, n (%)	85 (59.9)	56 (38.6)	p<0.001	
Tertiary, n (%)	16 (11.3)	84 (57.9)	p<0.0001	

4.1.4 Marital Status

The marital status of patients enrolled into the study is presented in Table 4.4. Married patients were in the majority at both sites but more CDE participants were married vs. those at CMJAH (67.8% vs. 47.9%; p<0.0001). It should be noted that the Single category includes a number of unmarried subjects in stable, long-term relationships.

Table 4.4 Marital status differences of study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values (pairs)	p-values (group)
Single, n (%)	29 (20.7)	16 (11.0)	p<0.05	p<0.001
Married, n (%)	67 (47.9)	99 (67.8)	p<0.0001	
Divorced, n (%)	11 (7.9)	9 (6.2)	NS	
Widowed, n (%)	33 (23.6)	22 (15.1)	NS	

4.1.5 Employment Status

The employment status of patients attending CMJAH and CDE can be found in Table 4.5. Significantly more patients attending CDE were employed vs. those attending CMJAH (54.1% vs. 39.4%; p<0.01). Similar numbers were retired (32.4% CMJAH vs. 35.6% CDE). Although not reported in the Table, the mean age of retirement by site was 66.3 vs. 73.2 years for patients attending the CMJAH and CDE respectively (p<0.01).

Table 4.5 Employment status differences of study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values (pairs)	p-values (group)
Unemployed, n (%)	40 (28.2)	15 (10.3)	p<0.001	
Employed, n (%)	56 (39.4)	79 (54.1)	p<0.01	p<0.01
Retired, n (%)	46 (32.4)	52 (35.6)	NS	

4.2 Access

Issues of access to care are detailed in the text and tables below.

Table 4.6 Access differences of study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values
Citizenship/Residence			
'ID Document'*, n (%)	138 (95.8)	143 (97.9)	NS
Transportation			
Public, n (%)	88 (62.4)	1 (0.7)	p<0.0001
Private, n (%)	53 (37.6)	145 (99.3)	p<0.0001
Travel Time			
<30minutes, n (%)	49 (34.3)	92 (66.2)	p<0.0001
>30minutes, n (%)	94 (65.7)	47 (33.8)	p<0.0001
Medical Aid			
Medical Insurance, n (%)	9 (6.3)	145 (99.3)	p<0.0001

***National Identification Document for Citizens and Permanent Resident Status for non-South Africans**

4.2.1 South African Citizenship/Residence Status

Since lack of a South African identification document of citizenship or permanent residence is reported by some as being a barrier to access to clinical services, particularly in the public sector (CMJAH: personal communication), it is important to record possession of such a document. Almost all patients attending the two sites had such documentation (95.8% CMJAH vs. 97.9% CDE).

4.2.2 Transportation

More study patients at CDE reported having private means of transport vs. CMJAH patients (99.3% vs. 37.6%; p<0.0001). In contrast, more patients attending CMJAH made use of public transport (62.4% vs. 0.7%; p<0.0001). Of the 88 CMJAH patients who travelled by means of public transportation to the hospital, 74 (84.1%) utilized minibus taxis whilst 14 (15.9%) used regular buses. In contrast, only 1 CDE patient utilized minibus taxis and none used regular bus. All 53 (100.0%) of the CMJAH patients with access to private transportation utilized their own car to get to the hospital whilst 142 (97.9%) and 3 (2.1%) of CDE patients utilized their own car and metered cabs, respectively.

4.2.3 Travel Times

The self-reported travel times from home to clinic can be found in Table 4.6. Only one-third of CMJAH study patients travelled fewer than 30 minutes in order to reach the clinic vs. two-thirds of CDE patients (34.3% vs. 66.2%; $p<0.0001$).

4.2.4 Medical Insurance

Study patients were questioned regarding membership of a medical aid scheme (i.e. private medical insurance cover). Almost all study patients attending CDE had private cover (99.3%) vs. only 6.3% of CMJAH patients ($p<0.0001$).

4.2.5 Specific Patient-reported Access Barriers

Barriers encountered by patients attending CMJAH or CDE were recorded at interviews (Appendix I). Overall, CMJAH patients encountered more access barriers than those attending CDE: median 1.0 (range: 0–9) vs median 0 (range: 0–5), $p<0.00001$. Of the 13 barriers considered, two fell into a personal category (e.g. had more important things to take care of), three fell into the financial category (e.g. high transport costs), and eight indicated difficulty in accessing the facility itself (e.g. could not take time off work) or in accessing services within the facility (e.g. long waiting times).

4.2.6 Comments on Demographics and Access

In summary, the results present a picture of a CDE group that appears to be advantaged in terms of socioeconomic status, education and access to employment and clinical services. In contrast, the CMJAH group appears to be socioeconomically and educationally disadvantaged, encountering a broad range of barriers that may impede access to care and impact on outcome.

4.3 Processes of Care

4.3.1 Frequency of Annual Healthcare Professional Visits

Table 4.7 shows the recorded frequency of visits by patients attending CMJAH and CDE. At both sites the most frequently consulted healthcare professionals were the doctors, and the sites had similar annual rates. More nurse consultations per year were recorded at CMJAH than at CDE.

Table 4.7 The median and range differences in frequency of annual healthcare professional visits in study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values
Doctor	3.0 (0-8)	3.0 (0-12)	p<0.05
Nurse	3.0 (0-8)	0 (0-4)	p<0.001
Dietician	0 (0-4)	1.0 (0-6)	p<0.001
Podiatrist	0 (0-3)	1.0 (0-10)	p<0.001
Ophthalmologist	0 (0-4)	0 (0-2)	NS
Optometrist	0 (0-4)	0 (0-2)	NS
Biokineticist	0	0 (0-14)	p<0.001

4.3.2 Frequency of Annual Tests Performed

Table 4.8 shows the frequency of laboratory tests that were performed in patients attending CMJAH and CDE. The median frequency of HbA1c was tested per patient per year and showed that more patients at CMJAH were tested for HbA1c. In contrast, more CDE patients had their blood lipid levels and renal function tested per year. HbA1c testing per year occurred more frequently than other tests at both settings. This is not surprising as it is the primary monitor of diabetes management and control.

Table 4.8 The median and range differences in frequency of annual tests performed in study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values
HbA1c	3.0 (0-5)	2.0 (0-6)	NS
Lipid Profile	1.0 (0-4)	2.0 (0-4)	p<0.001
Renal	1.0 (0-4)	2.0 (0-5)	p<0.001

4.3.3 Medications

The treatment for glycaemic control or agents prescribed for patients attending CMJAH and CDE are shown in Table 4.9 and Table 4.10. No patients attending CMJAH were recorded as using dietary modification alone as a means of lowering HbA1c vs. 7 CDE patients. A combination of insulin and oral hypoglycaemic agents was used at both sites, although larger numbers of patients using this combination were seen at CMJAH (63.2% vs. 34.2%; p<0.0001). More use of biguanide was seen at CMJAH (88.2% vs. 70.5%; p<0.001), whilst sulphonylureas were prescribed to a greater extent at CDE (29.5% vs. 16.0%; p<0.01) (Table 4.10).

Table 4.9 The % of patients using treatment for glycaemic control at Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values (pairs)	p-values (group)
Diet only, n (%)	-	7 (4.8)	p<0.05	
1 oral, no insulin, n (%)	22 (15.3)	43 (29.5)	p<0.01	
≥2 oral, no insulin, n (%)	22 (15.3)	27 (18.5)	NS	
Insulin, n (%)	15 (10.4)	23 (15.8)	NS	p<0.0001
Combination–Orals/ Insulin, n (%)	91 (63.2)	50 (34.2)	p<0.0001	

Table 4.10 The percentage of patients using treatment for glycaemic control at Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values (pairs)
Orals			
Biguanides, n (%)	127 (88.2)	103 (70.5)	p<0.001
Sulphonylureas, n (%)	23 (16.0)	43 (29.5)	p<0.01
Thiazolidinediones, n (%)	-	2 (1.4)	-
***DPP-4 inhibitors, n (%)**	4 (2.8)	17 (11.6)	p<0.05
Injectables			
****GLP-1 agonists, n (%)**	2 (1.4)	6 (4.1)	NS
Human insulin, n (%)	106 (73.6)	16 (11.0)	p<0.0001
Human insulin analogue, n (%)	-	55 (37.7)	-
Analogue + non-analogue, n (%)	-	2 (1.4)	-

*Dipeptidyl peptidase; ** Glucagon-like peptide

The numbers of hypertensive patients and antihypertensive agents prescribed at CMJAH and CDE are presented in Table 4.11. Overall, more patients at CMJAH were hypertensive in comparison with those at CDE (79.2% vs. 56.2%; p<0.0001). The medications used for blood pressure control differ substantially between the two sites.

Table 4.11 The percentage of hypertensive patients and those using antihypertensives at Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values (pairs)
Median Use of Antihypertensives, n (%)	2 (0-5)	1 (0-4)	p<0.01
Frequency of patients on the following number of agents			
1	21 (18.4)	28 (34.1)	p<0.05
2	43 (37.7)	40 (48.8)	p<0.05
3	36 (31.6)	12 (14.6)	NS
≥4	14 (12.3)	2 (2.4)	NS
ARB, n (%)	11 (9.6)	46 (56.1)	p<0.0001
ACE-inhibitors, n (%)	65 (57.0)	11 (13.4)	p<0.0001
Calcium Channel Blockers, n (%)	75 (65.8)	20 (24.4)	p<0.0001
Diuretics, n (%)	73 (64.0)	37 (45.1)	p<0.0001
B-Blockers, n (%)	7 (6.1)	17 (20.7)	**p=0.053**

ARB = Angiotensin Receptor Blockers; ACE = Angiotensin Converting Enzyme; CCBs = Calcium Channel Blockers

In Table 4.12 the frequencies of lipid, anti-platelet and thyroid treatments are presented for patients attending CMJAH and CDE. In terms of lipid-lowering therapy (i.e. statins), significantly more patients attending CMJAH were treated with this class of drug (81.3% vs. 52.7%; p<0.0001). Almost one-fifth of patients attending CMJAH were prescribed antiplatelet therapy vs. one-third at CDE (18.8% vs. 34.9%; p<0.01).

Table 4.12 The differences in pharmacological treatments in study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values (pairs)
Statins, n (%)	117 (81.3)	77 (52.7)	p<0.0001
Simvastatin	80 (55.6)	32 (21.9)	P<0.01
Atorvastatin	37 (25.7)	35 (24.0)	NS
Rosuvastatin	-	9 (6.2)	-
Pravastatin	-	1 (0.7)	-
***Cholesterol absorption inhibitor**	-	5 (3.4)	-
Fibrates	-	1 (0.7)	-
Antiplatelet, n (%)	27 (18.8)	51 (34.9)	p<0.01
Thyroid, n (%)	16 (11.1)	18 (12.3)	NS

*Ezetimibe

4.3.4 Comments on Processes of Care

Significantly more patients at CMJAH made use of nurses as clinical educators and 'case managers' while at CDE there was greater access to dieticians and to podiatrists for care of specific problems. Frequency of consultations with other healthcare providers was low at both sites. Frequency of blood tests differed between sites. Management of blood sugar and hypertension involved different pharmacological approaches at the two sites.

4.4 Outcomes

4.4.1 Complications

Overall, no statistically significant differences in complication rates (i.e. micro- or macrovascular disease) could be found between patients attending CMJAH and CDE. Rates of strokes and/or transient ischaemic attacks were low at both sites (Table 4.13).

Table 4.13 Complication differences in study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values (pairs)	p-values (group)
Cardiovascular Disease, n (%)	23 (16.0)	23 (15.8)	NS	
Stroke or TIA, n (%)	4 (2.8)	3 (2.1)	NS	
Retinopathy, n (%)	20 (13.9)	27 (18.5)	NS	NS
Neuropathy, n (%)	17 (11.8)	26 (17.8)	NS	
Nephropathy, n (%)	14 (9.7)	13 (8.9)	NS	

TIA = Transient Ischaemic Attack

4.4.2 Blood Pressure

Rates of hypertension differed significantly between CMJAH and CDE (79.2% vs. 56.2%; p<0.0001). Overall, more patients attending CDE were normotensive than those attending CMJAH. Table 4.14 shows that the systolic blood pressure target of <140mm Hg was achieved by 78.7% of patients attending CDE vs. 51.7% of CMJAH patients (p<0.0001). In contrast, diastolic blood pressure (<80 mm Hg) was achieved by more patients attending CMJAH (57.3% vs. 43.0%; p<0.05).

Table 4.14 Blood pressure outcome differences of study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values (pairs)
Systolic Blood Pressure, n (%)*	74 (51.7)	107 (78.7)	p<0.0001
Diastolic Blood Pressure, n (%) **	82 (57.3)	58 (43.0)	p<0.05
Pulse Pressure (mmHg)	64 (20.4)	51 (12.3)	p<0.0001

***(<140mm Hg); ** (<80mmHg)**

4.4.3 Biochemical Outcomes

Table 4.15 shows that HbA1c targets (<7%) were achieved more frequently at the CDE vs. CMJAH (HbA1c 45.5% vs. 27.3%; p<0.01). Statistically significant differences were found for triglycerides across the two settings, but not for total cholesterol. Details of other lipid outcomes i.e. LDL-C and HDL-C are provided in Appendix O.

Table 4.15 Biochemical outcome differences of study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH	CDE	p-values (pairs)
HbA1c (<7%), n (%)	38 (27.3)	66 (45.5)	p<0.01
Triglycerides (<1.7 mmol/l), n (%)	52 (57.1)	48 (42.5)	P<0.05
Total Cholesterol (<4.5 mmol/l), n (%)	58 (61.7)	76 (63.3)	NS

Denominator may vary for % calculations

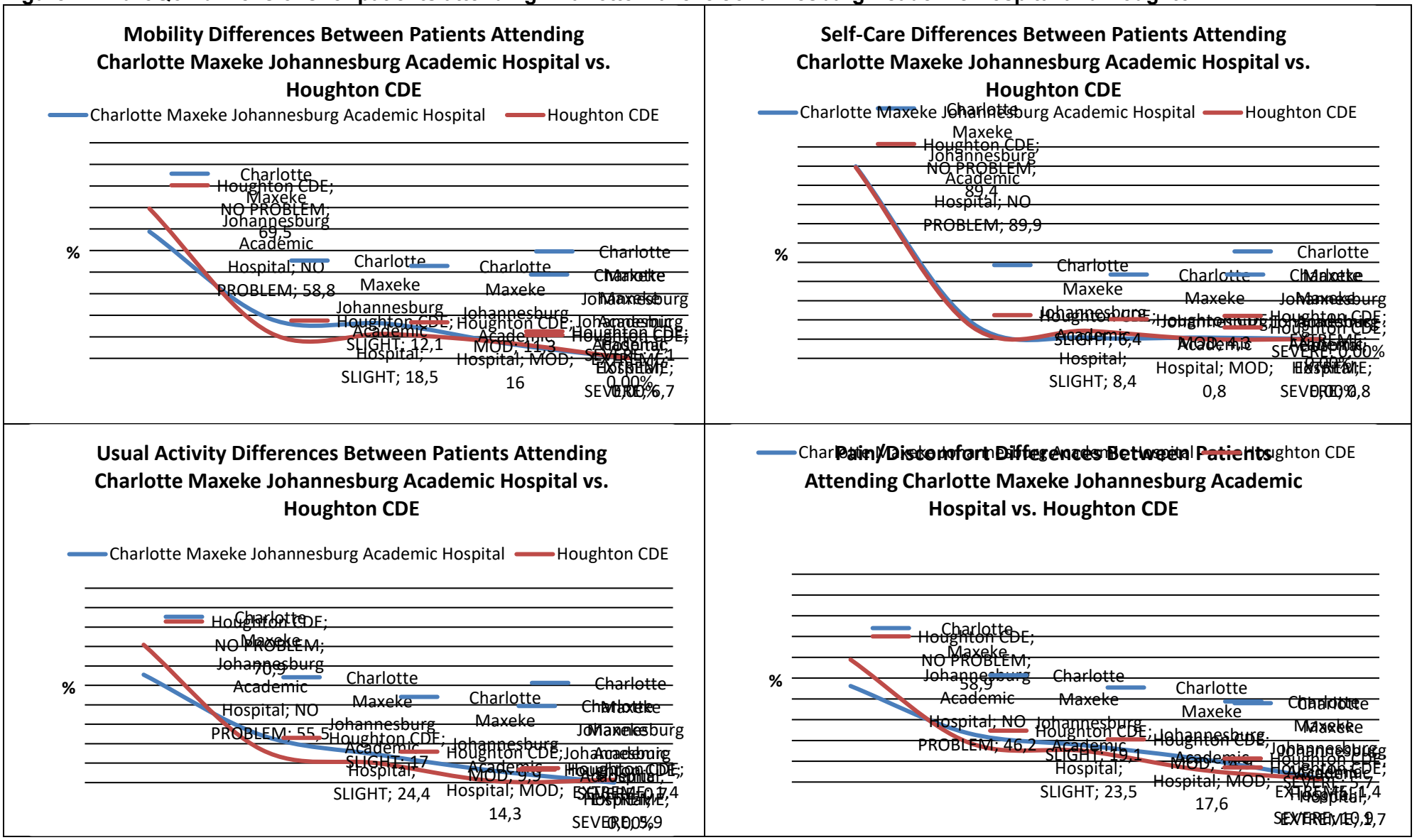
4.4.4 Health Related Quality Of Life

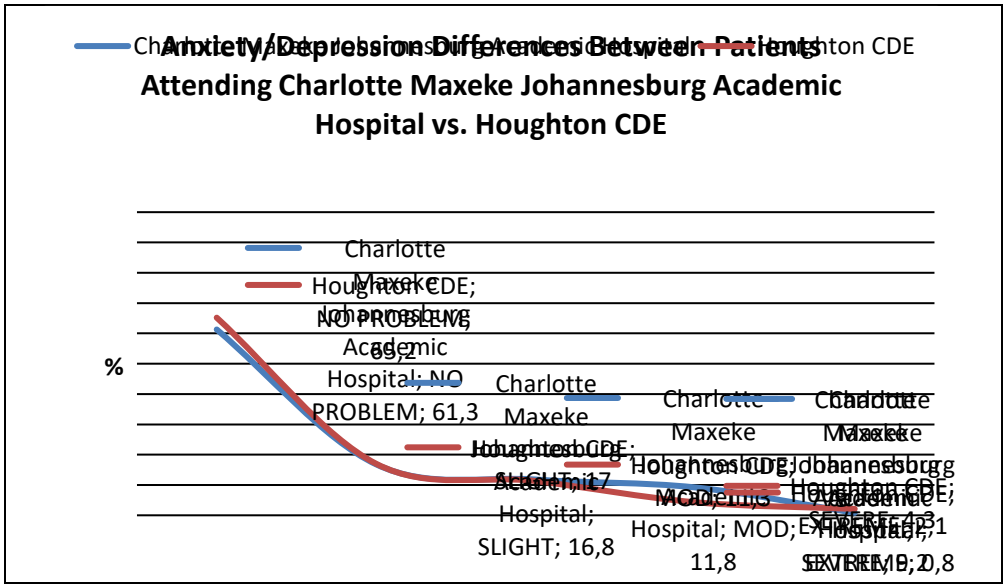
Each participant was interviewed for impact of diabetes in 5 health-related quality of life dimensions, with impact scored from 1 - 5 using the EuroQoL tool (EQ-5D-5L). The 5 dimensions include: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Levels within each dimension from 1 - 5 are: no problems, slight problems, moderate problems, severe problems and unable to perform the function. The dimension scores are converted into an overall HRQoL score for each subject and individual scores are combined into a mean score for each site. Composite results for CMJAH and CDE are shown in Table 4.16. More patients within the CDE completed the EQ-5D-5L vs. CMJAH patients (98.6% vs. 87.5%). Frequency analysis demonstrated that the sites were similar, although 'usual activities' had a p-value of 0.06. Figure 4.1 shows that diabetes impacted similarly on CMJAH and CDE participants. Patients at both sites reported to have had the least amount of problems with 'Self-Care' (CMJAH 89.9% and CDE 89.4%) in comparison with the rest of the 5 dimensions. Pain/discomfort problems at the various levels were encountered slightly more frequently than other problems at both sites. When comparing the five dimensions in terms of patients with no problems or ≥1 problem across the two study sites, two dimensions viz. usual activities and pain/discomfort were found to be significantly different between the sites ($p<0.05$). Overall, HRQoL scores were not statistically different between the two sites (CMJAH 0.75 ± 0.22 vs. CDE 0.80 ± 0.23; $p=0.06$).

Table 4.16 Differences in study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

EuroQoL Dimensions n (%)	CMJAH	CDE	p-values (group)
MOBILITY			
I have no problems in walking about	70 (58.8)	98 (69.5)	
I have slight problems in walking about	22 (18.5)	17 (12.1)	
I have moderate problems in walking about	19 (16.0)	16 (11.3)	NS
I have severe problems in walking about	8 (6.7)	10 (7.1)	
I am unable to walk about	0.0	0.0	
SELF-CARE			
I have no problems washing or dressing myself	107 (89.9)	126 (89.4)	
I have slight problems washing or dressing myself	10 (8.4)	9 (6.4)	
I have moderate problems washing or dressing myself	1 (0.8)	6(4.3)	NS
I have severe problems washing or dressing myself	1 (0.8)	0.0	
I am unable to wash or dress myself	0.0	0.0	
USUAL ACTIVITIES			
I have no problems doing my usual activities	66 (55.5)	100 (70.9)	
I have slight problems doing my usual activities	29 (24.4)	24 (17.0)	
I have moderate problems doing my usual activities	17 (14.3)	14 (9.9)	NS (p=0.06)
I have severe problems doing my usual activities	7 (5.9)	1 (0.7)	
I am unable to do my usual activities	0.0	2 (1.4)	
PAIN / DISCOMFORT			
I have no pain or discomfort	55 (46.2)	83 (58.9)	
I have slight pain or discomfort	28 (23.5)	27 (19.1)	
I have moderate pain or discomfort	21 (17.6)	21 (14.9)	NS
I have severe pain or discomfort	13 (10.9)	8 (5.7)	
I have extreme pain or discomfort	2 (1.7)	2 (1.4)	
ANXIETY / DEPRESSION			
I am not anxious or depressed	73 (61.3)	92 (65.2)	
I am slightly anxious or depressed	20 (16.8)	24 (17.0)	
I am moderately anxious or depressed	14 (11.8)	16 (11.3)	NS
I am severely anxious or depressed	11 (9.2)	6 (4.3)	
I am extremely anxious or depressed	1 (0.8)	3 (2.1)	

Figure 4.1 EuroQoL dimensions for patients attending Charlotte Maxeke Johannesburg Academic Hospital and Houghton CDE




Anxiety/Depression Differences Between Patients Attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE
%
Charlotte Maxeke Johannesburg Academic Hospital; NO PROBLEM; 61,3
Houghton CDE; NO PROBLEM; 65,2
Charlotte Maxeke Johannesburg Academic Hospital; SLIGHT; 16,8
Houghton CDE; SLIGHT; 17
Charlotte Maxeke Johannesburg Academic Hospital; MOD; 11,8
Houghton CDE; MOD; 11,3
Charlotte Maxeke Johannesburg Academic Hospital; SEVERE; 10,8
Houghton CDE; SEVERE; 4,3
Charlotte Maxeke Johannesburg Academic Hospital; EXTREME; 1
Houghton CDE; EXTREME; 2

4.4.5 Comment on Outcomes at CMJAH and CDE

Blood pressure and blood glucose were better controlled at CDE than at CMJAH. On the other hand, microvascular and macrovascular complication rates appeared to be similar. More patients at the CDE achieved systolic blood pressure and HbA1c targets whilst CMJAH had more patients at goal for diastolic blood pressure and triglycerides. The EuroQoL tool showed similar impact of diabetes on the 5 dimensions at CMJAH and CDE. While there was a small trend towards diabetes impacting on HRQoL scores in CMJAH patients to a greater extent than in CDE patients, the difference was not statistically significant.

4.4.6 Multivariate Logistic Regression Analysis

Continuous variables included in the analysis were age, duration of diabetes, total cholesterol, triglycerides, LDL-C, HDL-C, number of annual lipid profile and renal tests and number of annual healthcare professional visits (doctor, nurse and dietician). The following were explored as categorical variables: gender, ethnicity, education, requirement for insulin treatment and antihypertensive treatment, presence or absence of barriers to care, HRQoL and presence or absence of micro- and macrovascular complications (as defined in Table 4.17). The cut-point for HRQoL (0.80) was derived from the literature for T2DM.[250] As site was the variable of specific interest it was included in all multivariate regression analyses.

Variables were included as per the Donabedian categories of Access, Processes and Outcomes of Care, but as described in the Methodology, additional patient data were included (demographics). Certain factors were not entered into the multivariate analysis; for example, because HbA1c and requirement for insulin essentially measured the same clinical status of the patient and were correlated (r=0.54, $p<0.01$), 'requirement for insulin' was included as a measure of disease severity and HbA1c level was excluded. Similarly, 'requirement for anti-hypertensive therapy' was included as a measure of disease severity and other measures of blood pressure (i.e. systolic, diastolic or mean blood pressure) or need for specific anti-hypertensive agents were excluded.

Table 4.17 Variables selected for data analyses of study patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Demographics	Access	Process	Outcomes
Age (years)	Site (CMJAH = 0 /CDE = 1)	Annual lipid profile tests (no.)	HRQoL (<0.80 or ≥0.80)
Duration of diabetes (years)	Barriers (Y/N)	Annual renal function tests (no.)	Microvascular disease (Y/N)
Gender (M/F)		Annual Dietician appointments (no.)	Macrovascular disease (Y/N)
Ethnicity (Black African/Mixed-Ancestry = 0, Caucasians/Asian = 1)		Annual Nurse appointments (no.)	
Education (none/primary = 0, secondary/tertiary = 1)		Annual Doctor appointments (no.)	
Insulin requirement (Y/N)			
Anti-hypertensive treatment (Y/N)			
Total Cholesterol (mmol/L)			
Triglycerides (mmol/L)			
LDL-C (mmol/L)			
HDL-C (mmol/L)			

Based on the sample size and the consequential requirement to include only an appropriate number of variables in the multivariate analysis, only key variables were included. In addition, where some numbers were small within the categories of ethnicity and education, the groups were combined e.g. African and Mixed-Ancestry were combined and secondary/tertiary education were combined. The plethora of drug types for management of HbA1c, blood pressure and lipids, and the relatively small numbers of patients within each therapeutic group also resulted in these variables not being included in the multivariate analysis.

Independent variables from the univariate analysis with $p \leq 0.20$ were included in the multiple logistic regression models. As stated above, if the p-value for site was >0.20 it was also included in each of the analyses for the major outcomes. Similarly, if p-values for demographic variables (age, gender, ethnicity) and measures of disease severity were >0.20 then these were also included in the modelling in order to interrogate the effect that the intersite patient differences would have on variables which were already included (i.e. those with $p \leq 0.20$). Potentially significant interactions were also explored, and where variables were correlated (e.g. site and nurse consultations; $r=0.68$, $p<0.01$), multivariate analysis was repeated with and without each of the correlating variables.

Table 4.18 Health Related Quality of Life vs. Demographic, Access, Process and other indicators for combined group of patients attending Charlotte Maxeke Johannesburg Academic Hospital and Houghton CDE

	Unadjusted/Univariate models				Adjusted/Multivariate model			
Covariates	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value
Age	1.025	1.004	1.047	0.019	1.022	0.997	1.048	0.083
Duration of Diabetes	0.377	0.230	0.620	0.001	0.471	0.270	0.822	0.008
Nurse Visits	1.133	0.989	1.299	0.072	1.026	0.831	1.267	0.813
Dietician Visits	0.798	0.643	0.990	0.040	0.886	0.690	1.136	0.339
Site								
0= CMJAH	Ref				Ref			
1 = CDE	1.984	1.222	3.224	0.006	1.216	0.487	3.033	0.675
Education								
0 = None/Primary	Ref				Ref			
1 = Secondary/Tertiary	4.300	1.953	9.468	0.001	2.767	1.107	6.915	0.029
Barriers								
0 = None	Ref				Ref			
1 = One or above	0.293	0.177	0.484	0.001	0.296	0.164	0.535	0.001
Insulin Drug								
0 = None	Ref				Ref			
1 = On insulin	0.631	0.385	1.034	0.068	0.779	0.433	1.403	0.406
Antihypertensive								
0 = Negative	Ref				Ref			
1 = Positive	0.606	0.363	1.010	0.055	0.750	0.412	1.364	0.346
Gender								
0 = Female	Ref				Ref			
1 = Male	1.244	0.770	2.011	0.373	1.110	0.638	1.928	0.712
Ethnicity								
0 = Black African/Mixed*	Ref				Ref			
1 = Caucasian/Asian	0.985	0.607	1.598	0.952	0.514	0.260	1.016	0.056

***Mixed = Mixed-Ancestry**

Nine of the 18 possible independent variables shown in Table 4.17 with significance at the p≤0.2 level, and two of the adjusted variables (gender and ethnicity) were included in the subsequent multivariate analysis (Table 4.18). After adjusting for site, demographic variables and severity of disease, results of the multivariate model show that an HRQoL score of ≥0.80 was associated with: a shorter duration of diabetes (OR 0.471; 95%CI: 0.27, 0.82; p=0.008), an increased level of education (OR 2.767; 95%CI: 1.11, 6.92; p=0.029) and fewer barriers to care (OR 0.296; 95%CI: 0.16, 0.54; p=0.001). The variables in the above model contribute favourably towards the goodness of fit (Hosmer Lemeshow = 8.441, p-value = 0.392). Removing the demographic variables of gender and ethnicity (both of which had a p>0.20) from the model have little effect on the other statistically significant variables (Table 9.3 in Appendix Q), and goodness of fit values do not change. Intuitively one might expect a correlation between age and duration of disease, however the correlation coefficient is low (r=0.25) and removal of age does not alter the results. Similarly, site and education show low correlation (r=0.34) and correlation between site and barriers is minor (r=0.35). In fact, removal of site from the model has little effect on statistically significant variables.

Table 4.19 Microvascular Complications vs. Demographic, Access, Process and other indicators for combined group of patients attending Charlotte Maxeke Johannesburg Academic Hospital and Houghton CDE

	Unadjusted/Univariate models				Adjusted/Multivariate model			
Covariates	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value
Age	0.980	0.958	1.002	0.071	0.997	0.967	1.028	0.837
Duration of Diabetes	0.977	0.946	1.008	0.147	1.112	0.564	2.192	0.760
Nurse Visits	1.258	1.075	1.474	0.004	1.426	1.085	1.875	0.011
Triglyceride	0.828	0.643	1.065	0.141	0.872	0.655	1.163	0.352
Annual Renal Tests	0.850	0.674	1.072	0.169	0.932	0.665	1.306	0.682
Site								
0= CMJAH	Ref				Ref			
1 = CDE	1.768	1.049	2.979	0.032	0.831	0.304	2.277	0.720
Insulin Drug								
0 = None	Ref				Ref			
1 = On insulin	1.870	1.073	3.259	0.027	2.797	1.296	6.035	0.009
Antihypertensive								
0 = Negative	Ref				Ref			
1 = Positive	1.672	0.937	2.983	0.082	1.989	0.902	4.386	0.088
Ethnicity								
0 = Black/Mixed*	Ref				Ref			
1 = Caucasian/Asian	1.553	0.915	2.637	0.103	1.436	0.636	3.246	0.384
Gender								
0 = Female	Ref				Ref			
1 = Male	1.037	0.619	1.739	0.889	0.719	0.363	1.424	0.344

***Black = Black African, Mixed = Mixed-Ancestry**

Once again, 9 of the 18 potential independent variables (on the basis of p-values of ≤0.20) as well as the adjusted variable (gender) were included in the multivariate analysis (Table 4.19). Results of the multivariate model show that the diagnosis of microvascular disease was significantly associated with severity of diabetes (i.e. requirement for insulin had an OR 2.797; 95%CI: 1.30, 6.04; p=0.009) and increased nurse visits (OR 1.426; 95%CI: 1.09, 1.88; p=0.011). The variables in the above model contribute favourably towards the goodness of fit (Hosmer Lemeshow = 5.755, p-value = 0.675). To assess the interaction between site and nurse visits (r=0.68), removal of the nurse variable from the model had little effect. This observation of the association between nurse consultations and microvascular disease will be addressed in the Discussion section of the thesis. Removal of the gender variable from the model did not impact on statistically significant variables (Table 9.4 in Appendix Q).

Table 4.20 Macrovascular Complications vs. Demographic, Access, Process and other indicators for combined group of patients attending Charlotte Maxeke Johannesburg Academic Hospital and Houghton CDE

	Unadjusted/Univariate models				Adjusted/Multivariate model			
Covariates	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value
Age	0.962	0.936	0.989	0.006	0.963	0.924	1.003	0.072
Duration of Diabetes	0.941	0.907	0.976	0.001	0.717	0.301	1.709	0.453
Triglyceride	0.771	0.582	1.021	0.069	0.878	0.617	1.251	0.472
HDL-C	3.339	1.110	10.041	0.032	2.444	0.606	9.865	0.209
Site								
0= CMJAH	Ref				Ref			
1 = CDE	1.033	0.559	1.910	0.917	0.402	0.148	1.094	0.074
Insulin Drug								
0 = None	Ref				Ref			
1 = On insulin	2.187	1.086	4.402	0.028	3.121	1.155	8.429	0.025
Antihypertensive								
0 = Negative	Ref				Ref			
1 = Positive	2.087	0.992	4.389	0.053	1.960	0.685	5.608	0.209
Ethnicity								
0 = Black/Mixed*	Ref				Ref			
1 = Caucasian/Asian	2.445	1.235	4.839	0.010	4.215	1.468	12.102	0.008
Gender								
0 = Female	Ref				Ref			
1 = Male	2.344	1.249	4.400	0.008	2.240	0.898	5.591	0.084

***Black = Black African, Mixed = Mixed-Ancestry**

Nine of the 18 potential independent variables were considered following univariate analysis (Table 4.20). Results of the multivariate analysis showed that a diagnosis of macrovascular disease was associated with the following: increased severity of diabetes as shown by requirement for insulin (OR 3.121; 95%CI: 1.16, 8.43; p=0.025) and Caucasian/Asian ethnicity (OR 4.215; 95%CI: 1.47, 12.10; p=0.008). The variables in the above model contribute favourably towards the goodness of fit (Hosmer Lemeshow = 5.657, p-value = 0.686). No further adjustment for demographics or disease severity was necessary as all were already included on the basis of p≤0.2 (age, gender, ethnicity and severity of disease).

Table 4.21 Systolic Blood Pressure vs. Demographic, Access, Process and other indicators for combined group of patients attending Charlotte Maxeke Johannesburg Academic Hospital and Houghton CDE

	Unadjusted/Univariate models				Adjusted/Multivariate model			
Covariates	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value
Age	0.986	0.965	1.007	0.181	0.978	0.943	1.015	0.244
Dr	0.891	0.753	1.054	0.178	0.865	0.663	1.130	0.289
Nurse	0.727	0.628	0.842	0.000	1.020	0.752	1.383	0.898
Duration of Diabetes	2.138	1.293	3.532	0.003	1.435	0.658	3.126	0.364
LDL-C	0.810	0.604	1.087	0.160	0.696	0.477	1.014	0.059
Site								
0= CMJAH	Ref				Ref			
1 = CDE	0.291	0.172	0.492	0.001	0.509	0.162	1.597	0.247
Education								
0 = None/Primary	Ref				Ref			
1 = Secondary/Tertiary	0.230	0.117	0.451	0.001	0.273	0.103	0.723	0.009
Insulin Drug								
0 = None	Ref				Ref			
1 = On insulin	1.936	1.142	3.282	0.014	2.058	0.900	4.708	0.087
Ethnicity								
0 = Black/Mixed*	Ref				Ref			
1 = Caucasian/Asian	0.270	0.161	0.453	0.001	0.267	0.109	0.654	0.004
Barriers								
0 = None	Ref				Ref			
1 = One or above	1.946	1.183	3.202	0.009	0.914	0.418	2.000	0.822
Gender								
0 = Female	Ref				Ref			
1 = Male	0.833	0.506	1.370	0.471	0.897	0.414	1.944	0.783

***Black = Black African, Mixed = Mixed-Ancestry**

While not included among the primary outcomes of interest, analysis was also carried out for control of blood pressure (above or below 140 mmHg) and control of HbA1c (above or below 7%). In these analyses, drug treatment for the variable under consideration (insulin or antihypertensive therapy respectively) was excluded. In the multivariate analysis of blood pressure control, of the 10 variables entered into the model (with p≤0.20 as the cut-off) and with the addition of gender (at p=0.471), the systolic blood pressure above 140 mmHg was associated with less education (OR 0.273; 95%CI: 0.10, 0.72; p=0.009) i.e. those who had secondary/tertiary education were less likely to have higher systolic blood pressure compared with those with no or primary level education (Table 4.20). Higher systolic blood pressure was less likely among Caucasians/Asians (OR 0.267; 95%CI: 0.11, 0.65; 95%CI: p=0.004). The variables in the above model contribute favourably towards the goodness of fit (Hosmer Lemeshow = 4.629, p-value = 0.796). Removal of the gender variable from the model resulted in little difference (Table 9.5 in Appendix Q).

Table 4.22 Glycated Haemoglobin vs. Demographic, Access, Process and other indicators for combined group of patients attending Charlotte Maxeke Johannesburg Academic Hospital and Houghton CDE

	Unadjusted/Univariate models				Adjusted/Multivariate model			
Covariates	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value
Age	1.030	1.009	1.053	0.006	1.031	1.006	1.055	0.012
Duration of Diabetes	0.946	0.913	0.980	0.002	1.930	1.136	3.278	0.015
Nurse Visits	0.780	0.673	0.903	0.001	0.841	0.684	1.033	0.100
Dietician Visits	1.213	0.990	1.486	0.063	1.090	0.865	1.374	0.463
Site								
0= CMJAH	Ref				Ref			
1 = CDE	0.450	0.274	0.739	0.002	1.013	0.434	2.368	0.976
Barriers								
0 = None	Ref				Ref			
1 = One or above	1.807	1.097	2.975	0.020	1.434	0.821	2.504	0.205
Antihypertensive								
0 = Negative	Ref				Ref			
1 = Positive	1.438	0.863	2.395	0.163	1.255	0.715	2.203	0.429
Ethnicity								
0 = Black/Mixed*	Ref				Ref			
1 = Caucasian/Asian	0.617	0.376	1.014	0.057	0.979	0.525	1.826	0.947
Gender								
0 = Female	Ref				Ref			
1 = Male	0.949	0.584	1.542	0.831	1.155	0.680	1.963	0.595

***Black = Black African, Mixed = Mixed-Ancestry**

In the multivariate analysis of HbA1c control, of the 8 variables entered into the model (at a cut-off of p≤0.20) and with the addition of gender (at p=0.831), higher HbA1c (>7.0%) was associated with: increased age (OR 1.031; 95%CI: 1.01, 1.06; p=0.012) and increased duration of diabetes (OR 1.930; 95%CI: 1.14, 3.28; p=0.015) (Table 4.21). The variables in the above model contribute favourably towards the goodness of fit (Hosmer Lemeshow = 3.771, p-value = 0.877). Removal of the gender variable from the model showed little difference (Table 9.6 in Appendix Q).

5. DISCUSSION

Diabetes mellitus is a major health problem in South Africa and is one of the leading causes of morbidity and mortality.[109] Healthcare systems are critical to a successful response to DM, yet most healthcare systems across sub-Saharan Africa are overwhelmed by both communicable and non-communicable diseases, and are therefore underprepared for the rapidly increasing burden of DM.[160] In addition, most studies in sub-Saharan Africa have focused on the epidemiology rather than on exploring the broad-based healthcare systems needed for effective management of DM and its associated risk factors.[160] To the knowledge of the researcher, the present study represents one of only a few that explores differences of diabetes care across the two major healthcare systems in South Africa, and is the only one to simultaneously compare clinical and quality of life outcomes between the two systems.

One of the first findings to emerge from this study was the differences in characteristics of the two study sites (i.e. CMJAH and CDE) (Table 3.1). The CDE was found to be better resourced than the CMJAH. For instance, patients attending the aesthetically-superior CDE had access to reminders, more frequent communication on disease management, as well as regular invitations to diabetes camps/meetings. In comparison with the CMJAH, the CDE ran more weekly clinics, employed more specialist doctors (i.e. Endocrinologists), provided a wider selection of allied health disciplines (e.g. Dieticians, Biokineticists and Clinical Psychologists) and delivered continuing medical education to clinical and non-clinical staff. The CDE facilities also provided patients with a structured referral mechanism and access to a wider selection of drug classes (i.e. not restricted to the national EDL). Electronic patient management systems at the CDE provided advantages in terms of reduced patient waiting times, and enabled scheduling of consecutive appointments with multiple healthcare professionals at a single visit. Hence, as shown by sub-analyses of this study's data, patients at the CDE generally reported having fewer problems accessing clinic-related services (CDE 1.3% of patients vs. CMJAH 36.8%; $p<0.0001$). Specifically, waiting times of >1 hour for consultations were experienced more frequently by CMJAH patients when waiting for nurses (CDE 28.8% of patients vs. CMJAH 43.1%; $p=0.01$) and also for doctors (CDE 2.7% of patients vs. CMJAH 84.0%; $p<0.0001$). Perhaps patients at the CMJAH who received State-subsidised healthcare thought it was 'acceptable' or 'normal' practice to experience such extended waiting times, which may mean that the above numbers are in fact an underestimate of the existing problem.[227] It was also observed by the researcher during his interviews with study subjects, that most patients spent fewer than 4 hours at the CDE with back-to-back appointments (laboratory, consultations and pharmacy), almost the entire time used

productively, and little time wasted in between appointments. In contrast, CMJAH patients spent more than half of their day at the CMJAH, with the majority of their time spent waiting, rather than receiving healthcare. Previous research into care in a setting comparable to that of the CMJAH showed that patients could wait for as long as 90-180 minutes for their consultation with healthcare professionals, which when it finally did occur, would last <5 minutes.[194] A study by Ndlovu evaluating service delivery within the KwaZulu-Natal's public sector also found similar barriers, for example, 13.0%, 18.8%, 20.9% of patients waited an hour or more for medications (at the pharmacy), a nurse and a doctor, respectively.[251] Likewise, in the General Household Survey (GHS), 33.8% of patients reported that they had waited 'too long' for service in the public sector healthcare facilities. Another advantage of the CDE was the dedicated onsite laboratory which would allow for test results to be readily available to treating doctors. They could then base their treatment decisions on information provided almost immediately (i.e. HbA1c levels), rather than having the patient wait for the next scheduled appointment, which would further risk possible diabetes-related complications and/or hospitalisations. Hence patients at the CMJAH often have their past, rather than their current results treated. The National Health Laboratory Services (NHLS) provides laboratory services to the CMJAH. These services are 'shared' across all hospital clinics including the diabetes clinic, which does not enjoy preference over other clinics. Therefore, in Donabedian terms, patients at the CMJAH appear to be disadvantaged by several 'structural' and access factors in comparison with CDE patients. The better accessibility and availability of diabetes-related services could potentially influence and contribute towards patient outcomes.

In terms of demographics of the CMJAH and CDE groups, the present study showed that patients attending the CMJAH (mostly Black Africans) were on average significantly younger than (mostly Caucasian) patients attending the CDE (58.6 ± 10.9 vs. 63.2 ± 12.2 years; $p<0.001$). Further, though statistically insignificant, patients at the CMJAH had a slightly longer duration of DM in comparison with CDE patients: CMJAH 11.0 (1-47) vs. CDE 10.0 (1-48) years, (Table 4.1). The data therefore suggest that Black Africans from the CMJAH manifest T2DM earlier in comparison with the Caucasians from the CDE. This is supported by another local study which found that Africans with T2DM attending a diabetes clinic in Johannesburg were on average 6 years younger, and had a younger age of diagnosis, than the Caucasian diabetics.[252] A possible explanation for some of this phenomenon is that populations who historically have been subjected to periods of nutritional starvation may develop an efficient way of storing fat as a survival advantage through activation of the 'thrifty gene'.[253] Such fat storage would sustain the person

until food became available again, and if such a population subsequently resides in a land of plenty, then the same genetic trait for efficient fat storage could lead to insulin resistance, a major risk factor for the development of T2DM.[253] This hypothesis might apply to the CMJAH population, given the important role that historical deprivation and subsequent urbanization have on unhealthy lifestyle choices which potentially drive the earlier onset of DM.[254] Another contributing factor may have been a susceptibility to intrauterine growth retardation (IUGR) among the African population, which has also been reported to be associated with earlier development of DM in adulthood.[255,256,257] Intrauterine growth retardation and low birth weight may also be a manifestation of the 'thrifty gene' or a consequence of the 'foetal insulin hypothesis'. This latter hypothesis refers to genetic or epigenetic variations which affect foetal pancreatic development, resulting in reduced foetal growth and a higher risk of T2DM later in life due to the underlying problem of compromised β-cell mass.[258]

The present study also revealed a larger proportion of females attending the CMJAH in comparison with the CDE (66.0% vs. 46.6%; $p<0.001$) (Table 4.1). This could possibly be related to health-seeking behaviours which determine how health services are used, and in turn affect the health outcomes of populations.[259] Perhaps 'traditional masculine behaviour' prevented men from receiving care at CMJAH as a result of 'denial' of their disease.[260] This is supported by research which has shown that men avoid going for routine medical check-ups, preventive care or health counselling, and often ignore symptoms or delay seeking medical attention when sick, in pain, or even when their lives are in grave danger.[261] Similarly, according to Galdas and Boman, there is a growing body of research in the US which suggests that men are less likely than women to seek help from health professionals for problems as diverse as depression, substance abuse, physical disabilities, and stressful life events.[260,262] Imaginably, the different roles that men and women traditionally have within the family structure also affect health-seeking behaviour, with women often taking on greater responsibility for family health.[263] Overweight/obesity among the Black African females attending the CMJAH may also have played a role in the relative excess of females at the site. In this study the average weight of Black African females at CMJAH was 90.4 ± 22.1 vs. 82.6 ± 19.7 kg among the other females ($p<0.05$). While BMI was not calculated because of poor capturing of height, the mean weight of 90.4kg is higher than desirable. This tendency to overweight or obesity among females attending CMJAH suggests that the group had deleterious lifestyle habits and/or (epi)genetic susceptibilities. Quite perversely, perhaps one of the contributors to obesity in South Africa's Black African population is the HIV/AIDS epidemic. Here the postulate is that because weight loss and wasting are commonly associated with

advanced AIDS, the cultural perception of a bulkier body size (representing good health) leads to purposive weight gain.[119,120] Therefore, in addition to poor lifestyle choices, the utilization of a healthcare system may depend on social and/or medical factors, and how diabetic patients perceive their disease.

Ethnicity has long been recognized as a risk factor for the development of DM.[264] Within the two study sites the ethnic distributions largely represent the populations served by the public and private sectors respectively. The largest group represented at CMJAH was Black African (63.9%) whilst at the CDE, Caucasians made up the majority (63.0%). Mixed-Ancestry patients were least represented at both CMJAH (6.3%) and CDE (4.1%). According to a 2013 report from the Human Sciences Research Council, the majority of Black Africans (75.5% or 25.2 million) and more than half (56.1% or 3.1 million) of Mixed-Ancestry people rely on the public health sector, whilst in contrast, 83.4% (3.6 million) of Caucasians and 65.5% (970 000) of Indian/Asians have access to the well-resourced private health sector.[265] Yet due to modern lifestyle factors, direct genetic propensity or gene-environmental interactions, Black Africans and Mixed-Ancestry people are particularly susceptible high-risk ethnic groups with higher DM prevalence rates and earlier onset of disease in comparison with other ethnic groups (Table 1.2).

Data from this research also show that CMJAH patients are less educated, more likely to be single, and more likely to be unemployed (Tables 4.3 - 4.5). All of these differences pose risk. For example, lower education levels have been associated with less favourable health behaviours such as higher rates of sedentary lifestyle, obesity, smoking and alcohol consumption, all of which are recognized risk factors for the development or worsening of diabetes.[14,67,266] In the present study, more patients attending the CMJAH reported secondary education as their highest level, whilst more CDE patients reported having tertiary education vs. CMJAH patients (57.9% vs. 11.3%; $p<0.0001$). These results may be reflective of past racist socio-political and socio-economic policies which ultimately led to a race-based division of health and education services.[265]

A statistically significant larger portion of individuals attending the CDE were married in comparison with those attending the CMJAH (67.8% vs. 47.9%; $p<0.0001$). In terms of the impact of marital status on health, several studies indicate that personal relationships such as marriage offer individuals ‘protective’ or ‘health-enhancing attributes’ against loneliness, depression, risky health habits, poorer physical and cognitive function, poor self-rated health and increased risk of

institutionalization.[73,78,79] In this study more patients attending CDE were employed vs. those attending the CMJAH (54.1% vs. 39.4%; p<0.01). In this regard, a number of studies have postulated a convergence between unemployment patterns in relation to the development of chronic diseases such as T2DM.[84,85,86] There is also evidence that individuals who lose their job are at greater risk of developing chronic diseases.[84] The rate of cardiovascular mortality is doubled in those who are unemployed in comparison with employed people, particularly in the first year of unemployment.[85,86] Unemployment may elevate lifestyle risk factors such as low nutrient diets, lack of exercise, increased smoking and alcohol abuse.[87]

Further evidence of socioeconomic disadvantage is the lack of medical insurance among CMJAH patients, and also reliance on public transportation (which likely also impacts negatively on travel time to the clinic) (Table 4.6). These latter factors have also been shown locally and internationally to interfere with optimal management of T2DM where, due to the chronic nature of this disease, there is a need for regular provider visits, medication supply and modification of treatment plans.[177,187] In fact, data from several studies suggest that patients who had no access to private transportation had a higher likelihood of missing, delaying or forgoing care.[177] In the current study, the majority of CDE patients but only one-third of CMJAH patients had access to private transportation (99.3% vs. 37.6%, p<0.0001). This likely affected the longer travel time of >30 minutes which was largely experienced by the CMJAH vs. CDE patients (65.7% vs. 33.8%; p<0.0001), although longer travel time might also reflect distance from CMJAH. Data from a previous South African study supports the above, showing that the lowest income quintiles of South Africans were more likely to live further away from their nearest health facility.[226]

In terms of medical insurance, the majority of study patients attending CDE had private cover in comparison with only a few CMJAH patients (99.3% vs. 6.3%; p<0.0001). This again could be to the disadvantage of the CMJAH patients, given the nature of the public sector in general, which has been described as being in a state of disarray, with infrastructure often run-down and dysfunctional due to lack of funds, poor management and years of neglect.[167] This situation is not unique to South Africa, as uninsured populations regularly experience barriers to quality healthcare.[188,189] Nelson et al[187] found that in comparison with insured diabetics, those who are uninsured monitor daily blood glucose less frequently and have fewer annual dilated eye exams, foot examinations, and HbA1c tests. Data from the 2009 National Health Interview Survey showed that due to the cost implications, uninsured diabetics were six times more likely to forgo necessary medical care in comparison with those who were continuously insured.[188] Along similar lines, not

having a standard site for care and/or substituting an emergency department for the site which should be regularly utilized for healthcare, were associated more with uninsured patients with diabetes than with those who were insured (47.5% vs. 7.7% and 7.1% vs. 1.1%; p<0.001).[189]

Almost all participants in this research were either South African citizens or were registered as permanent residents (95.8% CMJAH vs. 97.9% CDE) (Table 4.6). This leaves several unanswered questions as to whether non-citizens and unregistered diabetics do not seek help, are not referred to these centres for care, or are turned away on the basis of ineligibility or inability to pay.[219] In this regard, some immigrants have reported to have experienced 'medical xenophobia' which included hospital security staff declining non-nationals entrance into a health facility, health professionals placing non-nationals in longer queues, and/or forcing immigrants to pay more for healthcare.[220] Other research also shows that immigrants face challenges accessing healthcare services. For example, South Asian immigrants of the UK (i.e. Indians, Pakistanis, Bangladeshis etc) and Latin populations of the U.S. (i.e. Puerto Ricans, Mexicans etc) also experience barriers to care which ultimately result in poor health outcomes.[175,176] Access barriers experienced by immigrant groups could have major public health implications, leaving such individuals vulnerable, despite the need to access healthcare as much, if not more than the citizens of a particular country.

In addition to the objective barriers, the perceived barriers to care were also assessed. The CMJAH patients encountered more access barriers than those attending CDE: 1.0 (0–9) vs 0 (0–5), p<0.00001. Available evidence from the South African GHS showed that users of public hospitals reported low levels of satisfaction and high levels of problems associated with access.[267,268] The most commonly-experienced barriers at the CMJAH were: 'transportation costs', followed by 'delays in being seen/getting an appointment', 'difficulty scheduling/long waiting times', 'healthcare services too expensive' and 'had more important things to take care of'. Patients at the CDE also reported several perceived barriers such as 'healthcare services too expensive', 'having more important things to take care of', 'transportation costs', 'could not take time off from work' and 'too sick to attend' but in almost all cases, perceived barriers were significantly more frequent for the CMJAH patients. Hence individuals at different income levels may experience variable access barriers with respect to healthcare and competing priorities. Both sites raised transportation costs as barriers, which is understandable given the multiple costs associated with maintenance of vehicles, the ever-rising cost of fuel, the further distances CMJAH patients travelled, and taxi- or bus fares.

Due to the complex nature of T2DM and its associated multiple comorbidities, there are diverse challenges that individual clinicians may find difficult to manage, consequently various specialists in a multidisciplinary team should function together through identification of shared roles and responsibilities, whilst contributing uniquely to patients in order to achieve the desired outcomes.[269] It is now well established from a variety of studies that regular medical visits and preventive care practices, such as self-monitoring of glycaemic control, regular foot care, and ophthalmic examinations, can help to reduce both the incidence and progression of diabetic complications.[269] In addition, compared to non-integrated care, interdisciplinary team care involving a variety of HCPs such as nurses, podiatrists and endocrinologists has been shown to reduce the risk of lower limb amputation by 34-47%, end-stage renal disease in patients with T2DM nephropathy, and risk of mortality.[269]

In the present study, it was found that differences existed in terms of the frequency of consultations and laboratory testing between the two sites (i.e. CMJAH and CDE) (Table 4.7 and 4.8). For instance, more nurse consultations were recorded at CMJAH per year than at CDE: 3.0 (0-8) vs. 0 (0-4); $p<0.001$. This may be explained by the fact that nurses at the CMJAH took on the roles of dieticians and dedicated diabetes educators in addition to regular nurse responsibilities (i.e. measuring blood pressure, weight and point-of-care blood testing). On the other hand, more allied healthcare staff were available at the CDE than at the CMJAH, hence patients at the CDE received more consultations from dieticians 1.0 (0-6) vs. 0 (0-4); $p<0.001$, podiatrists 1.0 (0-10) vs. 0 (0-3); $p<0.001$ and biokineticists 0 (0-14) vs. 0; $p<0.001$. According to Bayless et al[270] the role of non-physicians as part of an integrated, interdisciplinary approach to chronic disease management provides evidence for the benefits of team care as it pertains to attaining clear metabolic outcomes.

Given the complex nature of T2DM and its associated risk factors, guidelines have incorporated several well-standardised biomarkers which are used to monitor/manage/guide/determine treatment(s) and/or predict outcomes.[3] Tests such as HbA1c, lipid profile and creatinine not only provide a reliable measure of chronic hyperglycaemia, cholesterol and renal function, but also correlate with the risk of long-term diabetes complications. As shown in Tables 4.8 and 4.15, patients at CMJAH were tested more frequently for HbA1c 3.0 (0-5) tests per year vs. 2.0 (0-6); (not statistically significant) but also achieved target HbA1c levels of <7% less frequently than CDE patients (27.3% of patients vs. 45.5%; $p<0.01$). The figure of 27.3% is similar to that reported

in a study from Tshwane, South Africa and slightly higher than that reported for Cape Town.[125,128] In Donabedian terms this raises the question of whether these results are due to inherent patient factors (e.g. demographics), access to services, or processes within the two clinics. In terms of patient factors, issues such as obesity and traditional diet have already been discussed for CMJAH patients. Access to services, as already shown by reliance on public transportation and greater travel times to CMJAH may impact on HbA1c management as shown by research indicating that prolonged travel time is an obstacle to management of disease. For instance, two studies found that patients with T2DM who lived closer to their healthcare providers tended to have better glycaemic control than those who lived further away.[183,184] It has also been found that the further the driving distance for individuals with DM, the lower the likelihood of being an insulin user.[183] A reason cited for the latter was that providers worried about the detrimental risk of hypoglycaemia in patients who live in remote areas and may not have access to emergency if required. Another factor at CMJAH could have been that patients had their past (from their previous visit) rather than a current HbA1c result treated, and this may have led to increased testing in order to be more cautious. However, other differences between the CMJAH and CDE might relate to T2DM management at the two sites and between clinic visits. Here it is important to note the CDE 'business model', which is a capitation-based, risk-sharing, service contract with medical schemes that is essentially driven by well-managed HbA1c control in order to prevent hypo- or hypoglycaemic episodes (for which the CDE and not the medical aid will pay if the patient is admitted to hospital). There is thus a significant vested interest in HbA1c management. Furthermore, while medical schemes contract with CDE on behalf of patients, there is no restriction on such patients also accessing T2DM-related services outside of the CDE and complementing their T2DM management. In order to obtain an indication of the extent of the latter phenomenon, the researcher approached the administrators of a major open medical scheme and requested anonymised data for 150 randomly-selected T2DM members who were similar to the CDE sample in this study in terms of eligibility criteria, were registered with CDE for diabetes care, and were also accessing additional medical services. Review of the medical scheme data showed that 38.7% of the sample claimed for additional glucose testing strips at a total cost of R64 063, and 27.3% had additional HbA1c tests done in order to optimise their blood sugar and HbA1c management. One can safely assume that the public sector patients at CMJAH would not have been in a position to access (and self-fund) the additional services to 'fine-tune' their control. At the CMJAH, fewer patients were managed by diet alone, fewer received a single oral drug, and more patients required combination therapy of oral drug and insulin (Table 4.9). Here, one should also consider the possible impact of variable drug supply at CMJAH where drugs dispensed to

patients are sourced from different manufacturers. This may be the result of 'drug stock-outs' or the frequent changes of suppliers of generic medicines in the public sector which is driven by awarding of tenders to different pharmaceutical companies.[171] Evidence has suggested that excipients used in a generic formulation are not required to be identical to those in the originator formulation.[271] Small changes in excipients can alter the properties of a formulation (e.g. lead to differences in particle size, or modify the shelf-life) and hence affect drug efficacy and safety.[271]

There are many examples in the published literature in which studies have shown marked variation in dissolution times between supposedly bioequivalent drugs.[271] Apart from the problems with drug availability there is also the relatively restricted State formulary i.e. the EDL. In this regard, more biguanide use was seen at CMJAH (88.2% vs. 70.5%; $p<0.001$), whilst sulphonylureas were prescribed to a greater extent at CDE (29.5% vs. 16.0%; $p<0.01$). The sulphonylurea agents prescribed for CDE patients were likely the newer, longer acting formulations which have lower risk of hypoglycaemic events and which were not accessible to CMJAH patients (due to EDL restrictions; see Appendices D & E).

More patients at CMJAH were hypertensive in comparison with those at CDE (79.2% vs. 56.2%; $p<0.0001$). Perhaps among the complex and multifactorial contributors to hypertension, more CMJAH patients were hypertensive due to factors relating to urbanization and adoption of unhealthy lifestyles.[98] The data from the current study are supported by a study by Kalk et al[272] in which Africans had a higher prevalence of hypertension than Caucasians (83.3% vs.47.1%; $p<0.001$). Once again, the question arises as to whether there are patient factors leading to more hypertension in the CMJAH population, or access/process issues.

As stated above, data from studies support a predisposition to hypertension in Black Africans.[252,272] In terms of processes of care, far more ARBs were prescribed to CDE patients vs. those at CMJAH (56.1% vs. 9.6%; $p<0.0001$) who were prescribed more ACE-inhibitors (57.0% vs. 13.4%; $p<0.0001$). These differences can partly be explained by the EDL restrictions at the CMJAH whereby only the highly-genericized ACE inhibitors are available to the majority of patients, whilst the newer ARB agents are only available on a 'motivational' basis (i.e. individuals who experience intolerance to ACE inhibitors and therefore require ARBs). In a Cochrane Collaboration Review which compared ACE inhibitors and ARBs in a head-to-head manner, there was no evidence of a difference in total mortality or cardiovascular outcomes for ARBs as compared with ACE inhibitors, while ARBs were associated with fewer withdrawals due to

adverse effects (WDAEs) than ACE inhibitors.[273] In addition, despite evidence for lower circulating renin levels and a less significant fall in blood pressure in response to renin angiotensin system (RAS) inhibitors in Black Africans, data from several clinical trials support the efficacy of RAS inhibitors to improve clinical outcomes in this population, especially in those with hypertension and risk factors for cardiovascular and related diseases (i.e. chronic renal disease and/or proteinuria).[274]

Turning to the higher use of calcium channel blockers at CMJAH, CCBs have been recommended for Black African patients as initial therapy for hypertension.[275] Hence a large proportion of CMJAH patients were using this class of agent (65.8%) vs. only 24.4% at the CDE. In order to effectively lower blood pressure in hypertensive patients, an evidence-based, widely accepted practice is to use combinations of antihypertensive classes. In fact, patients with T2DM typically require 3-4 classes of antihypertensives in order to achieve blood pressure targets.[205,276] Hence, in the current study, diuretics were often combined with other agents in order to help patients achieve target blood pressure levels. Patients from both study sites were similarly prescribed diuretics as their second most frequently chosen class of antihypertensive within their setting, although these differed by site (64.0% vs. 45.1%, $p<0.0001$). Beta-blocker use across both sites was similar, although used in lower numbers overall which may perhaps be due to their potential properties of masking potential hypoglycaemic events.[277]

Blood lipid levels were tested more frequently at CDE over the year 2.0 (0-4) vs. 1.0 (0-4); $p<0.001$ and renal function tests were also more frequent 2.0 (0-5) vs. 1.0 (0-4); $p<0.001$. As shown in Table 4.15, similar numbers of patients at CDE and CMJAH achieved target levels of total cholesterol (63.3% vs. 61.7%, respectively). Further exploration of lipid levels in a sub-analysis of HDL cholesterol levels in women at the two sites showed that differing numbers of women achieved HDL target levels of >1.2 mmol/l (CMJAH 33.9% vs. CDE 55.8%; $p<0.05$). Previous research has shown that despite a greater prevalence of obesity and lower HDL concentrations in black South African women, they were relatively protected against ischaemic heart disease.[278] One-fifth of patients attending CMJAH were prescribed antiplatelet therapy vs. one-third at CDE (18.8% vs. 34.9%; $p<0.01$). Optimal vascular protection is achieved through a multifactorial approach (i.e. use of antiplatelet therapy, ACE inhibitors, metformin, and statins) thereby offering risk reduction in patients with T2DM. In terms of thyroid replacement therapy, both sites had equally low numbers of patients using this class of agent which is most commonly prescribed to patients with hypothyroidism.[279]

Overall, the data from the current study clearly demonstrate that the cohort attending the public sector (i.e. CMJAH) was disproportionately more disadvantaged and apparently at greater risk for T2DM-related morbidity and mortality than the CDE group in terms of demographics, access and processes of care. For instance, the CMJAH group had more patient risk factors such as earlier age of DM onset and higher body weights (particularly in Black African females). The CMJAH group may also have experienced more socioeconomic difficulties compared with CDE patients. This was noted by their lower levels of education, higher likelihood of being single and unemployed. In addition, the CMJAH patients also suffered from limitations in accessing healthcare which may have been attributed to being uninsured, more reliant on public transportation (but also traveling further distances) and experiencing various other perceived barriers (e.g. delays being seen and financial worries). In comparison with the CDE cohort, the CMJAH group was further deprived of access to a full multidisciplinary team of HCPs, were treated to the levels of previous test results and restricted to an EDL of highly genericized medications which are often liable to substitution by the CMJAH dispensary. Finally, the CMJAH group also emerged as having more hypertensive disease than those at CDE, and fewer patients reached HbA1c targets, which again will increase the risk of future diabetes-related complications. Hence, all the evidence thus far in the present study suggests that in comparison with the CDE patients, the odds appear to be stacked against the CMJAH patients. However, as per Donabedian principles one must turn to the outcomes to obtain the complete picture.

In the T2DM condition it is the clinical outcomes and complications in particular that are the key determinants and predictors of morbidity and mortality.[1] If left untreated, these can lead to microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (cardiovascular and stroke) diseases which further affect multiple physiological systems and lead to poor patient outcomes.[41] Very important in the present study is the finding that there were no statistically significant differences in major complication rates (i.e. micro- or macrovascular disease) between CMJAH and CDE patients (Table 4.13). Also of note is that the complication rates found in the two sites study are all within the ranges identified in various South African studies (Table 5.1), with most in this study being towards the lower end of the ranges. The latter is of interest given that all the patients in the present study were being treated in specialised care environments, i.e. most likely representing the more-severely affected patients.

Table 5.1 A comparison of complication rates across several South African diabetes

mellitus studies

Study	Retinopathy (%)	Neuropathy (%)	Nephropathy (%)	Stroke/TIA (%)	CVD (%)
Webb[125]	29.0	11.0	7.4	-	±17
Pinchevsky[126]	6.3	7.1	11.7	3.0	15.5
Pillay[127]	6.4	45.2	20.0	-	-
Levitt[128]	55.4	27.6	5.3-36.7	-	-
Klisiewicz[280]	-	-	-	-	21.3
Current Study (CMJAH vs. CDE)	13.9 vs. 18.5	11.8 vs. 17.8	9.7 vs. 8.9	2.8 vs. 2.1	16.0 vs. 15.8

CVD = Cardiovascular Disease; TIA = Transient Ischaemic Attack

Patients with T2DM who either have or don't have complications may experience changes in lifestyle and reduced HRQoL.[210,211] For example, the UKPDS Group directly assessed health utility scores in T2DM and found that subjects with microvascular complications had slightly, but not significantly, lower scores than patients without complications, and subjects with macrovascular disease.[216] Similarly, Redekop et al[281] assessed HRQoL scores in a sample of Dutch T2DM subjects who participated in the Cost of Diabetes in Europe - Type 2 (CODE-2) study and found that older age, obesity, female sex, insulin therapy, and presence of complications were associated with lower health utility scores. In the current study, the majority of patients completed the EQ-5D-5L (96.6% and 82.6% at the CDE and CMJAH respectively). As shown in Figure 4.1, the results of the 5 HRQoL dimensions were virtually superimposed on one another, and the overall HRQoL scores were not statistically different between the two sites (CMJAH 0.75 ± 0.22 vs. CDE 0.80 ± 0.23). These HRQoL scores were generally in keeping with those from other DM studies.[216] Thus in terms of clinical and quality of life assessments at the two study sites, contrary to expectations, key clinical outcomes appeared to be equivalent.

In order to establish more clearly which characteristics within the clinic populations and services were related to the outcomes of interest, the CMJAH and CDE datasets were combined and subjected to multivariate logistic regression analysis.

In terms of HRQoL scores, three major associations/determinants appeared. The first was with access barriers which were inversely related to the HRQoL score as determined by means of the EQ-5D instrument. The perceived barriers as assessed in this research were derived from the literature and it is interesting to note their significant association with the score. In this regard it should be noted that it was specifically access to the clinic, services within the clinic and financial issues that were independently found to be associated with the HRQoL score. Along these lines,

a study conducted across six European countries demonstrated that longer waiting or travel times to healthcare providers resulted in a reduction in a patient's HRQoL.[282] In addition, a study by Glasgow et al[283] reported a markedly lower HRQoL in those with no medical insurance vs. those with private insurance as the former group experienced greater barriers to accessing care.

A shorter duration of disease also appeared to have a positive influence on the HRQoL of study patients. With long-term consequences of DM having a substantial impact on HRQoL, this result is logical. Indeed, several studies have found similar results.[284,285] Higher HRQoL scores were also found to be associated with increased education levels in the present study. Since 'education' in the context of this thesis relates to patients' historical level of education, the variable is likely to be a proxy for several other factors that are associated with higher quality of life. For example, recent South African data show clearly the inverse relationship between level of education and likelihood of unemployment (the unemployment rate for those with less than matriculation in comparison with university graduates is 31.9% vs. 6.9%, respectively).[286] While unemployment itself has been shown to impact on quality of diabetes care,[84,85,86] in general one can assume there is a relationship between education, employment, personal income, greater access to housing, and higher quality of life.[287] On the other hand, as suggested by a recently-conducted Swiss study in >500 subjects, perhaps a better-educated patient is simply more likely to get an appointment directly with a specialist or to remind his general practitioner to refer him,[288] either/both of which might improve care and consequently also quality of life.

At this point it is important to recognise that HRQoL is an appropriate measure for a cross-sectional study such as this one as it relates a score to an individual's experiences and perceptions at a point in time. The same cannot apply to the other outcomes in this study viz. microvascular and macrovascular complications, which are the result of sustained pathophysiological inputs and would require a longitudinal study in order to adequately identify determinants. Nevertheless, the multivariate analyses applied in this study are important in identifying factors associated with the outcomes and possible areas for future intervention.

In the present study the presence of microvascular disease was positively associated with an increased number of nurse consultations and greater insulin use (which was included as a marker of severity of diabetes). Although nurse visits are highly correlated with site, removal of the variable from the multivariate logistic model did not elevate site to significance, and the association between nurse consultations and microvascular disease must therefore be addressed

on its own. Here there is the possibility that patients with microvascular disease make more appointments to see nurses. Alternatively it is possible that at a site in which microvascular disease is not always detected, the patients are directed to management by nurses rather than by doctors, or it is possible that patients seen predominantly by nurses are not referred and/or screened as aggressively for markers of microvascular disease. While site did not emerge as a significant factor in the multivariate logistic model, the odds ratio does however point in the direction of more microvascular disease at CDE. Taking the latter arguments into account one must consider the possibility that microvascular disease is relatively under-diagnosed at CMJAH. This potentially-important finding is being specifically flagged for further study. The association between presence of microvascular disease and severity of diabetes is logical, but also introduces the need for the patients' disease being managed better in the future e.g. by improved glucose control and management of factors known to predispose to microvascular disease.[195]

In the current study the presence of macrovascular disease was found to be associated with Caucasian/Asian ethnicity and severity of diabetes as reflected by requirement for insulin. In terms of ethnicity, the findings from the current study are similar to those of Kalk and Joffe who described higher prevalence rates of coronary artery disease in White diabetic subjects than in Black diabetic South Africans.[272] As is the case in the present study, these latter authors found lower triglyceride levels in their Black African patients. The median triglyceride levels in this study were 1.86mmol/l in Caucasian/Asians and 1.49mmol/l in Black African/Mixed-Ancestry subjects ($p<0.001$). A relationship has been established for triglycerides and macrovascular disease, and also for triglycerides and insulin resistance.[289,290,291] The latter relationships between sub-groups of patients suggests strongly that genetic, epigenetic and/or environmental factors influence how DM patients manifest disease and/or respond to treatment. For example, in a Swedish analysis which stratified newly diagnosed patients with diabetes (n=8980) according to six variables (glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c, and estimates of β-cell function and insulin resistance), the researchers were able to identify subgroups of individuals who were at increased risk of developing complications and would therefore benefit from timely tailored and targeted treatment in order to prevent diabetic complications from arising.[292] In terms of how external and internal environments might influence DM, much work is currently focused on the gut biome which refers to the multitude of gastrointestinal microbes and can be considered a separate endocrine organ.[293] The composition and richness of the gut microbiota depends on the symbiotic relationship with the host. They are modulated by the diet, host health, age, ethnicity and genetics, and thus are unique and highly variable among individuals.[294] In addition to the

metabolic capability of enterocytes and hepatocytes, it is now increasingly accepted that the gut microbiota influence metabolism and also drug pharmacokinetics and correspondingly bioavailability, efficacy or adverse effects. Modulating the microbiome, either through exogenous replacement (probiotics) or curtailing interventions, such as antibiotics or specific inhibitors, affords exciting opportunities to improve healthcare outcomes and advance personalised medicine.[295]

The association between presence of macrovascular disease and severity of diabetes is logical, and again introduces the need for the severity of disease being managed better in the future e.g. by improved glucose control management of factors known to predispose to macrovascular disease.[195] An additional consideration in terms of the association between macrovascular disease and requirement for insulin is the possibility that the insulin itself plays a role in the atherosclerosis/restenosis of patients who have macrovascular disease. However, this is a highly contested and controversial area of research.[296]

It should be noted that site did not emerge as a significant independent variable with any of the abovementioned outcomes in this research.

Noting the significant differences in HbA1c and blood pressure control at the two sites, additional analyses were performed. In the multivariate analysis with blood pressure control as the dependent variable, site was not significant but lower education level (OR 0.273; 95%CI: 0.10, 0.72; p=0.009) and Black African/Mixed-Ancestry (OR 0.267; 95%CI: 0.11, 0.65; 95%CI: p=0.004) were associated with higher blood pressure measurements. According to a meta-analysis comprised of 242 studies with 1,494,609 adults from 45 countries by Sarki et al[297], those without formal education compared with those who were educated were more likely to be hypertensive (49.0% vs 24.9%, P<0.00001). While ‘education’ in the present study applied to historical education, there is likely also a case for ‘real time’ focused educational programmes for patients with various chronic diseases. For example, there are data showing that health education may in itself lower blood pressure in patients.[298] In terms of the association between hypertension and ethnicity, higher blood pressure in Black Africans/Mixed-Ancestry patients has commonly been found.[252,299,300]

In the analysis of HbA1c as the dependent variable, age (OR 1.031; 95%CI: 1.01, 1.06; p=0.012) and duration of diabetes (OR 1.930; 95%CI: 1.14, 3.28; p=0.015) were found to be statistically

significant. Site was not a statistically significant independent variable. However, while process of care issues such as insulin type or frequency of tests were not included in the model, if these factors were statistically relevant, one would have expected them to reflect in 'site' and elevate that variable towards significance. Several studies have shown a significant positive correlation between HbA1c and age, and also with duration of diabetes.[301,302,303,304] The exact mechanism for the tendency of increasing age to raise HbA1c levels is unknown, but it could involve processes such as glycation and red blood cell lifespan.[301] Kilpatrick et al[305] reported that age affected fructosamine levels less than it did HbA1c levels, and Cohen et al[306] found that the known heterogeneity in red cell lifespan would be sufficient to alter HbA1c levels. Other studies, however, have shown that increasing age is associated with a reduction in red cell lifespan; if true, such a trend would tend to lower rather than raise HbA1c with increasing age (because circulating red blood cells would be exposed to circulating glucose for a shorter period of time). Alterations in glucose metabolism (resulting in insulin resistance) have also been shown to occur as a result of the ageing process.[307,308,309,310] Potential explanations include: 1) increased abdominal fat mass, 2) decreased physical activity, 3) sarcopenia, 4) mitochondrial dysfunction, 5) hormonal changes, and 6) increased oxidative stress and inflammation.[311]

6. CONCLUSION

This study was a quantitative audit and analysis which set out to measure and compare the quality of diabetes care associated with T2DM management of patients attending either a specialised public (CMJAH) or private (CDE) healthcare facility within urban Johannesburg. The major objectives of the study were to evaluate the demographics, the perceived barriers to access of diabetes-related healthcare, the processes of care associated with diabetes management and the clinical outcomes and HRQoL attained by patients with T2DM attending either the public or private sector facility.

Demographics and Access to Care:

- The CMJAH group was younger, consisted of a larger proportion of overweight/obese females and had a slightly longer duration of DM (therefore earlier onset age of DM) in comparison with the CDE group.
- The CDE group was advantaged in terms of socioeconomic status, education and access to employment and clinical services.
- A broader range of barriers (e.g. less private transportation, longer travel time and less medical insurance) impeded access to care for the CMJAH group in comparison with the CDE group.
- The CDE group had access to a greater variety of healthcare staff in comparison with the CMJAH group which meant greater access to dieticians and to podiatrists for care of specific problems. Hence, the latter group made more use of nurses as clinical educators and ‘case managers’. In addition, CDE patients made use of providers beyond the CDE for management of their disease.

Processes of Care:

- The frequency of blood tests differed between sites, with more patients at CMJAH tested for HbA1c and full blood count, whilst more CDE patients had their blood lipid levels and renal function tested.
- The management of blood sugar involved similar pharmacological approaches at the two sites, whereas pharmacological management differed substantially for management of hypertension. Differential access to medications between the two study sites almost certainly played a role in the effectiveness of management of blood glucose and blood pressure.

- Despite the differences between the sites, HRQoL scores were similar between the sites, as were rates of microvascular and macrovascular complications.

Results of multivariate logistic regression analysis are summarised (Table 6.1).

Table 6.1 Primary Outcomes vs. Demographic, Access, Process and other indicators for combined group of patients attending Charlotte Maxeke Johannesburg Academic Hospital and Houghton CDE

Outcome	Patient-related	Access to care	Process of care
HRQoL	▪ Duration of diabetes ▪ Education*	▪ Barriers*	
Microvascular	▪ Severity of diabetes*		▪ Nurse visits*
Macrovascular	▪ Ethnicity ▪ Severity of diabetes*		

*Represent potentially modifiable factors

Overall, the multivariate analyses describe two major findings:

1. The first is that a number of factors are potentially modifiable. Access barriers found in this study such as delays in being seen or getting an appointment, too few healthcare providers available, lack of trust in healthcare providers, or healthcare providers seemingly lacking interest in patients and treating patients poorly, appear to be important and could specifically be addressed by clinic staff. The severity of disease in patients could also be addressed by a focus on improving the control/management of blood glucose and blood pressure, particularly in identified high-risk groups.

2. Most of the factors emerging from this study as being related to the outcomes of interest or control of HbA1c and hypertension are related to patient demographics and severity of disease. This highlights the relatively inadequate performance of the widely-accepted 'access/structure and process'-focused Donabedian model in measuring clinical outcomes.[172] Here it should be noted that HQA, the sole South African body measuring and reporting on the quality of care for almost 7 million of the nearly 9 million privately-covered individuals in contracted medical schemes, does not include measures of disease severity.[234] Critics of the Donabedian model state that adequate evaluation requires large

sample populations, adjustments by case mix and also requires long-term follow-up, as outcomes may take considerable time to become observable".[312] Consequently any model that excludes variables of age, gender, ethnicity, disease duration and severity (essentially 'case mix') has the potential to invalidate the results.

With an estimated 7.0% of the South African population plagued by the burden of DM, an appropriate and successful response is critical.[1] Yet, as South Africa's Gini coefficient increases (from 0.593 in 1993 to 0.630 in 2014) disparities in healthcare systems (i.e. public and private) continue to widen.[313] With a larger proportion (70%) of South Africa's doctors working full-time in the resource-rich private sector (serving approximately 16% of the more-affluent population), the majority who are from a lower socioeconomic standing/status and are most likely to be more vulnerable/at higher risk of developing costly complications, have no choice but to obtain their healthcare from what has been described as a 'dysfunctional and run-down' healthcare system'.[167] Although in the present study complication rates and HRQoL outcomes were found to be similar between the two study sites, the differences in characteristics between the sites showed that each week the CDE served twice as many patients as at the CMJAH's diabetes clinic (Table 3.1). Hence, despite the potentially larger burden of disease faced by the CMJAH, a smaller number of this hospital's population receives the services/care they so desperately require. Much of the hope in addressing the abovementioned disparities rests on the promises embedded into/plans described by the NHI white paper, which proposes a system that has the potential to bring both sectors together to build a system that suits everyone's needs and provides quality care to all.[171] However under the NHI, the contemplated establishment of 'centres of excellence' could result in only the more-complex patients being managed at central hospitals. These academic hospitals would be under the control of the NDOH and would form the platform for the training of health workers and conducting research. As such they risk being separated to an extent from other academic hospitals, regional hospitals and district health services. This strategy could actually lead to even fewer patients accessing specialised care, particularly if patient selection criteria at these hospitals are stringent (i.e. only the extremely complicated cases to be treated/managed). This risk demands that one evaluates greater use of care beyond the specialised centres and engages the experts in outreach programmes. Achieving treatment objectives for T2DM requires close cooperation between the patient, the physician, and other members of the diabetes care team during the long course of the diabetic illness. In this regard, recommendations from the 2017 Lancet Commission on Diabetes in Sub-Saharan Africa indicate that there is value in modifying care plans towards a benefit-based tailored treatment (BTT).[160]

Hence, the implementation of a more 'patient-centered care' approach that would include modifiable patient factors identified in this study, could lead to enhancements in patient education, empowerment and improvement in the healthcare treatment experience which might lead to reductions in complications and/or cost savings. However, results from this thesis introduce a major caveat in that a question arises as to whether predominantly nurse-based care, even in a tertiary diabetes clinic, adequately identifies complications such as microvascular disease.

In any discussion about care in the two healthcare sectors in South Africa one cannot avoid the matter of cost. It was beyond the scope of this study to ascertain the cost-per-patient at the two sites. The main reason for exclusion of this element was the difficulty in accurately assessing such costs. Granted it is theoretically a simple matter to obtain costs at the CDE because as an audited, tax-paying, for-profit entity it is obliged to declare all income and expenditure, and costs-per-patient could be calculated with relative ease. However, given the widespread criticism of private sector providers who operate on a fee-for-service basis and are perceived as earning excessive salaries, the CDE was not enthusiastic about disclosing its financial statements. On the other hand, even with such information one would have had to go deeper into the costs of CDE patients who also paid contributions to medical aid schemes and whose diabetes management extended beyond the CDE (see above for review of "administrators of a major open medical scheme"). Similarly, costs at CMJAH are difficult to establish for reasons that include an inability to assess costs for specific out-patient areas in terms of salaries and operational expenditure. Maintenance and infrastructural costs are also difficult as they are the responsibility of a different provincial department, and again cannot be identified for a specific out-patient area within the hospital. There are also systematic distortions that are built into the two healthcare systems, for example the State tender system guarantees lower drug prices for the public sector and lower laboratory costs for services from the National Health Laboratory Services vs. the for-profit private sector laboratories. While accurate cost-per-patient data could not be determined, at a macro level one can once again cite the national statistics that indicate roughly equivalent expenditure of R200bn by each of the sectors, but the public sector spending is on ±47 million citizens while the private sector covers only ±8 million.[115] These statistics strongly suggest that private sector diabetes-related per-patient costs are substantially higher in the private sector.

7. RECOMMENDATIONS

Thus, how can the current situation be improved? A few possibilities are mentioned, although further research on each of these is still required.

7.1 Results from the present study suggest that certain high-risk groups require specific interventions:

a) Management of risk factors in high-risk groups e.g. attention to HbA1c in relation to macrovascular disease in Caucasians/Asians, attention to blood pressure control particularly in Black African/Mixed-Ancestry patients. Blood pressure might also be improved through attention to patient education. The weight profile, particularly of black females could also be addressed in terms of education (regarding diet and lifestyle modification).
b) Addressing the 'severity of diabetes' i.e. improving control of HbA1c, particularly of the CMJAH cohort to 'acceptable' levels, but taking into account the logistical problems such as distance from the clinic, and not below levels which place patients at risk for hypoglycaemia. No doubt there would be advantages in obtaining HbA1c results on the day of clinic attendance rather than responding to the result at the next visit. Constant attention to the most appropriate insulin regimen is necessary, which might also include attention to the variable supply of drugs in the public sector. The latter relates not only to frequent product changes from different suppliers but also to the problems of 'stock-outs.'
c) Optimising drug management of hypertension, again particularly at CMJAH where specific drugs may be more appropriate for the population served, but access to such drugs requires additional effort in terms of 'motivations' to hospital management.

7.2 The HRQoL of patients could be addressed by paying attention to access barriers, particularly in terms of enhancing patient experiences and improving services within the clinics.

7.3 The possibility of underdiagnosis of microvascular disease at CDE requires investigation.

7.4 With the country's commitment to NHI and a future that will involve the State contracting with private and public facilities, it is important that when performance of the facilities in the two sectors is assessed, the variables that are included do not only include access to care and processes of care but also include the case-mix of the populations served.

8. LIMITATIONS

Although cross-sectional and observational in nature, this study provides useful information on the quality of diabetes care received in the two specialised healthcare settings. However, some limitations should be noted:

- Only those patients who attended the study sites were included in the study. Patients who dropped out of care/treatment at a site for reasons such as a severe complication (e.g. disability through angina, stroke or peripheral vascular disease) were likely not included. Intuitively, in this regard, it can be assumed that the CMJAH patients would be more affected than CDE patients e.g. more difficulty with accessing care for someone with one of the abovementioned conditions. However, results from this study indicate that complications occurred at similar rates and HRQoL scores were similar. In other words, if there was a loss of sicker patients from the CMJAH group in comparison to the CDE, one would have expected this to manifest as lower HRQoL scores at CMJAH and/or as higher frequency of complications.
- Sample size is always a concern in a study of this nature. Perhaps with a larger sample some results may have differed with more comparisons reaching statistical significance.
- Full exploration of the roles of various drugs available at the two sites for glucose and blood pressure control was not carried out and is an area for future research.
- Whilst the primary objective of the present study was to assess the quality of care and outcomes in T2DM patients attending a public vs. a private specialised care clinic, the results are limited to these two settings. Given that South Africa has a burden of approximately 2.3 million adults with T2DM, one cannot confidently extrapolate the results of the ±300 patients in this study either to other public or private treatment sites or to the general population. However, of note in this regard is that the results of this study represent ‘real life’ practice, i.e. there was no Hawthorne Effect of the sites operating under specific study conditions.[314] Data were collected from patients, and consequently there was no awareness among healthcare providers that access to their services or their processes of care were being observed.
- Body Mass Index could not be assessed because height was not recorded for all patients. Weights alone suggest that BMI are in obese range at CMJAH (especially for the females), possibly related to lifestyle ‘lack of exercise’ and those on insulin treatment (regardless of daily dosage) as recently shown in a study.[315]

- Clinical assessment of ocular, retinal and renal complications may be more rigorous at CDE (fundal photography by a trained technician; renal disease on the basis of microalbuminuria or proteinuria-positive. Not all patients CMJAH have annual microalbuminuria tested). As such there is the possibility of relative under-diagnosis at CMJAH, particularly of early complications. This may also apply to other screening methodologies e.g. for vascular disease and sexual dysfunction. On that note, eye screening, foot care/screening, screening for vascular disease and screening for sexual dysfunction were not explored fully in the study but rather assumed to have occurred through ophthalmologist, podiatrist, doctor visits etc. Hence further studies, which take these variables into account, will need to be undertaken.
- Since the cross-sectional study design only allowed for the last recorded patient history, laboratory measurement values and medications to be captured during the study period, the researcher could not account for longitudinal trends of patients attending each setting.

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Appendix A - Management of Glycaemia in Diabetic Patients

All diabetics : HbA1c between 6.5 and 7 with no hypoglycaemia. If < 6.5 consider decreasing therapy.

HbA1c < 6.5 acceptable if on metformin monotherapy.

Individualize HbA1c target with consultant in following groups of patients:

1. Severe microvascular disease: End Stage Renal Disease, proliferative retinopathy
2. Established comorbid macrovascular disease: Ischaemic heart disease, stroke.
3. Age > 70
4. Hypoglycaemic unawareness
5. Frequent hypoglycaemia
6. Severe comorbid disease: metastatic malignancy, NYHA IV CCF on therapy, chronic kidney disease not for renal replacement therapy, end stage lung disease.
7. Poor functional status.

HbA1c targets to be reviewed in conjunction with a consultant annually.

Methods of glycaemic control

Type 1 DM

- Basal Bolus insulin using short acting insulin preprandial (TDS) and basal intermediate insulin either nocte or BD
- BD premixed is to be avoided unless already on premixed insulin with HbA1c at target.
- Alternate to conventional basal bolus to be considered in conjuction with a consultant if any of the following:
    - Severe comorbid macrovascular or microvascular disease
    - Poor baseline function
    - Hypoglycaemic unawareness

Type 2 Diabetics

Initial therapy guided by **baseline** HbA1c

HbA1c < 9	:	Diet + Metformin 850mg BD
HbA1c 9-11	:	Diet + Metformin 850mg BD + Gliclazide 80mg BD

HbA1c < 11/ketoacidosis : Diet + Metformin 850mg BD + insulin therapy.

If patient achieves target HbA1c within 12 months or diminishing insulin requirements to maintain target HbA1c patient to be considered for de-escalation to oral dual agent therapy.

Insulin Therapy

Titrate insulin dose to achieve fasting HGT between 4-7 and HbA1c between 6.5-7.0%. Increase dose by between 10-20% until HbA1c < 7.5 then increase dose more cautiously. Measure HbA1C every 3rd month until target attained.

Step 1: start nocte NPH insulin at 0.2u/kg

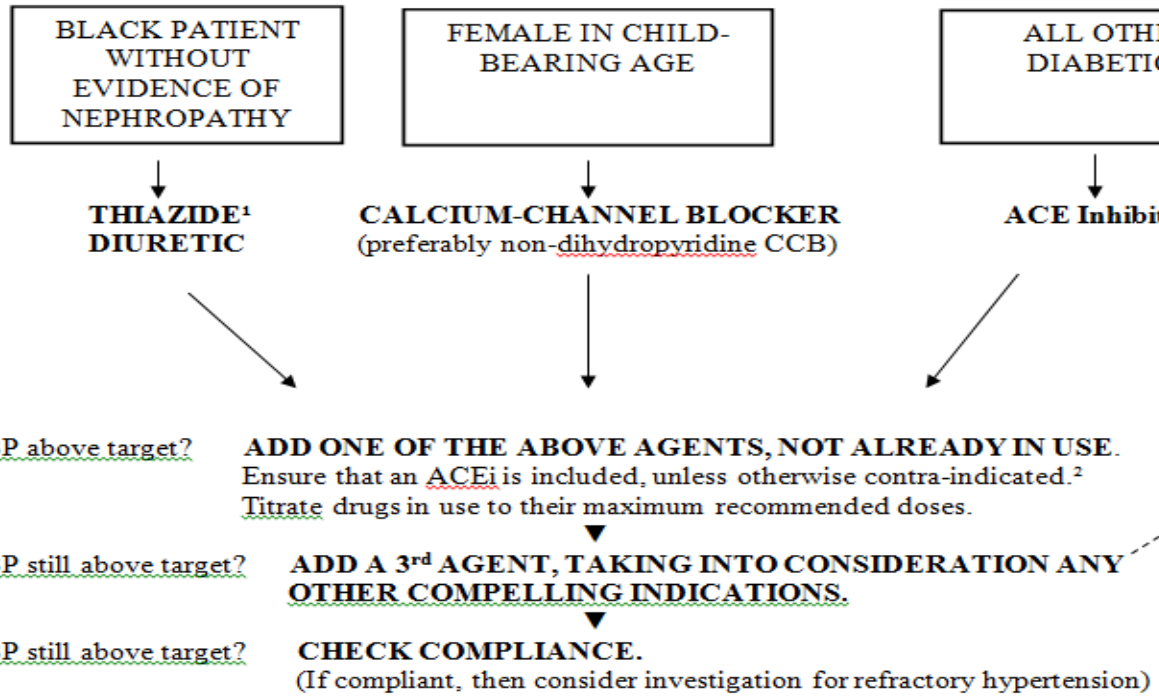
Step 2: BD NPH insulin at 0.3u/kg

Step 3: Titrate NPH dose to maintain fasting HbA1c between 4-7. Increase dose until 0.6u/kg

Step 4: If HbA1c not at target consider BD Actraphane increasing total dose of insulin by 10-20%.

Step 5: Basal insulin BD with addition of prandial short acting insulin TDS.

Appendix B - Management Of Hypertension In Diabetic Patients



Initiate 2 anti-hypertensive agents (ACEi *plus* thiazide) if:

- Stage III hypertension on presentation
- Black patient with microalbuminuria
- History of previous CVA

DRUG	COMPELLING INDICATIONS	CONTRAINDICATION
B- Blockers	History of angina, MI, CCF, tachyarrhythmias.	Peripheral vascular disease, bradycardia, Asthma, COPD Pregnancy
Loop diuretics	Hypertension assoc. with volume overload or a reduced GFR (CCF, nephrotic syndrome).	
Aldosterone antag.	Heart failure, post MI.	Renal failure Hyperkalaemia
Calcium Channel Blockers	Non-dihydropyridine CCB useful in the presence of heavy proteinuria not responsive to ACE inhibition alone.	± Anti-retroviral therapy ± Cardiac failure (for dihydropyridine agents)
Alpha Blockers	Benign prostatic hypertrophy	

BP TARGETS:

- *In the presence of micro-albuminuria:* **SP < 120mmHg, DP < 70mmHg**
- *If no micro-albuminuria:* **SP < 130mmHg, DP < 80mmHg**

Once target BP has been attained, monitor BP every 4-6 months.

[1] Thiazide diuretics are ineffective when GFR < 30ml/min/1.73m². Avoid use in patients with gout.

[2] For a person with intolerance to an ACE inhibitor (other than renal deterioration or hyperkalaemia), substitute an ARB for the ACEi. Monitor serum potassium and creatine in all patients, particularly if ACEi, ARBs or diuretics are prescribed.

Appendix C - Management of Dyslipidaemia in Diabetics

Lifestyle Modification for all patients: Diet and Exercise

Priority 1: Optimize LDL-C

LDL-C TARGETS	
ALL T2DM (Primary Prevention)	< 2.5 mmol/L
T2DM + Established Macrovascular Disease (IHD/CAD, TIA,CVA,PVD)	< 1.8 mmol/L

Exclude secondary causes:
Hypothyroidism, Nephrotic Syndrome , CKD, Alcohol, HIV

If not at target and patient adherent to treatment move to next step

STEP 1: Simvastatin 10mg nocte

STEP 2: Simvastatin 20mg nocte

STEP 3: Simvastatin 40mg nocte

STEP 4: Atorvastatin 40mg nocte

STEP 5: Atorvastatin 80mg nocte

IF HIV and on Efavirenz start with Atorvastatin 10mg

Priority 2: Optimize Triglycerides (Evaluate fasting level)

If newly diagnosed diabetic or presentation with acute hyperglycaemia (e.g. DKA, HONK) then institute glycaemic control (oral agents or insulin) and re-evaluate after 3-6 months

If on glucose lowering therapy and **triglycerides > 5mmol/L** then start fibrate (Bezafibrate SR 400mg daily) irrespective of LDL level.

If triglycerides < 5mmol/L then optimize LDL and glycaemic control (HBA1C = 7.0%) first.

Once LDL at target and if **triglycerides > 2.3mmol/L and HDL < 0.8mmol/L** then consider combination treatment: statin plus fibrate.

IDEAL TARGETS	
Fasting Triglyceride	< 1.7 mmol/L
HDL-C (male)	> 1.0 mmol/L
HDL-C (female)	> 1.2 mmol/L

If no contra-indication Aspirin (75mg - 150mg) is indicated for:

1. Secondary prophylaxis in all patients with established macrovascular disease (IHD/CAD, TIA,CVA,PVD)
2. Primary prophylaxis in males older than 50 or females older than 60 **AND** one or more risk factors: HT, smoking, dyslipidaemia, family history of CVD, albuminuria.

Appendix D – Essential Drug List 2014

Chapter 9: Endocrine conditions

9.2 TYPE 2 DIABETES MELLITUS

9.2.1 TYPE 2 DIABETES MELLITUS, IN ADOLESCENTS

E11.9

DESCRIPTION

The majority of adolescent diabetics are of type 1. However, an increasing number of adolescents are being diagnosed with type 2 diabetes mellitus.

Criteria for screening for diabetes in children

» Body mass index > 85th percentile for age and sex.
» Family history of type 2 diabetes mellitus.
» Presence of hyperlipidaemia, hypertension or polycystic ovarian syndrome.

AND

» Physical signs of puberty **or** age > 10 years of age.

DIAGNOSIS

» Symptoms of diabetes plus a random blood glucose ≥ 11.1 mmol/L.
– Random is defined as any time of day without regard to time since last meal. - The classic symptoms of diabetes mellitus include polyphagia, polyuria and polydipsia.

» Fasting plasma glucose ≥ 7.0 mmol/L.
  – Fasting is defined as no caloric intake for ≥ 8 hours.

It is difficult to distinguish type 2 from type 1 diabetes mellitus, as many type 1 diabetics may be overweight, or have a family history of type 2 diabetes mellitus, given the increasing prevalence of both obesity and type 2 diabetes mellitus. The diagnosis of type 2 diabetes mellitus in adolescents should be made in consultation with a specialist.

REFERRAL

All.

9.2.2 TYPE 2 DIABETES MELLITUS, ADULTS

E11.9

DESCRIPTION

Type 2 diabetes mellitus is a chronic debilitating metabolic disease characterised by hyperglycaemia with serious acute and chronic complications. It is an important component of the metabolic syndrome (see Section 9.5.1: Obesity in diabetes).
Most adults with type 2 diabetes mellitus are overweight with a high waist to hip ratio. In adults the condition might be diagnosed only when presenting with complications, e.g.:

» ischaemic heart disease
» peripheral artery disease
» stroke
» deteriorating eyesight
» foot ulcers
» erectile dysfunction

CLINICAL PRESENTATION

Symptoms of hyperglycaemia are:
» thirst, especially noticed at night
» polyuria
» tiredness
» periodic changes in vision due to fluctuations in blood glucose concentration
» susceptibility to infections, especially of the urinary tract, respiratory tract and skin

Note: It is important to distinguish type 2 diabetes mellitus from type 1 diabetes mellitus. Suspect type 1 diabetes mellitus among younger patients with excessive weight loss and/or ketoacidosis.

DIAGNOSIS

» Symptoms of diabetes plus a random plasma glucose ≥ 11.1 mmol/L.
– Random is defined as any time of day without regard to time since last meal.
» Fasting plasma glucose ≥ 7.0 mmol/L.
– Fasting is defined as no caloric intake for ≥ 8 hours.

MONITORING

<u>At every visit:</u>
» Finger-prick blood glucose.
» Weight.

» Blood pressure.

Baseline:
» Serum creatinine concentration (and calculate estimated glomerular filtration rate (eGFR)).
» Serum potassium concentration, if on ACE-inhibitor or eGFR < 30 mL/min.
» Urine protein by dipstix.
– If dipstix negative, send urine to laboratory for albumin: creatinine ratio, unless already on an ACE-inhibitor. (See Section 9.4.3: Diabetic nephropathy).
– If dipstix positive, see Section 9.4.3: Diabetic nephropathy.
» Blood lipids (fasting total cholesterol, triglycerides, HDL and LDL cholesterol).
» Foot examination.
» Eye examination to look for retinopathy.
» Abdominal circumference.

Annually:
» Serum creatinine concentration (and calculate eGFR).
» Serum potassium concentration, if on ACE-inhibitor or eGFR < 30 mL/min.
» Urine protein by dipstix.
– If dipstix negative, send urine to laboratory for albumin: creatinine ratio, unless already on an ACE-inhibitor. (See Section 9.4.3: Diabetic nephropathy.)

LoE: III[iv]

» HbA1c, in patients who meet treatment goals (3–6 monthly in patients whose therapy has changed, until stable).
» Eye examination to look for retinopathy.
» Foot examination.

Treatment targets

Parameter	Optimal	Acceptable	Additional action suggested
Finger prick blood glucose values:			
– fasting (mmol/L)	4–7	<8	> 8
– 2-hour post-prandial (mmol/L)	5–8	8–10	> 10
Glycosylated haemoglobin (HbA1c) (%)	< 7	7–8	> 8
Blood pressure Systolic	< 140 mmHg		
Diastolic	< 90 mmHg		

» In the elderly, the increased risk of hypoglycaemia must be weighed against the potential benefit of reducing microvascular and macrovascular complications.
» Prevent acute complications, e.g. hyperglycaemic and hypoglycaemic coma.
» Management of type 2 diabetes mellitus includes:
– Treatment of hyperglycaemia.
– Management of chronic conditions associated with diabetes. For treatment of hypertension and dyslipidaemia after risk-assessment, see Section 4.7: Hypertension and Section 4.1: Prevention of Ischaemic heart disease and

atherosclerosis.
– Prevention and treatment of microvascular complications. See Section 9.4: Microvascular complications of diabetes.
– Prevention and treatment of macrovascular complications. See Section 9.5: Cardiovascular risk in diabetes.

GENERAL MEASURES

» Lifestyle modification, including self-care practices.
» Education about diabetes and its complications.
» Increased physical activity, aim for 30 minutes 5 times a week.
» Appropriate weight loss if weight exceeds ideal weight.
» Discourage smoking.
» Moderate or no alcohol intake (≤ 2 standard drinks per day for males and ≤ 1 for females).
» Education about foot care.
» All patients should wear a notification bracelet.

Diet

» Consider the following for a person-centred approach to diet therapy:
– Weight.
– Lifestyle and physical activity.
– Cultural, social and economic issues.
» Dietary emphasis for improved glycaemic control should be on:
– Even and regular meal consumption.
– Low-glycaemic and high fibre foods. These foods are digested slowly resulting in a slow and steady rise in blood glucose concentrations.
– Reduced amounts of fat, sweets, sugary foods and sugar-containing beverages.

Fruit and vegetables

» Eat a variety of fruit and vegetables – 4 to 5 portions on a daily basis.
– One portion of which is a good source of vitamin C, e.g. tomato, cabbage family, citrus fruit and guavas.
– One portion, a dark green vegetable e.g. broccoli, green beans, spinach and baby marrow.
– One dark yellow/orange vegetable, e.g. carrots, pumpkin and butternut prepared without butter.
» Eat only one fruit (fresh) at a time.
– Fruit must preferably be eaten with a meal or as a snack.
– When eating dried fruit, limit the portion to the equivalent of a fresh fruit, e.g. 2 dried pear halves = 1 pear.

Carbohydrate

» Make starchy foods the basis of most meals.
» At least half of the grain intake should be from wholegrain products e.g. whole wheat, brown or rye bread, oats, whole wheat cereals, brown rice, whole wheat pasta.

Fat and cholesterol

» Reduce total intake of fat, saturated and transfat.

– Unhealthy fats include: animal fat, hard margarine, butter, cheese, and any type of oil heated to a high temperature.

– Use healthy types of fat, e.g. avocado pear, nuts, canola oil, canola margarine, olive oil and olives.

– Soft low fat margarine (in the tub) should preferably be used instead of butter or hard margarine.

– Never use 2 “fats” on bread e.g. when using a spread containing fat, do not use margarine as well.

– Use low fat dairy products e.g. low fat/fat free milk, low fat cheese.

– Limit the intake of cheese to a 30 g portion (a matchbox size or a third cup grated cheese) three times per week.

– Grilled or steamed fish/chicken (without the skin) should be eaten in preference to red meat.

– Eat at least 2 servings of fish per week.

– Small amounts of red meat (lean portions) ≤ three times per week.

– Protein source alternatives include legumes, e.g. peas and beans, lentils and soya products.

» Restrict food high in cholesterol, e.g. egg yolks, tripe, liver, processed meat (sausages), cheese, butter, fast food (fried chicken, hamburgers).

Salt

» Salt restriction may help to control blood pressure.

» Remove the salt from the table.

» Gradually reduce added salt in food preparation.

» Avoid processed foods.

MEDICINE TREATMENT

Oral blood glucose lowering agents

Stepwise approach:

» Add metformin to the combination of dietary modifications and physical activity/exercise.

» Combination therapy with metformin plus a sulphonylurea is indicated if therapy with metformin alone (together with dietary modifications and physical activity/exercise) has not achieved the HbA1c target.

» For persisting HbA1c above acceptable levels and despite adequate adherence to oral hypoglycaemic agents: add insulin and withdraw sulphonylurea.

» Ensure patient is adherent at each step.

» Oral agents should not be used in type 1 diabetes mellitus, renal impairment or clinical liver failure.

STEP 1

Lifestyle modification plus metformin

Entry to Step 1	Treatment and duration	Target
» Typical symptoms - thirst, tiredness, polyuria. **AND** » Random plasma glucose >11.1mmol/L. **OR** » Fasting plasma glucose ≥ 7 mmol/L.	» Lifestyle modification for life. » Appropriate diet. » Weight loss until at ideal weight. Initiate therapy with: • Metformin. » Assess monthly.	» 2-hour post-prandial finger-prick blood glucose: 8–10 mmol/L. **OR** fasting finger-prick blood glucose: 6–8 mmol/L. **AND/OR** » HbA1c:7–8%.

- Metformin, oral, 500 mg daily with meals.
  - Titrate dose slowly depending on HbA1c and/or fasting blood glucose concentrations to a maximum dose of 850 mg 8 hourly.
  - Contraindicated in:

– uncontrolled congestive cardiac failure
– severe liver disease
– patients with significant respiratory compromise

In patients with renal impairment, adjust dose according to table:

eGFR	Action
>30–60 mL/minute	» Continue use » **50% of dose (maximum 500 mg 12 hourly)** » Increase frequency of renal function monitoring (3–6 monthly)
<30 mL/minute	Stop metformin

LoE:III[V]

STEP 2

Add sulphonylurea:

Entry to Step 2	Treatment and duration	Target
» Failed step 1: HbA1c > 8 % or fasting finger-prick blood glucose > 8 mmol/L despite adherence to treatment plan in step 1 and maximal dose of metformin for 2–3 months. **OR** » 2-hour post-prandial finger-prick blood	» Lifestyle modification. **AND** » Combination oral hypoglycaemic agents, i.e.: • Metformin. **AND** • Sulphonylurea.	» 2-hour post-prandial finger prick blood glucose <8–10 mmol/L. **OR** » fasting finger prick blood glucose: 6–8 mmol/L. **AND/OR** » HbA1c:7–8%.

glucose > 10 mmol/L despite adherence to treatment plan in step 1 and maximal dose of metformin for 2–3 months.		

- **Sulphonylurea derivatives: glimepiride or glibenclamide.**

- Glimepiride, oral with or before breakfast.
  - Initially 1 mg daily, adjusted according to response in 1 mg increments at 1 to 2 week intervals.
  - Maximum dose of 4 mg daily.
  - Preferred in the elderly.

OR *LoE:III*[vi]

Glibenclamide, oral, 2.5 mg daily 30 minutes before breakfast.
- Titrate dose slowly depending on HbA1c and/or fasting blood glucose levels to a maximum of 15 mg daily.
- When ≥ 7.5 mg per day is needed, give $^{2}/_{3}$ of the total dose in the morning and $^{1}/_{3}$ at night.
- **Avoid in the elderly and patients with renal impairment**

LoE:III[vii]

Both glimepiride and glibenclamide should be avoided in patients with renal impairment i.e. eGFR< 60 mL/minute.

LoE:III[viii]

Sulphonylureas are contraindicated in:
» severe hepatic impairment
» pregnancy

Missing meals while taking sulphonylureas may lead to hypoglycaemia.

STEP 3
Insulin therapy: See Section 9.1.2: Type 1 diabetes mellitus, in adults.
» Insulin is indicated when oral combination therapy fails.
» Continue lifestyle modification.
» Insulin therapy must be initiated and titrated by a doctor, until stabilised.
» Stop sulphonylurea once insulin therapy is initiated but continue metformin.

LoE: III

Education for patients on insulin therapy:
» Types of insulin.
» Injection technique and sites of injection.
» Insulin storage.
» Self-monitoring of blood glucose and how to self-adjust insulin doses.
» Diet:
– Meal frequency, this varies according to the type and frequency of insulin, e.g. patients may need a snack at night about 3–4 hours after the evening meal.
– Consistent carbohydrate intake for patients receiving fixed mealtime doses of insulin.

» Recognition and treatment of acute complications, e.g. hypoglycaemia and hyperglycaemia.

Insulin type	Starting dose	Increment
Add on therapy: • Intermediate to long-acting	10 units in the evening before bedtime, but not after 22h00.	If 10 units not effective: increase gradually to 20 units (2–4 units increase each week).
Substitution therapy: • Biphasic	Twice daily. Total daily dose: 15 units divided as follows: ○ $^{2}/_{3}$ of total daily dose, i.e. 10 units, 30 minutes before breakfast. ○ $^{1}/_{3}$ of total daily dose, i.e. 5 units, 30 minutes before supper.	4 units weekly. First increment is added to dose before breakfast. Second increment is added to dose before supper.

LoE: III[IX]

REFERRAL

Urgent (same day)

» Acidotic breathing.
» Dehydration and hypotension.
» Nausea, vomiting and abdominal pain.
» Ketonuria (more than 1+).
» Hyperglycaemia > 25 mmol/L .
» Gangrene.
» Sudden deterioration of vision.
» Serious infections.

Note: Consider IV infusion with sodium chloride 0.9%, before transferring very ill patients.

Non-urgent

» Pregnancy.
» Failure of step 3 to control diabetes.
» eGFR < 30 mL/minute.
» Ischaemic heart disease.
» Cerebrovascular disease.
» Refractory hypertension.
» Progressive loss of vision.

9.3 DIABETIC EMERGENCIES

DESCRIPTION

Diabetics may present with a decreased level of consciousness owing to:

» hyperglycaemia diabetic ketoacidosis (DKA) or hyperosmolar hyperglycaemic state(HHS), or
» hypoglycaemia.

DIAGNOSIS

Check blood glucose concentration and test urine for ketones, immediately.

	Hyperglycaemia		Hypoglycaemia
	DKA	HHS	
Blood glucose	≥ 11.1 mmol/L		≤ 4mmol/L
Urine test for ketones	Usually positive and > 1+	Negative/ positive	usually negative

If a diagnosis cannot be made, treat as hypoglycaemia and refer urgently.
Low blood glucose presents the most immediate danger to life.

9.3.1 HYPOGLYCAEMIA IN DIABETICS

E10.0/E11.0

DESCRIPTION

Diabetic patients on therapy may experience hypoglycaemia for reasons such as intercurrent illness (e.g. diarrhoea); missed meals; inadvertent intramuscular injections of insulin or miscalculated doses of insulin or progressive renal failure leading to decreased insulin clearance; alcohol ingestion; and exercise without appropriate dietary preparation.
Risk factors include age < 6 years of age, low HbA1c and longer duration of diabetes.

Hypoglycaemia in diabetic patients can be graded according to the table below:

Mild/moderate hypoglycaemia	Severe hypoglycaemia
» Capable of self-treatment*.	» Semi-conscious **or** Unconscious/comatose.
» Conscious, but requires help from someone else.	» Requires medical help.

*Except children < 6 years of age.

Autonomic symptoms/signs	Neurological symptoms/signs
» Tremors	» Headache
» Palpitations	» Mood changes
» Sweating	» Low attentiveness
» Hunger	» Slurred speech
» Fatigue	» Dizziness
» Pallor	» Unsteady gait
	» Depressed level of consciousness/ convulsions

***Note:**

» Children, particularly < 6 years of age, generally are not capable of self-management and are reliant on supervision from an adult.
» Patients may fail to recognise that they are hypoglycaemic when neuroglycopenia (impaired thinking, mood changes, irritability, dizziness, tiredness) occurs before autonomic activation.

DIAGNOSIS

» Blood glucose < 4 mmol/L with symptoms in a known diabetic patient.
» Blood glucose concentrations should be measured with a glucometer to confirm hypoglycaemia.

Hypoglycaemia must be managed as an emergency. If a diabetic patient presents with an altered level of consciousness and a glucometer is not available, treat as hypoglycaemia.

EMERGENCY TREATMENT

» Measure blood glucose concentration with glucometer/testing strip, immediately.

Conscious patient, able to feed

Breastfeeding child

– give breast milk

Older children

– A formula feed of 5 mL/kg

OR

– oral sugar solution
  - Dissolve 3 teaspoons of sugar (15 g) in a 200 mL cup of water – administer 5 mL/kg

OR

– sweets, sugar, glucose by mouth

Adults

– sweets, sugar, glucose by mouth

OR

– oral sugar solution
  - Dissolve 3 teaspoons of sugar (15 g) in a 200 mL cup of water.

Conscious patient, not able to feed without danger of aspiration

Administer via nasogastric tube:

- Dextrose 10%, 5 mL/kg
  - Add 1 part 50% dextrose water to 4 parts water to make a 10% solution.

OR

– milk

OR

– sugar solution
  - Dissolve 3 teaspoons of sugar (15 g) in a 200 mL cup of water – administer 5 mL/kg.

Unconscious patient

Children

- Dextrose 10%, IV, 2–5 mL/kg.
  - 10% solution e.g. add 1 part 50% dextrose water to 4 parts water for injection to make 10% solution.

IV administration of dextrose in children with hypoglycaemia:

» Establish an IV line. Do not give excessive volumes of fluid: usually can keep line open with 2mL/kg/hour.
» Take a blood sample for emergency investigations and blood glucose.
» Check blood glucose.
– **If low, i.e. < 2.5 mmol/L or if testing strips are not available, administer 2–5 mL/kg of 10% dextrose solution IV rapidly.**
In the majority of cases an immediate clinical response can be expected.
» Recheck the blood glucose after infusion.
– If still low, repeat 2 mL/kg of 10% dextrose solution.
» After recovery, maintain with 5–10% dextrose solution until blood glucose is stabilised.
» Feed the child as soon as conscious.

Adults

LoE: III[X]

- Dextrose 50%, IV, 50 mL immediately and reassess.
  - If there is no clinical response, give a second 50% dextrose bolus.
  - Followed with dextrose 10% solution.
  - In the majority of cases an immediate clinical response can be expected.
  - Maintain with 5% dextrose solution after recovery until blood glucose is stabilised.

LoE: III[XI]

Alcoholics

- Thiamine, IV/IM, 100mg immediately.

CAUTION

Thiamine should preferably be administered prior to intravenous glucose to prevent permanent neurological damage.
Do not delay the dextrose administration in a hypoglycaemic patient.

REFERRAL

Urgent

» All hypoglycaemic patients on oral hypoglycaemic agents.
» Hypoglycaemic patients who do not recover completely after treatment.
» All children with documented hypoglycaemia unless the cause is clearly identified and safe management instituted to prevent recurrence.

9.3.2 DIABETIC KETOACIDOSIS (DKA)

E10.1/E11.1

DESCRIPTION

Clinical features of DKA include:

» dehydration
» abdominal pain
» vomiting
» deep sighing respiration
» drowsiness, confusion, coma
» acetone/fruity smelling breath
» elevated blood glucose

MEDICINE TREATMENT

Adults

Average deficit 6 L, and may be as much as 12 L.
Be cautious in renal and cardiac disease.
In the absence of renal or cardiac compromise:

- Sodium chloride 0.9%, IV, 15–20 mL/kg in the first hour
  - Subsequent infusion rate: 10 mL/kg/hour with 20 mL/kg boluses if shocked.
  - Do not exceed 50 mL/kg in the first 4 hours.
  - Correct estimated deficits over 24 hours.

LoE: III[xii]

Refer urgently with drip in place and running at planned rate.

When referral will take more than 2 hours and a diagnosis of diabetes with hyperglycaemia is confirmed:

- Insulin, short acting, IM, 0.1 unit/kg.
  - When giving insulin IM, do not use insulin needle.

CAUTION

Do not administer IV short-acting insulin if the serum electrolyte status, especially potassium is not known.
Continue with IV fluids but delay giving insulin in these cases in consultation with referral facility as this delay should not negatively affect the patient, but hypokalaemia with resultant cardiac dysrhythmias definitely will.
See Section 21.12: Hyperglycaemia and ketoacidosis

Children

If in shock:

- Sodium chloride 0.9%, IV, 20 mL/kg as a bolus.

» If shock not corrected, repeat the bolus.
» If a 3rd bolus is required, consult with paediatrician.

If no shock or aftershock is corrected

- Sodium chloride 0.9%, IV.

Fluid rates of sodium chloride 0.9%, IV (if no shock) in children awaiting transfer.		**Check regularly for shock or increasing dehydration**
Weight range kg		**Rate** (mL/hr) (2–10 kg: 6 mL/kg/hr) (>10-–20 kg: 5 mL/kg/hr) (>20–40 kg: 4 mL/kg/hr)
4	<6	25
6	<10	40
10	<15	60
15	<20	85
20	<30	100
30	<45	150
45	<80	200

LoE: III[xiii]

Refer urgently with drip in place and running at planned rate.

When referral will take > 2 hours and a diagnosis of diabetes with hyperglycaemia is confirmed and provided glucose is monitored hourly:

- Insulin, short acting, IM, 0.1 units/kg after 1st hour of infusion of saline ○ When giving insulin IM, do not use insulin needle.

9.4 MICROVASCULAR COMPLICATIONS OF DIABETES

9.4.1 DIABETIC NEUROPATHY

E10.2/E11.2/N08.3

DESCRIPTION

Neuropathies are a common complication of diabetes. They play an important role in the morbidity and mortality suffered by people with diabetes.
There are three major categories:

» peripheral neuropathy
» autonomic neuropathy
» acute onset neuropathies

GENERAL MEASURES

» Educate patient regarding appropriate footwear and good foot care.
» Patients with neuropathy should have their feet examined at every visit.

MEDICINE TREATMENT

Ensure appropriate glycaemic control.
Exclude or treat other contributory factors e.g.:

» alcohol excess
» vitamin B_{12} deficiency, if suspected,
» uraemia, and
» HIV infection.

Pain:

- Amitriptyline, oral, 10–25 mg at night increasing to 100 mg, if necessary.

LoE: III[XIV]

AND/OR

- Paracetamol, oral, 1 g 6 hourly as needed.

Gastroparesis:

- Metoclopramide, oral, 10 mg 8 hourly before meals.

LoE: III[XV]

REFERRAL

For further treatment if the above measures do not control symptoms adequately.

9.4.2 DIABETIC FOOT ULCERS

E10.5/E11.5

DESCRIPTION

Ulcers develop at the tips of the toes and on the plantar surfaces of the metatarsal heads and are often preceded by callus formation.

If the callus is not removed then haemorrhage and tissue necrosis occurs below the plaque of callus which leads to ulceration. Ulcers can be secondarily infected by staphylococci, streptococci, coliforms, and anaerobic bacteria which can lead to cellulitis, abscess formation, and osteomyelitis.

DIAGNOSIS

The three main factors that lead to tissue necrosis in the diabetic foot are:
» neuropathy,
» infection, and
» ischaemia.

GENERAL MEASURES

» Metabolic control.
» Treat underlying comorbidity.
» Relieve pressure: non-weight bearing is essential.
» Smoking cessation is essential.
» Frequent (e.g. weekly) removal of excess keratin by a chiropodist with a scalpel blade to expose the floor of the ulcer and allow efficient drainage of the lesion.
» Cleanse with sodium chloride 0.9% solution daily and apply non-adherent dressing.

MEDICINE TREATMENT

- Amoxicillin/clavulanic acid 875/125 mg oral 12 hourly for 10 days.

LoE: III[xvi]

REFERRAL

Urgent

Threatened limb, i.e. if the ulcer is associated with:
» cellulitis,
» abscess,
» discolouration of surrounding skin, or
» crepitus.

Non-urgent

» Claudication.
» Ulcers not responding to adequate treatment.

9.4.3 DIABETIC NEPHROPATHY

E10.2/E11.2/N08.9

DESCRIPTION

Screening

» Check annually for proteinuria using dipstix.
» A diagnosis of nephropathy can be made on either a positive dipstix or, if dipstix negative, send urine to laboratory for albumin:creatinine ratio. If ratio > 3 mg/mmol, diagnose nephropathy.
» Measure serum creatinine annually, and estimate eGFR.

LoE: III[xvii]

Diet and lifestyle

» Limit protein intake < 0.8 g/kg daily, if proteinuric.

» Advise smoking cessation.

MEDICINE TREATMENT

» Start treatment with an ACE-inhibitor and increase gradually to maximal dose if tolerated.

- ACE-inhibitor, e.g.:
- Enalapril, oral, initiate with 5mg 12 hourly.
  - Increase to 20 mg 12 hourly, as tolerated.
  - Monitor potassium, at baseline, within 1 month, and annually.

LoE: I[xviii]

Persistent proteinuria

See Chapter 9: Kidney and urological disorders.

Hypertension

Target BP: < 140/90 mmHg. See Section 4.7: Hypertension.

Diabetes mellitus

Target HbA1c < 7.5%.

- Intensify other renal and cardiovascular protection measures (not smoking, aspirin therapy, lipid lowering therapy).

REFERRAL

To specialist: When eGFR < 30 mL/minute or earlier if symptomatic.

9.5 CARDIOVASCULAR RISK IN DIABETES

E10.69/ E11.69

DESCRIPTION

The metabolic syndrome is a cluster of risk factors:

» impaired glucose metabolism
» central obesity
» dyslipidaemia
» hypertension

DIAGNOSIS

There is still some controversy as to whether the metabolic syndrome is a true syndrome or a cluster of risk factors. There are also varying diagnostic criteria around the world. The more components of the syndrome, the higher the risk.

MEDICINE TREATMENT

Aspirin therapy (Doctor initiated).

» Use aspirin therapy in adult Type 1 and Type 2 diabetic patients with a history of cardiovascular disease i.e.
  - ischaemic heart disease
  - peripheral vascular disease
  - previous thrombotic stroke

- Aspirin, orally, 150 mg (½ tablet) daily.

9.5.1 OBESITY IN DIABETES

E66.9

» Abdominal obesity, i.e. waist circumference > 94 cm in men, and > 80 cm in women.
» BMI: determined by weight in kg/height in m^2.

BMI (kg/m^2)	
18.5–24.9	normal
25.0–29.9	overweight
30.0–34.9	mildly obese
35.0–39.9	moderately obese
>40	extremely obese

GENERAL MEASURES

A decrease in food intake together with an increase in physical activity is crucial to losing weight.

MEDICINE TREATMENT

Treat the metabolic risk factors, i.e. dyslipidaemia, hypertension, and hyperglycaemia.

9.5.2 DYSLIPIDAEMIA IN DIABETES

E78.5

DESCRIPTION

Dyslipidaemia in type 2 diabetes is usually characterised by increased fasting plasma triglycerides (> 1.7 mmol/L), decreased HDL cholesterol (< 1.0 mmol/L in men and < 1.30 mmol/L in women) and to a lesser extent, increased LDL cholesterol. In those with type 1 diabetes, triglycerides, and to a lesser extent cholesterol concentrations, are usually increased.

MONITORING

See Section 9.2.2: Type 2 diabetes mellitus, in adults.

MEDICINE TREATMENT

Dyslipidaemia may successfully be treated through lifestyle modifications alone.

▪ HMGCoA reductase inhibitor (statin) therapy should be added to lifestyle modifications, regardless of baseline lipid concentrations, for all type 2 diabetic patients, who:

– are > 40 years of age
– have had diabetes for > 10 years
– have existing cardiovascular disease
– have chronic kidney disease (eGFR < 60 mL/minute)

• e.g. Simvastatin, oral, 10 mg at night.

In patients < 40 years of age, risk assess as for dyslipidaemia. See Section 4.1: Prevention of ischaemic heart disease and atherosclerosis.

LoE: III[xix]

REFERRAL

» Random cholesterol > 7.5 mmol/L.
» Fasting (14 hours) triglycerides > 10 mmol/L.

9.5.3 HYPERTENSION IN DIABETES

I15.2

BP lowering in hypertensive patients reduces cardiovascular risk. The diagnosis of hypertension is confirmed if the blood pressure remains > 140/90 mmHg on 2 separate days. See Section 4.7: Hypertension.

9.5.4 HYPERGLYCAEMIA

R73.9

See Sections 9.1.2: Type 1 diabetes mellitus, in adults and 9.2.2: Type 2 diabetes mellitus, in adults.

9.6 HYPOTHYROIDISM

9.6.1 HYPOTHYROIDISM IN NEONATES

E03.9

DESCRIPTION

Congenital deficiency of thyroid hormone due to aplasia/hypoplasia of the thyroid gland, defects in thyroid hormone biosynthesis or intrauterine exposure to antithyroid medicines. Congenital hypothyroidism is one of the common treatable causes of preventable mental retardation in children. Congenital hypothyroidism must be treated as early as possible to avoid intellectual impairment.

DIAGNOSIS

Clinical

» prolonged jaundice
» feeding difficulties
» lethargy
» constipation
» swollen hands, feet and genitals
» decreased muscle tone
» delayed achievement of milestones
» enlarged tongue

REFERRAL

All patients for investigation and initiation of therapy.

9.6.2 HYPOTHYROIDISM IN CHILDREN AND ADOLESCENTS

E03.9

DESCRIPTION

Hypothyroidism in children causes decreased growth, lethargy, cold intolerance and dry skin. Physical signs may include goitre, short stature, bradycardia and delayed deep tendon reflexes.
Congenital hypothyroidism may present in childhood. Acquired hypothyroidism in children and adolescents may be caused by:

» chronic lymphocytic thyroiditis
» iodine deficiency
» surgery
» radioactive iodine
» infiltrations

DIAGNOSIS

Elevated TSH and low T4 concentrations.

MEDICINE TREATMENT

- Levothyroxine, oral, 100 mcg/m^2 once daily, preferably on an empty stomach (Doctor initiated).

LoE: III[xx]

REFERRAL

All cases for investigation and initiation of therapy.

9.6.3 HYPOTHYROIDISM IN ADULTS

E03.9

DESCRIPTION

Hypothyroidism causes general slowing of metabolism, which results in symptoms that include fatigue, slow movement and speech, hoarse voice, weight gain, constipation, cold intolerance, depression and impaired memory. Physical signs may include bradycardia, dry, coarse skin, hair loss and delayed relaxation of deep tendon reflexes.

Common causes of primary hypothyroidism are:

» thyroiditis
» amiodarone
» post surgery
» radio-active iodine

Secondary hypothyroidism (< 1% of cases) may be due to any cause of anterior hypopituitarism.

DIAGNOSIS

» Check TSH concentration. If elevated, check T4 concentration.
» If TSH is elevated, and T4 is low, diagnose hypothyroidism.

MEDICINE TREATMENT

- Levothyroxine, oral, 100 mcg daily, preferably on an empty stomach.
  - If there is a risk of ischaemic heart disease, start at 25 mcg daily and increase by 25 mcg every 4 weeks.
  - In the elderly, start at 50 mcg daily, increased by 25 mcg at 4 week intervals, according to response.
  - Check TSH and T4 after 2–3 months and adjust dose if required.
  - Once stable, check TSH andT4 annually.

LoE: III[xxi]

REFERRAL

» Suspected hypopituitarism.
» Hypothyroidism in pregnancy.

9.7 HYPERTHYROIDISM

9.7.1 HYPERTHYROIDISM IN CHILDREN AND ADOLESCENTS

E05.9

DESCRIPTION

Hyperthyroidism is a pathological syndrome in which tissue is exposed to excessive amounts of circulating thyroid hormones. The most common cause is Grave's disease, although thyroiditis may also present with thyrotoxicosis.

DIAGNOSIS

Clinical

- » fatigue
- » nervousness or anxiety
- » weight loss
- » palpitations
- » heat insensitivity
- » tachycardia
- » warm moist hands
- » thyromegaly
- » tremor

REFERRAL

Urgent

All patients.

9.7.2 HYPERTHYROIDISM IN ADULTS

E05.9

DESCRIPTION

Most common cause of hyperthyroidism is Graves' disease, which is an autoimmune condition resulting from the presence of thyroid stimulating autoantibodies. Other common causes are toxic single or multinodular goitre and sub-acute thyroiditis.

DIAGNOSIS

Suppressed TSH and elevated T4

Note: T4 may be normal in hyperthyroidism.

REFERRAL

Urgent

All patients.

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Appendix E – CDE Clinical Guidelines 2015

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Clinical Guidelines 2015

The Use of Antibody Testing in the Management of Diabetes Mellitus

When should the Antibody Test be used?

If a patient has clinical symptoms of type 2 diabetes with early manifestation, below the age of 55 years, confirm diagnosis with antibody tests (i.e. If there is any doubt in Type-classification, perform the test).

LADA classification: If a type 2 patient is suspected of being LADA, perform the antibody test to detect for an autoimmune response, with impending insulin dependency.

What is the Antibody Test?

Detection of antibodies raised against GAD and IA-2 are both good indicators of an autoimmune response (type 1 diabetes).

Euroimmune Anti-GAD and Anti-IA-2 ELISA kits are run approximately once per week (once sufficient samples have been received) by most commercial labs. The test takes 2 days to complete.

Where do I Send the Samples?

Contact your local pathology laboratory for further details on the

requirements and procedure Sample required is usually a 7 ml clotted SST

tube.

When should the Antibody Test NOT be used?

Type 1 risk assessment: Do not use as a routine predictive tool of type 1 diabetes in related family members. To date there are no early intervention treatment guidelines available, so there is no clinical relevance. Testing for predictive purposes is considered ethically unacceptable.

Type 2 patients with oral treatment failure should be placed directly onto insulin, if required, without prior antibody testing.

The Treatment of Patients in Mild to Moderate Diabetic Ketoacidosis

On Admission:

 Assess level of consciousness (Glasgow Coma Scale) and symptoms of nausea / presence of vomiting

 Check

- BP
- Pulse
- Respiratory Rate
- Temperature
- Blood glucose (finger prick)
- Urine for ketones

 Contact the attending doctor and report findings whilst the following is done:

 Start intravenous therapy of Normal Saline, 1 litre to run over 1 hour

 Take venous blood for

- Urea & Electrolytes
- Creatinine

 Administer 6 IU **short / rapid acting** (Humulin R / Humalog / NovoRapid / Apidra) insulin as a stat IVI bolus.

Thereafter:

 Monitor Capillary Blood Glucose (finger prick) every 2 hours (continue nursing observations as required)

 Check **ALL** urine passed for ketones

 Intravenous therapy: Continue with normal saline

- Rate to be determined by Doctor
- KCl replacement to be determined by Doctor

 Insulin: 6 IU **short / rapid acting** insulin IVI as bolus hourly

Continue above regimen until blood glucose is below 12 mmol/l on 2-hourly blood glucose testing. As soon as a blood glucose of below 12 mmol/l is documented, change to the following regimen:

Intravenous therapy: **-** 5 % Dextrose Water, 1 litre + 1.5 g (20 mmol) KCl
Alternating with
- 5 % Dextrose Saline, 1 litre + 1.5 g (20 mmol) KCl, 8 hourly

Insulin: short / rapid acting insulin to be given as IVI bolus hourly as per 2-hourly capillary blood glucose measurements according to the last measured blood glucose as per the following scale:

Blood Glucose (mmol/l)	No. of Units short / rapid acting Insulin to be given Hourly
< 4	Nil
4.1 – 10.0	5u
10.1 – 16.0	6u
16.1 – 20.0	8u
> 20.0	10u

Note:

- Intravenous Dextrose and hourly insulin to be continued until urine is free of ketones
- Intermediate / Long-acting insulin may be prescribed in addition to the IV insulin – this must be administered **subcutaneously**
- Blood gas estimations are not done routinely – only on instruction from Doctor
- Patients are treated in a Medical Ward unless the Doctor requests transfer to ICU
- **ALL** urines to be tested for ketones

The Perioperative Management of Diabetes Mellitus

Introduction

Many different regimens have been described and used with varying amounts of success in managing diabetes during surgery. The commonest regimen utilizes the continuous intravenous infusion of insulin and glucose. However, this requires very good nursing care, unfortunately seldom found in our hospitals today. It is usually utilized only in the following circumstances:

1. With major surgery, (e.g. coronary artery bypass, vascular surgery etc.)
2. It requires an anaesthetist who fully understands the regimen.

3. Patients are usually nursed in an Intensive Care Environment post-op.

Unless one has fully trained nursing staff and an anaesthetist and surgeon all of whom understand insulin infusion techniques, it is best to use a simpler approach.

Surgery is divided into *major* and *minor* and for the purposes of this approach, they are defined as follows:

- *Major surgery*: patient unable to eat post-op
- *Minor surgery*: patient able to eat post-op

All surgery in patients with diabetes should be scheduled for first thing in morning if possible! There are thus four possible scenarios -

1. Minor Surgery in a patient on Oral Agents:

- This should be scheduled for first thing in the morning.
- Patient omits Oral Agents in the morning. Takes them with a light meal as soon as he / she recovers from anaesthetic.
- NO Intravenous glucose to be given
- If patient requires IV therapy, it should be Normal Saline.

2. Major Surgery in a patient on Oral Agents:

Before theatre:

- Check blood glucose (finger prick)
- Start IV 5 % Dextrose-Water alternating with 5 % Dextrose-Saline 8 hourly
- Add KCl as necessary (Usually 1 amp / 1.5 g per litre).
- Give empirical dose of 30 IU of a basal insulin (Protaphane, Humulin N, Lantus or Levemir) sub cut.
- Repeat this daily until IV therapy discontinued. (Dose can be adjusted depending on response).
- Use additional **short / rapid acting** insulin (Actrapid / Humulin R / Humalog / NovoRapid / Apidra etc) subcutaneously 6 hourly according to 6 hourly finger prick blood glucose - see scale of "top-up" insulin doses below.

- Today many units have developed their own algorithms for IV insulin infusions and these are now considered the “gold standard” of care, provided they are understood and implemented by trained staff.

Post-Op:

Continue as above. As soon as patient off IV therapy, stop insulin and resume OHA's.

3. Minor surgery in patients on insulin:

This must be done first in morning if problems are to be avoided.
Give normal insulin dose the day and night before surgery.
Omit insulin on morning of surgery

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Before theatre:

- Check blood glucose
- If over 10 mmol/l, give ↓ dose of normal morning insulin.
- If <10 mmol/l, no insulin.
- If IV therapy necessary, use Normal Saline only NOT Dextrose.

Post-Op:

As soon as patient awake, give normal morning insulin dose and follow with Breakfast.

4. Major Surgery in patients on Insulin:

Before theatre:

- Give normal insulin dose the day or night before surgery.
- On the morning of surgery check finger prick blood glucose
- Commence 5 % Dextrose-Water + 1.5 g (1 amp) KCl and alternate this with 5 % Dextrose-Saline + 1.5 g KCl 8 hourly.

Post-Op: There are three options depending on extent / seriousness of surgery and patients general condition:

a) Today many units have developed their own algorithms for IV insulin infusions and these are now considered the “gold standard” of care, provided they are understood and implemented by trained staff.

b) Give ↓ amount of patients TOTAL insulin dose (Add total 24 hour insulin doses together and divide by 3) as NPH (Protaphane or Humulin N) when IV therapy commenced

and give second equivalent dose as NPH in evening before bed. **Or** give 2/3 the total dose as once daily Lantus or Levemir. To this, add 6 hourly **short / rapid acting** insulin according to 6 hourly finger prick blood glucose as per "top-up' scale below. Continue this until patient able to discontinue IV and eat.

c) Give **short / rapid acting** insulin 6 IU IVI hourly and monitor finger-prick blood glucose hourly. Titrate dose of insulin up or down by 2 IU to "clamp" blood glucose between 6-8 mmol/l. This is the preferred regimen for unstable patients, more major surgery, and delivery / Caesarean for pregnant women. However, it requires trustworthy nursing and proper instruction of nursing staff.

Suggested "Top-up" Scale (as per 2. & 4)

Blood Glucose (mmol/l)	Short / rapid acting Insulin Dose (IU)
<6	Nil
6.1– 8	4
8.1 – 10	6
10.1– 15	8
15.1– 20	10
>20	12

This scale can be adjusted up or down by 2 IU across the board depending on patient response

Protocol for the Treatment of Type 1 Diabetes In Patients on the CDE Diabetes Management Programme

The treatment of type 1 diabetes is highly individualised and the treatment regimens used depend on a number of factors, including the patients age, level of literacy, work situation, family support systems and the presence or absence of both microvascular and macrovascular complications. As such, a detailed protocol for the treatment of type 1 diabetes is neither possible nor desirable. However, certain key management procedures are specified and need to be adhered to:

1. Patient Education: Every patient with type 1 diabetes must undergo adequate diabetes education, The amount of education provided will depend upon the individual patient's needs and requirements, but will be not less than:

i. a detailed training in the cause, management and prevention of hypoglycaemia and ketonuria / ketoacidosis,

ii. insulin action and insulin adjustment,

iii. the performance of home blood glucose monitoring and the interpretation of results, and

iv. The importance of and means of attaining and maintaining diabetes control.

Thereafter, patients will be expected to attend a session with the diabetes educator at least twice a year. More intensive education programmes will be provided for patients who request or are deemed suitable for this.

2. Emergency Care: Every accredited Preferred Provider (Diabetes Centre) is contractually obliged to provide a 24-hour emergency telephone contact number ("Hotline') so that all patients have emergency access when and if needed. Every patient must be given a Glucagon Hypo kit and urine ketone testing strips to enable community management of acute diabetes complications.

3. Other Health Care professionals: All patients must have access to and consult with a dietician, podiatrist and ophthalmologist as per the "Minimum Care Guidelines".

4. Insulin Regimens: Type 1 diabetes is a condition that results in a total lack of endogenous insulin. For survival, insulin replacement therapy must be given. Any insulin regimen used must take into account prandial as well as basal insulin requirements and must be administered at least twice daily. The insulin to be used is not circumscribed as there are numerous options available. The selection of an appropriate regimen is very individualised, dependant on a number of factors and should be a joint decision of the doctor, diabetes educator and the patient. As a general principle, a multiple injection regimen is preferred, using either human or analogue insulins and dependent upon the patient's individual requirements.

Insulin infusion pump therapy can be considered when indicated, as specified in the "CDE Insulin Pump Guidelines".

5. Home Glucose Monitoring: every patient will be supplied with a blood glucose monitoring meter and sufficient testing strips for their needs. Patients should be expected to test at least 3 times a day and should receive between 100 and 150 testing strips per month. More will be supplied in specific instances when required, such as pregnancy, adolescence, patients on insulin pumps or intercurrent illness.

6. Doctor's Responsibilities: These are outlined in the "Minimum Care Guidelines". Every patient will see the doctor at least once every 6 months. However, when deemed necessary, such as unstable or uncontrolled patients, children and adolescents, and in pregnancy, visits that are more frequent are expected, as often as the individual situation requires. The patient's doctor also shares risk, being responsible for hospital costs for any acute diabetes admission, as outlined in the "Minimum Care Guidelines.

Targets: The following treatment targets are recommended, but may vary dependant on individual patient circumstances

	Adults	Hypoglycaemic unawareness	16-18 years	6-16 years	2-5 years	<2 years
HbA_{1c}	<7 %	<8.5 %	<7.5 %	7-8.5 %	7.5-9 %	7.5-9 %

Fasting Glucose	4-6.7 mmol/l	4-8 mmol/l	4.4-6.7 mmol/l	4.4-10 mmol/l	5.5-12 mmol/l	5.5-14 mmol/l

Protocol for the Treatment of Type 2 Diabetes In Patients on the CDE Diabetes Management Programme

Objectives of the Diabetes Management Programme

A. To Promote a sense of Well-being in Patients who have Diabetes

- Patient education to permit patients to understand their condition, the importance of maintaining adequate glycaemic control and the means of achieving it.
- Promote patient self-empowerment in the management of their condition,
- Provide a sense of security for members of the Programme via constant availability and a 24-hour "Hotline" facility.
- Provide psychological support to patients in both coming to terms with a chronic condition and managing the necessary life-style changes. This may be achieved through rapport with the help of a psychologist if needed, but is supported by the dietician and rapport with the diabetes educator.
- Achieve satisfactory glycaemic control, not only rendering the patient asymptomatic, but also controlling blood glucose levels to an individualised target range that provides the optimum balance between the reduction in risk of microvascular complications of uncontrolled diabetes and the cardiovascular and other risks of hypoglycaemia.
- Avoid hospitalisation and reduce work / school absenteeism.
- Encourage healthy lifestyle, exercise and sport.

B. Prevent or Delay Complications:

- Discourage Smoking
- Define and treat additional risk factors (Lipids; Blood Pressure; Obesity etc as laid out in "Therapeutic Goals" (next page).)
- Attain and maintain optimal glycaemic control

C. Detect, Manage Or Refer For Management Any Complications That Might Arise:

- Ophthalmologist
- Cardiologist
- Vascular Surgeon
- Neurologist, Etc.

The CDE Diabetes Management Programme is only contracted to manage Diabetes. Some of the patients joining the Programme are already under the management of their current Family Practitioner or Specialist Physician and wish to remain under their own doctors for non-diabetes care. It is therefore sometimes necessary to refer these patients back to their own doctors for management of these co-morbidities. Wherever feasible, however, *CDE* doctors should attempt to provide total care to their patients under the Programme.

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Treatment Protocol for Type 2 Diabetes

Therapeutic Goals:

1. Glycaemic Control:

Glycaemic targets need to be **individualized**. Generally, the following HbA_{1c} targets apply:

- <6.5 % - Ideal for a newly diagnosed, younger and / or otherwise healthy individual
- <7.0 % - Recommended target for the majority of patients
- <7.5 % - Acceptable for elderly, high-risk individuals and those who are hypoglycaemia unaware
- <8.5 % - May be acceptable in some patients (E.g. The very elderly, those with a terminal illness)
- >8.5 % - Unacceptable

Recommended Blood Glucose Profiles on Home Monitoring		
	Ideal	Acceptable
Fasting	4.0-7.0 mmol/l	6.5-8.0 mmol/l
Random	4.0-7.0 mmol/l	5.0-10 mmol/l

Blood Glucose (Home monitoring) is recommended as following:

For patients on OHA's: 3-5 times a week

- 3 times weekly fasting
- 1-2 times weekly random, preferably before supper or 2 hours post-prandial

Patients on Insulin: At least 1-2 times daily, but more if control unstable.

2. Attainment of Acceptable Body Weight:

Do not set unrealistic targets.

- If overweight (BMI>26) - Aim for 5-10 % reduction in mass. More, only if possible.
- If normal weight (BMI<26) - Maintain adequate nutrition.

3. Achieve optimal blood lipid concentrations:

- Initially by dietary manipulation
- The majority of patients with type 2 diabetes will require statin therapy to attain lipid goals.

Aim for

- Total Cholesterol <4.5 mmol/l
  - LDL <1.8 mmol/l
  - TG <1.7 mmol/l
  - HDL >1.0 mmol/l (men), >1.2 mmol/l (women)

4. Adequate blood Pressure control:

Aim for <140/85 mmHg. If proteinuria / microalbuminuria present, aim for 120/70 mmHg.

In view of the CDE contractual obligations to the relevant Medical Aid and Medical Aid Administrators, the following treatment protocols concentrate solely on the treatment of the Diabetes / Glycaemia. However, it is inherent in our obligation to our patients that all other aspects of care, in particular those outlined above (e.g. Lipids, hypertension etc), will be appropriately and adequately assessed and treated according to accepted treatment guidelines and protocols.

All aspects of diabetes care and treatment will be funded from the Capitation fee (see "Minimum Care Guidelines" in CDE Association Contract). Additional therapies will be prescribed and administered according to the requirements, rules and drug formularies of the patients Medical Aid. As a gesture of good faith for those Medical Aids that have joined the CDE Programme, CDE doctors will at all times attempt to attain the best possible treatment outcomes in a cost-effective manner for treatments not included in the Diabetes Programme package. However, the patient's best interests must be given priority at all times.

CDE Clinical Guidelines 2015

A. Treatment protocol for People with Type 2 Diabetes

The CDE follows the 2012 South African guidelines published by SEMDSA

The 2012 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) Guideline for the Management of type 2 diabetes (Revised). JEMDSA 2012; 17 (2) (Supplement 1): S1-S95.

These guidelines are extremely comprehensive and current and should be carefully and fully read.

ANNEXURE 1

Protocol for use of Oral Hypoglycaemic Agents in Type 2

Diabetes In all patients, Metformin should be started on

diagnosis.

NOTE: ***It is the expressed intention of the Diabetes Management Programme that Centres are NOT dictated to as to which drugs to use and which sulphonylureas to select. This is left to the servicing doctor to decide, based on his own clinical experience. Since individual doctors are directly responsible for their own patient's well being and control, they must be comfortable with the agents they elect to use. The details below are therefore only recommendations and a guide to correct practice.***

A. INSULIN SENSITIZERS

Recent recommendations suggest that sensitizers should probably be prescribed de novo (On diagnosis)

- **Metformin**

a) ***Glucophage –*** recommended

b) ***Generics*** – Many available. In our experience, those that are not enteric coated tend to have more Gastrointestinal side effects. Therefore, if generics are used the enteric coated generics are suggested.

Recommended starting dose: 500 mg bd.
If excessive gastrointestinal effects occur, try taking after meals. With slow titration upwards, patients may be able to adapt to side effects.
Optimal dose 1g bd. - a dose of up to 3 grams daily may occasionally be tried in very obese patients. 1 g tablets are now available.
Comment: Theoretically can precipitate lactic acidosis and should not be used in the very elderly or those with significant renal or hepatic impairment or in the presence of established myocardial ischaemia.

c) Glucophage XR 500 mg- Slow-release format. Equipotent with standard metformin. Better intestinal absorption and less GIT side effects. Can be given once daily in a dose up to 4 tabs (2g) daily.

- **Thiazolidinediones (TZD's)**

Have different site and mode of action to metformin and work on both peripheral and hepatic insulin resistance. Had much promise on release, but are now being, or have been withdrawn. Should **NOT** be used.

Rosiglitazone has been linked to increased incidence of Coronary Heart Disease. Withdrawn from market.

Pioglitazone (15 mg and 30 mg) has been associated with increased fracture risk in women and increased incidence of bladder cancer. Has been removed from the South African Guidelines.

B. INSULIN SECRETOGOGUES

- **Sulphonylureas**

1) **Glibenclamide**

a) ***Daonil; Euglucon***

b) ***Glycomin; Glyben; Numerous other generics: -*** In our experience, all Glibenclamide generics are acceptable. However, Glibenclamide has fallen into disrepute because of tendency to cause severe hypoglycaemia. Better sulphonylureas are available.

Comment: Considered the most potent of the sulphonylureas and the most likely to cause hypoglycaemia, which may then be severe and protracted. Should no longer be used and has been removed as a sulphonylurea option in the SA Guidelines.

2) **Gliclazide**

a) ***Diamicron***

b) ***Ziclin; Glucomed; Rolab-Gliclazide; Diaglucide (Biogaran) & other generics*** **-** Our experience suggests that all these available generics are acceptable and seem to have a similar efficacy profile to the original. Can be used.

Recommended starting dose 40 mg ($^1/_2$ tablet) bd.
The maximum effective dose is probably not more than 80 mg bd. Higher doses are not recommended.
Comment: As with all sulphonylureas, can cause hypoglycaemia.

c) ***Diamicron MR 30 mg*** and ***60mg tablets***: a modified release formulation of gliclazide in which gliclazide release from the tablet better matches the circadian variation in glycaemia of the patient with type 2 diabetes. This modified release formulation also allows for once daily dosing leading to improved patient compliance. Patients changed from twice-daily gliclazide to once daily Modified Release had lower HbA_{1c} levels after the switch. Diamicron MR does not interfere with the protective effects of ischaemic preconditioning and

is associated with a low risk of hypoglycaemia. It is available in 30 mg and 60 mg tablets and is always given *once daily*. Diamicron 80 mg may be changed to DIAMICRON MR on a tablet for tablet basis i.e.: 1 x 80 mg TABLET Diamicron = 1 x 30 mg Diamicron MR. The dose can be increased to 120 mg daily.

d) ***Diaglucide MR 30 mg*** is a generic of Diamicron MR and is equivalent in all respects but cheaper. Can be recommended. Other generics now available.

3) **Glipizide**

Minidiab - No generic equivalent available
Recommended starting dose 2.5 mg (1/2 tab) bd.
Maximum effective dose is probably not more than 5 mg (1 tab) bd. Doses higher than 7.5 mg bd.
or 5 mg t.d.s not recommended.
Comment: Shortest acting of all the sulphonylureas and may have a place in treating the very elderly because of potentially reduced duration of hypoglycaemia, if it occurs. Because of the short half-life, it should be taken at least 2 or 3 times daily, which may be a disadvantage. Not often used.

4) **Glimepiride**

a) ***Amaryl;***

b) ***Glamaryl & other generics*** Recommended starting dose
1 mg daily

Maximum effective dose probably 4 mg daily and dose above 6 mg daily not recommended.
Comment: True once-a-day dosage schedule, less hyperinsulinaemia and weight gain and lower incidence of hypoglycaemia. Glimepiride can be taken before, during or after meals unlike the other sulphonylureas, which need to be taken before meals. Therefore could be indicated in elderly patients and those who are obese but need the addition of a sulphonylurea.

C. NON-SULPHONYLUREA INSULIN SECRETAGOGUES

1) **Repaglinide**

NovoNorm - No generic available. Ultra-short acting and taken with meals as often per day as the patient eats. Works on the sulphonylurea receptor and promotes acute phase insulin release. Comment: A relatively weak hypoglycaemic agent, not convincingly better than available sulphonylureas. Requires multiple daily doses (before all meals). May promote bad eating habits, but equally may be useful for occasional patients who are unable to eat regularly.

2) **Nateglinide**

Starlix - A unique amino acid derivative that restores the physiological pattern of early phase insulin secretion, resulting in a reduction in postprandial hyperglycaemia. Usual dose: 120 mg, 1-30 minutes before meals.
Comment: The most expensive of available insulin secretagogues. Although a different agent, has similar indications and dosing schedule to NovoNorm.

D. DPP4-INHIBITORS

- Do not cause weight gain and do not cause hypoglycaemia if used without a sulphonylurea or insulin.
- Correct place in therapeutic protocol would be second-line as an alternative to sulphonylurea, particularly in the very overweight patient.
- An expensive alternative to sulphonylureas.
- Can be tried as triple oral therapy before starting insulin.

1) Vildagliptin

a) ***Galvus:*** Starting dose 50 mg daily to be increased to 50 mg bd.

(Requires monitoring of hepatic enzymes before starting therapy and regularly thereafter - see package insert).

2) Saxagliptin

a) ***Onglyza:*** Only one dose of 100 mg daily (Liver function test monitoring not required.)

3) Sitagliptin

a) **Januvia**: Dose 100 mg daily. 25 and 50 mg doses are available for use with reduced renal function.

Comment: All three agents very similar in efficacy and price.

E. GLP-1 Agonists

- Injectable agents which have the advantage of causing weight loss together with a reduction in HbA1c.
- Do not cause hypoglycaemia.
- High incidence of GIT side effects, particularly nausea and vomiting.

- Extremely expensive.
- Recommended place is in patients with BMI >35 kg/m^2 on maximum effective doses of oral agents.
- Unfortunately being used widely by the general public as a weight-reducing drug.

1) Exenatide

a) ***Byetta:*** Dose 5 µg bd by subcutaneous injection for 1 month, then 10 µg bd.

2) Liraglutide

a) ***Victoza:*** Dose 0.6 mg daily by subcutaneous injection for 1 week, then 1.2 mg daily. Can go up to1.8 mg daily in selected individuals.

F. OTHER AGENTS

1) **Acarbose:**

Glucobay - no generic available
Recommended starting dose 25 mg ($^1/_2$ tablet) daily or bd., taken with meals and increasing slowly over several weeks to 50-100 mg t.d.s.
Maximum dose usually 100 mg t.d.s but very few patients are able to tolerate this dosage.
Comment: Works primarily by reducing post- prandial hyperglycaemia and has a fairly "weak" effect on overall blood glucose control. Cost / benefit ratio is dubious. It has a high incidence of gastrointestinal side effects, which many patients find unacceptable. Indication for use probably confined to patients with slight hyperglycaemia confined mostly to post-prandial glucose peaks. Does not add much to patients already approaching secondary failure and therefore of doubtful use as an "add-on" agent in patients already on optimal doses of other agents and inadequately controlled.

G. FIXED COMBINATION AGENTS

To reduce the tablet load in patients on polypharmacy, a number of combination tablets are now available

1) Glucovance

This is the first fixed combination oral agent to enter the South African market. It is a complimentary combination of the biguanide, metformin and the sulphonylurea, glibenclamide. It addresses the two core defects of type 2 diabetes (Insulin resistance and β-Cell dysfunction) and comes in the following strengths:

- 250 mg / 1.25 mg
- 500 mg / 2.5 mg

- 500 mg / 5 mg

Because the drug has a dual mode of action, lower dosing of the individual components is possible. This tends to improve tolerability. Improved compliance is expected with simplification of the treatment regimen. Good cost / efficacy ratio. If used, the prescribed strength must be stated carefully. The fact that it utilizes glibenclamide as the sulphonylurea is a disadvantage (see above).

2) Janumet

A combination of Januvia and metformin. Available in three strengths:
50/500, 50/850 and 50/1000 mg.
To be taken twice daily.
If used, the prescribed strength must be stated carefully

3) Galvus Met

A combination of Galvus and Metformin. Available in two strengths, 50/850 and 50/1000.
To be taken twice daily.
If used, the prescribed strength must be stated carefully

4) Amaryl Combi

A combination of Amaryl and metformin. Available in two strengths, 1/250 and
2/500, To be taken twice daily.
If used, the prescribed strength must be stated carefully

GENERAL COMMENTS

1. All patients will eventually require dual therapy with an insulin sensitizer and a secretagogue.

2. It is generally better to use lower doses of each agent in combination than increasing one agent to maximum effective dose before adding the second. An exception to this may be the massively obese patient where higher doses of metformin may be preferable to adding a sulphonylurea.

3. There is no purpose in combining two sulphonylureas in one patient.

4. If adequate glycaemic control is NOT being achieved on optimal doses of combination OHA's, it is better to accept the need for insulin therapy rather than use excessive doses of OHA's.

ANNEXURE 2

Insulin Therapy in Patients with Type 2 Diabetes

Criteria for commencing Insulin Therapy in a Patient on Optimal OHA Therapy:

1. Generally, insulin should be commenced in any patient who has an HbA_{1c} >7 % and / or Fasting Blood Glucose on Home Monitoring averaging >6.5 mmol/l. These targets may be individually adjusted if:

- Patient very elderly and asymptomatic
- Patient has another terminal disease.
- Patient lives alone and is incapable of self-management and/or is unable to recognize hypoglycaemia.

2. After myocardial infarction or revascularization procedure, irrespective of control, unless otherwise not indicated.

In all cases, insulin therapy in people with type 2 diabetes can and should be commenced on an outpatient basis by the Diabetes Educator. Adequate education into insulin therapy, injection technique and hypoglycaemia detection and management is essential. All patients should be supplied with Glucagon and a member of the family taught how to use it.

Suggested Insulin Regimens:

a) Combination therapy with Nocté NPH + OHA

Useful in patients as a starting regimen. Therefore this regimen works best when instituted fairly early.

Also useful as a "halfway" negotiation to wean resistant patients on to Insulin therapy - i.e. use this form of combination therapy for a few weeks before converting patients onto a more conventional bd. regimen.

Recommended Protocol: Start with 0.2 IU/kg body weight and increase by 4 IU every 3-4 days (under the guidance of the Diabetes Educator) until the fasting glucose is generally below 6.5 mmol/l. This can sometimes require a large dose of insulin to achieve and doses as high as 100+ IU NPH Insulin nocté have been recorded, without untoward effects. Patients should be advised to check their blood glucose at 3 AM once every 10 days until a stable dose has been established.

b) Combination therapy with once-daily insulin glargine (Lantus) or insulin detemir (Levemir) + OHA

This is an alternative first-line insulin therapy for people with type 2 diabetes. Glargine can be given at any consistent time of the day, as convenient for patient, but is usually instituted at night. Levemir, however, should be given at bedtime. Recommended as the first choice insulin for failed OHA patients, provided cost is not an issue. Should be used if patients experience nocturnal hypoglycaemia on NPH insulin.

Recommended Protocol: Add glargine or detemir to current OHA regimen, using same dose schedule as for NPH (above).

c) "Basal Plus" Regimen

If target Fasting Glucose levels are being achieved on a basal insulin regimen but the HbA_{1c} remains >7 %, the implication is that the post-prandial glucose levels are elevated. Start a short-acting analogue before the biggest meal of the day, titrating the dose to achieve a post-prandial glucose of <7.8 mmol/l. If target HbA_{1c} is still not achieved, introduce a second dose of short acting analogue before the second largest meal of the day etc.

d) Multiple Injection Regimens:

In some young and non-obese people with type 2 diabetes, a multiple injection regimen may be more acceptable to their lifestyle.

Recommended Protocol: Patients should be treated as for type 1 diabetes in all respects.

e) Combination therapy with before-supper pre-mixed insulin + OHA.

Occasionally used in patients who have large suppers and in whom the bedtime glucose level is too high, but with adequate glycaemic control during the day. This regimen is used often in the USA instead of nocté NPH or Lantus / Levemir.

f) Twice-daily Premixed Insulin

Probably the commonest, but not necessarily the best, insulin regimen used in type 2 diabetes. With the Pen-injectors it is easy to administer and simple to use. Good glycaemic control can be achieved with this in most patients with type 2 diabetes. A 30/70 Mix is usually employed (Humulin 30/70, Insuman Comb 30/70 or Biosulin 30/70). Humalog Mix25 / NovoMix 30 are also effective for this regimen and may be more convenient for some patients as they are able to inject at the time of the meal (and not 30-45 min before). Humalog Mix25 / NovoMix 30 may also control post-breakfast and post-supper hyperglycaemia better than the other premixed insulin's. Humalog Mix50 can be used three times a day in appropriate patients.

Recommended Protocol: Start with 0.3 IU/Kg body weight and with 2/3 before breakfast and 1/3 before supper (if patient follow European pattern of eating, or a 50:50 split for patients following a traditional South African meal pattern, where supper is the largest meal). Increase by 2-4 IU every 3-4 days according to the results of twice-daily (fasting and pre- supper) home glucose monitoring. NOTE: Due to the pathophysiology of type 2 diabetes and the tendency in this country for a large supper, morning glucose levels are often higher than evening levels and it is not unusual for patients to eventually require more insulin in the evening than in the morning

If adequate Glycaemic control or a satisfactory quality of life is not being achieved on a twice-daily regimen, conversion to a multiple injection regimen should be considered.

In some patients in whom 2 injections of pre-mix are not achieving the required result but who are resistant to a formal 4-injection per day basal-bolus regimen. Humalog Mix 50 given 3 times a day pre-meal may be an alternative.

Note: Once pre-prandial insulin (in the form of either a short acting analogue or premixed insulin) is instituted, there is no longer any place for the ongoing use of

sulphonylureas and they should be stopped. Metformin, however, should be continued indefinitely.

Appendix F – Ethics Clearance Certificate

R14/49 Mr Yacob Pinchevsky

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150140

NAME: (Principal Investigator)	Mr Yacob Pinchevsky
DEPARTMENT:	Pharmacy and Pharmacology Johannesburg Metropolitan Primary Care Clinics Associated with the University
PROJECT TITLE:	The Cost and Consequences of Treatment Failure in South Africa Type 2 Diabetics Across Different Healthcare Settings
DATE CONSIDERED:	30/01/2015
DECISION:	Approved unconditionally
CONDITIONS:	Additional Study Site : Centre for Diabetes and Edocrinology (CDE)
SUPERVISOR:	Dr Neil Butkow
APPROVED BY:	Professor P. Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	03/06/2016

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 Research Office Secretary in Room 10\004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised 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 to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in January and will therefore be due in the month of January each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix G – Approval of Title

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

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

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

03 June 2016
Person No: 0404881D
PAG

Mr Y Pinchevsky
P O Box 10643
Vorna Valley
1686
South Africa

Dear Mr Pinchevsky

Doctor of Philosophy: Approval of Title

We have pleasure in advising that your proposal entitled *A comparison of diabetes care of patients attending Charlotte Maxeke Johannesburg Academic Hospital and Houghton Centre for diabetes & endocrinology* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix H – Study Site Letter

To whom it may concern,

Please allow me to introduce myself - my name is Jan Pinchevsky and I am a researcher from the Department Of Pharmacy and Pharmacology, Faculty Of Health Science, University Of The Witwatersrand.

Under the supervision of Dr. N Butkow, we are currently involved in diabetes research. This research project is titled: "***A Comparison Of Diabetes Care Of Patients Attending Charlotte Maxeke Johannesburg Academic Hospital And Houghton Centre For Diabetes & Endocrinology***"

This study has objectives, and these are to determine:
1. The perceived barriers to access of diabetes-related healthcare in patients with type 2 diabetes mellitus attending either a public or private sector facility.
2. The processes of care associated with diabetes management that is provided to patients with type 2 diabetes mellitus attending either a public or private sector facility, using guideline derived, evidence-based targets.
3. The outcomes (primarily glycated haemoglobin, blood pressure, low density lipoprotein cholesterol and hospitalizations) attained in patients with type 2 diabetes mellitus attending either a public or private sector facility, using guideline derived, evidence-based targets.

For more details concerning the study, please refer to the attached protocol which is to be submitted and reviewed by the Wits Post Graduate Committee. Ethical approval for the study will also be sought by the University of the Witwatersrand's Human Research Ethics Committee.

The reason we have approached you is to request access to your clinic/hospital as a study site. We would like to collect patient information on diabetic patients at your clinic/hospital. Very importantly, the patient's information will be kept strictly confidential and will only be requested upon signed consent being granted. The information will be captured into case report forms and transferred to a secure database at the University for analysis.

All of the study's findings will be shared with the clinic/hospital and any other colleagues. None of the patient's files or records will be physically removed from the clinic/hospital premises.

If you would be willing to allow us access to your clinic– we would be most grateful. We are happy to assist you complete any forms/documents needed by your administration department for the study to occur. If there is any further information needed from our side, we are always available to answer. We appreciate your time and look forward to working with you.

Sincerely,

Jan Pinchevsky
PhD Student
082-837-4082
0404881D@students.wits.ac.za

Neil Butkow
PhD Supervisor
(011) 717-2371
Neil.butkow@wits.ac.za

Appendix I – Patient Questionnaire - Clinical

Study: "A Comparison Of Quality of Diabetes Care At Charlotte Maxeke Johannesburg Academic Hospital And Houghton Centre For Diabetes & Endocrinology"

Participant code:
Capture date (today's date):
Do you have diabetes (Y/N)?
How long have you had diabetes for (years)?
Healthcare Setting: [ ] CMJAH [ ] CDE Houghton
How long have you been treated at the above setting (months/years)?

Demographics

Instructions: please choose **one answer only**, unless requested to select more than one.

	Gender	[ ] Male [ ] Female	
	Date of birth	YYYY MM DD	
	Ethnicity (self-reported)	[ ] African [ ] Caucasian [ ] Asian/Indian [ ] Mixed-Ancestry (Coloured)	
	Education level (highest qualification achieved)	[ ] None [ ] Primary (Grade 1 – 7) [ ] Secondary (Grade 8 – 12) [ ] Tertiary (College, University)	
	Marital Status	[ ] Married [ ] Single [ ] Divorced [ ] Separated [ ] Widowed	
	Employment status	[ ] Unemployed [ ] Self-employed [ ] Retired [ ] Employed full-time [ ] Employed part-time	
	Current Suburb of Residence	(specify)	
	Do you have a South African ID?	[ ] Yes [ ] No	
	Are you a South African Resident?	[ ] Yes [ ] No [ ] Temporary Resident [ ] Permanent Resident	
	Are you a South African Citizen?	[ ] Yes [ ] No: (specify)	
	Which healthcare professionals do you normally see for your diabetes care/treatment at this clinic/hospital?	[ ] Doctor [ ] Nurse [ ] Dietician or Nutritionist [ ] Podiatrist [ ] Ophthalmologist [ ] Optometrist [ ] Biokineticist [ ] Psychologist [ ] Psychiatrist [ ] Physiotherapist [ ] Occupational therapist [ ] Pharmacist [ ] Emergency/Casualty department [ ] Other (please state):	
	Which of the following tests do you normally receive at this clinic/hospital, and also, how often per year?	[ ] HbA1c [ ] Lipogram [ ] Renal or microalbuminuria [ ] Full blood count [ ] Don't know	Frequency_____ Frequency_____ Frequency_____ Frequency_____
	Where, **apart** from at this clinic/hospital do you receive routine diabetes care/treatment?	[ ] Traditional healer practice [ ] Other public clinic [ ] Other public hospital [ ] Other private clinic [ ] Other private hospital [ ] Other (please state):	

	If yes, from which healthcare professional specifically?	[ ] Traditional healer [ ] Private doctor [ ] Nurse [ ] Dietician or Nutritionist [ ] Podiatrist [ ] Ophthalmologist [ ] Optometrist [ ] Biokineticist [ ] Psychologist [ ] Psychiatrist [ ] Physiotherapist [ ] Occupational therapist [ ] Pharmacist [ ] Emergency/Casualty department staff [ ] Other (please state):
	Medical aid status	[ ] Have (Yes) [ ] Don't have (No) If answered <u>Yes</u> above, please state: Medical aid name:_____ Plan name:_____ Plan cover (benefits): [ ] High [ ] Middle [ ] Low
	How do you pay for your appointments/laboratory tests/medications at this clinic/hospital?	<u>Private Sector</u> [ ] I pay in full without medical aid paying [ ] Medical aid and a co-payment from me [ ] Paid in full by my medical aid <u>Public Sector</u> [ ] I pay in full using cash/credit card [ ] I pay for only some of the costs: H1- H3 [ ] I don't pay, paid in full by government: H0, pensioner, unemployed [ ] Medical aid (IPLEASE USE PRIVATE SECTOR HEADINGS TO INDICATE HOW)
	Separate to the above, do you have to pay for **<u>additional diabetes-care related products or services</u>** not covered/provided by your medical aid/ government clinic (more than 1 answer possible)	[ ] Glucose meter [ ] Glucose test strips [ ] Ketone test strips [ ] Needles [ ] Lancets [ ] Syringes [ ] Glucagon [ ] Doctor [ ] Nurse [ ] Dietician or Nutritionist [ ] Podiatrist [ ] Ophthalmologist [ ] Optometrist [ ] Biokineticist [ ] Psychologist [ ] Psychiatrist [ ] Physiotherapist [ ] Occupational therapist [ ] Pharmacist [ ] Emergency/Casualty department [ ] Other (please state): [ ] Additional care/treatment, please state:
	What transport do you use to get to this clinic/hospital?	[ ] Walk [ ] Bicycle [ ] Minibus taxi [ ] Train [ ] Own car [ ] Bus (e.g Rea Vaya) [ ] Metered cab
	Cost of transport to get to this clinic and back home (excluding petrol)?	[ ] R0 [ ] <R5.00 [ ] R6.00 – R10.00 [ ] R11-R15.00 [ ] R16.00 – R20.00 [ ] R21 – R25.00 [ ] >R26.00 [ ] Other R_____
	Since the time you have been treated at this clinic/hospital, have you ever been	(please write out procedure date, procedure type and hospital name)

	hospitalized for a **diabetes related complication, procedure or treatment?** e.g. short stay (cataract removal, hypoglycaemia, dialysis), longer stay (DKA, diabetic coma, MI, stroke, amputation).	
Instructions: **More than one** answer may be selected. (Have you ever had difficulties receiving your diabetes care at the clinic/hospital because of…)		
	Inability to get to clinic:	[ ] Limited public transportation (e.g. taxi strike) [ ] You could not take time off from work [ ] You were too sick [ ] You didn't have a way to get there [ ] You had responsibilities to take care of someone [ ] You were afraid to leave home because of personal safety [ ] You had more important things to take care of
	Limited health care supply:	[ ] Limited number of doctors [ ] Delays in being seen and getting an appointment [ ] No appointment available [ ] There were problems being enrolled/registered (e.g. foreigner, necessary identification documents such as ID, passport not available)
	Lack of quality health care:	[ ] Inaccurate diagnosis [ ] Lack of trust in health care providers [ ] Lack of interest in patients [ ] Difficulty scheduling/long waiting times [ ] No decisions made last time by HCP/Previous negative experience [ ] Poor treatment by the healthcare professional
	Financial constraints:	[ ] Health care services too expensive [ ] Inadequate health care coverage (plan benefits/formularies/lab tests/consults) [ ] High cost of prescription medications [ ] Transport costs [ ] Payment to babysitter [ ] Sometimes I go without the medical care I need because it is too expensive [ ] Sometimes it is a problem to cover my share of the cost for a medical visit [ ] Had to use money for food, clothing , housing instead of healthcare
Instructions: please choose **one answer only**, unless requested to select more than one.		
	Travel time: On average, how long does it take you to get to this medical center/office?	[ ] <15 minutes [ ] 15-30 minutes [ ] 31-45 minutes [ ] 46-60 minutes [ ] 1 – 2 hours [ ] 2-3 hours [ ] 3-4 hours [ ] >4 hours
	Urgent appointment time: If you get sick and need to be seen before any appointment you already have in this	[ ] I can be seen without an appointment [ ] 2 days or less [ ] 3 days to 1 week [ ] 1–2 weeks [ ] 3-4 weeks

	clinic/hospital, how long does it take for you to get an extra appointment?	[ ] more than 4 weeks

	Waiting time: Once you get to this clinic/office, how long do you usually have to wait to see the healthcare professional								
Healthcare Professional	**Times**	<15 minutes	15-30 minutes	31-45 minutes	46-60 minutes	1-2 hours	2-3 hours	3-4 hours	>4 hours
	Doctor								
	Nurse								
	Dietician or Nutritionist								
	Podiatrist								
	Ophthalmologist								
	Optometrist								
	Biokineticist								
	Psychologist								
	Consultation length: What is the average duration of time spent with the healthcare professional								
Healthcare Professional	**Times**	<5 minutes	6-10 minutes	11-15 minutes	16-20 minutes	21-25 minutes	26-30 minutes	30-45 minutes	>45 minutes
	Doctor								
	Nurse								
	Dietician or Nutritionist								
	Podiatrist								
	Ophthalmologist								
	Optometrist								
	Biokineticist								
	Psychologist								

Appendix I – Patient Questionnaire – Dimensions & Visual Analogue Scale

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

100

We would like to know how good or bad your health is TODAY.

95

This scale is numbered from 0 to 100.

90

100 means the best health you can imagine.

85

0 means the worst health you can imagine.

80

Mark an X on the scale to indicate how your health is TODAY.

75

Now, please write the number you marked on the scale in the box below.

70

65

60

55

50

45

40

35

30

25

20

15

10

5

0

Appendix J – (Medical Record)

Study: "A Comparison Of Diabetes Care Of Patients Attending Charlotte Maxeke Johannesburg Academic Hospital And Houghton Centre For Diabetes & Endocrinology"

Participant code:
Capture date (today's date):
Participant's last appointment date in file:
Study time period date using participant's medical record:
Setting: [ ] CMJAH [ ] CDE Houghton
Date of Birth: YYYY MM DD **Gender:** [ ] Male [ ] Female **Diabetes Duration (years):**
Waist Circumference (cm): **Weight (Kg):** **Height (m):**
Ethnicity: [ ] African [ ] Caucasian [ ] Asian/Indian [ ] Mixed-Ancestry (Coloured)
Cardiovascular Disease: [ ] Stroke [ ] MI [ ] PVD [ ] Angina [ ] TIA [ ] Left Ventricular Hypertrophy [ ] Heart Failure [ ] Acute Coronary Syndrome
Microvascular Disease: [ ] Retinopathy [ ] Neuropathy [ ] Nephropathy
Cardiovascular Interventions: [ ] Bare-Metal Stent [ ] Drug-Eluting Stent [ ] PTCA [ ] CABG [ ] Carotid Endo-Artectomy [ ] Peripheral Vascular Disease
Family History: [ ] Familial Hypercholesterolaemia [ ] Premature CHD (<55 ♂ / <65 ♀)
Risk Factors for Coronary Heart Disease: [ ] Hypertension [ ] Hyperlipidaemia [ ] Obesity [ ] Smoking
Please record only the latest measurement of the following:

Current Blood Pressure (mmHg)	
Fasting / Random Blood Glucose (mmol/l)	
HbA1c (%)	
Total Cholesterol (mmol/l)	
Triglycerides (mmol/l)	
High Density Lipoprotein (HDL-C) (mmol/l)	
Low Density Lipoprotein (LDL-C) (mmol/l)	

Co-morbidities (e.g. Menopause, Gout, COPD, RVD)**:**

Hospital admission/Procedure Please indicate if the patient has any record of being hospitalized for a **diabetes related complication, procedure or treatment** since the time they have been treated at this clinic/hospital e.g. short stay (cataract removal, DKA hypoglycaemia, diabetic coma), long stay (MI, stroke, amputation), dialysis.	(please write out event and date of the event)	
Consultation (How many of the following consultations has the patient had in the 12 months/1 year **prior** to the last recorded appointment within the system? E.g. last appointment was 16/02/2016, therefore study period: 16/02/2015 - 16/02/2016)	Doctor	[ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] ___
	Nurse Educator (Basic Diabetes Knowledge/Self-Management)	[ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] ___
	Nutritionist (Diet)	[ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] ___
	Podiatrist (Foot Examination)	[ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] ___
	Optometrist (Eye Examination)	[ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] ___
	Ophthalmologist (Eye Examination)	[ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] ___
	Biokineticist (Exercise Prescribed)	[ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] ___
	Clinical Psychologist	[ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] ___
	Additional consultations outside the system (please write out HCP & frequency):	
Laboratory Tests (How many of the following tests has the patient had within the system in the **above study time period**?)	HbA1c	[ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] ___
	Lipogram	[ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] ___
	Renal function, microalbuminuria, creatinine	[ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] ___
	Full blood count	[ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] ___

Appendix K - EuroQoL Value Sets

Gerben Bakker <bakker@euroqol.org>
to me, Bianca

Dear Mr. Pinchevsky,

Thank you for your email.

In the absence of a value set for South Africa, we recommend to use the directly elicited value set for England / UK:
http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html

Best regards,

Gerben Bakker
User Support Officer
EuroQol Research Foundation

T: + 31 88 4400189
E: bakker@euroqol.org
W: www.euroqol.org

Appendix L – EuroQoL Study Registration

On Thu, Jun 2, 2016 at 10:19 AM, Bianca Smit <smit@euroqol.org> wrote:

Dear Ms. / Mr. Yacob Pinchevsky,

Thank you for registering your research at the EuroQol Research Foundation's website.

As the study "A Comparison Of Diabetes Care Of Patients Attending Charlotte Maxeke Johannesburg Academic Hospital And Houghton Centre For Diabetes & Endocrinology" you registered involves low patient numbers (302) you may use the EQ-5D-5L Paper version free of charge. Please note that separate permission is required if any of the following is applicable:

- Funded by a pharmaceutical company, medical device manufacturer or other profit-making stakeholder;
- Routine Outcome Measurement;
- Developing or maintaining a Registry;
- Digital representations (e.g. PDA, Tablet or Web)

Please find attached the Afrikaans (South Africa), English (South Africa), Sesotho (South Africa), Xhosa (South Africa), Zulu (South Africa) EQ-5D-5L Paper version (in MS Word format). A brief user guide is downloadable from the EuroQol website (www.euroqol.org).

Best regards,

Bianca Smit
Communications Officer
EuroQol Research Foundation

T: + 31 88 4400190
E: smit@euroqol.org
W: www.euroqol.org

Appendix M - Patient Information Sheet

Study: "A Comparison Of Diabetes Care Of Patients Attending Charlotte Maxeke Johannesburg Academic Hospital And Houghton Centre For Diabetes & Endocrinology"

Patient Information Sheet

Dear Patient,

The following information will allow you to familiarize yourself with the study:

WHO WE ARE:

Mr. Y Pinchevsky and Dr. N Butkow are scientists at the University Of The Witwatersrand, Faculty Of Health Science, Department Of Pharmacy and Pharmacology, currently working on diabetes research. This research will allow us to learn the answer to a question. This research project is headed under Dr. N Butkow and Mr. Y Pinchevsky for the purposes of a doctoral degree and will not replace the normal care you are receiving at your clinic or hospital.

WE KNOW THAT:

Diabetes is a disease of raised blood sugar (glucose).

WHAT WE WANT TO KNOW:

How you as an individual are experiencing care and management of your diabetes?

WHY?

Many studies have shown that when people with diabetes are managed correctly for their condition, they develop far less complications for their disease over time. What we want to know is, how does the management and care of South African people with Type 2 Diabetes compare with the diabetes care available in other countries.

BENEFITS?

We would like to know how South African diabetics are being managed for their disease. Once we have analysed the necessary information obtained, we will be able to determine where the challenges lie and will then be able to make recommendations to health care professionals such as doctors on where they should focus their attention more.

HOW CAN YOU HELP?

We are inviting you to take part in this research study.

If you agree to participate, we will simply ask you some questions about your diabetes management using a questionnaire. We will also need to capture information from your medical record from the clinic/hospital into a case report form. This will allow us to capture how your type 2 diabetes is being managed at the clinic/hospital and compare these findings with settings in other countries. We will only require 10 minutes of your time for this to happen.

We cannot offer any participant compensation for their involvement in this study, as he or she will not incur any additional cost in participation of this study.

Your information will only be filled into a case report form only ONCE you have agreed to participate (see below for specific information needed).

We will only need to capture your details on the day you agree to participate in the study and this will only occur one time. No further action is needed from your side.

If you do not wish to participate in this study, you will not be subject to penalty, loss of your normal routine medical treatment or loss of any other benefits.

At any stage of this study you may withdraw yourself from the study. If you do so you will not be subject to penalty, loss of your normal routine medical treatment or loss of any other benefits. In order to withdraw yourself as a participant from this study, please contact Y Pinchevsky (number below) for removal of your information from the database.

HOW WILL THIS STUDY BE DONE?

This study is an “observational” or “audit” type study, looking at diabetic medical information from the past year. The study is only taking place in the Gauteng area and we would like to have participants from different health care settings in the study.

Please note:

NONE OF YOUR PERSONAL INFORMATION WILL BE REQUIRED FOR THE STUDY (e.g. ID number, physical address)

1. Measurements

If you agree to participate in this study, the following information will be required:

- Demographical information (age, gender, ethnicity)
- Duration of diabetes
- Education level
- Socioeconomic status
- Employment status
- Medical aid status
- Waist circumference
- Weight
- Height
- Pre-existing disease
- Interventions e.g. surgery
- Family history
- Risk factors
- Current and previous blood pressure
- Glucose (sugar) or glycated haemoglobin (HbA1c) levels
- Cholesterol levels
- Diet intervention
- Exercise intervention
- Current medication

Questionnaire:

- The frequency of diabetes-related consultations, laboratory tests and care that you receive from healthcare professionals both within and outside of your normal healthcare facility every year.

- How your diabetes care is normally paid for.
- The reasons relating to why you were unable to get to the clinic in the past (if any).
- The reasons relating to why you have ever experienced problems with your healthcare supply or quality of healthcare relating to your diabetes care or treatment (if any).
- Travel times to the clinic/hospital for your diabetes care.
- Costs associated with travel to the clinic/hospital for your diabetes care.
- Waiting times associated with your diabetes care.
- Consultation duration times associated with your diabetes care.
- Your quality of life will be assessed using the WHOQOL-BREF, which is a validated tool created by the World Health Organization (WHO).

If you agree to participate in this study, your measurements (listed above) will be filled into a case report form or a questionnaire. The information from the case reports and questionnaire will then be placed into a database for analysis. The analysis will enable us to study how your Type 2 Diabetes is being managed.

Please also note that if we find that we have captured your data into the case report form or questionnaire incorrectly, we will need to get in touch with you once again to confirm the information. We may exclude any participant which does not meet the study's criteria, even if this has changed after the participant's consent has been obtained.

2. Confidentiality of Records

Your form will be given a unique participant code, which we will create when capturing your information. This means that only we will be able to match your code with your form. This will ensure that your medical information remains completely safe and secure.

Efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law.

3. Obtaining Additional information

You are encouraged to ask us any additional questions that occur to you at this time or at any other time during your participation in this study.

You will be given a copy of this information sheet to keep and refer to at a later stage.

Please don't hesitate to call us if you desire more information regarding this study (details below).

RISKS?

None. By participating in this research project, you will not be subjected to any pain nor will your personal information be used. Your participation will be voluntary, meaning that you may withdraw at any time. Withdrawal from this study will not result in any consequences WHATSOEVER.

Furthermore, if there are any significant new findings developed during the course of this study, we will contact the participant and make him/her aware of these findings and allow them the opportunity to decide if they are still willing to participate in the study.

WHAT HAPPENS AFTER THE STUDY?

Once we have analysed the necessary information obtained, we will be able to find where the challenges lie and will then be able to make recommendations to doctors on where they should focus their attention.

The results of this study will be published in medical journals for participants and their treating doctors to see or use.

THANK YOU

Contact Numbers

Mr. Y Pinchevsky
082 837 4082 (office hours)
0404881D@students.wits.ac.za

Dr. N Butkow
(011) 717 2371 (office hours)
Neil.butkow@wits.ac.za

Research Ethics Committee - 011-717-1234/1252/2700 (office hours)

Appendix N - Volunteer Consent Form

Study: "A Comparison Of Diabetes Care Of Patients Attending Charlotte Maxeke Johannesburg Academic Hospital And Houghton Centre For Diabetes & Endocrinology"

VOLUNTEER CONSENT FORM

Participant Code: _____

I have read the patient information sheet and have had an opportunity to ask any questions. All of my questions regarding the study have been answered. I have been given a copy of the information sheet as well as this consent form.

Signature: _____ Print Name: _____

Date: _____
(Participant)

I, the undersigned, have fully explained the relevant details of this study to the participant named above. I am qualified to perform this role.

Signature: _____ Print Name: _____
(Investigator)

Date: _____

Mr. Y Pinchevsky
082 837 4082 (office hours)
0404881D@students.wits.ac.za

Dr. N Butkow
(011) 717 2371 (office hours)
Neil.butkow@wits.ac.za

Appendix O – Lipid Outcomes

Biochemical Outcome Differences Of Study Patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH (n = 96)	CDE (n = 104)	p-values (pairs)
LDL-C (<2.5mmol/l), n (%)	60 (62.5)	70 (67.3)	NS
HDL-C (>1.0mmol/l), n (%)*	3 (9.1)	20 (32.3)	p<0.05
HDL-C (>1.2mmol/l), n (%)**	19 (33.9)	29 (55.8)	p<0.05

*** = men; ** = women; NS = Non-significant.**

Appendix P – Missing Data

Missing data were subjected to analysis to assess whether age, gender, ethnicity, duration of disease and disease severity were different in populations in which data were recorded or missing. Most variables were at or close to 100% complete. The highlighted variables below were found to be p>0.05 (therefore missing at random) with the exception of triglycerides at CDE which differed in terms of mean age (61.2 ± 11.4 vs. 68.3 ± 13.4 years; p=0.006). This latter finding is unlikely to have affected the results in terms of the multivariate analysis.

Table 9.2 Data available of Study Patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

Characteristic	CMJAH (n=144)	CDE (n=146)	Total (n=290)
Age, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Gender, n (%)	143 (99.3)	145 (99.3)	288 (99.3)
Duration of Diabetes, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Weight, n (%)	135 (93.8)	137 (93.8)	272 (93.8)
Ethnicity, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Education Level, n (%)	142 (98.6)	145 (99.3)	287 (99.0)
Marital Status, n (%)	142 (98.6)	146 (100.0)	288 (99.3)
Employment Status, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Specific Patient-reported Access Barriers, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Annual Dietician appointments, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Annual Nurse appointments, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Annual Doctor appointments, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Annual lipid profile tests, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Annual renal function tests, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Insulin, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Anti-hypertensive treatment, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Microvascular disease, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Macrovascular disease, n (%)	144 (100.0)	146 (100.0)	290 (100.0)
Systolic Blood Pressure, n (%)	143 (99.3)	136 (93.2)	279 (96.2)
Total Cholesterol, n (%)	94 (65.3)	120 (82.2)	214 (73.8)
Triglycerides, n (%)	91 (63.2)	113 (77.4)	204 (70.3)
LDL-C, n (%)	96 (66.7)	104 (71.2)	200 (69.0)
HDL-C, n (%)	89 (61.8)	114 (78.1)	203 (70.0)
HbA1c, n (%)	139 (96.5)	145 (99.3)	284 (97.9)
HRQoL, n (%)	126 (87.5)	144 (98.6)	270 (93.1)

Appendix Q – Multivariate Results

Table 9.3 Health Related Quality Of Life of Study Model Patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

	Unadjusted/Univariate models				Adjusted/Multivariate model			
Covariates	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value
Age	1.025	1.004	1.047	0.019	1.022	0.998	1.048	0.076
Duration of Diabetes	0.377	0.230	0.620	0.001	0.450	0.259	0.783	0.005
Nurse Visits	1.133	0.989	1.299	0.072	1.018	0.826	1.253	0.869
Dietician Visits	0.798	0.643	0.990	0.040	0.885	0.690	1.135	0.336
Site								
0= CMJAH	Ref				Ref			
1 = CDE	1.984	1.222	3.224	0.006	0.924	0.394	2.168	0.856
Education								
0 = None/Primary	Ref				Ref			
1 = Secondary/Tertiary	4.300	1.953	9.468	0.001	2.539	1.036	6.223	0.042
Barriers								
0 = None	Ref				Ref			
1 = One or above	0.293	0.177	0.484	0.001	0.303	0.169	0.543	0.001
Insulin Drug								
0 = None	Ref				Ref			
1 = On insulin	0.631	0.385	1.034	0.068	0.830	0.464	1.487	0.532
Antihypertensive								
0 = Negative	Ref				Ref			
1 = Positive	0.606	0.363	1.010	0.055	0.802	0.444	1.447	0.463

Table 9.4 Microvascular Complications Model of Study Patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

	Unadjusted/Univariate models				Adjusted/Multivariate model			
Covariates	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value
Age	0.980	0.958	1.002	0.071	0.997	0.967	1.028	0.843
Duration of Diabetes	0.977	0.946	1.008	0.147	1.130	0.576	2.219	0.722
Nurse Visits	1.258	1.075	1.474	0.004	1.390	1.062	1.820	0.017
Triglyceride	0.828	0.643	1.065	0.141	0.888	0.668	1.181	0.415
Annual Renal Tests	0.850	0.674	1.072	0.169	0.942	0.673	1.319	0.727
Site								
0= CMJAH	Ref				Ref			
1 = CDE	1.768	1.049	2.979	0.032	0.841	0.306	2.311	0.737
Insulin Drug								
0 = None	Ref				Ref			
1 = On insulin	1.870	1.073	3.259	0.027	2.736	1.278	5.860	0.010
Antihypertensive								
0 = Negative	Ref				Ref			
1 = Positive	1.672	0.937	2.983	0.082	1.953	0.891	4.280	0.095
Ethnicity								
0 = Black /Mixed*	Ref				Ref			
1 = Caucasian/Asians	1.553	0.915	2.637	0.103	1.405	0.624	3.165	0.412

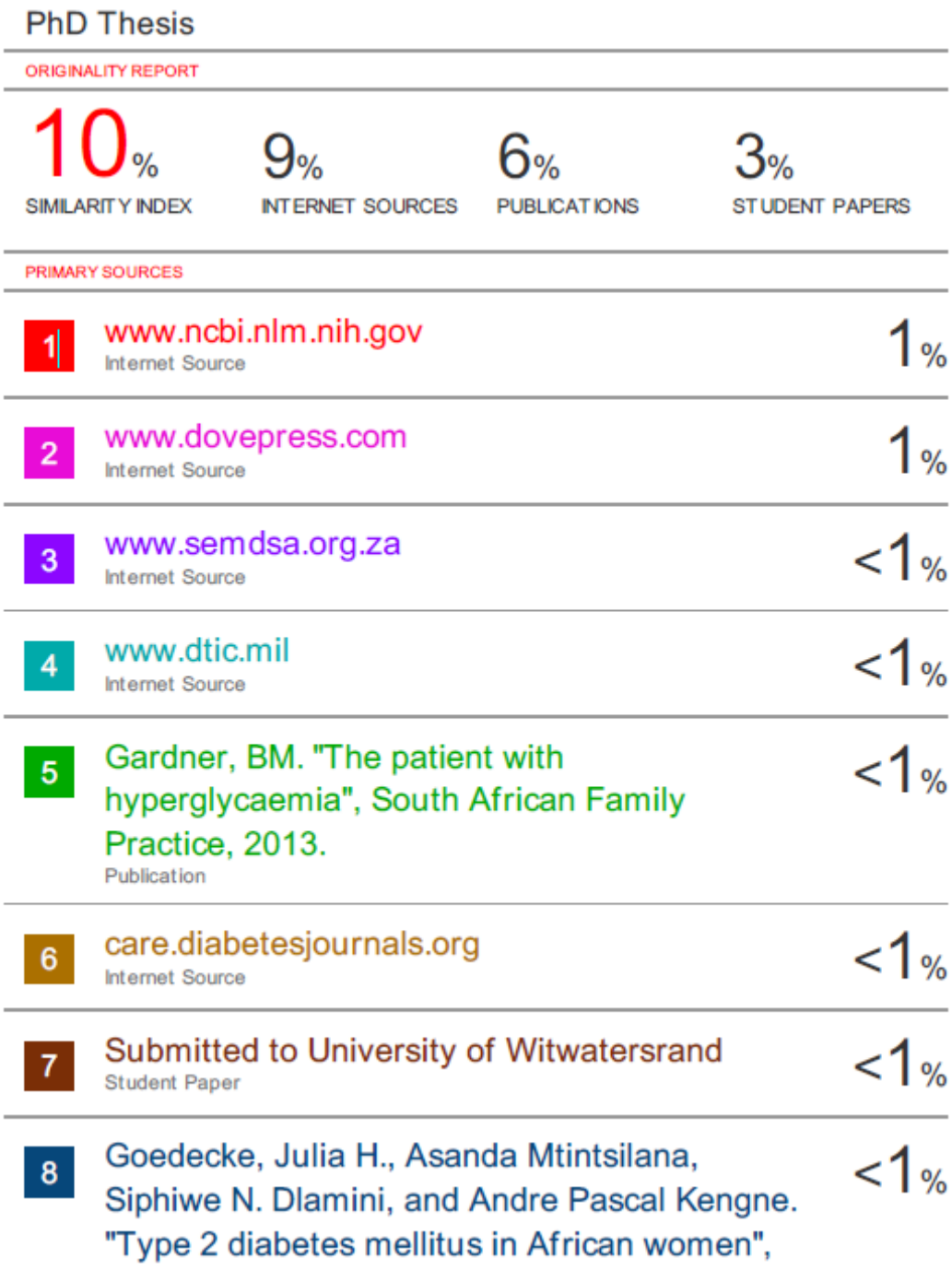
Table 9.5 Systolic Blood Pressure Model of Study Patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

	Unadjusted/Univariate models				Adjusted/Multivariate model			
Covariates	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value
Age	0.986	0.965	1.007	0.181	0.978	0.943	1.015	0.243
Dr	0.891	0.753	1.054	0.178	0.865	0.662	1.130	0.287
Nurse	0.727	0.628	0.842	0.000	1.011	0.750	1.362	0.944
Duration of Diabetes	2.138	1.293	3.532	0.003	1.450	0.668	3.145	0.347
LDL-C	0.810	0.604	1.087	0.160	0.696	0.478	1.015	0.059
Site								
0= CMJAH	Ref				Ref			
1 = CDE	0.291	0.172	0.492	0.001	0.508	0.162	1.597	0.246
Education								
0 = None/Primary	Ref				Ref			
1 = Secondary/Tertiary	0.230	0.117	0.451	0.001	0.273	0.103	0.724	0.009
Insulin Drug								
0 = None	Ref				Ref			
1 = On insulin	1.936	1.142	3.282	0.014	2.042	0.895	4.655	0.090
Ethnicity								
0 = Black /Mixed*	Ref				Ref			
1 = Caucasian/Asians	0.270	0.161	0.453	0.001	0.267	0.109	0.654	0.004
Barriers								
0 = None	Ref				Ref			
1 = One or above	1.946	1.183	3.202	0.009	0.911	0.416	1.994	0.815

Table 9.6 Glycated Haemoglobin Model of Study Patients attending Charlotte Maxeke Johannesburg Academic Hospital vs. Houghton CDE

	Unadjusted/Univariate models				Adjusted/Multivariate model			
Covariates	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value	Odds Ratio	Lower CL 95%	Upper CL 95%	*p*-value
Age	1.030	1.009	1.053	0.006	1.031	1.007	1.055	0.011
Duration of Diabetes	0.946	0.913	0.980	0.002	1.929	1.135	3.276	0.015
Nurse Visits	0.780	0.673	0.903	0.001	0.846	0.690	1.039	0.111
Dietician Visits	1.213	0.990	1.486	0.063	1.095	0.869	1.379	0.442
Site								
0= CMJAH	Ref				Ref			
1 = CDE	0.450	0.274	0.739	0.002	1.032	0.443	2.406	0.942
Barriers								
0 = None	Ref				Ref			
1 = One or above	1.807	1.097	2.975	0.020	1.424	0.816	2.485	0.213
Antihypertensive								
0 = Negative	Ref				Ref			
1 = Positive	1.438	0.863	2.395	0.163	1.268	0.724	2.222	0.407
Ethnicity								
0 = Black /Mixed*	Ref				Ref			
1 = Caucasian/Asians	0.617	0.376	1.014	0.057	0.981	0.527	1.829	0.953

Appendix R – TURN-IT-IN Report



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