Guideline compliance in type 2 diabetes care: Regional hospital outpatient department in the Dr Kenneth Kaunda District

DE Venter
orcid.org / 0000-0002-5087-9354

Dissertation accepted in fulfilment of the requirements for the degree Master of Pharmacy in Pharmacy Practice at the North West-University

Supervisor: Dr JM du Plessis
Co-Supervisor: Dr J Joubert
Co –Supervisor: Mrs M Vorster

Graduation: October 2019
Student number: 23509414
PREFACE

This research dissertation is presented in the form of four chapters with the results of the empirical study compiled in two drafted manuscripts. The first chapter is a brief overview of the study as a whole, and contains the problem statement, research methodology and ethical considerations of the study.

Chapter 2 contains the literature review wherein the literature objectives as stated in Chapter 1 were achieved. It provides an overview of the nature of type 2 diabetes mellitus, as well as the management practices of type 2 diabetes care, a picture of guideline compliances and patient outcomes both nationally and internationally.

The results of the empirical study are compiled in Chapter 3 and discussed in the form of two manuscripts. Manuscript one is intended for publication in the journal: Primary Care Diabetes. Manuscript two is intended for publication in the journal: Diabetes Research and Clinical Practice. Both of these manuscripts were structured according to the author guidelines stipulated by each journal. The two manuscripts are titled:

- Type 2 diabetes care: A gap in clinical care guidelines and clinical care practice.
- Glycaemic control at primary healthcare level: Regional hospital outpatient department in the Dr Kenneth Kaunda District.

Chapter 4 comprises the conclusions of both the literature review and empirical study, research limitations and recommendations for further research on the subject of guideline compliance in type 2 diabetes care.

A list of references and annexures contains any and all information not discussed in the chapters mentioned above.
ACKNOWLEDGEMENTS

Psalm 121: 2-3

My help comes from the Lord, the Maker of heaven and earth;

He will not allow your foot to slip. . . (HCSB)

I would first like to honour God, who has helped me and carried me through the course of this study. I would also like to thank the following people, without whom this study would not have been possible. Their guidance and support cannot be measured and therefore I would like to give a special thanks to all those who contributed to the completion of this study:

Dr Jesslee du Plessis, my supervisor, and my co-supervisors, Dr Rianda Joubert and Ms Martine Vorster for all their support, patience, feedback and input throughout the course of completing this study.

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The North-West University (NWU) and the research entity: Medicine Usage in South Africa (MUSA) for the financial and technical support.

The hospital research committee of the selected regional hospital for your willingness to allow my research to take place using patient records of patients treated at your medical outpatient department.

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My fellow master’s students and friends, Jo-Ancobe Jaquire and Nericke Olivier. Your prayers and support will stay with me for the rest of my life. Thank you for the friendship that has grown in the office where we all worked and laughed together.

My wonderful husband, Ivan Venter. Thank you for your love, patience, encouragement and countless prayers. You have been a rock on which I could lean during the entire course of this study. This is our work.
I would also like to thank my mother and father, Trudie and Cobus de Beer for their support and encouragement.
ABSTRACT

Title: Guideline compliance in type 2 diabetes care: Regional hospital outpatient department of the Dr Kenneth Kaunda District.

Keywords: Type 2 diabetes mellitus, guideline compliance, complications, care, management, clinical practice

The aim of this study was to assess healthcare provider compliance with the South African Primary Healthcare Standard Treatment Guidelines and Essential Medicines List 2014 edition (also referred to as the national type 2 diabetes care guidelines) with an emphasis on the recommended monitoring and treatment practices.

A literature review and empirical study were conducted in order to achieve the aim. The literature review was based on the following objectives: To give an overview of the nature of type 2 diabetes mellitus (T2DM), the management protocols for T2DM with a national and international scope, to investigate healthcare provider compliance with T2DM management protocols and the number of patients who reach therapeutic targets set by these protocols.

The empirical study was a quantitative non-experimental descriptive study with a retrospective longitudinal approach where hard copy patient records were reviewed for data relevant to the objectives of the study. The objectives of the empirical study were to assess healthcare provider compliance with the PHC STG EML 2014 recommendations for the monitoring and management of adult T2DM patients. This was done through a retrospective evaluation of patient records for evidence of clinical parameters tested and whether action was taken when indicated and if the actions taken were according to the recommendations of the PHC STG EML 2014. The next objective was to assess healthcare provider compliance with the recommendations for the management of specifically hyperglycaemia of adult T2DM patients. The target population consisted of all diabetes mellitus patients who received care at the selected regional hospital and the study population comprised all patient records who met the inclusion and exclusion criteria. All-inclusive sampling of the study population was done.

A total of 192 patient records met the inclusion criteria and were evaluated during the data collection period. The number of patient visits to the medical outpatient department (MOPD) were 1657 in number. The statistical analyses of the monitoring of specific guideline parameters were completed according to the number of these patient visits. Finger-prick blood glucose testing and blood pressure measurements were the only parameters that were monitored at more than 91% of the expected number of visits. Waist circumference measurement and albumin:creatinine ratio
testing were never performed for any of the patients. Baseline monitoring and annual monitoring were also sub-optimal and the monitoring of eye function and for neuropathy was done in reaction to the presence of microvascular complications. Action was taken when indicated and the majority of these actions in the form of pharmacologic treatment were performed according to the recommendations of the PHC STG EML 2014.

Healthcare provider compliance was optimal and showed a well-organised approach to the monitoring and care of hypertension and hyperglycaemia at every visit (which included monitoring of blood pressure and monitoring of blood glucose by means of a finger-prick blood glucose test). Healthcare provider compliance with the pharmacologic management of hypertension, dyslipidaemia, hyperglycaemia and microvascular complications was optimal. Healthcare provider compliance with the baseline and annual monitoring of guideline specific parameters at baseline and annually was sub-optimal with evidence of reactive care rather than proactive care and poor monitoring of glycosylated haemoglobin. The monitoring of these parameters is important and can be indicative of the presence of microvascular complications. The monitoring of glycosylated haemoglobin is also important as it is a superior indication of a patient’s blood glucose levels. Therefore, based on the sub-optimal compliance to the monitoring of these parameters, the overall compliance of healthcare providers with the PHC STG EML 2014 was sub-optimal, as the goals of the T2DM management were not met. These goals are to treat hyperglycaemia, hypertension and dyslipidaemia, to prevent the development of complications and to treat the complications that were present.
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<td>ACEi</td>
<td>Angiotensin converting enzyme inhibitor</td>
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<td>ADA</td>
<td>American Diabetes Association</td>
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<tr>
<td>AER</td>
<td>Albumin excretion rates</td>
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<td>AGE</td>
<td>Advanced glycosylation end products</td>
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<td>ARB</td>
<td>Angiotensin receptor blocker</td>
</tr>
<tr>
<td>b.i.d.</td>
<td>Twice daily</td>
</tr>
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<td>BMI</td>
<td>Body mass index</td>
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<td>BP</td>
<td>Blood pressure</td>
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<td>CDA</td>
<td>Canadian Diabetes Association</td>
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<td>CHD</td>
<td>Coronary heart disease</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CV</td>
<td>Curriculum vitae</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>d</td>
<td>Daily</td>
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<tr>
<td>DAG</td>
<td>Diacylglycerol</td>
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<td>DKKD</td>
<td>Doctor Kenneth Kaunda District</td>
</tr>
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<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>DN</td>
<td>Diabetic neuropathy</td>
</tr>
<tr>
<td>DPP-4</td>
<td>Glugagon-like polypeptidase-4 inhibitors</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<td>EML</td>
<td>Essential Medicines List</td>
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<td>FFA</td>
<td>Free fatty acids</td>
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<td>FPG</td>
<td>Fasting plasma glucose</td>
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<td>G6-P</td>
<td>Glucose-6-phosphatase</td>
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<td>GLUT</td>
<td>Glucose transporter</td>
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<td>GMD</td>
<td>Gestational diabetes mellitus</td>
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<td>GSH</td>
<td>Glutathione</td>
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<td>GSIS</td>
<td>Glucose stimulate insulin secretion</td>
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<tr>
<td>HbA1c</td>
<td>Glycosylated haemoglobin</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
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<tr>
<td>HCP</td>
<td>Healthcare provider</td>
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<td>HPCSA</td>
<td>Health Professionals Council of South Africa</td>
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<td>HREC</td>
<td>Health Research Ethics Committee</td>
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<td>IDDM</td>
<td>Insulin dependent diabetes mellitus</td>
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<tr>
<td>IDF</td>
<td>International Diabetes Federation</td>
</tr>
<tr>
<td>ID number</td>
<td>Identity document number</td>
</tr>
<tr>
<td>IFG</td>
<td>Impaired fasting glucose</td>
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<td>IGT</td>
<td>Impaired glucose tolerance</td>
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<tr>
<td>IHD</td>
<td>Ischaemic heart disease</td>
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<td>IL-6</td>
<td>Interleukin-6</td>
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<tr>
<td>IRS</td>
<td>Insulin receptor substrate</td>
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<td>LDL</td>
<td>Low density lipoprotein</td>
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<td>MI</td>
<td>Myocardial infarction</td>
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<td>Definition</td>
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<tr>
<td>MOPD</td>
<td>Medical outpatient department</td>
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<td>MPS</td>
<td>Medical Protection Society</td>
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<tr>
<td>MUSA</td>
<td>Medicine Usage in South Africa</td>
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<tr>
<td>NAD⁺</td>
<td>Nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NADPH</td>
<td>Nicotinamide adenine dinucleotide phosphate</td>
</tr>
<tr>
<td>NCD</td>
<td>Non-communicable disease</td>
</tr>
<tr>
<td>NIDDM</td>
<td>Non-insulin dependent diabetes mellitus</td>
</tr>
<tr>
<td>NWU</td>
<td>North-West University</td>
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<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<tr>
<td>PDK</td>
<td>Phosphoinositide dependent kinase</td>
</tr>
<tr>
<td>PEPCK</td>
<td>Phosphoenolpyruvate carboxykinase</td>
</tr>
<tr>
<td>PG</td>
<td>Plasma glucose</td>
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<tr>
<td>PHC</td>
<td>Primary healthcare</td>
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<tr>
<td>PI3K</td>
<td>Phosphoinositide 3-kinase</td>
</tr>
<tr>
<td>PKC</td>
<td>Protein kinase C</td>
</tr>
<tr>
<td>PPAR-γ</td>
<td>Peroxisome proliferator-activated receptor gamma</td>
</tr>
<tr>
<td>PPG</td>
<td>Post prandial plasma glucose</td>
</tr>
<tr>
<td>PPRM&amp;E</td>
<td>Policy, Planning, Research, Monitoring and Evaluation</td>
</tr>
<tr>
<td>RAAS</td>
<td>Renin-angiotensin aldosterone system</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
</tr>
<tr>
<td>RSA</td>
<td>Republic of South Africa</td>
</tr>
</tbody>
</table>
SAS® Statistical Analysis System
SDH Sorbitol dehydrogenase
SEMDSA Society for Endocrinology, Metabolism and Diabetes of South Africa
SGLT2i Sodium-glucose co transporter inhibitor
SHD Sorbitol dehydrogenase
SMBG Self monitoring of blood glucose
STG Standard Treatment Guidelines
TC Total cholesterol
TG Triglycerides
t.i.d. three times daily
T1DM Type 1 diabetes mellitus
T2DM Type 2 diabetes mellitus
WHO World Health Organization
UK United Kingdom
US United States
**LIST OF DEFINITIONS**

<table>
<thead>
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<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Aetiology</td>
<td>The cause or origin of a disease (Merriam-Webster, 2019).</td>
</tr>
<tr>
<td>Baseline</td>
<td>Baseline variables are measured before treatment is started and are used to characterise the patients and to measure patient outcomes after treatment is given (Assmann <em>et al.</em>, 2000:1033; Liu <em>et al.</em>, 2009:2509). For the case of this study, the baseline parameters were the first data of specific parameters measured within the study period.</td>
</tr>
<tr>
<td>Blood lipids</td>
<td>All blood lipids including cholesterol circulate in the blood in the form of lipoproteins. Cholesterol circulate in the blood as chylomicrons, very low-density lipoprotein, low-density lipoprotein and high-density lipoproteins. The low-density lipoproteins deliver cholesterol to the cells and high-density lipoproteins remove excess cholesterol from the blood and cells and deliver it to the liver in order to be excreted in the bile (Costanza <em>et al.</em>, 2012:131; Graham <em>et al.</em>, 1951:666; Widmaier <em>et al.</em>, 2016:557).</td>
</tr>
<tr>
<td>Clinical inertia</td>
<td>Failure to initiate or intensify treatment in a timely manner according to evidence-based clinical practice guidelines in patients who may potentially benefit from such initiation or intensification (Khunti <em>et al.</em>, 2018:428; Khunti <em>et al.</em>, 2013:3411; Phillips <em>et al.</em>, 2001:825).</td>
</tr>
<tr>
<td>Diabetes care</td>
<td>Involves a number of interventions for the treatment of hyperglycaemia (through a combination of diet, physical exercise and, if necessary, medication) and that of macrovascular risk factors such as hypertension and dyslipidaemia. Diabetes care also includes regular screening for damage to the eyes, feet and kidneys in order to facilitate early treatment.</td>
</tr>
</tbody>
</table>
Diabetes mellitus
A chronic disease that occurs when the pancreas does not produce enough insulin or when the body cannot effectively make use of the insulin that it produces (WHO, 2018).

Dyslipidaemia
A condition marked by abnormal concentrations of lipoproteins in the blood, such as increased low-density lipoprotein and decreased high-density lipoproteins (Mancini et al., 2018:178).

Fasting plasma glucose levels
Plasma glucose levels measured after no caloric intake for a period of eight hours or more (RSA, 2014:9.6; Sacks et al., 2002:436).

Gangrene
Death and decay of part of the body due to deficiency or cessation of blood supply. Causes include disease, injury and atheroma in major arteries, frostbite, severe burns and diseases such as diabetes mellitus. Two types of gangrene exist, namely: dry gangrene caused by cessation of local blood circulation and wet gangrene caused by bacterial infection (Oxford Concise Medical dictionary, 2015:305).

Glucose
Carbohydrates are absorbed from the gastrointestinal tract in the form of simple sugars, such as fructose, galactose and glucose. Glucose is the body’s major source of energy. Much of the glucose that is absorbed is catabolised to carbon dioxide and water providing energy for adenosine triphosphate formation. Glucose that was not catabolised is converted to glycogen, which is then stored for future use (Widmaier et al., 2016:565).

Glycaemic control
System of treating hyperglycaemia using a management protocol in order to reduce blood
glucose levels to sufficiently relieve symptoms of hyperglycaemia, but also to prevent or delay the onset of microvascular and macrovascular complications (SEMDSA type 2 diabetes guidelines expert committee, 2017:s34).

<table>
<thead>
<tr>
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<th>Definition</th>
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<tr>
<td>Glycosylated haemoglobin</td>
<td>Glycosylated haemoglobin is formed from the binding of glucose to amino groups of haemoglobin. Glycosylated haemoglobin values reflect the average blood glucose, including post-prandial blood glucose spikes over a period of two to three months (Little &amp; Sacks, 2009:113; Selvin et al., 2010:805).</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>Hyperglycaemia is defined as plasma glucose levels above 11.1 mmol/L (Hirsch, 2002:975).</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Abnormally high arterial blood pressure measured at three separate occasions over a period of two days, indicated by adult systolic blood pressure of 140 mmHg or a diastolic blood pressure of 90 mmHg or higher (Pinchevsky et al., 2015:82; RSA, 2014:4.15).</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>Blood glucose levels lower than 3.9 mmol/L (ADA, 2005:1245).</td>
</tr>
<tr>
<td>Idiopathic diabetes mellitus</td>
<td>Type 1 diabetes in which there is no known aetiology or pathogenesis of the destruction of beta-cells (Magliano et al., 2015:5).</td>
</tr>
<tr>
<td>Immune-mediated diabetes mellitus</td>
<td>Type 1 diabetes mellitus caused by chronic auto-immune destruction of pancreatic islets, thought to be mainly mediated through autoreactive, cytotoxic T-lymphocytes (Yoon &amp; Jun, 2005: 580; Graham et al., 2012:149).</td>
</tr>
</tbody>
</table>
| Incretin effect                           | Effect mediated by gastro-intestinal peptides such as glucagon-like peptide-1, which leads to the
increased secretion of insulin as well as the suppression of glucagon secretion (Amod et al., 2012:s26).

**Insulin resistance**

An abnormal biologic response to insulin, whether endogenous or exogenous; therefore, insulin has a limited ability to reverse a hyperglycaemic metabolic state. Insulin resistance is manifested by an increase in fasting and post-prandial blood glucose levels (Petersen & Shulman, 2002:11G; Sattar et al., 2015:339; Tabák et al., 2009:2218).

**Macrovascular complications**

Macrovascular complications are caused by damage to large vessels of the circulatory system (Fowler, 2008:77; Kaul et al., 2012:8).

**Microvascular complications**

Microvascular complications are defined as damage to small blood vessels, which contributes to diabetic neuropathy, nephropathy and retinopathy (Fowler, 2008:77; Kaul et al., 2012:8).

**National type 2 diabetes care guidelines**

For the purpose of this study, the national type 2 diabetes care guidelines were taken as the management of type 2 diabetes mellitus defined by the Primary Healthcare Standard Treatment Guidelines and Essential Medicines List (PHC STG EML) for South Africa, 2014 edition (RSA, 2014:9.7).

**Nephropathy**

Damage to the kidney, characterised by a progressive rise in microalbuminuria and elevated glomerular blood pressure (Kaul et al., 2012:9).

**Neuropathy**

The presence of signs and/or symptoms of dysfunction of the peripheral nerve in patients with diabetes mellitus, after any other causes have been excluded (Boulton, 2012:61).

**Pathogenesis**

<table>
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<tr>
<th>Patient record</th>
<th>Any relevant record made by health practitioners at the time of or subsequent to a consultation and examination or the applications of health management. A patient record contains the information about the healthcare of an identifiable individual (HPCSA, 2008:1). For the purpose of this study, all patient records are hard copies.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-prandial plasma glucose</td>
<td>Plasma glucose levels measured two hours after a glucose load (ADA, 2015:s8).</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Microvascular complications that damage the retinal vasculature, which is also a leading cause of blindness (Tarr et al., 2012:88).</td>
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<tr>
<td>Type 1 diabetes mellitus</td>
<td>Previously known as insulin dependent diabetes and is characterised by complete deficiency in insulin production, which requires daily insulin administration (ADA, 2014:s81; WHO, 2018).</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>Progressive disease characterised by hyperglycaemia caused by either insulin resistance or deficient insulin secretion or both (ADA, 2014:s81).</td>
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CHAPTER 1 RESEARCH PROTOCOL

1.1 Introduction

There is a continuous rise in the global incidence of diabetes mellitus (DM) (IDF, 2015:11; NCD-RisC, 2016:1521), to the extent of reaching epidemic proportions (Kharroubi & Darwish, 2015:850), affecting every country, age group and economy across the world (Home et al., 2013:92; IDF, 2015:11). While there are multiple forms of diabetes, the majority of all diabetes cases are type 2 diabetes mellitus (T2DM) (Desphande et al., 2008:1255; Mogre et al., 2016:s79). Type 2 diabetes mellitus is a progressive disease characterised by hyperglycaemia, caused by either insulin resistance, decreased compensatory insulin secretion or both, leading to impaired glucose tolerance (IGT) and ultimately T2DM (ADA, 2014:s81; Dunkley et al., 2015:923; Ozougwu et al., 2013:53). Good diabetes care, with the use of a standardised protocol, has the potential to prevent the development of complications associated with diabetes and maintain a good quality of life (Home et al., 2013:92; WHO, 2016:47). The majority of patients diagnosed with DM are uncontrolled and do not reach therapeutic targets (Amod & Berg, 2012:1; Igbojiaku et al., 2013:449). This leads to an increased incidence of complications, morbidity, healthcare costs and mortality of the disease (Desphande et al., 2008:1225; Giaccio & Brownlee, 2010:1058; Tripathi & Srivastava, 2006:RA138). Healthcare provider (HCP) compliance to diabetes care guidelines for the treatment of T2DM is sub-optimal (Braga et al., 2012:457; Pinchevsky et al., 2015:81). This leads to a gap between the clinical practice and the diabetes care guidelines (Home et al., 2013:93), which then impairs patient outcomes (such as blood glucose, glycosylated haemoglobin (HbA1c), blood lipids, creatinine clearance and glomerular filtration rate) (Amod & Berg, 2012:1; Pinchevsky et al., 2015:81).

1.2 Background

Diabetes mellitus is a collective term for a group of metabolic disorders characterised by hyperglycaemia (elevated blood glucose levels) resulting from defective insulin secretion and inadequate action to the produced insulin in target tissues (ADA, 2013:s67). There are different forms of DM, of which the majority can be categorised into either type 1 diabetes mellitus (T1DM) or T2DM (ADA, 2014:s81). Type 1 diabetes mellitus, also known as insulin dependent diabetes mellitus (IDDM), is caused by an absolute lack of insulin production and accounts for up to 10% of all diabetes cases (Ozougwu et al., 2013:47). Type 1 diabetes mellitus is treated with insulin therapy only (RSA, 2014:9.3). Type 2 diabetes mellitus, also known as non-insulin dependent diabetes mellitus (NIDDM) (ADA, 2014:s81), is caused by either impaired insulin secretion, insulin resistance or both (Ozougwu et al., 2013:52). This form of diabetes is the most prevalent globally.
and accounts for up to 90 to 95% of all patients diagnosed with DM (Mogre et al., 2016:s79). Gestational diabetes is a form of hyperglycaemia present during pregnancy (Desphande et al., 2008:1255), and might dissipate after birth (IDF, 2015:26). Other types of DM are caused by chemicals or disease (Desphande et al., 2008:1255).

Type 2 diabetes mellitus is a progressive and chronic disease that can affect many different organ systems in the body (Desphande et al., 2008:1257). The progression of T2DM starts with exposure to both modifiable and non-modifiable risk factors leading to impaired insulin secretion, insulin resistance or both. Both insulin resistance and impaired insulin secretion can lead to IGT that, if left untreated, leads to T2DM (Fonseca, 2008:s3). Patients with T2DM are at an increased risk for the development of serious complications (Forbes & Cooper, 2013:138). The development of these complications can be attributed to multiple risk factors such as hyperglycaemia, dyslipidaemia and hypertension (Raal & Blom, 2012:s57; RSA, 2014:9.7; Simò & Hernàndez, 2002:846). These complications can be divided into macrovascular complications and microvascular complications (Desphande et al., 2008:1257). Macrovascular complications include ischaemic heart disease (IHD), cerebrovascular disease and peripheral arteriopathy (damage to the arterial wall) (Jüllig et al., 2010:3367; Tripathi & Srivastava, 2006:RA137-RA138). Arteriopathy, in turn, could lead to the development of slow healing wounds, gangrene and ultimately amputation (Desphande et al., 2008:1257). Microvascular complications include retinopathy, nephropathy and neuropathy (Desphande et al., 2008:1257; Fonseca et al., 2009:s151-152). The overall microvascular complications of T2DM are caused by prolonged exposure to hyperglycaemia (Giacco & Brownlee, 2010:1059). Therefore, optimal glycaemic control assists to reduce the incidence of microvascular complications, while in the case of macrovascular complications, it is seen merely as risk factor management (Giacco & Brownlee, 2010:1058; Tripathi & Srivastava, 2006:RA138). Therefore, the goals of the diabetes care guidelines are to avoid acute decompensation, prevent or delay the appearance of late disease complications, decrease mortality, and maintain a good quality of life (Simò & Hernàndez, 2002:845).

Diabetes mellitus is a disease with one of the highest social and healthcare costs (Simò & Hernàndez, 2002:845). The disease accounted for up to 12% of the global health expenditure in 2015 (IDF, 2015:11), dedicated to the treatment of both the disease and its complications (Home et al., 2013:92). The global incidence of DM was 415 million patients in 2015 and has risen to 422 million in 2016 (IDF, 2015:11-13; WHO, 2018). The greatest rise in the incidence of DM can be seen in countries where there have been economic transitions, particular in the Middle East, sub-Saharan Africa, China and India (Home et al., 2013:92; Ozougwu et al., 2013:81). This increase
has the potential to put severe strain on healthcare systems in these countries (Home et al., 2013:92).

Despite the increasing burden of this disease, the HCP compliance with diabetes care guidelines continues to be sub-optimal and the goals for therapy are not met in the primary care setting, where most patients receive their care (Braga et al., 2012; Home et al., 2013:93). In South Africa, a large number of patients are not well controlled, with fewer than 10% of DM patients reaching targeted blood pressure (BP), blood lipids and blood glucose levels (Amod & Berg, 2012:1; Amod et al., 2012:81). Pinchevsky et al. (2015:81) stated that despite the strong evidence of improved outcomes through lifestyle and medication effectiveness, there is often sub-optimal compliance with risk factor management of T2DM. Sub-optimal diabetes care guidelines compliance was also seen in a study of the compliance with Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) diabetes care guidelines at a regional hospital in KwaZulu-Natal, South Africa (Igbojiaku et al., 2013:449). Inadequate diabetes care guidelines compliance could lead to difficulty in reaching therapeutic targets in clinical practice (Nam et al., 2011:2). There are a number of factors that contribute to poor diabetes care guidelines compliance, which cause a reduction in the quality of care due to a gap in clinical practice and the recommended guidelines (Braga et al., 2012:457; Home et al., 2013:93). These factors include (Home et al., 2013:93):

- The number of internationally recognised guidelines for the care of DM
- Continual updates
- Poor access to the guidelines
- Reduced access to healthcare resources of the target population.
Diabetes care guidelines are intended to provide clinicians, patients, researchers and payers with the components of diabetes care and tools to evaluate quality of care (ADA, 2010:s11; RSA, 2014:xviii). These guidelines ensure standardised care, reduce practice variation, improve patient outcomes and reduce morbidity due to T2DM (Woolf et al., 1999:527). Good diabetes care guidelines require maintaining simultaneous control of hypertension, dyslipidaemia and hyperglycaemia (RSA, 2014:9.7; Strain et al., 2014:303). The World Health Organization (WHO) (2016:50) states that good diabetes care guidelines should cover five basic principles:

- **Lifestyle interventions**: promoting a healthy lifestyle through a healthy, balanced diet, physical activity and the avoidance of tobacco use and alcohol abuse.

- **Glycaemic control interventions**: use of medication such as oral hypoglycaemic agents and/or insulin.

- **Macrovascular disease risk interventions**: use of medication to control cardiovascular disease risk.

- **Complication detection interventions**: regular all-inclusive eye- and feet assessments and urine protein analysis.

- **Patient referral interventions**: ensuring standard referral lines for primary- through to tertiary care.

The South African Primary Healthcare Standard Treatment Guidelines and Essential Medicines List 2014 edition (PHC STG EML 2014) (hereafter referred to as the national type 2 diabetes care guidelines) has been designed to provide care at clinics, community healthcare centres and primary healthcare (PHC) clinics, including the study setting, and contains the standard for management and care for conditions treated at the PHC level, including T2DM (RSA, 2014:xviii). These guidelines comply with the WHO requirements as stated above (RSA, 2014:9.8-9.22). The national type 2 diabetes care guidelines for adults provide management and monitoring guidelines for the care of patients with T2DM. Management of these patients includes the treatment of hyperglycaemia, hypertension and dyslipidaemia for the prevention of IHD and atherosclerosis, as well as the prevention and treatment of micro- and macrovascular complications (RSA, 2014:9.7). The monitoring guidelines include the measurement of specific parameters (blood glucose, BP, blood lipids, urine proteins, eye and foot assessments), done at every visit, at baseline (first data of specific parameters measured within the study period) and/or annually (refer to Annexure A (adapted from RSA, 2014:9.7-9.22; Amod & Berg, 2012:s57). The national type 2 diabetes care guidelines further provide the cut-off values at which treatment should be initiated and the steps to be taken should patients not reach therapeutic targets (RSA, 2014:9.7-9.22).
1.3 Problem statement

There is a constant increase in the incidence of DM patients globally, mainly T2DM (IDF, 2015:13; Mogre et al., 2016:s57). The majority of these patients are poorly controlled and have difficulty reaching the targeted blood glucose, BP and blood lipid levels (Amod & Berg, 2012:1; Igbojiaku et al., 2013:449). The poor control of these patients leads to the development of complications that increase the morbidity, healthcare costs and mortality (Desphande et al., 2008:1225). Compliance with the national type 2 diabetes care guidelines overall is sub-optimal, leading to a gap between clinical practice and the guidelines (Pinchevsky et al., 2015:81). This gap, in turn, reduces the quality of care and impairs patient outcomes (Home et al., 2013:93). It was therefore important to investigate, within the medical outpatient department (MOPD) of the selected regional hospital in the Dr Kenneth Kaunda District (DKKD) of the North West Province, the compliance of the HCPs with the national type 2 diabetes care guidelines in adults (RSA, 2014:9.7-9.22), in order to address the above stated problem.

1.4 Research aim and objectives

The aim and objectives of the study that are specific to the literature review and the empirical study will be discussed next.

1.4.1 Research aim

The study aimed to assess HCP compliance with the selected measures of the national type 2 diabetes care guidelines for adult patients, in the MOPD of the selected regional hospital in the DKKD of the North West Province during the study period of 1 March 2016 to 28 February 2018.

1.4.2 Specific research objectives

The study took on a two-dimensional approach of a literature review and an empirical study. The specific literature objectives were to:

- Generate a general picture of the nature of DM with the focus on T2DM;
- Give an overview of the goals of T2DM treatment, therapeutic approaches and therapeutic outcomes according to the diabetes care guidelines, both nationally and internationally;
- Generate a general picture of HCP compliance with the type 2 diabetes care guidelines and possible factors that could negatively impact such compliance;
• Investigate the overall number of T2DM patients reaching therapeutic targets both nationally and globally.

The specific empirical objectives were to:

• Assess the HCP compliance with the monitoring and management guidelines as set out by the national type 2 diabetes care guidelines for adult patients in the MOPD of the selected regional hospital in the DKKD of the North West Province. This was done through the review and evaluation of the following evidence:

(a) Documentation on the monitoring and treatment measures;
(b) Determining whether action was taken when treatment targets were not met;
(c) Determining whether the actions taken (if any) were according to the guidelines.

• The study expanded to assess HCP compliance with the management of specifically hyperglycaemia, according to the guidelines.

1.4.2.1 Literature review

A literature review was conducted to create an overview of the nature of T2DM, along with the management protocols, both nationally and internationally. The literature review also investigated HCP compliance with diabetes care practices and the number of patients who reach treatment targets.

Literature from search engines and databases such as Google Scholar™, Science Direct® and EBSCOhost®, which can be found on the North-West University’s (NWU) library site (http://library.nwu.ac.za), was used in order to reach the research-specific objectives. The researcher made use of keywords or -phrases (both as single entities and in various combinations) such as: ‘diabetes’, ‘type 2’, ‘management’, ‘treatment’, ‘guideline compliance’, ‘outcomes’ and ‘pathophysiology’.

1.4.2.2 Empirical study

The empirical study was a quantitative, longitudinal study design to reach the outlined objectives of the empirical study.

The researcher applied for approval of the study from the Health Research Ethics Committee (HREC) of the NWU, Potchefstroom Campus and the North West Department of Health (DoH): Policy, Planning, Research, Monitoring and Evaluation (PPRM&E) committee and the hospital
research committee. The researcher obtained approval from the hospital research committee by means of a formal meeting with the members of the research committee (see Annexure C for the meeting agenda). The researcher retrospectively collected data relevant to the study from patient records of T2DM patients who met the inclusion criteria. The data were processed and used to reach the specific objectives of the empirical study. This was to assess HCP compliance with the monitoring and pharmacological management of T2DM recommendations of the national type 2 diabetes care guidelines, and to further assess HCP compliance with the management of hyperglycaemia.

1.5 Research methodology

This section will cover the study setting, target and study population, inclusion- and exclusion criteria and study design of the research project.

1.5.1 Study setting

The study took place at the MOPD of the selected regional hospital in the DKKD in the North West Province, South Africa. This hospital serves as a regional hospital in the district, and therefore it has been selected as the study setting. The MOPD treats up to 250 diabetes patients per month and receives referrals from all of the surrounding PHC clinics and general practitioners. The level of care provided to patients at the MOPD is considered at primary healthcare level, however should the need arise, patients are hospitalised and receive secondary and if needed tertiary care. The focus of this study is HCP compliance with the national type 2 diabetes care guidelines specific to primary healthcare.

1.5.2 Target and study population

The target population included all the records of patients diagnosed with DM receiving care in the PHC sector of the DKKD. The study population comprised DM patients receiving care at the selected regional hospital’s MOPD and who met the inclusion criteria.

1.5.2.1 Inclusion criteria

The inclusion criteria for the selected patient data for the determined period of 1 March 2016 to 28 February 2018 were as follows:

- All records of diabetes patients (including or excluding contingent illnesses) with at least two MOPD visits during the study period
- Ages 18 years and older, irrespective of gender.
1.5.2.2 Exclusion criteria

Exclusion to this study was based on the following:

- All types of diabetes that did not fall into the category of T2DM, such as gestational diabetes and T1DM (identified as patients using insulin only)

- Newly diagnosed patients without sufficient information (without data of at least two MOPD visits) to meet the inclusion criteria.

1.5.3 Study design

This study took on a quantitative, non-experimental, descriptive research design with a retrospective longitudinal approach. Maree and Pietersen (2016:162) stated that quantitative research is a process that is both objective and systematic in the use of numerical data from a selected population to generalise the finding to the population. This made the quantitative research approach applicable to the research, since the researcher made use of the numerical data to reach the specified research aims. Longitudinal studies are used to examine the way in which variables change over time (Brink et al., 2009:104-105). The researcher has observed patient records retrospectively. Data of patient visits to the MOPD within the two-year period have been evaluated in order to assess HCP compliance with the monitoring and pharmacologic treatment guidelines of the national type 2 diabetes care guidelines.

1.6 Data

The sources and data fields, along with the reliability and validity, will be discussed regarding the data of this research.

1.6.1 Sources and data fields

Study data were collected from the patient records of all adult T2DM patients after approval was granted by HREC as well as the North West Department PPRM&E committee and the selected hospital research committee. The data were collected by means of a structured electronic data collection tool, which had been developed to look into the actions that were either carried out or omitted by HCPs for the period of 1 March 2016 to 28 February 2018. It had related to different aspects, components or standards of care, as set out by the national type 2 diabetes care guidelines (see section 2.3.1) (RSA, 2014:9.7-9.22). No patient contact, testing or researcher interventions formed part of the study. The following fields have been collected for review/analysis. Demographic information had been recorded once off. Clinical/diagnostic data, however, have been recorded at three identified time intervals (as required by the stated
guidelines), at each visit, annually or at baseline (the first data for the specific parameters within the study period of 1 March 2016 to 28 February 2018 have been collected as baseline parameters):

- **Demographic information**
  
  (a) Sex
  
  (b) Age

- **Anthropometric information**
  
  (a) Weight
  
  (b) Length
  
  (c) Body mass index (BMI) was calculated by the researcher using the DoH Essential Medicines List Clinical (EML) Guide application (if both patient height and patient weight were recorded in the patient record and patient weight recorded within the study period)

- **Patient medication for the treatment of hyperglycaemia**
  
  (a) Active substances
  
  (b) Dosage
  
  (c) Dosage intervals
  
  (d) Date of prescriptions
  
  (e) Changes in medication

- **Clinical/diagnostic data including the dates when tests were done**
  
  (a) Finger-prick blood glucose levels (mmol/L)
  
  (b) Blood pressure (mmHg)
  
  (c) Blood lipid levels
    
    - Total fasting cholesterol (mmol/L)
    
    - Triglycerides (TG) (mmol/L)
• High-density lipoprotein (mmol/L)
• Low-density lipoprotein (mmol/L)

(d) Serum creatinine concentration (mg/dL)
(e) Estimate glomerular filtration rate (eGFR) (ml/minute) – calculated by the researcher using the eGFR tool of the DoH EML Clinical Guide Application
(f) Combination of serum potassium concentration (mmol/L) and eGFR in patients using angiotensin converting enzyme inhibitors (ACEi). Hyperkalaemia, high levels of potassium in the blood, is present with a renal impairment with the use of ACEi (Palmer, 2004:585)
(g) Urine protein – using dipsticks (positive/negative). This is done to detect renal failure (RSA, 2014:9.18)
  • If negative: look at creatinine:albumin ratio (mcg/L:mg/L)
(h) Glycosylated haemoglobin percentage (HbA1c)
(i) Eye assessments (any results or indication of referral)
(j) Foot assessments (any results or indication of referral).

1.6.2 Reliability and validity of data

Adequate patient records enable the researcher to reconstruct the essential parts of each patient contact without reference to memory (MPS, 2011:4). The data in patient records are entered by HCPs and were judged as reliable and valid. The Health Professionals Council of South Africa (HPCSA) states that patient records consist of handwritten notes taken by the HCP, as well as notes taken by previous HCPs, referral letters, laboratory reports and evidence. There are also factors that may compromise the validity and reliability of data found in patient records. Healthcare providers may fail to record negative outcomes, alter notes after the event and not consult the relevant records when seeing the patient (MPS, 2008:5).

1.7 Data collection tool

The data collection tool had been designed by the researcher, with the help of the biostatistician employed by the NWU Faculty of Health Sciences, for the sole use of the researcher. It was therefore in English only and required no training. The data collection tool had been developed
to, electronically, collect all data necessary to reach the research aim and objectives. Use of the data collection tool will be discussed under 1.8.3.

1.7.1 Development of data collection tool

The electronic data collection tool had been developed based on the recommendations of the PHC STG EML 2014 (RSA, 2014:9.7-9.22), as these are seen as the national type 2 diabetes care guidelines used in the PHC sector (refer to Annexure A for the guideline specific parameters). The electronic data collection tool was designed with the goal of convenient statistical analysis and can be seen in Annexure B.

1.7.2 Validity and reliability of data collection tool

The data collection tool was reviewed and controlled by the supervisor (Dr JM du Plessis) and co-supervisors (Dr R Joubert and Ms M Vorster), as well as the biostatistician employed by the NWU Faculty of Health Sciences (Ms M Cockeran). This ensured validity and reliability of the electronic data collection tool.

Reliability is the consistency of the instrument used and not the respondents (in this case the patient records). It is related to the reproducibility of the same results should the instrument be used repeatedly. Therefore, if a measuring tool was not reliable, the results gathered would have led to inaccurate conclusions. Validity relates to the instrument accurately measuring what it was supposed to have measured (Brink, 2009:159).

Content validity relates to whether the data collection tool represents all the components of the variable to be measured (Brink, 2009:160). For this study, the researcher had developed a data collection tool using the national type 2 diabetes care guidelines (PHC STG EML 2014). The management practices in the national type 2 diabetes care guidelines are evidence-based and assembled with the collaboration of numerous HCPs, the National DoH programmes and clinical societies (RSA, 2014:ii). Face validity relates to whether the instrument appears to measure what it was expected to have measured (Brink, 2009:160).

1.8 Data collection

The researcher considered the following regarding the data collection. The permission needed to have started data collection, the meeting in which the researcher explained the proposed study to the hospital research committee, as well as the data collection process and the selection of patient records.
1.8.1 Permission

Approval to perform the study was obtained from the North West DoH PPRM&E committee, after approval had been received by the HREC, Faculty of Health Sciences of the NWU, Potchefstroom Campus. Approval to perform the study at the selected regional hospital was also obtained, by means of a formal meeting, from the hospital research committee.

1.8.2 Initial meetings

Prior to the approval of the study, the researcher had an informal meeting with the hospital pharmacy manager at the study setting. The aim of the meeting had been to provide the hospital pharmacy manager with an informal overview of the study. This meeting covered the problem statement, along with the goals, motivations and objectives of the study. It was also aimed at familiarising the researcher with the study setting.

The researcher also scheduled a formal meeting with the hospital research committee, explained the study and provided an opportunity for them to ask any questions (refer to Annexure C for the complete meeting agenda).

1.8.3 Data collection process

The data collection process started after permission was granted by the HREC, North West DoH PPRM&E committee and the selected hospital research committee.

1.8.3.1 Process of obtaining informed consent

The researcher applied for permission to waive informed consent from the HREC, according to the National Health Act, 2003 section 16.1(b), which states that an HCP may examine a user’s health record for the purposes of study, teaching or research, with authorisation of the user, head of health establishment concerned and the relevant health research ethics committee. This, along with section 16.2, which states that if the study, teaching or research contemplated in subsection 1(b) reflects or obtains no information as to the identity of the user concerned, it is not necessary to obtain authorisations contemplated in that section. This study retained no personal, identifiable information of the participants who had been selected.

1.8.3.2 Selection of participants

The selection of patient records started after approval from the HREC and the North West DoH PPRM&E (subject to HREC approval) had been received, along with the approval from the hospital research committee of the selected regional hospital. The pharmacy staff identified the
diabetes patient records after having dispensed anti-diabetic drugs and placed the identified patient records into a box that had been marked for the researcher. The researcher then identified from those the patient records that met the inclusion criteria, based on the information found in the patient records.

1.8.3.3 Collecting data from patient records

All DM patients have received care and assessment by an HCP and had their prescriptions dispensed on Mondays (reserved by the selected regional hospital). These days were known as a “diabetes day”. The researcher was present on every “diabetes day”, for a total of 16 days, selected the patient records and collected the relevant data from those records. The pharmacy manager had instructed the pharmacy staff to identify DM patient records according to the anti-diabetic drugs prescribed (e.g. metformin, sulphonylureas and insulin). These patient records were placed in the box, which had been marked for the researcher. The researcher collected the box and moved into a private office. There the researcher selected the patient records according to the inclusion and exclusion criteria and electronically collected the data from the patient records. The entire patient record that met the criteria was studied for evidence of available monitoring and treatment parameters. Each record was marked with a coloured sticker (which prevented the duplication of data) and given a dummy number on the data collection tool, which ensured that the data collected were unique and ordered. The researcher alone collected data from the patient records and no identifiable data such as name, address or identification number (ID number) were collected and, in doing so, ensured patient confidentiality. The data that had been collected were stored and encrypted on the virus- and password protected computer of the researcher, kept on the researcher’s person until the collected data were transferred after the end of the “diabetes day”, for the whole data collection period. The data were transferred to a computer in the NWU, Faculty of Health Science at the School of Pharmacy building G23, which was also both password- and virus protected. This ensured data confidentiality and collaboration between the researcher and study leaders.

Data collection started after approval from the HREC of the NWU, Potchefstroom Campus and the PPRM&E committee was received and all goodwill permission forms had been signed.

1.9 Data analysis

The data collected were summarised and statistically analysed with the assistance of the biostatistician employed by the NWU, Faculty of Health Sciences. The data were used to assess HCP compliance with the national type 2 diabetes care guidelines (which was measured by blood
glucose levels, BP, blood lipid levels, serum creatinine- and serum potassium levels, eGFR, urine protein and eye- and foot assessments), see Table 1.1 for the statistical analysis.
<table>
<thead>
<tr>
<th>Assessment variables</th>
<th>Goals</th>
<th>Take action</th>
<th>Action to be taken</th>
<th>Statistical analysis</th>
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<td><strong>First data for variables measured</strong></td>
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<td><strong>Blood lipids</strong></td>
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<td>Fasting total cholesterol</td>
<td>&lt; 4.1 mmol/L</td>
<td>&gt; 5 mmol/L</td>
<td>Treat according to the national type 2 diabetic care guidelines</td>
<td>Frequencies (%)</td>
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<td>Triglycerides</td>
<td>&lt; 1.7 mmol/L</td>
<td>&gt; 1.7 mmol/L</td>
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<td>HDL</td>
<td>&gt; 1.5 mmol/L in both men and women</td>
<td>&lt; 1.0 mmol/L in men</td>
<td>&lt; 1.3 mmol/L in women</td>
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<td>LDL</td>
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<td>&gt; 3 mmol/L</td>
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<td>Serum creatinine concentration and estimate Glomerular Filtration Rate (eGFR)</td>
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<td>&lt; 30 mL/minute</td>
<td>Treat according to the national type 2 diabetic care guidelines</td>
<td>Frequencies (%)</td>
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<td>Assessment variables</td>
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<td>Serum potassium concentration (in patients on ACE-inhibitor) estimate eGFR</td>
<td>&lt; 30 ml/minute</td>
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<td>Variables measured continuously&lt;br&gt;Mean ± SD&lt;br&gt;95% CI&lt;br&gt;Median (25th percentile, 75th percentile)</td>
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<td>Urine protein</td>
<td>negative</td>
<td>Positive</td>
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<td>Albumin:creatinine</td>
<td>&gt; 3 mg/mmol</td>
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<tr>
<td>Abdominal circumference</td>
<td>&gt; 94 cm in men&lt;br&gt; &gt; 80 cm in women</td>
<td></td>
<td></td>
<td>Frequencies (%)&lt;br&gt;• Is the variable measured? (Yes/No)&lt;br&gt;• Is action taken when necessary? (Yes/No)&lt;br&gt;Variables measured continuously&lt;br&gt;Mean ± SD&lt;br&gt;95% CI&lt;br&gt;Median (25th percentile, 75th percentile)</td>
</tr>
<tr>
<td>Eye assessment</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Refer to ophthalmologist</td>
<td>Frequencies (%)&lt;br&gt;• Is the variable measured? (Yes/No)&lt;br&gt;• Is action taken when necessary? (Yes/No)&lt;br&gt;• Is the correct action taken? (Yes/No)</td>
</tr>
<tr>
<td>Assessment variables</td>
<td>Goals</td>
<td>Take action</td>
<td>Action to be taken</td>
<td>Statistical analysis</td>
</tr>
<tr>
<td>----------------------</td>
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<td>-------------</td>
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<td>---------------------</td>
</tr>
<tr>
<td>Foot assessment</td>
<td>Normal</td>
<td>Neuropathy</td>
<td>Treat according to the national type 2 diabetic care guidelines</td>
<td>Frequencies (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection</td>
<td></td>
<td>Is the variable measured? (Yes/No)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischaemia</td>
<td></td>
<td>Is action taken when necessary? (Yes/No)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Is the correct action taken? (Yes/No)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Continuous parameters</th>
<th>Blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>4-7 mmol/L &gt; 8 mmol/L Stepwise treatment according to the nation type 2 diabetic care guidelines: Entry to Step 1 includes a random plasma glucose &gt; 11.1 mmol/L or fasting plasma glucose ≥ 7 mmol/l Initiate therapy with metformin starting at 500 mg daily with meals, titrating up to a maximum dose of 850 mg eight hourly depending on HbA1c and/or fasting blood glucose. Target of Step 1: • 2-hour post prandial finger prick blood glucose of 8 - 10 mmol/L • Or fasting finger-prick blood glucose: 6 - 8 mmol/L • And/or HbA1c: 7 - 8%.</td>
</tr>
<tr>
<td>2-hour post prandial</td>
<td>5-8 mmol/L &gt; 10 mmol/L</td>
</tr>
<tr>
<td>Glycosylated haemoglobin (every three to six months whose therapy has changed until stable)</td>
<td>&lt; 7% &gt; 8%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment variables</td>
<td>Goals</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------</td>
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<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**Blood pressure**

<table>
<thead>
<tr>
<th>Systolic</th>
<th>&lt; 140 mmHg</th>
<th>&gt; 140 mmHg</th>
<th>Frequencies (%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Assessment variables</th>
<th>Goals</th>
<th>Take action</th>
<th>Action to be taken</th>
<th>Statistical analysis</th>
</tr>
</thead>
</table>
| Diastolic            | < 90 mmHg | > 90 mmHg  | Treat stepwise according to the national type 2 diabetic care guidelines | • Is the variable measured? (Yes/No)  
  • Is action taken when necessary? (Yes/No)  
  • Is the correct action taken? (Yes/No)  

Variables measured continuously  
Mean ± SD  
95% CI  
Median (25th percentile, 75th percentile) |
| Weight               |       |             |                    |                     |

**Variables measured on annual basis (if applicable):**

**Kidney function**

| Serum creatinine concentration and estimate Glomerular Filtration Rate (eGFR) | < 30 mL/min | Frequencies (%)  
|-------------------------------------------------------------------------------|-------------|-----------------|---------------------|
|                                                                               |             | • Is the variable measured? (Yes/No)  
  • Is action taken when necessary? (Yes/No)  
  • Is the correct action taken? (Yes/No) |
<table>
<thead>
<tr>
<th>Assessment variables</th>
<th>Goals</th>
<th>Take action</th>
<th>Action to be taken</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum potassium concentration (in patients on ACE-inhibitor) estimate eGFR</td>
<td>&lt; 30 mL/minute</td>
<td>Refer to ophthalmologist</td>
<td>Variables measured continuously</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median (25th percentile, 75th percentile)</td>
</tr>
<tr>
<td>Urine protein</td>
<td>positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin: creatinine</td>
<td>&gt; 3 mg/mmol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal circumference</td>
<td>&gt; 94 cm in men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 80 cm in women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye assessment</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Refer to ophthalmologist</td>
<td>Frequencies (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Is the variable measured? (Yes/No)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Is action taken when necessary? (Yes/No)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Is the correct action taken? (Yes/No)</td>
</tr>
<tr>
<td>Foot assessment</td>
<td>Normal</td>
<td>Neuropathy</td>
<td>Treatment according to the national diabetes guidelines</td>
<td>Frequencies (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection</td>
<td></td>
<td>Is the variable measured? (Yes/No)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischaemia</td>
<td></td>
<td>Is action taken when necessary? (Yes/No)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Is the correct action taken? (Yes/No)</td>
</tr>
</tbody>
</table>

All variables were expressed by the use of descriptive statistics, such as frequencies (n), percentages (%), means, standard deviations (SDs) and interquartile range. The data were analysed by the researcher and the statistician Ms M Cockeran, employed by the NWU, Faculty of Sciences, using Statistical Analysis Software (SAS®).
1.9.1 Independent variables

The following independent variables were considered by the researcher.

- Patient demographics
- Clinical tests and measurements (date and type)
- Medication prescribed (active substance, dosages and the date of each prescription and changes in the medication) for the treatment of hyperglycaemia.

1.9.2 Dependent variables

The researcher considered the results of the clinical tests and measurements as the independent variables as discussed in 1.6.1 under clinical/diagnostic data.

1.10 Ethical considerations

The ethical components that were considered by the researcher will be discussed below.

1.10.1 Permission and informed consent

The researcher gained access to the patient records by having applied for waived informed consent and permission from the following entities:

- The HREC of the Faculty of Health Sciences of the NWU for permission to waiver patient informed consent and consent to have conducted the study (see annexure D for approval letter)
- North West DoH PPRM&E committe, which was subject to HREC approval (see Annexure E for approval letter)
- Permission from the hospital research committee, which was subject to HREC approval (see Annexure F for the permission form).

1.10.2 Anonymity

The researcher collected data from patient records and therefore made no contact with any of the patients, nor did any testing or interventions of any nature form part of the study. The researcher took sole responsibility for the data collection process. All patient records were anonymised and a dummy number was allocated to the patient record on the data collection tool. All identifiable data were omitted during the data collection process. No patient record was removed from the hospital premises.
1.10.3 Confidentiality

The data that were collected by the researcher were viewed by the researcher, supervisors and the statistician. The researcher did not have any contact with the individual patient and, in doing so, preserved patient confidentiality.

1.10.4 Justification of research study

Risk factor management, as recommended by the national type diabetes care guidelines, is often neglected, as the majority of patients diagnosed with T2DM do not reach therapeutic targets. The study aimed to evaluate the compliance of the HCPs at the selected regional hospital's MOPD with the national type 2 diabetes care guidelines for the treatment and monitoring of patients diagnosed with T2DM.

1.10.5 Respect for research participants

The results of the study will be shared with the management of the selected regional hospital in the form of an oral presentation. The researcher will schedule the appointment ahead of time, during which the researcher will share the results of the study.

1.10.6 Benefit-risk ratio analysis

The level of risk that this study posed to the participant was a medium risk, due to the sensitive information contained in patient records, ID number, patient address, names and patient’s medical history. The benefits of the study, however, outweighed the risks because the researcher maintained patient confidentiality and anonymity.

1.10.6.1 Anticipated benefits

The anticipated benefits were the possible improvement of the HCPs compliance with the national type 2 diabetes care guidelines of the selected regional hospital’s MOPD.

1.10.6.2 Direct benefits

There were no direct benefits to the patients whose patient records were used. No patient was directly contacted by the researcher.

1.10.6.3 Indirect benefits

Possible improvements in compliance of the HCPs at the selected regional hospital’s MOPD with the national type 2 diabetes care guidelines, which might positively influence patient outcomes.
1.10.7 Anticipated risks and precautions

The anticipated risks that the research posed were the possibility of revealing patient identity and the loss of a patient record. The researcher prevented this by collecting data exclusively in a private office. All identifiable information was omitted during the data collection process. The researcher ensured that all patient records were returned to the pharmacy manager at the end of each data collection period and no patient record was removed from the hospital premises. Another anticipated risk was the possible financial implications to the participants. The researcher had no contact with the individual patients and did not influence the regular visits of the patients to the hospital.

There were no risks to the researcher during research.

1.10.8 Reimbursement of study participants

No provision was made for reimbursement to research participants as the researcher made use of patient records and had no contact with individual patients.

1.10.9 Data management

The processes of data management, during and after completion of the research, will be discussed below.

1.10.9.1 Data management during data collection

Patient records that met the inclusion criteria had been identified by the hospital pharmacy staff during the dispensing of anti-diabetic drugs and placed into a separate box marked for the researcher. The researcher collected the box and moved to a private office where data were collected from the participating patient records. The data were extracted from the participating patient records onto the electronic data collection tool, by the researcher exclusively. The researcher collected the data onto a personal password-protected computer, where after it was transferred to a password-protected computer to which only the researcher and research supervisors had access. This computer was on the NWU Potchefstroom Campus in building G23 - G04. The participating patient records were marked with a coloured sticker on the inside of the cover and given a dummy number on the data collection tool, which prevented the duplication of data. The researcher conducted the data collection process in a private office and removed no patient record from the hospital premises. The patient records were returned to the hospital pharmacy staff at the end of each data collection period. The hospital management staff, responsible pharmacist and research supervisors were aware of the information that was retrieved from the participating patient records and monitored the data collection process.
1.10.9.2 Data management after completion of the study

After completion of the study, electronic data will be stored on an external hard drive, which is stored at the MUSA research entity for safekeeping for a period of five years. Electronic data on the researcher’s personal computer will be destroyed and formatted under the direct supervision of the research assistant of MUSA and a legal document was signed that acknowledged such destruction.

1.10.10 Dissemination of research results

Results of the study were compiled into two draft manuscripts intended for two separate journals and a dissertation in order to complete the master’s degree in Pharmacy Practice. Direct feedback will not be provided to the individual patients, yet all the results of the study will be made available by means of a dissertation, journal articles, conference presentation and feedback to the North West DoH as well as the research committee of the selected regional hospital after the researcher has completed the Master of Pharmacy degree.

1.10.11 Role of the members in the research team

The research team have the necessary research- and professional competence to complete the study. The research supervisor of the study was Dr JM du Plessis, a general practitioner with experience on research in the public health sector. The researcher, Ms DE Venter, is registered for the Master of Pharmacy in Pharmacy Practice programme at the NWU Potchefstroom Campus. The co-supervisors of the study included Dr R Joubert and Ms M Vorster, both with experience in health research. Ms M Cockeran is a biostatistician employed by the NWU Faculty of Health Sciences and only assisted in the statistical processing of research results.

All of the above-mentioned people have up-to-date training in both ethics and biostatistics.

1.10.12 Study limitations

The study limitations included baseline parameters and annual parameters that were not measured within the study period.

1.10.12.1 Baseline parameters

Baseline parameters according to the national type 2 diabetes care guidelines are the parameters taken on the patient’s first visit. Therefore, for some patients, the baseline parameters did not fall within the study period, 1 March 2016 to 28 February 2018. The researcher used the first data
point within the study period as the baseline parameter. These parameters can be seen in Annexure A.

1.10.12.2 Annual parameters

Specific annual parameters must be captured during patient care. Some patients' annual parameters did not fall within the study period of 1 March 2016 to 28 February 2018. Therefore, the first data point that fell within the study period was taken as baseline and any other data points relevant to the monitoring recommendations of the national type 2 diabetes care guidelines and performed by the HCPs of the selected regional hospital’s MOPD were recorded as annual parameters. Annual parameters of newly diagnosed patients treated for a period shorter than 12 months were marked as not applicable on the data collection tool. The baseline parameters for these patients were recorded in the same manner as the other patients. Therefore, a not applicable (N/A) value was allocated to a newly diagnosed patient for annual parameters that could not be measured within the study period.

1.10.13 Conflict of interest

There was no known conflict of interest to the researcher partaking in the study.
CHAPTER 2 LITERATURE REVIEW

2.1 Introduction and brief overview of diabetes mellitus

Diabetes mellitus is a collective term for diseases with multiple metabolic disorders characterised by hyperglycaemia (excess of glucose in the bloodstream) and glucose intolerance (inability to properly metabolise glucose). This can be due to insulin deficiency, impaired effectiveness of insulin action or a combination thereof (Magliano et al., 2015:3). Diabetes mellitus has been described as a silent epidemic; its presentation can either be of rapidly emerging symptoms leading to complications, coma or death, or of a slow onset with asymptomatic progression leading to secondary complications (Nwaneri, 2015). This disease is affecting every nation and economy across the globe (WHO, 2016:4).

The prevalence of DM globally has increased from 108 million in 1980 to 425 million in 2017, partly as a result of increased prevalence, population growth and ageing, and partly due to interaction between these two factors (IDF, 2017:40; NCD-RisC, 2016:1513). During a study done in 2013 to estimate the global diabetes prevalence, it was revealed that though Africa has the lowest prevalence of DM, it is projected to have the largest proportional increase in the numbers of adults with DM by the year 2035 (Guariguata et al., 2014:140). Diabetes mellitus and its complications also hold an enormous economic loss to people with DM and their families, through direct medical costs and the loss of wages (WHO, 2016:6). According to the International Diabetes Federation (IDF), the global health expenditure related to DM was 727 billion USD (IDF, 2017: 51). The WHO estimated that 9.8% of the South African population have diabetes, resulting in a total of 5.3 million people (WHO, 2017). The estimated global prevalence (for adults over the age of 18 years), deaths due to DM and health expenditure per region (according to the IDF) for 2016 to 2017 are demonstrated in Table 2.1 below (adapted from IDF, 2017:40; WHO, 2016:25).
Table 2.1: Global health and economic burden of diabetes mellitus

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence of DM (million)</th>
<th>Deaths due to DM (million)</th>
<th>Health expenditure (billion USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa*</td>
<td>16 - 25</td>
<td>0.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Europe*</td>
<td>58 - 64</td>
<td>0.5</td>
<td>166.0</td>
</tr>
<tr>
<td>Middle East and North Africa*</td>
<td>39 - 43</td>
<td>0.3</td>
<td>21.3</td>
</tr>
<tr>
<td>North America and Caribbean</td>
<td>46</td>
<td>0.3</td>
<td>337</td>
</tr>
<tr>
<td>South and Central America</td>
<td>42</td>
<td>0.2</td>
<td>29.3</td>
</tr>
<tr>
<td>South East Asia*</td>
<td>82 - 96</td>
<td>1.</td>
<td>9.5</td>
</tr>
<tr>
<td>Western Pacific*</td>
<td>131 - 159</td>
<td>1.3</td>
<td>29.3</td>
</tr>
</tbody>
</table>

(* These regions are similar for both WHO and IDF)

Diabetes mellitus can be divided into a variety of categories, the majority being T1DM and T2DM (Desphande et al., 2008:1225). Type 1 diabetes mellitus, previously known as insulin-dependent diabetes, is associated with high prevalence in the youth and diabetes emergencies (Ramachandran et al., 2017:23; RSA, 2014:9.2). This form of DM is caused by an absolute lack of insulin due to auto-immune destruction of pancreatic beta-cells (Desphande et al., 2008:1255). The complete destruction of pancreatic beta-cells leads to total dependence on the administration of exogenous insulin for survival (Eisenbarth, 2005:399). Type 1 diabetes mellitus manifests in two manners, namely immune-mediated diabetes and idiopathic diabetes. Beta-cell destruction in immune-mediated diabetes is quite variable and can happen both rapidly or slowly in different patients (ADA, 2014:s82). Idiopathic diabetes has no known cause and is more prevalent in African and Asian populations (Magliano et al., 2015:5).

Type 2 diabetes mellitus, on the other hand, can range from predominant insulin resistance with relative insulin deficiency to prevailing defective secretion with insulin resistance (Kerner & Brückel, 2014:384). Type 2 diabetes mellitus is a progressive disease of slow-onset, characterised by the worsening of abnormal lipid and protein metabolism and loss of glycaemic control over time (Fonseca, 2008:s3; Shah & Vella, 2014:687). The loss of glycaemic control is presented by a progression from IGT (increase in glucose levels after a meal) to T2DM (Costa et al., 2002:205; Dunkley et al., 2014:923). There is also gestational diabetes mellitus (GDM), diagnosed by hyperglycaemia during pregnancy, which will often dissipate after birth (Desphande et al., 2008:1255) and diabetes caused by specific genetic defects of beta-cell function, insulin action, diseases of the pancreas, drugs or chemicals (ADA, 2014:s84-s85).
The diagnosis of a type of DM depends on the circumstances present at the time of diagnosis (ADA, 2014:s82). Type 1 diabetes is usually diagnosed when the patient seeks help from HCPs regarding weight loss, frequent urination, fatigue and thirst (all symptoms of hyperglycaemia) (Kerner & Brückel, 2014:385; WHO, 2016:48). Type 2 diabetes mellitus develops slowly leading to an asymptomatic period where the disease is present, without detectable symptoms and therefore most patients seek help from HCP due to complications such as difficulty to see, gangrene or a heart attack/myocardial infarction (WHO, 2016:48).

The factors that are considered during diagnosis include (ADA, 2014:s87; WHO, 2016:48):

- Fasting plasma glucose (FPG)
- 2-hour post-prandial plasma glucose (2hPG)
- Oral glucose tolerance test (OGTT)
- Random plasma glucose
- Glycated haemoglobin testing (HbA1c).

Fasting plasma glucose levels are an indication of the suppression of hepatic gluconeogenesis by insulin, and therefore of insulin action in the liver (Kaku, 2010:43). The 2hPG test or OGTT is an indication of insulin secretion and sensitivity (Ascaso et al., 2003:3320; Guthrie & Guthrie, 2004:113; Stumvoll et al., 2002:295). Glycated haemoglobin can be tested even if the patient is not in a fasting state and is an indication of the patient’s average glucose concentration over a period of three months (Selvin et al., 2010:801; WHO, 2016:47). When FPG is used to diagnose a patient with DM, the 2hPG test or OGTT is not necessary; however, should the patient be asymptomatic or have minimal symptoms and the FPG levels are not diagnostic, a 2hPG or OGTT must be performed (ADA, 2016:s13). According to the standards of the WHO, DM is diagnosed if FPG levels are higher than 7.0 mmol/L, 2hPG levels are higher than or equal to 11.1 mmol/L and HbA1c is more than or equal to 6.5% (WHO, 2016:83). Table 2.2 demonstrates the diagnostic criteria for DM, IGT, impaired fasting glucose (IFG) and GDM (table adapted from WHO, 2016:88). This table does not include the diagnosis of a type of DM.
**Table 2.2: Diagnostic criteria for diabetes mellitus**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Impaired glucose tolerance (IGT)</th>
<th>Impaired fasting glucose (IFG)</th>
<th>Gestational diabetes mellitus (GDM)</th>
<th>Diabetes mellitus (DM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG (mmol/L)</td>
<td>&lt; 7.0</td>
<td>6.1 - 6.9</td>
<td>5.1 - 6.9</td>
<td>≥ 7.0</td>
</tr>
<tr>
<td>2hPG (mmol/L)</td>
<td>≥ 7.8 and &lt;11.0</td>
<td>&lt; 7.8</td>
<td>&gt; 10.0</td>
<td>≥ 11.1</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
<td>≥ 6.5</td>
</tr>
</tbody>
</table>

Impaired glucose tolerance and IFG are often termed as pre-diabetes; these should not be viewed as clinical entities, but as risk factors for the development of DM (ADA, 2010:s66). The plasma glucose (PG) levels, as indicated in the table, for the diagnosis of DM, are the cut-off points for the risk of retinopathy (ADA, 2013:s72).

The management of DM differs specifically according to the type that is diagnosed. For the purpose of this study, and the remainder of this chapter, the focus will be on T2DM.

### 2.2 Type 2 diabetes mellitus

#### 2.2.1 History of type 2 diabetes mellitus

Diabetes mellitus (although only later named as such) is known throughout history as a disease associated with polyuria, sweet urine and even neuropathy and gangrene (Ahmed, 2002:373; Von Engelhardt, 1989:3). During a review of the history of DM, it was shown that the knowledge of DM developed over six eras (Nwaneri, 2015):

1. **Ancient times** – Era of recognition of the disease
   - 3000 - 1500 BC: The first recognition of diabetes was documented as polyuria in what is now known as the *Ebers Papyrus* (1500BC) (Nwaneri, 2015:2).
   - 500 BC: Two Hindu-Indian physicians, Susruta and Chakrat, recognised that DM was not a single disease, later to be named Type 1 and Type 2 DM (Lakhtakia, 2013:368; Tipton, 2008:1555). These physicians noted an association between this disease and obesity, lack of physical activity and indulging in sweet and fatty food (Tattersall, 2017:4).
(2) **1st century**: Era of description of causes

- **2nd century AD**: Aretaeus of Cappadocia first used the term diabetes, a Greek word for a syphon, to describe this disease characterised by polyuria (Nwaneri, 2015:3; Tattersall, 2017:4).

- **200 AD**: The triad of polydipsia, polyphagia and polyuria was noted in literature from China by Tchang Tchong-King (Karamanou et al., 2016:2; Nwaneri, 2015).


(3) **16th -18th century**: Era of clinical diagnosis

- **1621 - 1675**: The first time the term mellitus (meaning honey sweet (Ahmed, 2002:374)) was added by Thomas Willis who described the sweetness of urine as “*wonderfully sweet like sugar or honey*” (Tattersall, 2017:4; Von Engelhardt, 1989:4).

- **1735 - 1784**: The first description of hyperglycaemia was published by Matthew Dobson who found that both the serum as well as the urine of his patient tasted sweet (Nwaneri, 2015; Tattersall, 2017:4).

(4) **18th - 19th century**: Era of biochemical and pathological differences:

- **It was during this era that T2DM was clinically differentiated from T1DM** (Nwaneri, 2015:4).

- **1815**: French chemist proved that the ‘sweetness’ in urine and serum was glucose and proposed that glucose was not produced by the kidneys but was due to the inability of blood to utilise it correctly (Tattersall, 2017:6). This led to the explosion of experiments in biochemistry and clinical chemistry (Nwaneri, 2015).

- **1789 - 1858**: Extensive research of nephritis revealed that DM was not caused by kidneys, but that nephropathy was rather a complication of DM (Nwaneri, 2015).

- **1813 - 1878**: French physician Claude Bernard discovered through many experiments that animal metabolism of plants leads to the presence of glucose in the blood and later that glucose was also present in healthy animals, even when starved. This led to the discovery of endogenous glucose production by the liver and a starch-like substance he later named glycogen (Karamanou et al., 2016:4; Tattersall, 2017:7).
1869 - 1927: Paul Langerhans discovered what he described as heaps of islet cells in the pancreas with endocrine functions. It was Oscar Minowski, Joseph von Mering and Gustave-Edouard Laguesse who discovered the role of the pancreas in the development of DM, after experimental removal of a dog’s pancreas that led to permanent DM (Lakhtakia, 2013:368; Karamanou et al., 2016:5; Tattersall, 2017:7).

(5) 19th - 20th century: Era of insulin development and advancement


1922: The first time insulin was administered to a human; 14-year old Leonard Thompson. After the first injection, it was observed that his blood glucose level fell slightly without change in his symptoms. After a second injection, his blood glucose levels normalised. Morning injections for ten days led to marked clinical improvement (Karamanou et al., 2013:6; Nwaneri, 2015; Tattersall, 2017:12; Von Engelhardt, 1989:6).

1923: Insulin was widely available throughout North America and Europe (Tattersall, 2017:12).

1923: Founding of Novo Nordisk pharmaceutical industry that paved the way for the invention of modified slow- and fast-acting insulin (Nwaneri, 2015).

(6) Era of millennium developments

The 21st century heralded the revision of guidelines for the diagnosis and definitions of various stages of hyperglycaemia by the American Diabetes Association (ADA) and WHO.

Newer medications were found, which brought options and improved management of T2DM.


Some of the symptoms of DM, as documented in ancient scripts, coincide with the symptoms known today, which include polyuria, polydipsia and polyphagia (Ahmed, 2002:374; Motala, 2012:s5; RSA, 2014:9.6).
2.2.2 Risk factors and aetiology

The risk of developing T2DM increases if a patient is exposed to various risk factors. These can be divided into genetic and environmental risk factors (Desphande et al., 2008:1256; Scheen; 2003:335). There is an interrelationship between these risk factors. The genetic risk factors (with the exception of monogenic diabetes) (Bonnefond & Froguel, 2015:357) cannot lead to the development of the disease if the individual is not exposed to diabetes prompting environments (Temelkova-Kurktschiev & Stefanov, 2011).

The various risk factors for the development of T2DM interact in different ways to develop insulin resistance and beta-cell deficiency. The environmental risk factors (diet, physical activity, smoking, alcohol use and psychosocial factors) are mostly associated with the development of insulin resistance. Genetic risk factors are associated with decreased beta-cell function. Both insulin resistance and decreased beta-cell function are important in the progression of T2DM. Environmental and genetic risk factors also interact, leading to obesity. Obesity is associated with both the development of insulin resistance (due to metabolic by-products reducing insulin sensitivity) and decreased beta-cell function (due to inflammatory action). Figure 2.1 below demonstrates the interrelationship between environmental- and genetic risk factors, causing both obesity and, ultimately, T2DM (figure adapted from Kaku, 2010: 42).

![Diagram showing the interrelationship between environmental and genetic risk factors leading to obesity and type 2 diabetes mellitus](image)

**Figure 2.1:** Interaction of risk factors in the development of type 2 diabetes mellitus

The genetic risk factors include family history, age, ethnicity and genetic mutations (Fletcher et al., 2002:17). During the Framingham offspring study, the importance of family history was
demonstrated as the risk for developing T2DM was 3.5 times higher if one parent had T2DM and six times higher if both parents had T2DM (Meigs et al., 2000:2205; Radha & Mohan, 2014:317). Glucose tolerance diminishes with age, along with insulin action and secretion, which was decreased in the elderly when compared with young individuals (Basu et al., 2003:1743). There are certain ethnic groups that are more susceptible to the development of T2DM (Fletcher et al, 2002:19), such as Asian populations who develop T2DM at lower degrees of obesity than Western populations do (Hu, 2011:1249).

The genetics of T2DM can be regarded under two broad groups, namely genetics of monogenic forms of DM and genetics of polygenic forms of DM (Radha & Mohan, 2014:317). Monogenic diabetes is a rare form of T2DM, accounting for only 1 - 2% of all cases (Steck & Winter, 2011:252). Monogenic T2DM results from one or more defects in a single gene and is penetrant enough to cause T2DM alone (Bonnefond & Froguel, 2015:357). Monogenic DM is always diagnosed at an early age and is not related to auto-immunity (Vaxillaire et al., 2011:171) and manifests in two ways: either neonatal DM or maturity onset diabetes of the young (Radha & Mohan, 2014:317; Rubio-Cabezas et al., 2014:15; Steck & Winter, 2011:252; Vaxillaire et al., 2012:171). Neonatal DM is diagnosed within the first six months of an infant’s life and can either be permanent, needing lifelong treatment, or transient, which can dissipate at 18 months of age (relapse is also possible) (Flanagan et al., 2006:1190; Rubio-cabezas et al., 2014:47; Vaxillaire et al., 2012:172). Permanent neonatal diabetes mellitus is often caused by mutations in the beta-cell expressed adenosine tri-phosphate sensitive potassium channel (KATP channel) genes and in the preproinsulin gene (Shankar et al., 2012:174; Vaxillaire et al., 2012:172). Transient neonatal DM is caused by intra-uterine growth retardation and low birth weights (Vaxillaire et al., 2012:172). Mature onset diabetes of the young is known as a familial form of mild diabetes presenting during adolescence or in early adulthood (Rubio-Cabezas et al., 2014:48; Vaxillaire et al., 2012:177). Auto-immune destruction of beta-cells does not cause this form of T2DM and, while beta-cell function is impaired, the residual insulin secretion may be maintained for years after diagnosis. Therefore, administration of exogenous insulin is generally not necessary as treatment (Vaxillaire et al., 2012:177). Age at diagnosis of maturity onset diabetes of the young may differ widely and is rarely associated with obesity (Vaxillaire et al., 2012:178; Radha & Mohan, 2014:318). All known subtypes of this type of monogenic DM are caused by heterozygous mutations in genes important for the development and/or function of pancreatic beta-cells (Rubio-Cabesaz, 2014:48; Vaxillaire et al., 2012:178). Maturity onset diabetes of the young accounts for only 1 - 3% of all T2DM cases, but is the most common form of monogenic DM (Gardner & Taj, 2012:101; Radha & Mohan, 2014:318; Rubio-Cabezas, 2014:48).
Polygenic diabetes is the more common form of T2DM and develops due to complex interaction between multiple genes and the environment. None of the numerous genes are penetrant enough to cause T2DM alone (Bonnefond & Froguel, 2015:357). The multiple gene variants through single nucleotide polymorphisms, identified through genome-wide association studies, all play a role in beta-cell function and/or insulin resistance (Bonnefond & Froguel, 2015:378; Brunetti, 2014:131; Pánico et al., 2014:104). Genetic predisposition also accounts for monogenic obesity (which plays a major role in the development of T2DM (Yatura, 2011:79) in some individuals (Boutin & Froguel, 2001:391).

Environmental risk factors for the development of T2DM include (Ali, 2013:114; Desphande et al., 2008:1257; Khan, 2003:4; Shah & Vella, 2014:687):

- Increased body weight or obesity
- Diet high in refined carbohydrates and saturated fats
- Lack of physical activity
- Smoking
- Psychosocial factors (such as stress, depression etc.)
- Alcohol abuse

Being overweight or obese is strongly associated with the development of T2DM (Yatura, 2011:79), as the risk increases as BMI and weight circumference increase (Bergman & Ader, 2000: 351; Yatura, 2011:79). Not all patients with T2DM are obese and not all people who are obese have DM; however, significant numbers of people who are obese also have DM and many patients diagnosed with T2DM are also obese or overweight (Yatura, 2011:79). Apart from obesity, body fat distribution seems to be a critical aspect, especially central body fat distribution (Khan, 2003:5). Central body fat distribution or visceral adiposity is associated with insulin resistance, dyslipidaemia and hypertension, which also contributes to increased risk of cardiovascular disease and higher mortality of the disease (Esser et al., 2014:142). Visceral fat distribution occurs when an individual has overwhelmed his/her ability to store fat subcutaneously preceded by excess caloric intake (Sattar et al., 2015:343). When visceral fat accumulation happens, insulin resistance starts to occur in the vasculature, muscle and liver (Sattar et al., 2015:343). The adipocytes in visceral fat are also resistant to the antilipolytic effects of insulin, leading to increased release of free fatty acids (FFA) (Bergman & Ader, 2000:351). Elevated plasma-free fatty acids are common in T2DM and early changes in plasma may also be predictive
for the transition from IGT to T2DM (Boden & Shulman, 2002:14). Obesity is also often characterised by systemic inflammation, which is associated with beta-cell dysfunction (Kahn et al., 2014:1071). Components of the immune system are altered in obesity, with most changes occurring in adipose tissue of the liver, pancreatic islets, the vasculature and circulating leukocytes, leading to systemic inflammation associated with beta-cell dysfunction (Donath & Shoelson, 2011:98; Khan et al., 2014:1071). The inflammatory markers that are most commonly elevated in overweight patients and that predict the risk for the development of T2DM are tumour necrosis factor (TNF-α) receptor 2, interleukin-6 (IL-6) and C-reactive protein (CRP) (Donath & Shoelson, 2011:98; Hu et al., 2004:693; Pickup, 2004:813). These markers are closely associated with cardiovascular risk factors, non-cardiovascular and cardiovascular-related causes of death (Das, 2001:953).

Both obesity and T2DM are largely preventable with a change in lifestyle (Yatura, 2011:79). Diet and physical activity play important roles throughout the entire continuum of T2DM (Fletcher et al., 2002:18; WHO, 2016:50). Diet is made up of complex interactions between a variety of foods and nutrients determined by preference, culture and socioeconomic factors (Qiao et al., 2015:42). A person’s diet may either lead to or prevent the progression of T2DM, intake of food high in cereal fibre and polyunsaturated fat, which is associated with low incidence of T2DM (Hu et al., 2001:793); whereas intake of refined carbohydrates as well as saturated fat and trans-fatty acids may lead to an increased incidence of T2DM (Desphande et al., 2008:1257; Qiao et al., 2015:43). High intake of food with a high glycaemic index is associated with insulin resistance, decreased HDL levels and increased triglyceride levels in humans (Liu et al., 2000:1455; Smith, 1994:686s).

Physical activity is important during the prevention of T2DM in healthy people, as well as in the management of T2DM in patients (Adeniyi et al., 2015:101). In fact, exercise has been recommended as a strategy to promote the reduction in the sweetness of urine in patients by Indian physician, Sushrata, almost 2600 years ago (Riddel & Sigal, 2013:360). Physical activity of at least 30 minutes per day has been shown to decrease the progress of IGT to T2DM significantly (Hu et al., 2001:794). This can be seen because physical activity increases insulin sensitivity as well as insulin independent muscle glucose uptake (Sigal, et al., 2004:1520). During exercise, the fuel usage shifts from mainly the use of FFA by the muscle to a combination of FFA, glucose and muscle glycogen (Sigal et al., 2004:2519). This shift in fuel leads to increased fat oxidation in order to increase endogenous glucose production (Sigal et al., 2004:2520). The beneficial effects of exercise, however, wane significantly after exercised is ceased (Kahn, 2003:5; Prigeon et al., 1995:1259).
Smoking is an independent risk factor for the development of T2DM, which causes a decrease in insulin-mediated glucose uptake by up to 40% in men who smoke, compared to men who are non-smokers (Chang, 2012:399; Radzевичiene & Ostrauskas: 2006:559). In addition to causing increased insulin resistance, smoking also increases the risk of dyslipidaemia progression to atherosclerosis (Chang, 2012:400; Willi et al., 2007:2654). Active smoking is also known to increase inflammation and oxidative stress, which causes beta-cell dysfunction (Ding & Hu, 2007:2675). Therefore, smoking contributes to both insulin resistance and beta-cell dysfunction. Other environmental risk factors include psychosocial factors such as depression, increased stress, lowered social support and poor mental health (Desphande et al., 2008:1257). Alcohol use is considered an environmental factor in the risk of T2DM; however, it is not seen as a risk factor (Koppes et al., 2005:719; Carlsson et al., 2005:1051). Unlike the previous mentioned environmental factors that increase the risk of T2DM, light to moderate alcohol use has protective aspects that include increased insulin sensitivity and reduced risk of T2DM (by up to 30%) (Baliunas et al., 2009:2123; Carlsson et al., 2005:1051; Desphande et al., 2008:1257).

2.2.3 Pathophysiology

There are several pathogenic processes involved in the development of T2DM, which range from autoimmune destruction of pancreatic β-cells to abnormalities that result in resistance to insulin action (ADA, 2013:s67; Motala, 2012:s5). Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient and it is often unclear which abnormality is the primary cause of hyperglycaemia (ADA, 2013:s67; ADA, 2010:s62; Motala, 2012:s5). The severity of the symptoms of hyperglycaemia is dependent on both the type and duration of diabetes (ADA, 2013:s67; Kharrouri & Darwish, 2015:851), often leading to diabetes patients being undiagnosed until the manifestation of diabetes-related complications (IDF, 2015:23). As stated above, the hyperglycaemia that hallmarks T2DM is caused by either insulin resistance, inadequate insulin secretion or both. (Egan & Dinneen, 2014:679). The pathophysiology of T2DM has been extensively researched and debated. Most researchers agree that both decreases in insulin sensitivity (insulin resistance) and insulin secretion (beta-cell function) are important in the pathophysiology of T2DM (Chatterjee et al., 2017:2239; Hasstedt et al., 2001:537; Scheen, 2003:335) although disparity still exists in whether these two factors are in conjunction or different orders (Kaku, 2010:41). During a review done by Kahn (2003:4), it was suggested that, when consideration is given to the presence of a tightly regulated feedback system incorporating insulin sensitive tissues and beta-cells, both reductions in insulin sensitivity and beta-cell function are present early in the course of the development of T2DM.

Various organs play a role in the pathogenesis of T2DM. Disrupted communication between the endocrine pancreas and the liver, skeletal muscle, adipose tissue, gut and central nervous system
may lead to alterations in glucose homeostasis and the development of T2DM (Scheen, 2003:335).

2.2.3.1 Insulin resistance

Insulin has many roles in the body and acts on multiple types of tissues (Sattar et al., 2015:339). Insulin exerts action in muscle (cardiac and skeletal), adipose tissue, the liver, endothelium and immune cells (Sattar et al., 2015:339; Widmaier et al., 2011:561). At these sites, insulin stimulates a multitude of processes, such as (Codario, 2005:1; Sattar et al., 2015:339):

- Glucose metabolism in the muscle
- Limitation of hepatic triglyceride synthesis
- Suppression of hepatic gluconeogenesis
- Suppression of the release of FFA from adipose tissue
- Endothelial homeostasis
- Potential role in regulating inflammatory cascades.

Insulin secretion is mainly controlled by the blood glucose concentration in the form of a feedback loop, which implicates that when the blood glucose concentration increases after a meal, beta-cells of the islets of Langerhans secrete insulin, whereas a decrease in blood glucose concentration reduces the secretion of insulin by beta-cells (Widmaier et al., 2011:562).

Insulin resistance can be defined as an abnormal biologic response to insulin, whether endogenous or exogenous (Petersen & Shulman, 2002:11G; Sattar et al., 2015:339). Although the standard definition of insulin resistance still defines it in terms of the effects of insulin on glucose metabolism, the pathologic processes are acknowledged from a lipid-induced point of view (Savage et al., 2005:828; Morino et al., 2006:s9; Sattar et al., 2015:340). It is stated that abnormal metabolism of FFA could result in accumulation of FFA in muscle, liver and beta-cells, also known as lipotoxicity (Sesti, 2006:667). This visceral lipid accumulation is involved in the development of insulin resistance and impaired beta-cell function (Arner, 2002:s5; Boden & Shulman, 2002:14; Mlinar et al., 2007:21; Qatanani & Lazar, 2007:1443; Saini, 2010:68; Savage et al., 2005:828).

Glucose uptake through insulin-stimulated glucose transporters (GLUT) is the rate limiting step in glucose utilisation and storage (Morino et al., 2006:s9; Savage et al., 2005:829; Sesti, 2006:666).
Skeletal muscle accounts for the majority of insulin-stimulated glucose uptake, via GLUT4 and storage as glycogen (Savage et al., 2005:829; Sesti, 2006:666). During research done by Shulman (2000:171), it was found that skeletal muscle glycogen synthesis reduced by 50% in patients with T2DM and that this defective skeletal muscle glycogen synthesis plays a major role in causing insulin resistance in these patients. Therefore, skeletal muscle glucose transport represents an important element in both the pathogenesis and treatment of T2DM (Shulman, 2000:172; Savage et al., 2005:829).

Insulin binds to the insulin receptor and activates tyrosine kinase, which promotes the auto-phosphorylation of tyrosine kinase substrates (Saini et al., 2010:69; Schinner et al., 2004:675). This auto-phosphorylation step enables insulin receptor substrate (IRS) proteins, of which IRS-1 and IRS-2 are important in the regulation of glucose metabolism and pancreatic beta-cell growth and function (Schinner et al., 2004:675; White et al., 2002:E413). The phosphorylation of IRS activates phosphoinositide 3-kinase (PI3K), which generates phosphoinositides that bind to phosphoinositide dependent kinase (PDK), which has two substrates; protein kinase B (PKB) and protein kinase C (PKC). Protein kinase B mediates the effects of insulin by promoting glucose uptake via GLUTs and intracellular glucose metabolism in insulin sensitive cells (Saini, 2010:69; Schinner et al., 2004:675). This activation of PI3K leads to the translocation of intracellular GLUT4 to the plasma membrane, where it facilitates the transport of plasma glucose into the cell, mainly in that of skeletal muscle, heart and adipose tissue (Savage et al., 2005:831). See Figure 2.2 for an illustration of an insulin signalling pathway created for the purpose of illustrating the mechanism of insulin action.
Figure 2.2:  **Insulin signalling pathway**

In an environment of elevated plasma FFA, insulin action on GLUT4 decreases, resulting in decreased glucose uptake (Savage *et al.*, 2005:830). Elevated FFAs induce insulin resistance by inhibition of insulin stimulated IRS activation of PI3K (Dresner *et al.*, 1999:258; Saini, 2010:69). Free fatty acids and its metabolites serve as signalling molecules that activate protein kinases, which impairs insulin signalling by increasing serine phosphorylation of IRS (Qatanani & Lazar, 2007:1443). Insulin receptor substrate serine phosphorylation is part of the insulin feedback signalling in a time-controlled manner; however, when influenced by metabolic and inflammatory stresses, promotes insulin resistance (Tanti & Jager, 2009:753). Serine phosphorylation of IRS causes dissociation of insulin/IRS and/or IRS/PI3K, preventing activation of PI3Ki and furthermore the translocation of GLUT4 to the cell membrane, leading to a decrease in glucose uptake, as well as degradation of IRS (Saini, 2010:69; Mlinar *et al.*, 2007:25). Other causes of serine phosphorylation of IRS include inflammation, hyperglycaemia, hyperinsulinaemia and stress (Saini, 2010:70; Schinner *et al.*, 2004:679; Tanti & Jager, 2009:753; White, 2002:283).

The liver is an insulin sensitive organ, which plays an important role in maintaining the body’s energy homeostasis. Defective insulin signalling and the development of insulin resistance in the liver have important consequences. These consequences lead to the development of T2DM and its related complications such as hyperglycaemia and dyslipidaemia (Meshkani & Adeli, 2009:1331). Fasting hyperglycaemia results from reduced peripheral glucose uptake and increased glucose production by insulin resistant hepatocytes (liver cells) (De Fronzo *et al.*, 1989:387; Meshkani & Adeli, 2009:1334; Savage *et al.*, 2007:510). Insulin action in the liver is
similar to that of the muscle. Insulin binds to the insulin receptor, which leads to the same mechanism, up until the binding of PI3K to PDK and its substrate PKB; here, PKB promotes glycogen synthesis and inhibits gluconeogenesis (Samuel et al., 2010:2271). Insulin mediates its inhibitory effects of glucose production, by inhibiting phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6 phosphatase (G6-P), two key gluconeogenic enzymes via the action of PKB (Franke et al., 1997:665; Meshkani & Adeli, 2009:1334; Perry et al., 2014:84). Elevated FFA delivery to the liver (and specifically one of its metabolites; diacylglycerol (DAG)) promotes the translocation of PKC to the cell membrane where it inhibits the action of insulin (Perry et al., 2014:85). Hepatic insulin resistance leads to increased glucose production via increased gluconeogenesis and glycogenolysis and decreased glucose storage as glycogen via glycogen synthesis (Arner, 2002:s6). Insulin resistance also leads to the development of dyslipidaemia (Biddinger et al., 2008:131) by increasing the secretion of insulin. However, with reduced glucose uptake into skeletal muscle cells, the glucose is diverted to the liver where it is used for hepatic lipogenesis (Samuel et al., 2010:2271). Insulin action in the liver furthermore promotes lipid synthesis and inhibits lipolysis (Meshkani & Adeli, 2009:1335). Insulin resistance in adipose tissue results from reduced IRS1 action, which leads to reduced glucose uptake via GLUT4 and increased lipolysis. The increased lipolysis leads to an increased flux of FFA to the liver where it further promotes insulin resistance (Gustafson et al., 2015:195; Meshkani & Adeli, 2009:1335).

2.2.3.2 Beta-cell dysfunction

The beta-cell produces and secretes insulin in order to maintain circulation glucose concentrations within a narrow physiological range. Insulin secretion is maintained at a basal rate during the day and changes in response to changes in plasma glucose concentration (Gastaldelli, 2011:s61). The beta-cell exhibits both a high capacity insulin release (able to keep up with the insulin demand of a range of body sizes) and sensitivity in order to produce a rapid and robust response to glucose increments (Ferranini, 2010:349). Dysfunction of the pancreatic beta-cells plays a major role in the transition from normal glucose tolerance to hyperglycaemia and ultimately T2DM (Gastaldelli, 2011:s62). Beta-cell failure involves both a decrease in beta-cell mass and deterioration of beta-cell function (Muoio & Newgard, 2008:198). Beta-cell injury, on the other hand, is caused by a variety of factors that include obesity, insulin resistance, inflammation, over consumption of saturated fat and circulated free fatty acids (Cerf, 2013:37). Beta-cell loss is preceded by a progressive decline of beta-cell function that leads to beta-cell exhaustion (Cerf, 2013:37).
Loss of beta-cell function due to reduced secretory capacity and enhanced apoptosis is a key event in the pathophysiology of T2DM (Drews et al., 2010:703). Impaired insulin secretion is generally progressive involving glucose toxicity and lipo-toxicity. When left untreated, it contributes to the decrease in beta-cell mass (Kaku, 2010:43). In the progression of T2DM, there are five identified stages of beta-cell dysfunction (Weir & Bonner-weir, 2004:s16; Weir et al., 2001: s155):

(1) **Compensation**

The compensation stage is marked by increased insulin secretion in reaction to increased glucose stimulated insulin secretion (GSIS), following an intravenous glucose challenge. Much of the increase in the insulin secretion is caused by increased beta-cell mass.

(2) **Stable adaptation**

During the stable adaptation stage, the beta-cells are no longer able to compensate and a normal glucose range cannot be maintained. In this stage, the fasting glucose levels are maintained between 5.0 and 7.3mmol/L. As glucose levels rise to stage 2, important changes in both beta-cell function and differentiation occur. The most striking change is the loss of acute GSIS. Individuals can remain in stage 2 for years without developing T2DM.

(3) **Unstable early decompensation**

Due to a loss of beta-cell function at a critical stage, glucose levels rise rapidly from 7.3 mmol/L, through an unstable transient stage 3 of decompensation, to a stable stage 4 of 16-20 mmol/L.

(4) **Stable decompensation**

Individuals with T2DM in this stage typically have enough insulin secretion to remain in stage 4. This can last a lifetime in most cases, while the rapid auto-immune destruction in T1DM can lead to stage 5 relatively quickly.

(5) **Severe decompensation**

In this last stage, the beta-cell loss is so severe that people become ketotic and truly dependent on insulin for survival. Here glucose levels are typically > 22 mmol/L. In this stage, patients are dependent on insulin for survival. This stage is typically found in patients with T1DM or in patients with pancreatic islet transplant when beta-cells have been mostly destroyed by the immune system. Stage 5 can also occur in situations such as exposure to certain toxins or very severe pancreatitis.
In overt T2DM, insulin resistance is associated with abnormalities in beta-cell function. These abnormalities are manifested in the following manners (Ferrannini & Mari, 2014:1222):

- Increased fasting insulin secretion and total stimulated insulin output due to persistent hyperglycaemia, which positively correlates with IGT and insulin resistance
- Impaired glucose sensitivity
- Reduced sensitivity rate manifested as an inability to promptly respond to glucose increments
- Compromised incretin potentiation.

2.2.4 Complications

Type 2 diabetes mellitus is associated with a number of complications, both acute and chronic. The acute complications that are associated with mortality are keto-acidosis and coma. The chronic vascular complications are the most devastating (Forbes & Cooper, 2013:138). These complications result from damage to the blood vessels caused by chronic hyperglycaemia (Forbes & Cooper, 2013:139; Giacco & Brownlee, 2010:580). The vascular complications are divided into microvascular- and macrovascular complications (Desphande et al., 2008:1257; Fowler, 2008:77). Microvascular complications are chiefly caused by hyperglycaemia, while macrovascular complications by hypertension and dyslipidaemia (also associated with T2DM) (Mogre et al., 2016:79). Microvascular complications include retinopathy, nephropathy and neuropathy (Desphande et al., 2008:1257; Forbes & Cooper, 2013:138). Macrovascular complications include accelerated cardiovascular disease, resulting in myocardial infarction (MI) and cerebral diseases, which manifest as strokes (Forbes & Cooper, 2013:139).

2.2.4.1 Microvascular complications

Microvascular complications could have devastating effects, including blindness, end-stage renal failure and neuropathy that may lead to lower leg amputations, all of which could increase the cost of diabetes care (Girach & Vignati, 2006:229). Microvascular complications are mostly caused by prolonged exposure to hyperglycaemia (Giacco & Brownlee, 2010:1059).

The metabolic abnormalities of T2DM cause superoxide overproduction in the mitochondria of endothelial cells of both large and small vessels (Giacco & Brownlee, 2010:1058). Hyperglycaemia causes vascular damage through the following mechanisms (Giacco & Brownlee, 2010:1059; Madsen-Bouterse & Kowluru, 2008:319; Muthuppalaniappan et al., 2015:520; Vincent et al., 2004:617).
(1) *Increased polyol pathway flux*

Aldose reductase converts glucose to sorbitol. The sorbitol is then oxidised to fructose by sorbitol dehydrogenase (SHD) with nicotinamide adenine dinucleotide (NAD\(^+\)) as a cofactor (Vincent *et al.*, 2004:617; Giacco & Brownlee, 2010:1060; King & Loeken, 2004:333). Glucose is normally a poor substrate for aldose reductase, but in high quantities (as is the case in hyperglycaemia) much of the glucose is converted into sorbitol, activating the polyol pathway of glucose conversion to fructose (Vincent *et al.*, 2004:617). Aldose reductase is dependent on nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor, thereby depleting cytosolic NADPH (Vincent *et al.*, 2004:617). Increased NADP\(^+\) inhibits glutathione reductase, which regenerates reduced glutathione (GSH) (and because GSH is an important scavenger of reactive oxygen species (ROS) this leads to increased oxidative stress (Giacco & Brownlee, 2010:1060; Vincent *et al.*, 2004:617)). Sorbitol also produces a cellular osmotic stress that also leads to oxidative stress (Vincent *et al.*, 2004:617). Refer to Figure 2.3 for a schematic of the increased polyol pathway flux.

![Increased polyol pathway flux](image)

**Figure 2.3:** Increased polyol pathway flux
(1) **Advanced glycosylation end products (AGE)-mediated reactive oxygen species formation**

Advanced glycosylation end products are formed by a non-enzymatic reaction of glucose and amino acids in proteins, lipids and nucleic acids (Giacco & Brownlee, 2010:1060; Satirapoj, 2012:112; Vincent et al., 2004:617; Madsen-Bouterse & Kowluru, 2008:317). There are three general mechanisms by which AGE formation causes tissue damage. The first is the abnormal function of intracellular proteins modified by AGE. The second is the abnormal communication between AGE-modified extracellular matrix components with matrix receptors. Finally, AGE-modified plasma proteins that bind to AGE receptors on cells such as macrophages, vascular endothelial cells and vascular smooth muscle (Giacco & Brownlee, 2010:1060).

(2) **Activation of protein kinase C**

Protein kinase C is a family of at least 11 isoforms widely distributed in mammalian tissue (Giacco & Brownlee, 2010:1061). The activity of the classic isoforms is greatly enhanced by diacylglycerol (DAG), which is chronically elevated in hyperglycaemia (Geraldes & King, 2010:1320). Activation of several PKC isoforms mediates tissue damage by diabetes-induced reactive oxygen species (ROS) (Giacco & Brownlee, 2010:1061). The formation of PKC isoforms also decreases glycogen synthase, leading to increased glucose (Vincent et al., 2004:614).

(3) **Oxidative stress**

Oxidative stress plays an important role in the development of both microvascular and macrovascular complications (Rochette et al., 2014:2709). The definition of oxidative stress is excess endogenous oxidative species (especially ROS such as superoxide, hydrogen peroxide and hydroxyl radical ions), which damage cells and manipulate signalling pathways (Hurrle & Hsu, 2017:257).

2.2.4.1.1 Retinopathy

Retinopathy is the most common microvascular complication of T2DM and is characterised by a spectrum of lesions within the retina (Cheung & Wong, 2008:161; Forbes & Cooper, 2013:140; Fowler, 2008:77). Retinopathy is also a common cause of blindness and visual impairment (Forbes & Cooper, 2013:140; Tarr et al., 2012:88). This particular complication is slow to develop and can exist up to seven years before a clinical diagnosis is made (Desphande et al., 2008:1259). The assessment of retinopathy signs gives clinicians an opportunity to directly visualise the actual morphology of diabetic microvascular damage (Cheung & Wong, 2008:161). This is because the retina contains the only part of the vasculature that is easily visible (Shotliff &
Diabetic retinopathy can predict the presence of other vascular damage in both the microvascular- and macrovascular systems (Cheung & Wong, 2008:161).

Visual loss from retinopathy has two main causes: maculopathy and retinal ischaemia. Maculopathy is a disruption of the macular region of the retina, leading to impairment of central vision. While retinal ischaemia results in proliferative diabetic retinopathy (Ciulla et al., 2003:2563; Shotliff & Duncan, 2006:1). Other parts of the eye, apart from the retina, are also affected. Cataracts are more prevalent and there exists a link between diabetes and open angle glaucoma (Shotliff & Duncan, 2006:1). Early retinopathy is marked by changes in the structural and cellular composition of the microvasculature. Advanced retinopathy is characterised by the growth of abnormal retinal blood vessels in order to provide the hypoxic retina with oxygenated blood (Ciulla et al., 2003:2654; Cunha-vaz, 1978:351). The progression of retinopathy follows from no apparent retinopathy through to non-proliferative retinopathy and onto proliferative retinopathy (Ciulla et al., 2003:2654; Eshaq et al., 2017:2; Shotliff & Duncan, 2006:5). No apparent retinopathy has no clinically observable abnormalities, yet despite the normal appearances of the retina, early haemodynamic and histopathological changes can be found (Tarr et al., 2012:89). Non-proliferative retinopathy is associated with micro-aneurysms, haemorrhages appearing as small red dots, retinal ischaemia leading to intra-retinal microvascular abnormalities, retinal oedema, and venous beading and loops (Ciulla et al., 2003:2654; Forbes & Cooper: 2013:140; Fowler, 2008:78; Tarr et al., 2012:91). These changes in the retinal vasculature are strongly associated with worsening prognosis and progression to the proliferative phase (Forbes & Cooper, 2013:140). The proliferative phase is associated with the growth of new blood vessels known as retinal angiogenesis or neovascularisation (Shotliff & Duncan, 2006:9; Fowler, 2008:78). Maculopathy is associated with both proliferative and pre-proliferative retinopathy and is the most common cause of blindness in patients with T2DM (Tarr et al., 2012:92). Maculopathy is known by the presence of hard exudates caused by fluid accumulation at the macula due to increased vascular leakage (Ciulla et al., 2003:2655; Tarr et al., 2012:93).

2.2.4.1.2 Nephropathy

Nephropathy is the leading cause of renal failure, as well as end-stage renal disease in the Western world and affects 20 to 40% of patients with DM (Muthipalaniappan et al., 2015:520; Sharaf et al., 2017:363; Vinod, 2012:121). The classic definition of nephropathy is progressive albuminuria, from normoalbuminuria to overt proteinuria (Muthipalaniappan et al., 2012:520). Nephropathy progresses over a long period of time and is fatal if left untreated. Patients with nephropathy are at a higher risk of mortality, mostly due to cardiovascular complications, than other patients with T2DM (Satirapoj, 2012:108). The functional part of the kidney is the nephron
that serves to fulfil vital functions within the body, namely (MacIsaac & Watts, 2006:21; Pickett, 2016:686):

- Control of water and electrolyte metabolism;
- Regulation of arterial blood pressure;
- Excretion of both endogenously produced and exogenously ingested toxins.

The main site of pathophysiology in the nephron is the glomerulus (Satirapoj, 2012:113). The glomerulus is a filtration barrier that acts to separate large molecules and blood cells from small molecules and water (MacIsaac & Watts, 2006:23). Pathologic changes in the structure and function of this filtration barrier are manifested by glomerular hyperfiltration, glomerular- and tubular epithelial hypertrophy and the development of microalbuminuria (MacIsaac & Watts, 2006:24; Satirapoj, 2012:110; Sharaf El Din et al., 2017:364). This is followed by the development of glomerular basement membrane thickening, accumulation of mesangial matrix and overt proteinuria, which is a leading cause of glomerulosclerosis and end-stage renal disease (Vinod, 2012:110). Hyperglycaemia is the initiating event in the pathophysiological mechanisms that lead to structural and functional changes in the kidney (Satirapoj, 2012:121). In the pathophysiology of nephropathy, there are two main hyperglycaemia-induced pathways: the metabolic pathway and the haemodynamic pathway (Vinod, 2012:110)

Glomerular haemodynamic pathway changes occur very early the pathophysiology of the nephron and are driven by high intra-glomerular pressure caused by hyperfiltration and hyperperfusion (Forbes & Cooper, 2013:139; Satirapoj, 2012:111; Vinod, 2012:121). Decreased resistance in both the afferent and efferent arterioles (predominantly the afferent arteriole) leads to increased glomerular capillary pressure, which enhances trans-capillary hydraulic pressure and increase glomerular plasma flow (Vinod, 2012:122; Satirapoj, 2012:107). Defective autoregulation is partly caused by factors such as prostanoids, nitric oxide, vascular endothelial growth factors, transforming growth factor β1, endothelin and the renin-angiotensin aldosterone system (RAAS) (Muthuppalaniappan et al., 2015:520). These changes promote albumin leakage from the glomerular capillaries, overproduction of the mesangial matrix and glomerular basement thickening (Muthuppalaniappan et al., 2015:520; Satirapoj, 2012:110; Vinod, 2012:122).

The metabolic pathways are driven by hyperglycaemia and include oxidative stress caused by numerous abnormal metabolic pathways. These pathways include the polyl pathway, activation of PKCs and AGE formation (Satirapoj, 2012:110; Soldatos & Cooper, 2008:s76; Vinod, 2012:122).
Nephropathy develops in stages and is caused mostly by chronic exposure to hyperglycaemia. The early functional changes in nephropathy include glomerular hyperfiltration, glomerular- and tubular epithelial hypertrophy and development of microalbuminuria, followed by the development of glomerular basement membrane thickening and accumulation of mesangial matrix (Satirapoj, 2012:110):

- **Stage 1: Hyperfiltration**

  This stage is marked by increased albumin excretion rates (AER) leading to microalbuminuria and a rise in blood pressure, which may have started before microalbuminuria in T2DM. During this stage, GFR may increase by 20 to 50%.

- **Stage 2: Silent stage/ or microalbuminuria**

  Stage 2 may last for years with the majority of DM patients remaining in this stage throughout their lives. During this stage, there is normal AER with intermittent microalbuminuria leading to a false sense of normal renal function, yet structural abnormalities are already present.

- **Stage 3: Incipient or microalbuminuria**

  This stage is characterised by persistent microalbuminuria. In this stage, GFR can be preserved if the patients remain normotensive and the AER does not progressively rise. However, in T2DM, hypertension commonly precedes or accompanies this stage and also promotes a rise in AER and a decline in GFR.

- **Stage 4: Overt nephropathy or microalbuminuria**

  Stage 4 is also known as diabetic nephropathy. Clinically detectable proteinuria, hypertension and a subsequent decline in GFR characterise this stage. In untreated patients, GFR declines by approximately 10 to 15 ml/min each year during this stage.

- **Stage 5: End-stage renal disease**

  Patients in this stage progress to end stage renal failure, with GFR decreased to below 15 ml/min. This stage normally requires the commencement of renal replacement therapy.
2.2.4.1.3 Neuropathy

Diabetic neuropathy is the most troublesome complication of T2DM leading to the greatest morbidity and mortality and resulting in a huge economic burden of diabetes care (Vinik et al., 2013:747). Type 2 diabetes mellitus is the most common cause of neuropathy, and neuropathies are the most common complication of T2DM affecting up to 50% of patients with T2DM (Azzopardi et al., 2018:111; Otto-Buczkowska & Dryzalowski, 2016:142; Desphande et al., 2008:1260). This is a complication that encompasses both the somatic and autonomic divisions of the peripheral nervous system as well as damage to the spinal cord and the higher central nervous system, leading to impaired wound healing, erectile dysfunction and cardiovascular dysfunction in patients with DM (Forbes & Cooper, 2013:140; Pittinger & Vinik, 2003:275). Diabetic neuropathy is defined as the presence of symptoms and/or signs of dysfunction of the peripheral nerve in patients with DM after exclusion of other causes (Otto-Buczkowska & Dryzalowski, 2016:143). Diabetic neuropathy results from progressive nerve fibre damage affecting small nerve fibres early and involving large fibres later (Hershey, 2016:199). There are various factors that play a role in the development of diabetic neuropathy in the presence of DM (Pittenger & Vinik, 2003:271):

- Metabolic disruptions due to chronic hyperglycaemia, including the formation of AGE;
- Abnormal vascular function leading to loss of nutritive support for peripheral nerve fibres;
- Altered neurotrophic/growth factor availability;
- Autoimmune processes disrupting neuronal function;
- Neuronal loss and dysfunction caused by oxidative stress.

There are several types of diabetic neuropathy, which can be further categorised as diffuse or focal neuropathy (Farhat & Yezback, 2016:660). Diffuse neuropathies are more common in patients with T2DM and include peripheral and autonomic neuropathies. The symptoms of peripheral neuropathy vary depending on the involvement of small or large fibres. If the small fibres are involved, the symptoms include pain (either burning or stabbing) or dysesthesias (such as tingling), and if large fibres are involved, the symptoms could include numbness or loss of protective sensations (ADA, 2017:s93; Bril et al., 2018:s217). Peripheral neuropathy is the leading risk factor for foot ulcers, which is a major contributor to the morbidity, mortality and increased healthcare costs in T2DM (Embil et al., 2018:s222). Autonomic neuropathy could lead to the development of the following (ADA, 2017:s94; Verotti et al., 2014:2):
• Cardiac autonomic neuropathy presenting an orthostatic hypotension and decreased heart rate variability

• Gastrointestinal neuropathy, which includes gastroparesis, oesophageal dysmotility, diarrhoea and constipation

• Erectile dysfunction

• Urinary dysfunction

Focal neuropathies include mononeuropathy, cranial neuropathy, entrapment neuropathy, asymmetric lower limb motor neuropathy (amyotrophy), and radiculopathy/plexopathy. These are less common and usually self-limiting (Farhat & Yezback, 2016:660). Table 2.3 shows the classification of neuropathy (adapted from Matuszewski et al., 2013:156).

Table 2.3: Classification of neuropathy

<table>
<thead>
<tr>
<th>Diffuse symmetrical polyneuropathy</th>
<th>Focal and multifocal, non-symmetrical neuropathies</th>
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<tbody>
<tr>
<td>• Chronic sensorimotor neuropathy</td>
<td>• Cranial nerve neuropathy</td>
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<td>• Autonomic neuropathy</td>
<td>• Spinal nerve neuropathy</td>
</tr>
<tr>
<td>• Acute sensory neuropathy</td>
<td>• Focal limb neuropathies (including nerve compression syndromes)</td>
</tr>
<tr>
<td></td>
<td>• Proximal motor neuropathy</td>
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<tr>
<td></td>
<td>• Concomitant chronic neuropathy</td>
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</table>

2.2.4.2 Macrovascular complications

Macrovascular complications in patients with T2DM include various forms of heart diseases. Such diseases include epicardial coronary heart disease with manifestations that include sudden cardiac death and acute coronary syndrome comprising unstable angina pectoris and acute myocardial infarction; small vessel coronary artery disease; cerebrovascular disease; peripheral vascular disease; hypertension and congestive heart failure (Sober & Schneider, 2005:143). Cardiovascular disease is one of the main causes of death in patients with T2DM (Abdul-Ghani et al., 2017:813). The macrovascular complications of T2DM are the direct consequences of the effect of insulin resistance on lipid metabolism (Bardini et al., 2012:82). Atherosclerosis is the accumulation of lipids, cells and matrix components as well as the thickening and deformity of the
arterial wall (Stary et al., 1995:1356). This, in turn, led to the development of diseases in both the cardiovascular and cerebrovascular systems (Yuan et al., 1999:977). Insulin resistance contributes to the accelerated development of atherosclerosis due to increased concentrations of glucose and FFA as well as reduced nitric oxide production in muscle cells (Mangiapane, 2012:219).

2.3 Type 2 diabetes therapeutic goals

The WHO states that good management of DM using a standardised protocol can potentially prevent complications and premature death. A systemic approach to the organisation of diabetes care is essential, which includes well-trained and dedicated personnel, equipment that is functioning and calibrated, management and referral protocols, a continuous supply of necessary medication, a register of all patients, and legible patient records (SEMDSA type 2 diabetes guidelines expert committee, 2017:s20). Optimal care of T2DM involves a multifactorial approach comprising an inter-professional team addressing healthy behaviours, glycaemic control, blood pressure and blood lipid control in order to lower the risk of developing (and the progression) of complications for patients with T2DM (Houlden, 2018:s1). Clinical practice guidelines exist to provide involved parties, such as clinicians, patients, researchers etc., with the general goals of treatment and tools to evaluate quality of care (ADA, 2012:s11). Clinical practice guidelines further exist to increase knowledge, stimulate research and to promote better management of patients with T2DM (ADA, 2017:s1; SEMDSA type 2 diabetes guidelines expert committee, 2017:s1; RSA, 2014:ii). The goals of these guidelines (by various institutions or associations) are to prevent or delay the progression of both T2DM and its associated complications in order to reduce mortality and morbidity as well as to increase cost effectiveness (ADA, 2017:s52; RSA, 2014:9.7; SEMDSA type 2 diabetes guidelines expert committee, 2017:s34; WHO, 2016:46).

Type 2 diabetes mellitus management, according to the definitions posed by various care organisations, include (ADA, 2017:s57; RSA, 2014:9.7; SEMDSA type 2 diabetes guidelines expert committee, 2017:s20; WHO, 2016:60):

- The treatment of hyperglycaemia by the control of blood glucose levels expressed as FPG, 2hPG and HbA1c;
- The management of chronic conditions associated with T2DM such as hypertension and dyslipidaemia by control of blood pressure and total cholesterol levels;
- The treatment of microvascular complications;
- The treatment of macrovascular complications.
2.3.1 Therapeutic approaches

Type 2 diabetes care revolves around patient education, lifestyle modification (SEMDSA type 2 diabetes guidelines expert committee, 2017:s22), monitoring of T2DM patients for specific parameters (see Annexure A), and pharmacological treatment (RSA, 2014:9.9; SEMDSA type 2 diabetes guidelines expert committee, 2017:s34; ADA, 2017:s6). Lifestyle modifications in the T2DM care setting involves patient education regarding DM and complications, healthy diets, cessation of smoking and regular physical exercise (RSA, 2014:9.8; SEMDSA type 2 diabetes guidelines expert committee, 2017:s25-s30; WHO, 2012:22). The lifestyle component of T2DM care is essential as it can effectively delay the onset of disease progression of T2DM in high risk individuals, as well as prevent or delay the progression of associated microvascular- and macrovascular complications (Anderson et al., 2003:331; Klein et al., 2004:2067; Sievenpiper et al., 2018:s64; WHO, 2012:23). For the purposes of this study, the focus will be on the monitoring and pharmacological management of T2DM.

2.3.1.1 Treatment of hyperglycaemia

2.3.1.1.1 Monitoring of hyperglycaemia

The treatment of hyperglycaemia is the backbone of T2DM management (Inzucchi et al., 2015:140), the purpose of which is to reduce blood glucose levels in order to prevent or delay the development of microvascular complications (Imran et al., 2018:s42; SEMDSA type 2 diabetes guidelines expert committee, 2017:s51). Treatments of hyperglycaemia include the frequent monitoring of blood glucose levels by ways of either fasting, 2-hour post-prandial or at random finger prick testing and annual HbA1c% levels (ADA, 2017:s47; Berard et al., 2018:s47; RSA, 2014:9.7; SEMDSA type 2 diabetes guidelines expert committee, 2017:s35). Regular screening is recommended in order to achieve good glycaemic control (The Emerging Risk Factor Collaboration et al., 2014:1226). Finger-prick blood glucose levels are tested at each visit to the hospital/clinic (RSA, 2014:9.7; SEMDSA type 2 diabetes guidelines expert committee, 2017:s37). Glycated haemoglobin should be measured annually in stable patients and every three to six months in patients who are either newly diagnosed or in patients whose medication has changed (ADA, 2012:s18; Ismail-Beigi, 2012:1321; RSA, 2014:9.9; SEMDSA type 2 diabetes guidelines expert committee, 2017:s36). Frequent monitoring of blood glucose levels leads to better treatment of patients with T2DM as it can give an indication of whether patients are reaching glycaemic targets and whether patients are receiving appropriate therapy (ADA, 2016:s39; SEMDSA type 2 diabetes guidelines expert committee, 2017:s51). See Table 2.4 for a summary of the glucose monitoring practices as proposed in the guidelines by the CDA, ADA, SEMDSA.
and PHC STG EML (ADA, 2018:s49; Berard et al., 2018:s47; RSA, 2014:9.7; SEMDSA type 2 diabetes guidelines expert committee, 2017:s37).

Table 2.4: Summary of glucose monitoring practices

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Parameter</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDA 2018</td>
<td>HbA1c</td>
<td>Every three months if targets are not met. Every six months in patients whose glycaemic levels are consistently achieved.</td>
</tr>
<tr>
<td></td>
<td>Self monitoring of blood glucose (SMBG)</td>
<td>Individualised to each patient's unique circumstances.</td>
</tr>
<tr>
<td>ADA 2017</td>
<td>HbA1c</td>
<td>Measured at least biannually. Every three months in patients whose therapy changed or who are not reaching glycaemic targets. Measured as point of care testing.</td>
</tr>
<tr>
<td></td>
<td>SMBG</td>
<td>Individualised to each patient's unique circumstances.</td>
</tr>
<tr>
<td>SEMDSA 2017</td>
<td>HbA1c</td>
<td>Measured at the initial visit Every three months in patients whose therapy is changed or who do not meet glycaemic targets. Every six months in patients with stable control who are meeting their target goal.</td>
</tr>
<tr>
<td></td>
<td>SMBG</td>
<td>Individualised to each patient's unique circumstances.</td>
</tr>
<tr>
<td>RSA 2014</td>
<td>HbA1c%</td>
<td>Measured at initial visit. Measure at least annually in patients who are stable who reach treatment targets. Measured every three to six months in patients whose therapy has changed or who do not meet treatment targets.</td>
</tr>
<tr>
<td></td>
<td>Finger-prick blood glucose testing</td>
<td>Measured at every visit.</td>
</tr>
</tbody>
</table>
2.3.1.1.2 Pharmacological treatment of hyperglycaemia

The drugs used in the treatment of hyperglycaemia can be divided into insulin and anti-diabetic drugs. Insulin can further be divided into rapid or short acting insulin, intermediate acting insulin and slow or long acting insulin (Trevor et al., 2010:361; Wells et al., 2015:163). The non-insulin anti-diabetic drugs include (Klarenbach et al., 2011:E1214; Lipscombe et al., 2018:s88-s103; Nolte Kennedy, 2012:764; RSA, 2014:9.9; SEMDSA type 2 diabetes guidelines expert committee, 2017:s39-s48; Trevor et al., 2010:361; Zhang et al., 2014:1338):

- **Biguanide**

Biguanide drugs exert a glucose lowering effect by reducing hepatic and renal gluconeogenesis, ultimately decreasing the endogenous production of glucose (Pernicova & Korbonits, 2014:145; SEMDSA type 2 diabetes guidelines expert committee, 2017:s39). Side effects include gastrointestinal disturbances and lactic acidosis. The use of biguanide drugs is contraindicated in the presence of renal and liver dysfunction, irritable bowel syndrome and in the presence of hypersensitivity (Lipscombe et al., 2018:s88; Nolte Kennedy, 2012:764).

- **Sulphonylureas**

Sulphonylureas increases insulin secretion through the closure of potassium channels in pancreatic beta-cells (Beck-Nielsen et al., 1988:613; Rubaiy, 2016: 26) leading to a glucose lowering effect by reducing the circulating glucose and increasing glycogen, fat and protein formation. These drugs can only be used in patients with functioning beta-cells. The side effects include hypoglycaemia and possible weight gain. Use of sulphonylureas is contraindicated in patients with a history of severe or recurrent hypoglycaemia and advanced liver disease (Nolte Kennedy, 2012:764).

- **Alpha-glucosidase inhibitors**

Alpha-glucosidase inhibitors inhibit alpha-glucosidases in the intestine, thereby reducing conversion of starch to disaccharides and monosaccharides. Therefore, post-prandial hyperglycaemia is lowered (Bösenberg & van Zyl, 2008: 86; Nolte Kennedy, 2012:764).

- **Thiazolidinediones**

Thiazolidinediones reduce insulin resistance by regulated gene expression by binding to peroxisome proliferator-activated receptor gamma (PPAR-γ), found in muscle, fat and liver. The PPAR-γ modulates the expression of the genes involved in lipid and glucose metabolism, insulin transduction and adipocyte differentiation. Side effects include fluid retention, mild anaemia,

- **Amylin analogues**

Amylin analogues bind to amylin receptors, which modulate post-prandial glucose levels causing a reduction in post-prandial glucose excursions, lowering glucagon levels and slowing gastric emptying thereby decreasing appetite. The side effects include nausea, anorexia, hypoglycaemia and headache (Bösenberg & van Zyl, 2008: 87; Nolte Kennedy, 2012:764; Vella et al., 2002: 123).

- **Glucagon-like peptide-1 receptor agonist**

Glucagon-like peptide-1 receptor agonists increase the secretion of insulin and suppress glucagon by incretin effect. The use of these drugs could possibly lead to nausea and vomiting, pancreatitis and skin reactions. Contraindications for the use of these drugs include a history of pancreatitis or pancreatic tumour, history of medullary thyroid cancer or multiple endocrine neoplasia (Nolte Kennedy, 2012:764).

- **Glitinides**

Glitinides exert a glucose lowering effect in a similar manner than sulphonylureas, leading to a reduction in circulating glucose by increasing insulin secretion. Side effects include the possibility of hypoglycaemia (Bösenberg & van Zyl, 2008: 81; Nolte Kennedy, 2012:764).

- **Sodium-glucose co transporter inhibitors (SGLT2-i)**

Sodium-glucose co-transporter inhibitors inhibit the action of SGLT2, thereby reducing plasma glucose by increasing urinary glucose excretion. The side effects associated with the use of SGLT2-i include urinary tract infections and genital infections due to the increased urinary glucose excretion (Nolte Kennedy, 2012:764; Scheen, 2015:41).

- **Glucagon-like polypeptidase-4 inhibitors (DPP-4inhibitors)**

Glucagon-like polypeptidase-4 inhibitors block the degradation of glucagon polypeptides; this inhibition increases insulin secretion and inhibits glucagon secretion, while also delaying gastric emptying. Common side effects include headache, upper respiratory tract infections, anorexia and nasopharyngitis (Nolte Kennedy, 2012:764; Trevor et al., 2010: 366).

For further review of the anti-diabetic drugs, refer to Annexure I.
The most common of these drugs used for the treatment of hyperglycaemia, according to and suggested by various organisations, include: metformin (as a first line treatment) (ADA, 2017:s65; Rispin et al., 2009:34; RSA, 2014:9.8; SEMDSA type 2 diabetes guidelines expert committee, 2017:s40), sulphonylureas (used in combination with metformin) and insulin (Abdul-Ghani et al., 2015:686). Metformin is used as first-line treatment in most patients based on its effectiveness in lowering BG levels, relatively mild side effects and long-term safety record and possible negligible risk of inducing hypoglycaemia and not causing weight gain (Harper et al., 2013:s65; Inzucchi et al., 2015:144; Klarenbach et al., 2011:E1213). Metformin use is contraindicated in the presence of hepatic and renal dysfunction, irritable bowel syndrome and hypersensitivity (Pernicova & Korbonits, 2014:143; Rispin et al., 2009:31; SEMDSA type 2 diabetes guidelines expert committee, 2017:s40).

A variety of drugs are available for second-line treatment of hyperglycaemia. Sulphonylureas, however, are considered more often due to its effectiveness in lowering HbA1c, as well as its cost effectiveness. The use of sulphonylureas is recommended as the second step of treatment according to the PHC STG EML 2014 edition (RSA, 2014:9.11). When a patient’s blood glucose levels fail to improve, the dosage of the sulphonylureas may be increased or other oral anti-diabetic drugs may be added in combination or used to replace sulphonylureas (Klarenbach et al., 2011:E1217; Nathan et al., 2009:25; Ripsin et al., 2009:33; SEMDSA type 2 diabetes guidelines expert committee, 2017:s42). The next step in the treatment of hyperglycaemia, if oral anti-diabetic drugs failed to improve the patient’s glucose levels, is the use of insulin (Abdul-Ghani et al., 2015:686; ADA, 2017:s66; RSA, 2014:9.11; SEMDSA type 2 diabetes guidelines expert committee, 2017:s55).

### 2.3.1.2 Treatment of hypertension and dyslipidaemia

Cardiovascular disease (CVD) has the greatest capacity to cause sudden or premature death and/or devastating complications. Patients with T2DM have a two- to three-fold increased risk for the development of CVD (SEMDSA, 2017:s78). In all T2DM patients, CVD risk factors should be assessed systematically and annually. These risk factors include: hypertension, dyslipidaemia, smoking, family history of premature coronary disease, as well as the presence of albuminuria (ADA, 2017:s75). For the purposes of this study, only the monitoring and pharmacological management of hypertension and dyslipidaemia will be included/discussed. Table 2.5 provides a summary of the treatment of hypertension and dyslipidaemia (adapted from ADA, 2017:s75-s79; Mancini et al., 2018:s179; RSA, 2014:9.7; SEMDSA type 2 diabetes guidelines expert committee, 2017:s21; Tobe et al., 2018:s186)
Hypertension is a common comorbidity of T2DM, which is at a prevalence exceeding 70% in T2DM patients (Trudeau & Gilbert, 2018:113) and is one of the most preventable causes of morbidity and mortality in both developed and developing countries (Hashemizadeh & Sarvelayati, 2013:22). Blood pressure should be measured as often as each clinical visit according to accepted practices and be treated accordingly (ADA, 2017:s75; RSA, 2014:9.6; SEMDSA type 2 diabetes guidelines expert committee, 2017:s85). Treatment of hypertension includes multiple drug classes such as diuretics, beta-blockers and vasodilators (calcium channel blockers, angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blockers (ARB)), (Benowits, 2012:187-188). The first-line treatment of hypertension includes the use of ACEi, ARBs or calcium channel-blockers (Fares et al., 2018; RSA, 2014:4.15; SEMDSA type 2 diabetes guidelines expert committee, 2017:s87; Tobe et al., 2018:s187).

The use of ACEi and ARBs can reduce blood pressure as well as urine protein output. Angiotensin converting enzyme is responsible for converting angiotensin I to angiotensin II. Angiotensin II is the main effector of the RAAS (Satirapoj, 2012:116) and leads to increased vasoconstriction, which causes increased peripheral vascular resistance and ultimately increased blood pressure. Angiotensin II also stimulates the secretion of aldosterone, which leads to increased water and sodium retention and ultimately increased blood pressure (Benowitz, 2012:184). In the kidney of T2DM patients, glomerular hyperfiltration leads to the activation of the RAAS, which is important in the regulation of both blood pressure and proteinuria (Rüster & Wolf, 2006:2988; Satirapoj, 2012:115; Weir & Dzau, 1999:205s). Calcium channel blockers, specifically verapamil and diltiazem, decrease vascular tone by inhibiting calcium influx into arterial smooth muscle cells. Verapamil and diltiazem also have significant effects in lowering proteinuria (SEMDSA type 2 diabetes guidelines expert committee, 2017:s87). Some guidelines recommend a stepwise treatment plan that includes the use of multiple antihypertensive drugs from different classes (RSA, 2014:4.15-4.17; SEMDSA type 2 diabetes guidelines expert committee, 2017:s87).

Dyslipidaemia is a major contributor to macrovascular complications or atherosclerosis, which accounts for up to 70% of all mortalities in T2DM (Daya et al., 2017:1; SEMDSA type 2 diabetes guidelines expert committee, 2017:s78). Lipid phenotypes in T2DM patients vary and are subject to the same risk factors as in individuals without T2DM. The common pattern of dyslipidaemia in T2DM patients consists of slightly increased triglycerides, increased LDL and decreased levels of HDL (AL-Adsani et al., 2004:129; Blom, 2013:48; Daya et al., 2017:1; Mancini et al., 2018:s178; SEMDSA, 2017:s80). Statins used as monotherapy are the most potent total and LDL-cholesterol lowering agents, which, if added to dietary therapy, can lower total cholesterol with up to 30% (Wells et al., 2012:71). Considering the importance of dyslipidaemia in the risk of CVD in T2DM patients, it is important to both monitor and treat dyslipidaemia as part of the management of

- Older than four years of age
- Have had T2DM for longer than 10 years
- Have existing cardiovascular disease or chronic kidney disease.

<table>
<thead>
<tr>
<th>Table 2.5: Blood pressure and blood lipids monitoring practices</th>
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<tbody>
<tr>
<td><strong>Guideline</strong></td>
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<td><strong>CDA 2018</strong></td>
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2.3.1.3 Treatment of microvascular complications

Optimal glycaemic and blood pressure control contributes to the prevention of the development of microvascular complications, especially in retinopathy and nephropathy (ADA, 2017:s88). The management of complications will be discussed below.

2.3.1.3.1 Management of retinopathy

Diabetic retinopathy is the leading cause of new cases of blindness in both developed and developing countries; also, glaucoma, cataracts and other eye disorders occur earlier and more frequently in all patients with DM (ADA, 2017:s92; SEMDSA type 2 diabetes guidelines expert committee, 2017:s94). An estimated third of all DM patients worldwide will develop retinopathy, a condition that is by large preventable and/or treatable (SEMDSA type 2 diabetes guidelines expert committee, 2017:s94). Risk factors for the development of retinopathy include (Mohamed et al., 2007:902; Ting et al., 2016:262):

- Duration of DM
- Hyperglycaemia
- Hypertension
- Dyslipidaemia
- Nephropathy
- Obesity
- Smoking
- Physical inactivity
- Moderate alcohol consumption

Management of retinopathy therefore includes lifestyle interventions, cessation of smoking, glycaemic control, blood pressure control and treatment of dyslipidaemia (ADA, 2017:s92; Altomare et al., 2018:s210; Malek et al., 2012:635). Glycaemic control reduces the incidence of retinopathy, while the treatment of hypertension and dyslipidaemia reduces the progression of retinopathy and visual loss (Malek et al., 2012:635). Screening for diabetic retinopathy is recommended to be done at diagnosis and repeated annually in all T2DM patients (Altomare et al., 2018:s210; SEMDSA type 2 diabetes guidelines expert committee, 2017:s96). Frequent
screening for retinopathy can reduce the risk of vision loss, as retinopathy in patients can be asymptomatic until vision loss occurs (Altomare et al., 2018:s210; Hurley, 2017:s1; SEMDSA type 2 diabetes guidelines expert committee, 2017:s98)

2.3.1.3.2 Management of nephropathy

Nephropathy is the leading cause of end-stage renal disease affecting up to 20 to 30% of all T2DM patients (Ahmad, 2015:343; Gembardt et al., 2014:F317). Renal dysfunction and the development of end-stage renal disease remain major concerns in DM (Waanders et al., 2013:448). The main risk factors for the development of nephropathy include (Al-Rubeaan et al., 2014; McFarlane et al., 2018:s201; Raile et al., 2007:2523; SEMDSA type 2 diabetes guidelines expert committee, 2017:s89):

- Hyperglycaemia
- Hypertension
- The duration of T2DM
- Obesity
- Dyslipidaemia
- Smoking.

In order to effectively manage nephropathy, it is important to address these risk factors (ADA, 2017:s83; Gross et al., 2005:167; RSA, 2014:9.19). Optimal glycaemic control is organised according to hyperglycaemia treatment algorithms of the various DM care guidelines and blood pressure control is done through the blockade of the RAAS by the use of ACEi such as enalapril or ARBs (ADA, 2017:s91; Fried et al., 2013:1892; RSA, 2014:9.19; SEMDSA type 2 diabetes guidelines expert committee, 2017:s91). An important factor in glycaemic control is the adjustment of the pharmacological regime, when patients’ eGFR indicates a dose adjustment or change of drug (ADA, 2017; SEMDSA type 2 diabetes guidelines expert committee, 2017:s91; RSA, 2014:9.9). Patients with stages 3 to 5 of kidney disease (see section 2.2.4.1.2) are at an increased risk for developing hypoglycaemia due to decreased renal clearance of insulin and sulphonylureas as well as reduced gluconeogenesis. This has implications for the patients’ hyperglycaemia treatment (ADA, 2017:s90; RSA, 2014: 9.10; SEMDSA type 2 diabetes guidelines expert committee, 2017:s92) namely:
Metformin should be used with caution at stages 4 and 5 and completely avoided if eGFR is < 30 ml/min, as this patient carries the risk for developing lactic acidosis, which increases as eGFR decreases.

Only second-generation sulphonylureas (glipizide, gliclazide, glibenclamide, glimepiride) should be used, and only if the patient manages to avoid hypoglycaemic episodes.

Thiazolidinediones should only be used in patients without heart failure.

Insulin therapy should be administered with care to avoid hypoglycaemia.

Glucagon-like polypeptidase-4 inhibitor can be used with dose adjustments.

Glucagon-like peptide-1 receptor agonists should be avoided if creatinine clearance is ≤ 30 ml/min.

Some anti-diabetic drugs are also known to have direct effects on the kidneys apart from glycaemia (ADA, 2017:s90). Studies have shown that SGLT2i, such as empagliflozin, exhibit renal-protective characteristics by limiting hyperglycaemia-induced inflammation in the proximal tubule of the kidney and therefore ameliorates markers of renal injury (ADA, 2017:s90; Gembardt et al., 2014:F324; Panchapakesan et al., 2013). According to the SEMDSA 2017 guidelines, the progression of nephropathy can be decreased by optimal glycaemic control. The best approach, however, is to reduce blood pressure (SEMDSA type 2 diabetes mellitus guidelines expert committee, 2017:s91). The use of ACEi or angiotensin receptor blockers (ARB) can reduce the risk of nephropathy progressing to end-stage renal failure and is the preferred first-line treatment for hypertension in T2DM patients with an eGFR of < 60 ml/min (ADA, 2017:s91; Fried et al., 2013:1892; Mavrakanas et al., 2014:173).

Monitoring the progression of nephropathy in a T2DM patient includes the baseline and annual measurement of albumin excretion and the overall level of kidney function through an eGFR. Patients who are treated with ACEi should also have an annual measurement of serum potassium concentrations (ADA, 2017:s90; McFarlane et al., 2018:s202; RSA, 2014:9.7; SEMDSA type 2 diabetes guidelines expert committee, 2017:s91). Albumin excretion is an indication not only of the presence of kidney disease, but also the extent of the kidney disease (McFarlane et al., 2018:202; SEMDSA type 2 diabetes guidelines expert committee, 2017:s91).
2.3.1.3.3 Management of neuropathy

Neuropathy in T2DM patients is not definite and can be prevented by addressing the risk factors, which include hyperglycaemia, hypertension, dyslipidaemia, obesity and smoking (which are all modifiable) (Bril et al., 2018: s217; Papanas & Ziegler, 2015:48). The treatment of neuropathies includes management of pain, treatment of foot ulcers and symptomatic treatment of gastroparesis and erectile dysfunction. Few patients have complete relief of pain, and a 30 to 50% reduction in baseline pain is considered to be a clinically meaningful response (Bril et al., 2018: s218). Patients should have their feet examined at least annually and have their footwear examined at every visit (ADA, 2017: s93; RSA, 2014:9.17).

2.3.1.4 Treatment of macrovascular complications

Atherosclerotic cardiovascular disease in patients diagnosed with T2DM is the main cause of morbidity and mortality. Myocardial infarction and stroke account for up to 80% of deaths in T2DM (Ferrannini & DeFronzo, 2015:2289; Low Wang et al., 2016:2459). The main risk factors for the development of macrovascular complications such as atherosclerotic cardiovascular disease include hypertension and dyslipidaemia (ADA, 2017:s75; Stone et al., 2018:s165). Treatment of dyslipidaemia and hypertension has been shown to reduce the risk and decrease the development of macrovascular complications (ADA, 2017:s75; Stone et al., 2018:s163). Secondary prevention of macrovascular complications in patients with a history of cardiovascular events includes the use of aspirin at a dose of 150 mg daily (SEMDSA type 2 diabetes guidelines expert committee, 2017:s83).

For a summary of the management of microvascular and macrovascular complications, see Annexure H (adapted from ADA, 2017:s82-92; Altomare et al., 2018:s210; Bril et al., 2018:s217; Embil et al., 2018:s222; Macfarlane et al., 2018:s201; RSA, 2014:9.17-18; SEMDSA type 2 diabetes guidelines expert committee, 2017:s83-89; Stone et al., 2018:s162).

2.3.1.5 Therapeutic outcomes

Optimal outcomes for management of T2DM lead to the prevention and delay in the development of both microvascular and macrovascular complications. These outcomes include blood pressure targets of < 140/90 mmHg, HbA1c of < 7% and total cholesterol of < 4.5 mmol/L (ADA, 2017:s75; Imran et al., 2018:s42; SEMDSA type 2 diabetes guidelines expert committee, 2017:s80-s87; RSA, 2017:9.7).

Glycated haemoglobin targets should be individualised to each patient being treated. A target of ≤ 7% in most T2DM patients is beneficial in order to significantly decrease the risk of both
microvascular and macrovascular complications (Imran et al., 2018:s42). In adult patients who are at low risk of hypoglycaemia, a target of ≤ 6.5% should be strived for (ADA, 2017:s50; Imran et al., 2018:s43; SEMDSA type 2 diabetes guidelines expert committee, 2017:s36). For individualised HbA1c levels, refer to Table 2.6 (adapted from ADA, 2017:s40; Imran et al., 2018:s43; SEMDSA type 2 diabetes guidelines expert committee, 2017: s36).

### Table 2.6: Individualised HbA1c levels

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Individualised targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6.5</td>
<td>Adult patients with low risk of hypoglycaemia</td>
</tr>
<tr>
<td>≤ 7.0</td>
<td>Majority of adult patients</td>
</tr>
<tr>
<td>7.1 - 8.0</td>
<td>Functionally dependent patients</td>
</tr>
<tr>
<td>7.1 - 8.5</td>
<td>Frail or elderly patients with/or without dementia</td>
</tr>
<tr>
<td></td>
<td>Recurrent or severe hypoglycaemia</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia unawareness</td>
</tr>
<tr>
<td></td>
<td>Limited life expectancy</td>
</tr>
</tbody>
</table>

The recommended BP goal is 140/90 mmHg in the majority of patients. In patients at high risk for cardiovascular disease, an even lower BP target of 130/80 mmHg may be appropriate (ADA, 2017:s75; Brunstörm & Carlberg, 2016:5; RSA, 20014:9.7; Tobe et al., 2018:s186). According to the Brunström meta-analysis, the following outcomes associated with hypertensive treatment were observed (Brunström & Carlberg, 2016):

- All-cause mortality reduction with systolic BP lowered to 130 mmHG
- End-stage renal disease was only reduced if systolic BP before treatment was higher than 150mmHg and only if systolic BP was lowered to 140 - 150 mmHg
- Albuminuria was reduced by 29% when systolic BP was reduced to 130 - 140 mmHG
- Diastolic BP threshold was observed at 90 mmHg and an increased risk for cardiovascular mortality was seen if diastolic BP was lowered to less than 78 mmHg.

The primary target of lipid lowering therapy in T2DM is LDL cholesterol, which, if treated with the use of statins will reduce the risk of major cardiovascular events and reduce all-cause mortality (Mancini et al., 2018:s178; SEMDSA type 2 diabetes guidelines expert committee, 2017:s80).
Patients with T2DM are at an increased risk for cardiovascular diseases even if their LDL cholesterol is at normal levels. These patients are at an even higher risk if their LDL cholesterol is elevated. Low-density lipoprotein cholesterol should be reduced at least to < 2.0 mmol/L or to a > 50% reduction from baseline levels (Mancini et al., 2018:s178). The ideal lipid profile for a T2DM patient is as follows (SEMDSA type 2 diabetes guidelines expert committee, 2017:s80):

- Total cholesterol  < 4.5 mmol/L
- Triglycerides      < 1.7 mmol/L
- LDL cholesterol   < 1.8 mmol/L
- HDL cholesterol   > 1.0 mmol/L in men
                     > 1.2 mmol/L in women

2.4 Compliance to diabetes care guidelines

Clinical practice guidelines (such as diabetes care guidelines) are developed statements that assist HCPs to make healthcare decisions based on specific clinical circumstances (Argyriou et al., 2015:375). These guidelines exist to fill the gap between scientific evidence and implementation in clinical practice through standardisation of medical care in order to promote uniformity of clinical practice (Adedeji et al., 2015). Good T2DM management can be achieved through the use of a standard, evidence-based set of clinical care guidelines. These evidence-based guidelines recommend a set of generic medicines, patient education promoting self-management and implementation of healthy lifestyles, regular screening for early detection, and treatment of complications through a multidisciplinary team (Hull et al., 2014:171; WHO, 2016:47).

Guideline non-compliance is a global concern that negatively affects patient outcomes (Adedeji et al., 2015). Non-compliance can also be referred to as clinical inertia defined as the failure to initiate or intensify therapy in a timely manner according to evidence-based clinical practice guidelines in patients who may potentially benefit from such initiation or intensification (Khunti et al., 2018:428; Khunti et al., 2013:3411; Phillips et al., 2001:825). Clinical inertia was first defined by Phillips et al. (2001:825), who stated that, regardless of available guidelines that included well-defined goals of management and effective therapies, healthcare providers often failed to initiate or intensify therapy appropriately during patient visits. According to Phillips et al. (2001:826), good management of patients with T2DM, hypertension and/or dyslipidaemia involves two steps: the recognition of the abnormality and the initiation and intensifying of treatment until the therapeutic goals are reached.
2.4.1 Healthcare provider compliance to type 2 diabetes care guidelines

Research regarding healthcare provider compliance has been conducted on a global scale, suggesting that clinical inertia is affecting patients (especially with regard to glycaemic control) both nationally and internationally (Adedeji et al., 2015; Delavari et al., 2009: 494; Panatalone et al., 2018; Ratanawongsa et al., 2012:95; Reach, 2014: 241; Vinagre et al., 2012:774). A focused literature review that included studies from the United States (US), United Kingdom (UK) and Canada revealed that healthcare providers failed to initiate or intensify therapy even after HbA1c levels indicated action (Khunti et al., 2015:66). Studies conducted in the African regions also concluded that clinical inertia exists in the management of T2DM with regard to both monitoring of patients as well as initiation or intensification (Amod et al., 2012:89; Pinchevsky et al., 2015:81). A recent literature review focused on the initiation or intensification of insulin therapy in the UK also revealed challenges in healthcare provider compliance to the recommended guidelines regarding therapy (Khunti & Millar-Jones, 2017:10). In Indonesia, a study was conducted in order to determine the degree of awareness, agreement and adoption of clinical practice guidelines by HCPs and concluded that even with high levels of awareness of the existence and content of clinical practice guidelines, agreement and implementing of these guidelines are not guaranteed (Widyahening et al., 2014). Annexure J contains a detailed summary of examples of such studies ranging from clinical inertia in initiating or intensifying anti-diabetic drugs or insulin as well as clinical inertia in regular monitoring of patients.

2.4.2 Possible factors that contribute to clinical inertia

Clinical inertia exists due to multiple levels of barriers, i.e. clinician-level barriers, system-level and patient-level barriers (Zafar et al., 2014: 407). An example of a great clinician-level barrier is limited clinical awareness leading to an overestimation of both the quality of care and adherence to guidelines (Khunti & Millar-Jones, 2016:7; Philips et al., 2001:827); this was demonstrated by a qualitative study during which clinicians who viewed their performance as quite high, good or very good also had a lower quality of care (defined in this study as quality outcome framework (Zafar et al., 2014: 409). Physician-related barriers with regard to implementation in clinical practice also include a lack of requisite skill and expertise, being unaware of the existence of the clinical practice guidelines, a lack of confidence, disagreement with the clinical practice guidelines and a lack of expectancy that adherence will lead to the desired outcomes (Adedeji, 2015; Cabana et al., 1999:1461; Lugtenberg et al., 2009). Another contributing factor to clinician-level barriers may be the fact that chronic disease management is increasingly becoming the responsibility of primary healthcare, leading to general practitioners treating patients with multimorbidity (Khunti & Millar-Jones, 2016:7). This could also be a practical challenge that contributes to system-level barriers to clinical inertia.
Practical challenges that are part of any healthcare delivery system are known as system-level barriers. These challenges could include poor planning and communication between members of the healthcare team, inadequate supportive technologies, resource constraints and lack of clinical guidelines, all of which can lead to poor patient education, poor planning and execution of individualised care plans as well as improper use and understanding of available therapies (Reach et al., 2017:506; Ross, 2013:s38). Patient-level barriers include misconceptions, beliefs, health beliefs, financial resources, attitudes and fear regarding the complexity or need for therapy (Khunti & Millar-Jones, 2016:7; Nam et al., 2011:1; Polonsky & Jackson, 2004:147). Although patient-level barriers exist, clinical inertia remains the responsibility of the healthcare provider and is separate from patient-related factors (Philips et al., 2001:827) (see Table 2.7 for a summary of contributing factors to clinical inertia adapted from (Khunti & Millar-Jones, 2016:7; Reach et al., 2017:505)).

Table 2.7: Summary of contributing factors to clinical inertia at different levels.

<table>
<thead>
<tr>
<th>Clinician-level factor (50% contribution)</th>
<th>System-level (20% contribution)</th>
<th>Patient-level (30% contribution)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unawareness of guideline non-compliance</td>
<td>Lack of clinical guidelines</td>
<td>Health attitude</td>
</tr>
<tr>
<td>Failure to set clear treatment goals</td>
<td>Poor planning</td>
<td>Financial resources</td>
</tr>
<tr>
<td>Failure to initiate or intensify treatment</td>
<td>Lack of team approach to patient care</td>
<td>Complexity of treatment</td>
</tr>
<tr>
<td>Failure to identify and to treat comorbidities</td>
<td>Poor communication between physicians</td>
<td>Fear of side-effects</td>
</tr>
<tr>
<td>Reactive rather the proactive care</td>
<td>Lack of supporting technologies</td>
<td>Poor communication between patient and physician</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absence of symptoms</td>
</tr>
</tbody>
</table>

2.5 Outcomes of T2DM patients nationally and internationally

Clinical inertia is a global problem affecting the quality of care for patients, leading to poor patient outcomes and ultimately the development of complications, as well as increased morbidity, mortality and financial burden (Delavari et al., 2009:492; Braga et al., 2012:457; Reach et al., 2017:501). Good management with the use of evidence-based guidelines is aimed at improving patient outcomes, thereby reducing blood glucose levels, blood lipids and BP in order to prevent the development of diabetes-related complications. Studies done globally reveal that DM care is sub-optimal, with the majority of patients not reaching therapeutic targets and developing complications (Braga et al., 2012:457; Delavari et al., 2009:492; Mohan et al., 2013:14; Lian &
Liang, 2014:2233; Reach et al., 2017:501). Studies done on the quality of care revealed sub-optimal care for patients resulting in poor outcomes regarding blood glucose, blood lipid and BP:

- Braga et al. (2012:457) revealed that in a cohort of 3002 patients, only 19% achieved targeted BP, blood glucose and blood lipid levels.
- Delavari et al. (2009:493) revealed that of a total of 2692 patients in Iran, only 1.1% achieved a HbA1c of < 7%, 225 achieved an optimal LDL cholesterol and 65% achieved optimal BP levels.
- Pantalone et al. (2018) revealed that of a cohort of 7389 patients receiving care at the Cleveland clinic, 4577 patients had an HbA1C of > 7% and 1448 patients had an HbA1c of more than 9%. The study revealed that treatment was not intensified according to the recommendation of guidelines in the majority of patients.
- Stone et al. (2013:774) conducted a study with a total of 286 792 T2DM patients receiving care at primary care facilities in Catalonia. Of all the patients, only 31% had BP levels of ≤ 130/80 mmHg, 37.9% had LDL cholesterol levels of 2.59 mmol/L and 56% achieved an HbA1c of ≤ 7%.
- Pinchevsky et al. (2015:81) aimed to audit and compare the achievement of targets of individual parameters of a cohort of 666 T2DM patients receiving care at a South African tertiary hospital outpatient department over a period of four years. The parameters investigated included blood glucose, BP and blood lipids. Regarding glycaemic control, the study revealed a downward trend from 2009 to 2013: only 15.5% of patients achieved the targeted HbA1c level of < 7.0% in 2013 compared to the 25.4% in 2009. Blood pressure values improved with more patients reaching the target BP level of 140/80 mmHG and the same was seen with LDL cholesterol.

2.6 Chapter summary

This chapter focused on the importance of T2DM care. The pathophysiology of the development of T2DM and of diabetes complications was explored in order to demonstrate how the management of hyperglycaemia, hypertension and dyslipidaemia can prevent the development of complications. Healthcare provider compliance with type 2 diabetes care guidelines nationally and internationally was researched and revealed that clinical inertia is a global problem that affects patient outcomes as seen in section 2.5. Chapter 3 will focus on the results of the empirical study.
CHAPTER 3  MANUSCRIPTS

3.1  Manuscript one:

The title of the first manuscript is *Type 2 diabetes care in the primary care setting: A gap between clinical care guidelines and clinical care practice*. It is written according to the specifications of the journal: *Diabetes primary care* as an original research study.

This manuscript addresses the empirical research objective stated in Chapter 1, section 1.4.2. The objective was to assess HCP compliance with the monitoring and management guidelines as set out by the PHC STG EML 2014 for adult patients in the MOPD of the selected regional hospital in the DKKD for the North West Province of South Africa. This was done by review and evaluation of hard copy patient records for evidence of documentation on monitoring and treatment measures, in order to determine whether action was taken when treatment targets were not met and whether those actions were performed according to guideline recommendations.

3.1.1  Author guidelines

The specific guidelines for an original research paper are as follows (see Annexure K for the author guidelines):

- The maximum number of words is limited to 3000, excluding up to 50 references and a structured abstract not exceeding 200 words.
- The abstract is to be structured according to aims, method, results, conclusion and keywords.
- Papers should cover research or any other topics relevant to common diabetes conditions, chiefly clinical research with relevance to primary care and research implementation of evidence-based guidelines.
- The text should be divided into sections headed introduction, methods, results and discussion:
  - The introduction should state the objectives of the study and provide an adequate background, avoiding a detailed literature survey of a summary of the results.
  - The material and method section should provide sufficient details in order to allow the work to be reproduced by independent researcher. Methods that are already published should be summarised and cited. Use quotation marks and cite the source when directly quoting previously published methods.
  - Results should be written in a manner that is clear and concise.
  - Discussion should explore the significance of the results of the work and not repeat them. A combined results and discussion section is also appropriate. Also avoid extensive citations and discussions of published literature. Furthermore, the discussion section
should address difficulties encountered during the study, alternative methodologies that would have been helpful in answering the research question and new questions that arisen from the study.

- When writing the conclusion, it may be presented in a short conclusion section of the paper or as a subsection of the results and discussion section.
- Acknowledgements should be listed in a separate section. All individuals who provided help in the form of language help, writing assistance or proof reading of the article should be listed here.
- All sources should be cited in text by Arabic numerals within square brackets in the order of the first citation. The references must include authors’ surnames preceded by initials. List all authors if four or fewer or the first three followed by *et al.*, if there are five or more authors, the title of the article, title of the journal abbreviated according to the Index Medicus, volume (and supplement if appropriate), year of publication in parentheses, and the first and last page numbers.

The manuscript to be submitted to the journal *Primary care diabetes*, follows next.
Type 2 diabetes care: A gap between clinical guidelines and clinical practice at primary healthcare level

Authors: Danelle Elizabeth Venter a, b
Martine Vorster a, c
Rianda Joubert a, d
Jesslee Melinda Du Plessis a, e

a Medicine Usage South Africa, Faculty of Health Sciences, North-West University, Private Bag X6001, Potchefstroom, South Africa, 2520

b danelle.debeer@yahoo.com

c martine.vorster@nwu.ac.za

d rianda.joubert@nwu.ac.za

e jesslee.duplessis@nwu.ac.za

Corresponding author: Danelle Elizabeth Venter
Type 2 diabetes care: A gap between clinical guidelines and clinical practice at primary healthcare level

Abstract


Design: Patient records of 192 patients were retrospectively assessed for the study period of 1 March 2016 to 28 February 2018. Data of 1657 patient visits to the medical outpatient department were assessed for guideline-specific monitoring activities and the treatments prescribed.

Results: Monitoring of blood glucose and blood pressure was done at 91.5% and 91.9% of the total patient visits recorded and weight at 0.8%. Baseline monitoring of serum creatinine and serum potassium was performed at 58.9% and 57.3% of the expected number of visits, blood lipids at 71.3%, foot assessments at 25.5% and eye assessments at 22.4%. Annual monitoring of serum creatinine and serum potassium was performed at 37.5% and 36.5% of the expected number of visits, glycosylated haemoglobin at 42.7%, foot assessments at 50% and eye assessments at 54.2%. Recommended treatment for hyperglycaemia was prescribed in 81.3% of the prescriptions recorded, for hypertension in 62.7%, for dyslipidaemia in 83.9%, for nephropathy in 98.6% and for neuropathy in 95.5%.

Conclusion: Healthcare provider compliance was sub-optimal despite areas of optimal compliance.

Keywords: clinical inertia, type 2 diabetes mellitus, primary healthcare

1 Introduction

Clinical inertia, defined as a gap between the best clinical guidelines and clinical practice [1], is a global problem affecting type 2 diabetes mellitus (T2DM) patients in developing and developed countries [2-6] in all levels of care, specialised or at primary healthcare levels [1-7]. Identified areas of care that are impacted by clinical inertia include failure to monitor patient according to the recommendations of evidence-based guidelines [8-10] and failure to intensify or initiate treatment when indicated [1,11,12]. The major area of clinical inertia in T2DM care is glycaemic control.

Evidence-based guidelines recommend strategies to best manage T2DM in order to prevent the onset and delay the progression of diabetes-related complications [13-16], thereby reducing the
morbidity and mortality and ultimately healthcare costs associated with T2DM management [17,18]. These strategies include [13,15]:

- Treatment of hyperglycaemia;
- Treatment of hypertension and dyslipidaemia for the prevention of ischaemic heart disease and atherosclerosis;
- Prevention and treatment of microvascular- and macrovascular complications.

Failure of HCPs to comply with the recommendations of evidence-based guidelines undermines the goals of these guidelines and contributes to the development of complications, thereby increasing the morbidity and mortality and ultimately healthcare costs. Some of the contributors to clinical inertia are overestimation of care, reactive care rather than proactive care provided by HCPs as well as unawareness to guideline non-compliance [19]. By asking the question: “How compliant are the HCPs to the T2DM care guidelines?”, the level of care provided to patients will be highlighted, by revealing areas of compliance as well as areas of non-compliance. This will pave the way forward to better care for T2DM patients. The aim of this research was to assess HCP compliance with T2DM care guidelines. The guidelines used to achieve the objectives of this study were the PHC STG EML 2014. This evidence-based guideline is provided by the South African Department of Health and is implemented by primary healthcare facilities including the study setting. Annexure A provides a summary of the recommendations for the monitoring of specific parameters and management practices by the PHC STG EML 2014 [13].

2 Methods and materials

The methods and materials section will discuss the criteria used to select the participant patient records, the procedure whereby these patient records were evaluated and the type of data that were collected. The methods and materials furthermore include the standard used to assess HCP compliance with the monitoring and pharmacologic treatment guidelines as recommended by the PHC STG EML 2014, the materials needed to collect data for the patient records and the statistical analysis.
2.1 Participants

Patient records of adult DM patients receiving care at the regional hospital outpatient department in the Dr Kenneth Kaunda District of the North West Province in South Africa, irrespective of age and gender, were included according to the following inclusion criteria:

- Type 2 diabetes mellitus patients specifically, identified according to the anti-diabetic drugs prescribed.
- Patients who had at least two visits to the medical outpatient department (MOPD) during the study period of 1 March 2016 to 28 February 2018.

Patient records were excluded according to the following criteria:

- All types of DM other than T2DM such as gestational DM and T1DM (which was identified as patients being treated with insulin only).
- All newly diagnosed patients who did not have data of 2 MOPD visits during the study period.

2.2 Procedure

All selected patient records were retrospectively evaluated for evidence of HCP compliance with the monitoring and management practices of T2DM as stated in the PHC STG EML 2014:

- Did the HCP monitor specific parameters according to the recommendations of this guideline?
- Was an action taken when indicated?
- Was the action taken according the guideline recommendations?

2.3 Standard

The PHC STG EML 2014 provides a standard for the manner whereby the specific parameters should be monitored in T2DM, as well as the frequency of the monitoring of these parameters. This guideline furthermore provides the actions that are to be taken for the management of T2DM patients for the treatment of hyperglycaemia, hypertension and dyslipidaemia as well as the treatment of related complications. It is during patient visits to the MOPD that these guideline-recommended activities are performed. The PHC STG EML 2014 does not specify visit intervals for the management of T2DM; therefore, data for every patient visit to the MOPD were taken into account (see Table 1 for the guideline-recommended monitoring of specific parameters [13]).
Table 1: Monitoring intervals of clinical tests to be performed according to the PHC STG EML 2014

<table>
<thead>
<tr>
<th>At every visit</th>
<th>At baseline</th>
<th>Annual</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Finger-prick blood glucose testing</td>
<td>· Serum creatinine concentration testing (and calculate estimated glomerular filtration rate (eGFR)).</td>
<td>· Serum creatinine concentration testing (and calculate eGFR)</td>
</tr>
<tr>
<td>· Blood pressure measurement</td>
<td>· Serum potassium testing (if the patient is on an angiotensin converting enzyme inhibitors (ACEi) or eGFR is &lt; 30 mL/min.</td>
<td>· Serum potassium concentration testing (if patient is on an ACEi or eGFR is &lt;30mL/min).</td>
</tr>
<tr>
<td>· Weight measurement</td>
<td>· Urine protein testing by dipstick (If negative, albumin:creatinine should be measured unless the patient is treated with ACEi).</td>
<td>· Urine protein testing by dipstick (If negative, albumin:creatinine should be measured unless the patient is treated with ACEi).</td>
</tr>
<tr>
<td></td>
<td>· Blood lipid testing</td>
<td>· HbA1c testing</td>
</tr>
<tr>
<td></td>
<td>· Foot assessment</td>
<td>· Eye assessment</td>
</tr>
<tr>
<td></td>
<td>· Eye assessment</td>
<td>· Foot assessment</td>
</tr>
<tr>
<td></td>
<td>· Abdominal circumference measurement</td>
<td></td>
</tr>
</tbody>
</table>

For the two-year study period, 192 patient records contained data of 1657 patient visits to the MOPD. During these visits, specific guideline-recommended activities are expected to be performed by the HCPs. Blood glucose by ways of finger-prick testing, blood pressure and weight measurement should be performed at every visit, and therefore it is expected to see a total of 1657 finger-prick blood glucose tests, blood pressure and weight measurements recorded.

Baseline parameters are recorded as the first measurement that falls within the study period. Each patient should have an MOPD visit where these baseline parameters were tested, and therefore the expected number of patient visits during which a baseline measurement was performed should amount to 192 for each of these parameters.

Annual parameters are measured once a year, yet taking into consideration that the baseline parameter falls within the two-year study period, there should be one patient visit during which these annual parameters were monitored per patient record, resulting in 192 patient visits during which annual parameters were monitored. The PHC STG EML 2014 does not specify that glycosylated haemoglobin (HbA1c) should be measured at baseline, and therefore the total number of visits to the MOPD where HbA1c tests were recorded should amount to 384 for the
two-year study period if each of these patients’ HbA1c was measured annually (see Table 2 for the expected performance according to guidelines). It is important to note that within the study population, patient records of patients who were treated for a period shorter that one year within the study period were included. These patients’ annual parameters were marked with a not applicable (N/A) onto the data collection tool. Therefore, the number of visits where an annual parameter was performed should be the number of actual tests added to 23 N/A values for the patients who were treated for a period shorter than one year. There should be two N/A values for the 23 patient records for the two-year period for the monitoring of HbA1c. The N/A values were included in order to provide a true picture of HCP compliance with the PHC STG EML 2014.

Table 2: Expected number of recorded clinical tests for monitoring of patients according to the PHC STG EML 2014 recommendations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Expected number of recorded tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measured at every visit</strong></td>
<td></td>
</tr>
<tr>
<td>Finger-prick blood glucose</td>
<td>1657</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>1657</td>
</tr>
<tr>
<td>Weight</td>
<td>1657</td>
</tr>
<tr>
<td><strong>Measured at baseline</strong></td>
<td></td>
</tr>
<tr>
<td>Blood lipids</td>
<td>192</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>192</td>
</tr>
<tr>
<td>Serum potassium in patients using angiotensin inhibitors (ACEi)*</td>
<td>192</td>
</tr>
<tr>
<td>Urine protein using dipsticks</td>
<td>192</td>
</tr>
<tr>
<td>Albumin: creatinine ratio if urine tested negative for protein</td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>192</td>
</tr>
<tr>
<td>Eye assessment</td>
<td>192</td>
</tr>
<tr>
<td>Foot assessment</td>
<td>192</td>
</tr>
<tr>
<td><strong>Measured annually</strong></td>
<td></td>
</tr>
<tr>
<td>Glycosylated haemoglobin (HbA1c)</td>
<td>384</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>192</td>
</tr>
<tr>
<td>Serum potassium (measured in patients using ACEi)</td>
<td>192</td>
</tr>
<tr>
<td>Urine protein using dipsticks</td>
<td>192</td>
</tr>
<tr>
<td>Albumin: creatinine ratio if urine tested negative for protein</td>
<td></td>
</tr>
<tr>
<td>Foot assessment</td>
<td>192</td>
</tr>
<tr>
<td>Eye assessment</td>
<td>192</td>
</tr>
</tbody>
</table>

*Serum potassium was measured with serum creatinine regardless of ACEi use and is therefore treated the same as serum creatinine.
The PHC STG EML 2014 furthermore provides guidance on the recommended actions to be taken and when these actions are to be performed. The actions that were recorded for this research are limited to the pharmacological treatment of hyperglycaemia, hypertension, dyslipidaemia, nephropathy and neuropathy as outlined by the PHC STG EML 2014. These actions were included as evidence of a prescription prescribed by the healthcare provider on the same date of the MOPD visit regardless of whether a parameter was measured on the date of the MOPD visit or not. This was especially evident with the monitoring and management of nephropathy and neuropathy, where treatment was given, in the absence of a foot assessment or lab test performed to monitor kidney function.

2.5 Materials and data collection

All relevant data were captured from the hard copy patient records onto an electronic data collection tool in Microsoft Excel©. This tool was designed and developed by the researcher in order to collect and organise all data needed to achieve the research objectives. The tool was further evaluated by the institute’s biostatistician for validity and reliability.

2.6 Statistical analysis

Descriptive statistic such as frequency, percentage (%), mean and standard deviation (±SD) were considered during the statistical analysis. Demographic data such as gender, height, weight and calculated BMI are expressed according to the number of patient records and not according to the number of MOPD visits. Gender is expressed as a frequency and percentage. Patient length, weight and calculated body mass index (BMI) are expressed by means and standard deviations.

Data pertaining to HCP compliance with the recommendations of the PHC STG EML 2014 were analysed according to the number of MOPD visits recorded within the patient records. The data were expressed as frequencies and percentage. This data included:

- The number of clinical tests performed for monitoring
- The number of results that were at the treatment target
- The number of times that action was taken
- The number of actions taken that were according to the guidelines.
3 Results

The study population consisted of N = 192 patient records. Gender was recorded for 191 patient records, of which 63.4% (n=121) were female patients and 36.6% (n = 70) were male patients. Patient height was recorded in 10.9% (n = 21) of the patient records and patient weight in 6.8% (n = 13) patient records. The mean height ± standard deviation (SD) of these patients was 161.5 ± 16.1 cm, weighing average of 89.4 ± 19.9 kg. Body mass index was calculated for one patient as both height and weight were available in only one patient record, which resulted in 28.5 kg/m². The mean age of the study population was 62 years ± 12 years (see Table 3 for demographics of the study population).

Table 3: Demographics of the study population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (years)</td>
<td>62 ±12</td>
</tr>
<tr>
<td>*Male (% patients)</td>
<td>36.6</td>
</tr>
<tr>
<td>*Female (% patients)</td>
<td>63.4</td>
</tr>
<tr>
<td>Length, mean ±SD (cm)</td>
<td>161.5 ±16.1</td>
</tr>
<tr>
<td>Weight, mean ±SD (kg)</td>
<td>89.4 ± 19.9</td>
</tr>
</tbody>
</table>

*One gender value is reported missing. The proportion of male/female% is calculated using 191 patient records.

3.1 Healthcare provider compliance with the national guidelines for parameters measured at every visit

Finger-prick blood glucose testing was performed during 91.5% (n = 1516) of the recorded MOPD visits. Of these recorded tests, 54.7% (n = 830) were at the treatment target of ≤ 10.0 mmol/L. Action in the form of anti-diabetic drug prescriptions was taken during 84.4% (1398) of the recorded MOPD visits, of which 81.3% (n = 1137) were according to the guideline recommendations. Blood pressure was measured during 91.9% (n = 1523) of visits; these recorded blood pressure measurements 49.7% (n = 757) were at a combined target of < 140/90mmHg. Action in the form of anti-hypertensive drug prescriptions was taken during 76.4% (n = 1266) of the 1657 visits and 62.7% (n = 794) were prescribed according to the guideline recommendations. Weight was measured during 13 of the MOPD visits. Table 4 contains a summary of number of patient visits where the specific parameters to be monitored at each MOPD visit were performed.
Table 4: Healthcare provider performance regarding guideline specific parameters measured at every visit

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number of measurements performed (n)</th>
<th>Targets reached (n)</th>
<th>Action taken (n)</th>
<th>Actions taken according to guidelines (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finger-prick blood glucose</td>
<td>1516 (91.5%)</td>
<td>830 (54.7%)</td>
<td>1398 (84.4%)</td>
<td>1137 (81.3%)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>1523 (91.9%)</td>
<td>757 (49.7%)</td>
<td>1266 (76.4%)</td>
<td>794 (62.7%)</td>
</tr>
<tr>
<td>Weight</td>
<td>13 (0.8%)</td>
<td>3.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2 Healthcare provider compliance with the national guidelines for baseline and annual parameters

Baseline and annual parameters were expected to be monitored at 192 visits for both within the study population. HbA1c was expected to be monitored during 384 visits in total as the PHC STG EML 2014 did not specify that HbA1c should be monitored at baseline. The results for the monitoring of baseline and annual parameters were analysed according to the expected number of visits and not according to total patient visits recorded.

Table 5 provides a complete summary of the results for the monitoring of baseline and annual parameters. Serum creatinine was measured at baseline at 58.9% (n = 113) of the expected MOPD visits. Annually, serum creatinine was monitored during 49 patient visits and there were 23 N/A values; therefore, serum creatinine was monitored during 37.5% (n = 72) of the expected number of visits. The monitoring of serum potassium was regarded the same as serum creatinine, because it was measured in conjunction with serum creatinine for the majority of the clinical tests, regardless of the use of ACEi. At baseline, serum potassium was measured during 57.3% (n = 110) of the expected MOPD visits. The number of visits where serum potassium was monitored annually were 36.5% (n = 70) of the expected number of visits. Estimated glomerular filtration was calculated for 162 MOPD visits of which 96.3% (n = 156) were above the target of < 30 mL/min (at this value of eGFR, action by ways of treatment is recommended, no treatment target is specified). Action was taken during 72 visits of which 98.6% (n = 71) were according to the guidelines. Baseline urine protein was tested during 31.9% (n = 61) of the expected number of visits and annually during 47 of the expected visits, once again with 23 N/A values, and therefore annual monitoring of urine protein by dipstick was performed during 36.5% (n = 70) of the expected number of MOPD visits. The dipstick tests were negative for 89.8% (n = 96) of the recorded tests. Action was taken during 15 of the recorded visits and all of the actions taken were
according to the guidelines. Albumin:creatinine ratio was not monitored during any of the recorded patient visits.

The expected number of visits where a patient’s HbA1c should have been tested were two per patient within the two-year study period. Six of the patient records for patients treated for a period shorter than 12 months contained data of an MOPD visit where HbA1c was tested. Glycosylated haemoglobin was tested during 124 MOPD visits and there were 40 N/A values; therefore, HbA1c was monitored annually during 42.7% (n = 164) of the expected number of MOPD visits. The treatment target of < 7.0% was achieved by 21.8% (n = 27) of the recorded values. Action was taken during 116 visits, of which 89.7% (n = 104) were according to guideline-recommendations. Abdominal circumference was not measured at all.

Baseline eye assessments were recorded during 22.4% (n = 43) of the 192 expected visits. Annual eye assessments were performed during 82 visits, with one of the patients treated for a period shorter than 12 months who also received an additional eye exam other than at baseline, and therefore annual eye assessments were performed at 54.2% (n = 104) of the expected visits. Only 24.8% (n = 31) of the performed eye assessments were normal.

Baseline foot assessments were performed during 25.5% (n = 49) of the expected MOPD visits. Annual foot assessments were performed during 74 MOPD visits and once for a patient treated for a period shorter than 12 months, and therefore annual foot assessments were performed during 50% (n = 96) of the expected visits. Only 22% (n = 27) of the foot assessments performed were normal. Action was taken during 251 visits, of which 95.2% (n = 239) were according to the guidelines.

Blood lipids were measured during 71.3% (n = 137) of the expected MOPD visits, of which 33.1% (n = 45) were at the collective target of < 4.1 mmol/L for fasting total cholesterol, < 1.7 mmol/L for triglycerides, > 1.5 mmol/L for high-density lipoprotein in both men and women, and < 3 mmol/L for low-density lipoprotein. Action was indicated at 1583 of the patient visits, as treatment is indicated in all patients older than 40 years of age, or those with an eGFR < 60 ml/min, regardless of their blood lipid values. There were 80 patient visits to the MOPD of patients younger than 40 years and had eGFR values of > 60 ml/min, six of which were of patients whose blood lipids did not meet the treatment target. Action was taken during 1117 MOPD visits, of which 83.9% (n = 937) were according to the guideline-recommendations.
Table 5: Healthcare provider compliance with guidelines for the monitoring of baseline and annual parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of measurement performed</th>
<th>Target reached</th>
<th>Action taken</th>
<th>Action according to guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n) (%)</td>
<td>(n) (%)</td>
<td>(n)</td>
<td>(n) (%)</td>
</tr>
<tr>
<td>Kidney function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>113 (58.9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>110 (57.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Annual</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>49 (37.5%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>N/A</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum potassium</td>
<td>47 (36.5)</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Calculated estimate glomerular filtration rate</strong></td>
<td>156 (96.3)</td>
<td>72 (69.1%)</td>
<td>71 (72.2%)</td>
<td>98.6 (97.9%)</td>
</tr>
<tr>
<td><strong>Urine test by dipsticks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>61 (31.8)</td>
<td>97 (89.8)</td>
<td>15 (15.1%)</td>
<td>100 (100%)</td>
</tr>
<tr>
<td>N/A</td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Annual</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin: creatinine ratio (when urine tested negative for protein)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Glycosylated haemoglobin</td>
<td>124 (42.7)</td>
<td>27 (21.8)</td>
<td>116 (89.7)</td>
<td>104 (89.7)</td>
</tr>
<tr>
<td>N/A</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal circumference</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Eye function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline eye assessment</strong></td>
<td>43 (22.4)</td>
<td>31 (24.8)</td>
<td>94 (89.8%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Annual eye assessment</strong></td>
<td>82 (54.2)</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>N/A</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring for neuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline foot assessment</strong></td>
<td>49 (25.5)</td>
<td>27 (22.4)</td>
<td>251 (95.2)</td>
<td>239 (95.2)</td>
</tr>
<tr>
<td><strong>Annual foot assessment</strong></td>
<td>74 (50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline blood lipids</strong></td>
<td>137 (71.3)</td>
<td>45 (33.1)</td>
<td>1117 (95.2)</td>
<td>937 (88.9)</td>
</tr>
</tbody>
</table>
4 Discussion

Healthcare provider compliance at the regional hospital outpatient department was assessed by means of a retrospective evaluation of patient records for evidence of monitoring and treatment practices and whether those practices were conducted according to the PHC STG EML 2014. The information of 1657 MOPD visits was recorded onto an electronic data collection tool and analysed. Compliance with the recommendations of monitoring frequencies of specific parameters and the treatment of hyperglycaemia, hypertension, dyslipidaemia and complications were the focus of the study.

4.1 Healthcare provider compliance with guideline recommendations for parameters monitored at every visit

Healthcare providers performed finger-prick blood glucose tests and measured blood pressure at the majority of the visits. The majority of the treatments prescribed for the treatment of hyperglycaemia and hypertension were according to the recommendation of the PHC STG EML 2014. There was continuity of care, which was evidenced by the fact that treatment was continued when blood glucose and blood pressure values were at the target. It can therefore be concluded that HCPs are not only treating hyperglycaemia and hypertension, but also managing patients at the desired blood glucose and blood pressure levels. The high compliance with the monitoring of blood glucose and blood pressure at every visit indicates well-organised care with regard to glycaemic control and treatment of hypertension. Patient weight, however, was not measured according to guideline-recommendations. Therefore, HCP compliance with the monitoring frequency of weight measurements was sub-optimal. The lack of height- and weight measurements shows a poor approach to the monitoring of patient body weight, as BMI could only be calculated for one patient.

4.2 Healthcare provider compliance with guideline recommendation for parameters monitored at baseline and annually

Healthcare provider compliance with the recommendations for the monitoring of baseline and annual parameters was sub-optimal. The numbers of eye- and foot assessments were performed annually at more visits than at baseline with the majority of these assessments resulting in abnormal findings that require treatment. This indicates reactive care to the presence of complications rather than proactive care for the early detection of microvascular complications. Reactive rather than proactive care is evidenced to be one of the clinician-level barriers that contributes to clinical inertia [19]. Healthcare provider compliance was also sub-optimal with regard to the monitoring of HbA1c, which further undermines the goals of treatment as HbA1c can give an indication of patient blood glucose levels for the past three months (which serves to
give a more accurate picture of a patient’s condition) [21]. Waist circumference was not measured at any of the visits and neither were any of the albumin:creatinine ratios, when indicated. Healthcare provider compliance with the measuring of blood lipids was optimal, as the number of tests recorded were performed at more points during treatment than the recommended measurements by the PHC STG EML 2014 guideline of blood lipid testing at baseline.

Healthcare provider compliance with taking action when indicated was optimal and the majority of the prescribed treatments were according to the guideline recommendations. This can indicate a well-organised approach to the treatment of microvascular complications when indicated.

5 Conclusion

In conclusion, the overall compliance of HCPs was sub-optimal, despite some of the areas where compliance was good. The results show evidence of reactive care regarding the management of microvascular complications, which was evident by the fact that the majority of the eye- and foot assessments were abnormal and required action, as well as the fact that the number of annual assessments were greater than the number of baseline assessments. Healthcare providers were compliant with the recommended treatment approaches (actions that should have been taken). There is much room for improvement, especially regarding the annual and baseline monitoring as these are performed for early detection of complications.

Limitations

The use of hard copy patient records was a limitation during this study as it created a gap for human error during data collection resulting in missing data. The hardcopy patient records contained data of both in-hospital treatment and MOPD visits. Therefore, the researcher had to separate MOPD data from in-hospital data before it could be collected onto the data collection tool. This was a time consuming process, limiting the number of patient records that could have been evaluated.

Recommendations

Further research investigating the factors that influence HCP compliance would be beneficial in order to determine whether the sub-optimal compliance is the result of systemic factors or poor implementation of the care guidelines.

Conflict of interest

The authors declare that there is no conflict of interest.
REFERENCES


# ANNEXURE A: Guidelines specific monitoring and management practices

<table>
<thead>
<tr>
<th>Assessment parameters</th>
<th>Monitoring frequency</th>
<th>Treatment goals</th>
<th>Take action</th>
<th>Action to be taken</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>At every visit</td>
<td>4 - 7 mmol/L</td>
<td>&gt; 8 mmol/L</td>
<td></td>
</tr>
<tr>
<td>2hr post-prandial</td>
<td>At every visit</td>
<td>5 - 8 mmol/L</td>
<td>&gt; 10 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Glycosylated haemoglobin</td>
<td>Annually (every 3-6 months in patients whose medication changed until stable)</td>
<td>&lt; 7%</td>
<td>&gt; 8%</td>
<td>Adjust anti-diabetic treatment stepwise according to guidelines.</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic/diastolic</td>
<td>At every visit</td>
<td>&lt; 140/90 mmHg</td>
<td>&gt; 140/90 mmHg</td>
<td>Adjust anti-hypertensive treatment stepwise according to guidelines.</td>
</tr>
<tr>
<td><strong>Blood lipids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting total cholesterol</td>
<td>At baseline</td>
<td>&lt; 4.1 mmol/ L</td>
<td>&gt; 5 mmol/ L</td>
<td>Treat according to guidelines.</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>At baseline</td>
<td>&lt; 1.7 mmol/ L</td>
<td>&gt; 1.7 mmol/ L</td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>At baseline</td>
<td>&gt; 1.5 mmol/L in both men and women</td>
<td>&lt; 1.0 mmol/L in men</td>
<td>&lt; 1.3 mmol/ L in women</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>➢ Are older than 40 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>➢ Have an eGFR of &lt; 60 ml/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>➢ Have an existing cardiovascular disease.</td>
</tr>
<tr>
<td>LDL</td>
<td>At baseline</td>
<td></td>
<td>&gt; 3.0 mmol/L</td>
<td></td>
</tr>
<tr>
<td><strong>Kidney function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine and eGFR</td>
<td>At baseline and annually</td>
<td>&lt; 30 ml/minute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment parameters</td>
<td>Monitoring frequency</td>
<td>Treatment goals</td>
<td>Take action</td>
<td>Action to be taken</td>
</tr>
<tr>
<td>-----------------------------------------------------------------</td>
<td>----------------------------</td>
<td>-----------------</td>
<td>-------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Serum potassium and eGFR in patient using ACE-inhibitor</td>
<td>At baseline and annually</td>
<td></td>
<td>&lt; 30 ml/minute</td>
<td>Adjust treatment according to the guidelines</td>
</tr>
<tr>
<td>Urine protein using dipsticks</td>
<td>At baseline and annually</td>
<td></td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Urinary albumin: creatinine ratio if dipsticks are negative for urine protein</td>
<td>At baseline and annually</td>
<td></td>
<td>&gt; 3 mg/mmol</td>
<td></td>
</tr>
<tr>
<td>Abdominal circumference</td>
<td>At baseline</td>
<td></td>
<td>&gt; 94 cm in men</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; 80 cm in women</td>
<td></td>
</tr>
<tr>
<td>Eye assessments</td>
<td>At baseline and annually</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Refer to an ophthalmologist</td>
</tr>
<tr>
<td>Foot assessments</td>
<td>At baseline and annually</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Treat according to guidelines:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antibiotic treatment for infection and pain relief for neuropathy according to guidelines.</td>
</tr>
<tr>
<td>Weight</td>
<td>Every visit</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3.2 Manuscript two

The title of this manuscript is: *Glycaemic control at primary healthcare level: Regional hospital outpatient department in the Dr Kenneth Kaunda District*. It is written according to the specifications of the journal: *Diabetes research and clinical practice*

This manuscript addressed the empirical research objective stated in Chapter 1, section 1.4.2. The objectives of this manuscript were to assess HCP with the monitoring and management practices for the management of specifically hyperglycaemia in adult T2DM patients as recommended by the PHC STG EML 2014. This was done through the review and evaluation of hardcopy patient records for evidence of documentation of monitoring of blood glucose levels and of anti-diabetic drug prescriptions. This was done to determine whether blood glucose levels were monitored according to the guideline recommendations and whether the anti-diabetic drugs were prescribed according to the guideline recommendations.

3.2.1 Author guideline

Manuscript two will be submitted as an original research paper and is written according to the following guidelines (see Annexure L for the journal specific author guidelines):

- The word limit for an original research paper is 5000 words, not including the abstract and references. The abstract is should not exceed 200 words and must be divided into aim, methods, results, discussion and keywords.
- An original research paper should be divided into numbered sections; introduction, materials, subjects and methods, results, discussion, acknowledgements, references, and figures and tables.
  - The introduction should state the objectives, give an adequate background but avoid a detailed literature review. A summary of results should not be part of the literature review.
  - Materials, subjects and methods should provide sufficient details to allow the work to be reproduced by an independent research. Cite the source if methods of already published works are used. Use quotation marks and also cite the source if quoting a method directly.
  - Results should be clear and concise.
  - The discussion section should explore the significance of the results. Repetition of the results should be avoided. In some cases, a combined results and discussion section may be appropriate.
  - All contributors who did not meet the criteria to be writer should be acknowledged in the acknowledgements section. Examples of those who might be acknowledged are people who provided purely technical help, writing assistance or a department chair who provided
only general support. Authors should disclose whether they had any writing assistance and identify the entity that paid for the assistance.

- References that are cited in text should also be listed in the reference list. Any reference that is cited in the abstract should be given in full. There are no strict requirements for the style of references and any referencing style can be used as long as the style is consistent.

The manuscript to be submitted to the journal *Diabetes research and clinical practice* will follow next.
Glycaemic control at primary healthcare level: Regional hospital outpatient department in the Dr Kenneth Kaunda District

Authors: Danelle Elizabeth Venter a, b
Martine Vorster a, c
Rianda Joubert a, d
Jesslee Melinda Du Plessis a, e

a. Medicine Usage South Africa, Faculty of Health Sciences, North-West University, Private Bag X6001, Potchefstroom, South Africa, 2520
b. danelle.debeer@yahoo.com
c. martine.vorster@nwu.ac.za
d. rianda.joubert@nwu.ac.za
e. jesslee.duplessis@nwu.ac.za

Corresponding author: Danelle Elizabeth Venter
Glycaemic control at primary healthcare level: Regional hospital outpatient department in the Dr Kenneth Kaunda District

Danelle E Venter, Rianda Joubert, Martine Vorster, Jesslee M Du Plessis

a Medicine Usage South Africa, Faculty of Health Sciences, North-West University, Private Bag X6001, Potchefstroom, South Africa, 2520.

Abstract

Aim: The control of hyperglycaemia is an essential component of type 2 diabetes mellitus care, which is done by means of frequent monitoring of blood glucose levels and pharmacological treatment. The aim of this study was to assess healthcare provider (HCP) compliance with the management of hyperglycaemia according to monitoring and pharmacological treatment practices of the South African Primary Healthcare Standard Treatment Guidelines and Essential Medicines List 2014 edition (PHC STG EML 2014) published and distributed by the Department of Health. Method: Hardcopy patient records of 192 patients receiving care at the regional hospital in the Dr Kenneth Kaunda District were retrospectively evaluated for the study period 1 March 2016 to 28 February 2018. Results: Finger-prick blood glucose tests were performed at 91.5% of the patient visits. Glycosylated haemoglobin (HbA1c) was monitored in 50.5% of all patients. Only 15.7% of the patients whose treatment changed and 26.1% of newly diagnosed patients had their HbA1c monitored. A total of 1398 prescriptions were recorded of which 81.3% were prescribed according to the recommendations in the guidelines. Conclusion: Healthcare provider compliance with the management of hyperglycaemia was optimal; however, improvement is needed in the monitoring of HbA1c, which was sub-optimal

Keywords: glycaemic control, primary healthcare, type 2 diabetes
Glycaemic control at primary healthcare level: Regional hospital outpatient department in the Dr Kenneth Kaunda District

Danelle E Venter\textsuperscript{a}, Rianda Joubert\textsuperscript{a}, Martine Vorster\textsuperscript{a}, Jesslee M Du Plessis\textsuperscript{a}

\textsuperscript{a} Medicine Usage South Africa, Faculty of Health Sciences, North-West University, Private Bag X6001, Potchefstroom, South Africa, 2520

1.1 Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease characterised by a progressive increase in blood glucose levels leading to hyperglycaemia caused by abnormalities in both insulin secretion and insulin action at target sites [1-4]. Hyperglycaemia is the greatest contributing factor to the development and progression of microvascular complications such as nephropathy, retinopathy and neuropathy and to some degree macrovascular complications, e.g. peripheral vascular disease or cerebrovascular disease [5-7]. Glycaemic control is the backbone of T2DM management, where the management of hyperglycaemia revolves around frequent monitoring of blood glucose levels and pharmacological treatment in a stepwise manner [8-14]. Finger-prick blood glucose tests can be performed either after the patient has fasted overnight, at 2-hour post-prandially (after intake of a meal or a glucose load) or at random [13]. The recommended frequency for performing these tests in T2DM patients is: at every clinic visit for the finger-prick blood glucose test and annually for the HbA1c test, in stable patients, or every three to six months in newly diagnosed patients or in patients whose anti-diabetic drug regimen has changed until those patients' blood glucose levels stabilised [15]. Glycosylated haemoglobin is the most reliable method for assessing blood glucose levels, since HbA1c reflects an accurate estimate of the average blood glucose levels over three months, including post-prandial spikes with low intra-individual variability [15-20]. Glycosylated haemoglobin is furthermore a more superior indication of chronic glycaemia than that of finger-prick blood glucose tests, and is used to determine the appropriate adjustments in drug regimens in order to achieve treatment targets [15,19]. It is furthermore stated that HbA1c correlates well with the risk prediction of diabetes-related complications [20].

The number of therapeutic steps within the stepwise treatment protocol for hyperglycaemia vary between guidelines. The first step of the treatment protocol generally starts with metformin as monotherapy [9-12,16], moving towards both oral anti-diabetic drug combinations and oral- and injectable anti-diabetic drug combinations before moving towards the administering of exogenous insulin, which is the final step in the treatment of hyperglycaemia [9-12,14-16].
Diabetes mellitus patients across the world are poorly controlled and experience difficulty reaching targeted blood glucose levels [21-25]. Poor control of patients with T2DM is caused by a gap between clinical guidelines and clinical practice, also known as clinical inertia [22-25]. The majority of chronic disease control (including that of T2DM) is performed in the primary healthcare setting [22, 26], which is also true for patients with non-communicable diseases in South Africa (SA) [27]. In SA, patients receive care either in the public healthcare sector or in the private healthcare sector, where the public healthcare sector cares for 84% of the population [28]. The aim of this study was to assess HCP compliance with the PHC STG EML 2014 with a specific focus on the management of hyperglycaemia in the primary healthcare setting.

1.2 Method

In order to achieve the objectives, evidence of documentation of the monitoring of blood glucose levels and pharmacological treatment was evaluated according to the recommendations of the South African PHC STG EML 2014.

1.2.1 Study design

Hardcopy patient records of patients who received care at a regional hospital in the Dr Kenneth Kaunda District of the North West Province in South Africa were included in the study. The patient records of 192 patients were retrospectively evaluated for evidence of blood glucose monitoring by ways of finger-prick testing or measuring HbA1c as well as treatment in the form of anti-diabetic drug prescriptions according to the recommendations of the PHC STG EML 2014. Data of patient visits within the study period of 1 March 2016 to 28 February 2018 were collected. Patient records of all T2DM patients older than 18 years irrespective of gender with at least two visits to the medical outpatient department (MOPD) were included.

All data of patient visits to the MOPD within the study period were collected onto an electronic data collection tool designed specifically for this research using Microsoft Excel®. The data collection tool was assessed for validity and reliability by a biostatistician employed by the North-West University of South Africa.
1.2.1.1 Primary Healthcare Standard Treatment Guidelines and Essential Medicines List 2014 edition

Healthcare provider compliance with the PHC STG EML 2014 in T2DM patients was assessed according to the monitoring and pharmacological treatment guidelines for the management of hyperglycaemia. The standards for management according to these guidelines used to assess HCP compliance to the monitoring and pharmacological treatment were as follows:

1.2.1.1.1 Monitoring

Blood glucose parameters are measured at various intervals during the course of treatment. Blood glucose levels should be measured by ways of a finger-prick blood glucose tests at every patient visit to the MOPD. It can either be done at random, 2-hour post-prandial or after fasting. Glycosylated haemoglobin is measured annually or every three to six months in newly diagnosed patients or when patients’ drug regimen changed, up until those patients’ blood glucose levels stabilise. Annexure A summarises the guideline-recommended practice for the management of hyperglycaemia. The treatment target of fasting plasma glucose is 4 - 7 mmol/L and acceptable at < 8 mmol/L and for 2-hour postprandial and random is < 10 mmol/L. For HbA1c, the treatment target is < 7% [9]. (Refer to Annexure A).

1.2.1.1.2 Pharmacological treatment

The pharmacological treatment is recommended to be done in a stepwise manner during which there is a systematic intensification of treatment in order to help the patient reach the treatment targets. The first step in the pharmacological treatment of T2DM is the use of metformin. Metformin is globally recognised as first-line treatment, due to its low cost, proven safety and low risk of inducing hypoglycaemia [9,29]. Should a patient fail to reach the treatment target, step 2 should be initiated, which is the addition of a sulphonylurea, either glimepiride or glibenclamide. Sulphonylureas potentiate glucose-stimulated insulin secretion in the pancreas [30] and are the preferred second-line drug due to its cost-effectiveness [9,14,31]. Should a patient fail to reach therapeutic targets, step 3 is initiated whereby an insulin regimen is started and the sulphonylurea treatment ceased [9].

1.2.2 Statistical analysis

During the data collection period, a total of 192 patient records were included, which contained data of 1657 patient visits to the MOPD that were captured onto the data collection tool. The PHC STG EML 2014 does not specify the frequency of these visits; some patients were seen on a monthly basis and others on a three- to six-month schedule.
All variables are expressed through the use of descriptive statistics such as frequencies (n), percentages (%), mean, standard deviation (±SD), median and interquartile range. The statistical analysis was completed using both Microsoft Excel® and Statistical Analysis Software® (SAS). Finger-prick blood glucose tests and the anti-diabetic drug prescriptions were analysed according to the number of visits to the hospital's MOPD. Glycosylated haemoglobin monitoring was analysed according to the number of patient records.

1.2.3 Ethical considerations

The study was reviewed and approved by the North-West University's Health Research Ethics Committee (HREC) and allocated the ethics number NWU-00081-17-s1. Afterwards approval by the North West Department of Health: Policy, Planning, Research, Monitoring and Evaluation committee was granted as well as goodwill permission by the regional hospital’s research committee.

1.3 Results

The study population consisted of 192 patient records, where 63.4% (n = 121) belonged to female patients and 36.6% (n = 70) to male patients (the gender value of one patient record was unavailable). The mean (±SD) age of the study population was 62 ± 12 years. The mean height of the patients was 161.5 ± 16.1 cm, who weighed an average of 89.4 ± 19.9 kg. Both patient height and weight were available in only one patient record; therefore, body mass index (BMI) could only be calculated for that one patient. The calculated BMI of that patient was 28.5 kg/m².

1.3.1 Healthcare provider compliance to monitoring of blood glucose levels

Table 1 provides a complete summary of the results pertaining to HCP compliance with monitoring of finger-prick blood glucose levels. Finger-prick blood glucose tests were recorded during 91.5% (n = 1516) of the total MOPD visits, 54.7% (n = 830) of the tests resulted in blood glucose levels that were at the treatment target of ≤ 10.0 mmol/L. This target was used for all the finger-prick blood glucose test results, as no specifications were made in the patient records of whether they were performed at random, 2-hour post-prandial or at fasting. The average (±SD) blood glucose value was 10.6 ±5.2 mmol/L, which was above the treatment target and the median value was 9.4 mmol/L (interquartile range 6.9 mmol/L).

When looking at HbA1c monitoring in the study population, it was monitored in 50.5% (n = 97) of the patients, of which 75.2% (n = 73) had one HbA1c test recorded, 21.6% (n = 21) had two HbA1c tests recorded and 3.1% (n = 3) of the patients had three HbA1c tests recorded. Within the study population, there were 23 newly diagnosed patients who met the inclusion criteria, who
received treatment at the study setting for a period shorter than a year, and therefore the number of patients who were eligible for annual HbA1c monitoring resulted in 169. Only 75 (44%) out of the 169 patients' HbA1c was monitored annually. When evaluating the HbA1c monitoring practices in relation to changes in anti-diabetic drug prescription, it was observed that only 18 patients' HbA1c was monitored in response to such changes. When HbA1c monitoring was evaluated in newly diagnosed patients, it was seen that only six of the newly diagnosed patients who met the inclusion criteria had their HbA1c monitored within three to six months of being diagnosed. The total number of HbA1c tests were 124 in the 97 patients (refer to Table 2 for a summary of HCP compliance with the guideline recommended monitoring of HbA1c in T2DM patients).

A total of 118 patient records contained evidence of changes to anti-diabetic drug treatment. These included changes in the anti-diabetic prescribed drugs, changes in dosage and/or in dosage intervals. Of the patients whose treatment changed, 62.6% (n = 72) received an HbA1c test (irrespective of annual monitoring or monitoring in response to change). Glycosylated haemoglobin was tested within three to six months after changes to anti-diabetic drug prescriptions in merely 13.6% (n = 18) of the patients, which resulted in 25 HbA1c tests in total.

Within the study period, patient records of 23 newly diagnosed patients who met the inclusion criteria were included. Only 26.1% (n = 6) of these patients' HbA1c was monitored within three to six months after diagnosis, which resulted in a total of six HbA1c tests. The mean HbA1c of the study population was 9.6% (±2.8%), which was much higher than the recommended 7.0% or lower (refer to Table 2).

Healthcare provider compliance with annual monitoring of HbA1c within the study population was 44%, as only 75 patients out of 169 patients' HbA1c were monitored annually. Compliance with HbA1c monitoring every three to six months in response to changes in treatment was 13.6%, as only 18 of the 118 patients whose treatment changed had their HbA1c monitored accordingly. Healthcare providers were compliant with HbA1c monitoring of 26.1% of newly diagnosed patients, since six out of 23 patients' HbA1c was monitored within three to six months after diagnosis.
1.3.3 Healthcare provider compliance with the hyperglycaemia treatment recommendations

The patient records contained 1398 anti-diabetic prescriptions, which were limited to metformin, glimepiride a sulphonylurea and insulin. Three types of insulin were used, Humulin® 70/30 a premixed insulin, Humulin® N and Humulin® R. The prescriptions were categorised as mono-therapy, dual therapy and triple therapy. Mono-therapy existed of metformin, glimepiride or insulin (either Humulin® 70/30 or Humulin® N) alone. Dual therapy consisted of combinations of metformin and glimepiride, metformin and insulin or glimepiride and insulin. Triple therapy consisted of metformin, glimepiride and insulin (see Table 3 for a summary of the anti-diabetic prescriptions and HCP compliance with the PHC STG EML 2014 recommendations for the treatment of hyperglycaemia).

Metformin, glimepiride and insulin were prescribed in various doses and, in the case of metformin and insulin, at various dosage intervals. The maximum doses of metformin of 850 mg three times daily (t.i.d.) were not exceeded by any of the prescriptions. The PHC STG EML 2014 limits the dose of glimepiride to a maximum of 4mg daily. This dose was exceeded by 94 prescriptions in total, all of which were part of dual therapy in combination with metformin. The PHC STG EML 2014 does not provide a maximum dose for insulin therapy.

Of the 1398 prescriptions, 509 were for mono-therapy. Metformin was prescribed in 74.3% (n = 378) of mono-therapy prescriptions, insulin mono-therapy made up 22.6% (n = 115) of these prescriptions and 3.1% (n = 16) of the mono-therapy prescriptions were for glimepiride. Two types of insulin were prescribed as mono-therapy. Humulin® 70/30 was prescribed 112 times and Humulin® N was prescribed three times. Dual therapy was prescribed 854 times, of which 41.9% (n = 358) were a combination of metformin and glimepiride, 52.6% (n = 449) were a combination of metformin and Humulin® 70/30, 4.7% (n = 40) were of a combination of metformin and Humulin® N, six of the dual therapy prescriptions were of a combination of metformin and two types of insulin (Humulin® N and Humulin® R), and one prescription was of a combination of glimepiride and Humulin® 70/30. Triple therapy was prescribed 35 times, which was a combination of metformin, glimepiride and insulin (refer to Table 4 for a summary of the anti-diabetic drug prescriptions prescribed).

Anti-diabetic drug prescriptions were deemed correct according to the PHC STG EML 2014 if the correct combinations for dual therapy and the correct mono-therapy were used that did not exceed the maximum dosages of metformin or glimepiride. Metformin prescribed with a dosage not exceeding 850mg t.i.d. as mono-therapy is correct according to the PHC STG EML 2014. Dual therapy was correct according to guidelines when metformin in combination with glimepiride was
prescribed or metformin in combination with insulin. Dual therapy prescriptions of metformin and glimepiride, where the maximum dosage of either metformin or glimepiride is exceeded, were not according to the guideline recommendations. Insulin mono-therapy and glimepiride mono-therapy are not correct according to guideline-recommendations regardless of the dosage. Triple therapy using a combination of metformin, glimepiride and insulin is not correct according to guidelines regardless of the dosages.

By making use of the guidelines stating the recommended anti-diabetic drugs and dosage, the following was found in the prescriptions of the patients. The anti-diabetic drug prescriptions that were correctly prescribed according to guidelines were 81.3% (n = 1137) of the recorded prescriptions. The anti-diabetic drug prescription that was not according to the guidelines resulted in 18.7% (n = 261) prescriptions and consisted of 1.2% (n = 16) glimepiride mono-therapy prescriptions, 8.2% (n = 115) insulin mono-therapy prescriptions, 6.7% (n = 94) dual therapy prescriptions of metformin in combination with glimepiride exceeding the maximum dose of 4mg daily, one prescription of dual therapy of glimepiride in combination with Humulin® 70/30 and triple therapy, which resulted in 2.5% (n = 35) of the recorded prescriptions.

1.4 Conclusion

During this research, HCP compliance to hyperglycaemia management according to the PHC STG EML 2014 was assessed in the primary healthcare setting. Two components of glycaemic control were the focus of this study, i.e. the monitoring of blood glucose levels and the pharmacological treatment approach.

Compliance with the frequencies of finger-prick blood glucose tests was high, as finger-prick blood glucose tests were performed in 91.5% of the patient visits to the MOPD. This could be an indication of a well-organised approach to the monitoring of capillary blood glucose through finger-prick testing. The HCPs’ approach to the pharmacological treatment of hyperglycaemia was executed according to the national guidelines in 81.3% of all prescriptions. Healthcare providers were compliant to the medicine list provided for the treatment of hyperglycaemia, which included metformin, glimepiride, glibenclamide and insulin [9]. Metformin was prescribed in the majority of the prescriptions either as mono-therapy, or in combination with glimepiride or insulin. The maximum dosage of metformin was not exceeded by any of the prescriptions. The maximum dosage of glimepiride was exceeded when combined with metformin; however, the majority of the prescriptions with metformin and glimepiride combinations were according to the guidelines. The high compliance of HCPs with the pharmacological treatment of hyperglycaemia could possibly indicate an awareness of HCPs of the PHC STG EML 2014 guidelines, recommended anti-diabetic drugs, as well as the prescribing recommendations.
Healthcare providers’ compliance with the recommendations for the monitoring of HbA1c was sub-optimal. The sub-optimal compliance with monitoring HbA1c is a concern due to the value of HbA1c in determining a patient’s glycaemia and whether the patient’s treatment is adequate [17,20]. Healthcare providers displayed inappropriate response to the monitoring of HbA1c annually, in response to changes in patient treatment regimen and in patients who were newly diagnosed. Only 50.5% of the patient records contained data of HbA1c being monitored. The inappropriate response to changes in the drug regimens of patients is also concerning, as it can be concluded that drug regimen changes were based on the values of finger-prick blood glucose levels. Although this practice could be judged as appropriate according to the recommendations of the PHC STG EML 2014, using HbA1c as an indicator for drug regimen changes could have been more valuable and might have led to better patient outcomes [15,19]. There remains much room for improvement in the management of hyperglycaemia according to these guidelines.

Judging according to the neglect of HbA1c monitoring and the value of such monitoring not only to the therapeutic decisions, but also in predicting the risk of complications, it can be concluded that despite the optimal compliance with the monitoring of blood glucose through finger-prick testing and with the stepwise treatment regimen, the HCP compliance with the PHC STG EML 2014 guidelines needs to improve in order to manage hyperglycaemia in T2DM patients.

1.5 Limitations of the study

Data collection was completed by the researcher exclusively. This serves as a limitation to the study as a larger team could have evaluated patient records faster and more patient records could have been included. The use of hardcopy patient records was another limitation because data had to be collected from the records itself leaving a gap for human error seen in the missing gender value. The patient records also contained data of in-hospital treatment along with data from the MOPD, causing a break in the chronological order of MOPD data. This proved to be a great time constraint as the researcher had to seek out the relevant MOPD data, which may have led to data being left out. The use of hardcopy patient records also hindered the data collection process, as lab results were not always filed within the patient records. This research included T2DM patients of one study setting; the results can therefore not be generalised to the rest of South Africa.
1.6 Acknowledgements

We would like to acknowledge the regional hospital's research committee who allowed the study to take place on the premises. Further acknowledgements are reserved for the North-West University and Medicine Usage in South Africa for financial and technical support during this study.
REFERENCES


FIGURES AND TABLES

Table 1: Healthcare provider compliance with monitoring of finger-prick blood glucose at every visit

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>%</th>
<th>Mean</th>
<th>At target</th>
<th>Std. deviation</th>
<th>95% confidence interval</th>
<th>Median</th>
<th>Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finger-prick blood glucose (mmol/L) at every MOPD visit</td>
<td>1516</td>
<td>91.5</td>
<td>10.6</td>
<td>830</td>
<td>54.7</td>
<td>5.2</td>
<td>10.3, 10.8</td>
<td>9.4</td>
</tr>
</tbody>
</table>
Table 2: Healthcare provider compliance with the recommendations for the monitoring of HbA1c

<table>
<thead>
<tr>
<th>Monitoring frequency</th>
<th>Number of patients monitored</th>
<th>Number of HbA1c tests recorded</th>
<th>Percentage of patients monitored (%)</th>
<th>Mean (%)</th>
<th>SD (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Annual (out of 169 patients)</td>
<td>75</td>
<td>93</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three to six monthly after treatment changes (out of 118 patients)</td>
<td>18</td>
<td>25</td>
<td>13.6</td>
<td>9.6</td>
<td>2.8</td>
<td>9.1, 10.1</td>
</tr>
<tr>
<td>Three to six monthly in newly diagnosed patients (out of 23 patients)</td>
<td>6</td>
<td>6</td>
<td>26.1</td>
<td>9.6</td>
<td>2.8</td>
<td>9.1, 10.1</td>
</tr>
<tr>
<td>Total patients monitored (out of 192 patients)</td>
<td>97</td>
<td>124</td>
<td>50.5</td>
<td>9.6</td>
<td>2.8</td>
<td>9.1, 10.1</td>
</tr>
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</table>

*The number of patients expected to have had annual monitoring is the difference between the total study population of 192 patients and the 23 newly diagnosed patients. This is done as it cannot be expected for patients who were treated for a period shorter than 12 months to have annual monitoring of HbA1c.
Table 3: Healthcare provider compliance to hyperglycaemia treatment

<table>
<thead>
<tr>
<th>Therapy prescribed</th>
<th>Number of prescriptions</th>
<th>According to guidelines</th>
<th>Not according to guidelines</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Mono-therapy</td>
<td>509</td>
<td>378</td>
<td>27</td>
</tr>
<tr>
<td>Dual therapy</td>
<td>854</td>
<td>759</td>
<td>54.3</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>35</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total prescriptions recorded</td>
<td>1398</td>
<td>1137</td>
<td>81.3</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td>Anti-diabetic drugs used</td>
<td>Number of prescriptions (n)</td>
<td>Percentage of prescriptions (%)</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------</td>
<td>-----------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Mono-therapy</td>
<td>Metformin</td>
<td>378</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td>Metformin 250 mg b.i.d.</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metformin 500 mg d</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metformin 500 mg b.i.d.</td>
<td>77</td>
<td></td>
</tr>
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<td></td>
<td>Metformin 500 mg t.i.d.</td>
<td>17</td>
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</tr>
<tr>
<td></td>
<td>Metformin 500 mg q.i.d.</td>
<td>1</td>
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<tr>
<td></td>
<td>Metformin 850 mg d</td>
<td>5</td>
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<tr>
<td></td>
<td>Metformin 850 mg b.i.d.</td>
<td>42</td>
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<td>Metformin 850 t.i.d.</td>
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<td>Metformin 1000 mg b.i.d.</td>
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<tr>
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<td>Glimepiride</td>
<td>16</td>
<td>1.2</td>
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<td></td>
<td>Glimepiride 1 mg d</td>
<td>10</td>
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<td></td>
<td>Glimepiride 2 mg d</td>
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<td>Glimepiride 4 mg d</td>
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<td></td>
<td>Humulin® 70/30</td>
<td>112</td>
<td>8</td>
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<tr>
<td></td>
<td>Humulin® N</td>
<td>3</td>
<td>0.2</td>
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<tr>
<td>Dual therapy</td>
<td>Metformin/ Glimepiride</td>
<td>358</td>
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<td></td>
<td>Metformin 850 mg b.i.d./ Glimepiride 1 mg d</td>
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<td>78</td>
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<td>Metformin 850 mg d./ Glimepiride 2 mg d</td>
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<td>Metformin 850mg t.i.d./ Glimepiride 4 mg d</td>
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<td>Triple therapy</td>
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<td>7</td>
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<td>Metformin 850 mg t.i.d./Glimepiride 6mg d</td>
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</tr>
<tr>
<td>Metformin/ Humulin® N</td>
<td>Metformin 500 mg b.i.d./Humulin® N</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metformin 850 mg b.i.d./Humulin® N</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metformin 850 t.i.d./Humulin® N</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metformin/ Humulin® N/ Humulin® R</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glimepiride/ Humulin® 70/30</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metformin/ Glimepiride/ Humulin® 70/30</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

* b.i.d. Twice daily
* d Daily
* t.i.d. Three times daily
* q.i.d. Four times daily
3.3 Additional results

The results discussed in this section are compiled from data that were not included and discussed within the two manuscripts.

3.3.1 Patient demographics

The majority of patients were older than 40 years, with the oldest patient being 100 years old and the youngest 33 years of age. A mere six patients, 3.1% of the population, were younger than 40 years. Weight was measured in 6.7% (n=13) of the patients, with the mean weight being 89.4 kg ± 19.9 kg. Height was measured in 11% (n=21) of the study population of which the mean height was 161.5 cm ± 16.1 cm. Body mass index could only be calculated in one patient as both patient weight and height were available in that one patient, which resulted in 28.5 kg/m². The patient demographics, other than age and gender, cannot be used as a representation of the study population.

The mean blood glucose and HbA1c values were above the treatment targets and indicated the presence of hyperglycaemia in the majority of the study population. Similar studies on the clinical inertia in T2DM care also revealed the presence of hyperglycaemia within the study population (Braga et al., 2012:457; Delavari et al., 2009:493; Pantalone et al., 2018; Stone et al., 2013:774).

Blood pressure was monitored at the majority of the patient visits to the MOPD of which the mean systolic BP was 142.1 ± 24.7 mmHg and the mean diastolic BP value 77.5 mmHg ± 14.5 mmHg. Patient systolic BP was above the target value of 140 mmHg and diastolic BP below the target of 90 mmHg. The majority of the recorded BP values recorded, however, were not at the collective target of < 140/90 mmHg. The blood lipids were measured as total cholesterol, triglyceride, HDL and LDL. The mean total cholesterol was 4.5 mmol/L ± 1.2 mmol/L, which was just above the target of ≤ 4.1 mmol/L, the mean triglyceride value was 2.4 mmol/L ± 1.4 mmol/L, also above the targeted value of ≤ 1.7 mmol/L. The mean HDL value of 1.2 mmol/L ± 0.41 was below the target of 1.5 mmol/L, which is applicable to both male and female patients. Mean LDL was 2.3 mmol/L ± 0.9 mmol/L, which was above the target of ≤ 1.8 mmol/L. Low-density lipoprotein is generally increased in T2DM, according to the literature (AL-Adsani et al., 2004:129; Blom, 2013:48; Mancini et al., 2018:s178); this was also true for this study population as the mean LDL was 2.2 mmol/L ± 0.85 mmol/L.

Kidney function of patients was also tested during the course of this research by means of serum creatinine, serum potassium and eGFR. The minority of these patients exhibited the presence of nephropathy as only 3.7% (n=6) of the recorded eGFR values of < 30 mL/min, which are indicative of kidney dysfunction (Satirapoj, 2012:109). The mean calculated eGFR was 84.36 mL/minute ±
37.10 mL/minute. The presence of nephropathy is much higher within the general population of patients with T2DM globally. Nephropathy is prevalent in 20 to 40% according to the literature (Muthippaniappan et al., 2015:520; Sharaf et al., 2017:363; Vinod, 2012:121). For a complete summary of the additional results, refer to Table 3.1 for the additional results not discussed in the two manuscripts)
Table 3.1: Additional results for the study population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>95%</th>
<th>Median</th>
<th>Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>89.4</td>
<td>19.9</td>
<td>74.7, 104.2</td>
<td>86.0</td>
<td>26</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.5</td>
<td>16.1</td>
<td>154.1, 168.8</td>
<td>161.7</td>
<td>17.5</td>
</tr>
<tr>
<td>Calculated BMI (kg/m(^2))</td>
<td>28.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose (mmol/L)</td>
<td>10.6</td>
<td>5.2</td>
<td>10.8, 10.3</td>
<td>9.40</td>
<td>6.5</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>142.1</td>
<td>24.7</td>
<td>140.9, 143.4</td>
<td>139.0</td>
<td>32</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77.5</td>
<td>14.5</td>
<td>76.8, 78.3</td>
<td>77.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Glycosylated haemoglobin (%)</td>
<td>9.6</td>
<td>2.8</td>
<td>9.1, 10.1</td>
<td>9.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.5</td>
<td>1.2</td>
<td>2.6, 4.7</td>
<td>4.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.4</td>
<td>1.4</td>
<td>1.1, 2.6</td>
<td>1.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Low-density lipoprotein (mmol/L)</td>
<td>2.3</td>
<td>0.9</td>
<td>2.1, 2.4</td>
<td>2.1</td>
<td>1.2</td>
</tr>
<tr>
<td>High-density lipoprotein (mmol/L)</td>
<td>1.2</td>
<td>0.4</td>
<td>1.1, 1.2</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>91.9</td>
<td>41.5</td>
<td>85, 98.7</td>
<td>76.5</td>
<td>48.5</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>4.3</td>
<td>0.6</td>
<td>4.2, 4.4</td>
<td>4.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Estimate glomerular filtration rate (mL/minute)</td>
<td>84.9</td>
<td>37.2</td>
<td>78.7, 91.1</td>
<td>84.0</td>
<td>68.5</td>
</tr>
</tbody>
</table>
3.4 Discussion

According to the patient parameters, they tend to have hyperglycaemia, hypertension and dyslipidaemia. Only 9.4% (n = 18) of the patients in the study population achieve the combined blood glucose, blood pressure and blood lipid levels that were at the treatment targets. The presence of hypertension and dyslipidaemia is common in patients with T2DM (Daya et al., 2017:1; SEMDSA type 2 diabetes guidelines expert committee, 2017:s78; Trudeau & Gilbert, 2018:113). Dyslipidaemia is both a comorbidity of T2DM as well as a result of the processes of insulin resistance involved in the pathophysiology of T2DM (Biddinger et al., 2007:131; Gustafson et al., 2015:4; Meshkani & Adeli, 2009:1335). Hypertension in T2DM patients is a result of both nephropathy and lifestyle-driven risk factors that are present in T2DM patients (Benowits, 2012:184; Desphande et al., 2008:1256; Forman et al., 2009:401; Satirapoj 2012:115). The presence of hypertension and dyslipidaemia in this study population is in accordance with the literature. The minority of the patients had an eGFR value that indicated the presence of nephropathy, which is < 30mL/min.

3.5 Chapter summary

During this chapter, the results of the empirical study were outlined and presented in the form of two journal manuscripts. Any additional results of the empirical study that were not discussed in the manuscripts were discussed in section 3.3. The focus of the study was HCP compliance with type 2 diabetes care guidelines. The conclusions of the literature review and empirical study are discussed in Chapter 4.
CHAPTER 4 CONCLUSION, RECOMMENDATIONS AND LIMITATIONS

4.1 Introduction

The aim of this study was to assess healthcare provider compliance to the national type 2 diabetes care guidelines according with the PHC STG EML 2014 at the selected regional hospital outpatient department in the Dr Kenneth Kaunda District in the North West Province in South Africa. This chapter summarises the findings of both the literature review and empirical review after the specific objectives as stated in Chapter 1 were met. This chapter will furthermore discuss any limitations to the study as well as recommendations for future studies.

4.2 Conclusions: Literature review

The literature review served to create a general picture of the nature of T2DM, the management thereof, both nationally and internationally, by reviewing published diabetes care guidelines and healthcare provider compliance with diabetes care guidelines. The conclusions of each objective as stated in Chapter 1 paragraph 1.4.2 will be discussed in the subsequent paragraphs.

4.2.1 Generate a general picture of the nature of DM with the focus on T2DM

This objective was achieved in Chapter 2 section 2.2. Type 2 diabetes mellitus is an ancient disease that was first defined in 500 BC by Hindu physicians who associated the disease with obesity and a lack of physical activity and poor diet (Lakhtakia, 2013:368), now well-known as part of the risk factors in the progression of the disease. The development of T2DM is associated with risk factors that are either environmental or genetic. Environmental risk factors such as obesity, lack of physical activity and high caloric diets contribute to the development of insulin resistance (Ali, 2013:114; Esser et al., 2014:142). Genetic risk factors such as genetic predisposition, family history, age or gender, on the other hand, contribute to the decline in beta-cell function (Kaku, 2010: 42). Interaction between these two categories of risk factors is necessary for the progression of T2DM as both insulin resistance and beta-cell dysfunction are keys to the pathogenesis (Chatterjee et al., 2017:2239; Hasstedt et al., 2001:537; Kahn, 2003:4, Scheen, 2003:335).

Insulin resistance leads to hyperglycaemia through decreased muscle glycogen synthesis (Sesti, 2006:666; Shulman, 2000:171) and increased hepatic gluconeogenesis and glycogenolysis as well as decreased glycogen synthesis (De Fronzo et al., 1989:387; Meshkani & Adeli, 2009:1334; Savage et al., 2007:510). Insulin resistance further contributes to the development of
dyslipidaemia through increased hepatic lipogenesis, lipolysis and adipose tissue. Beta-cell dysfunction leads to hyperglycaemia because of decreased glucose stimulated insulin secretion in pancreatic beta-cells (Biddinger et al., 2007; Samuel et al., 2010:2271).

Microvascular and macrovascular complications develop in the environment of hyperglycaemia and dyslipidaemia created by the metabolic abnormalities that characterise T2DM (Bardini et al., 2012:82; Forbers & Cooper, 2013:139; Giacco & Brownlee, 2010:580). Microvascular complications such as retinopathy, nephropathy and neuropathy develop in an environment of chronic hyperglycaemia that causes oxidative stress in the microvasculature as described in section 2.2.3.1. Nephropathy contributes to the incidence of comorbid hypertension in DM patients, which increases the risk for macrovascular complications. Macrovascular complications develop in an environment of dyslipidaemia, hypertension and to a lesser extent due to the oxidative stress caused by hyperglycaemia. Both microvascular and macrovascular complications contribute to the morbidity and mortality of DM.

4.2.2 An overview of the goals of T2DM treatment, therapeutic approaches and therapeutic outcomes according to diabetes care guidelines, both nationally and internationally

It can be concluded that consensus exists nationally and internationally regarding the goals of T2DM management as discussed in section 2.3. Management revolves around the treatment of hyperglycaemia, hypertension and dyslipidaemia for the prevention of the development of diabetes-related complications and treatment of complications, should they exist in patients (ADA, 2017:s57; RSA, 2014:9.7; SEMDSA type 2 diabetes guidelines expert committee, 2017:s20).

Management of hyperglycaemia includes frequent monitoring of blood glucose levels by ways of finger-prick testing (at every visit) and annual testing of HbA1c (according to the South African guidelines) or biannually (according to the ADA and CDA guidelines) (see Table 2.4 for a summary of the monitoring practices for glycaemic control).

Pharmacological treatment is organised in a stepwise manner starting with the initiation of metformin as first-line treatment and moving on to the combination of oral anti-diabetic drugs and finally the use of insulin alone or in combination with metformin (according to the PHC STG EML 2014) or other oral anti-diabetic drugs with the exception of sulphonylureas (according to the SEMDSA 2017 guidelines as well as the ADA 2017 standards of care and the CDA 2018 guidelines). Although all guidelines conform to a stepwise manner of treatment, the number of steps differs from guideline to guideline, including or excluding oral anti-diabetic drugs (see Annexure G for the hyperglycaemia treatment algorithm).
There is a high prevalence of cardiovascular disease among T2DM patients, which can potentially lead to mortality (SEMDSA type 2 diabetes guidelines expert committee, 2017:s78; Trudeau & Gilbert, 2018:113). Therefore, guidelines recommend addressing the various risk factors associated with macrovascular complications. Frequent monitoring of BP, as often as each clinical visit, is recommended in the guidelines discussed in section 2.3. All guidelines agree on the therapeutic target of BP < 140/90 mmHg. The most common drug classes used in the treatment of hypertension include the use of ACEi and ARBs, calcium channel blockers, beta-blockers and thiazide diuretics (ADA, 2017:s75-s79; Mancini et al., 2018:s179; RSA, 2014:4.16; SEMDSA type 2 diabetes guidelines expert committee, 2017:s21; Tobe et al., 2018:s186). Stepwise treatment of hypertension is recommended and outlined by the PHC STG EML 2014, while international guidelines recommend monotherapy starting with ACEi or ARBs (ADA, 2017:s76; Tobe et al., 2018:s187). When patients fail to reach therapeutic targets, combination therapy is recommended with the addition of either calcium-channel blockers or thiazide diuretics (ADA, 2017:s76; Tobe et al., 2018:s187). All the guidelines discussed in section 2.3 agree and recommend statin use as monotherapy for the treatment of dyslipidaemia and according to the South African guidelines statin use is initiated in patients regardless of triglyceride levels according to specific parameters as seen in section 2.3.1.2.

The management of microvascular and macrovascular complications is discussed in section 2.3.1.3. All guidelines agree that prevention of microvascular complications includes addressing lifestyle driven risk factors, and the management of hyperglycaemia, hypertension and dyslipidaemia.

Management of retinopathy revolves around the prevention strategies as mentioned above. An annual eye test is recommended in order to monitor patients. Treatment of nephropathy is more specialised. While all the guidelines agree on the course of hypertension treatment, i.e. blockade of RAAS, variation occurs on which class of drugs to use. The available drug classes are either ACEi or ARB (ADA, 2017:s91; RSA, 2014:9.19; SEMDSA type 2 diabetes guidelines expert committee, 2017:s91). In the presence of kidney disease, dose adjustments of anti-diabetic drugs are recommended. All guidelines mentioned above are in agreement that if a patient’s eGFR is < 30 ml/min, metformin use should be withdrawn completely (ADA, 2017:s90; RSA, 2014:9.10; SEMDSA type 2 diabetes guidelines expert committee, 2017:s92). Regarding the use of sulphonylureas, the PHC STG EML 2014 recommends complete withdrawal if a patient’s eGFR is < 60 ml/min (RSA, 2014:9.11), whereas the other guidelines state that only second generation sulphonylureas be used provided that the patient can avoid hypoglycaemia. Monitoring of the patient is done annually by means of a urine dipstick and serum creatinine concentration and a serum potassium concentration if the patient is using ACEi. Neuropathy is managed through
asymptomatic treatment and pain relief. Further monitoring includes an annual foot assessment as well as an examination of footwear at every visit.

Management of macrovascular complications is centred on treatment of hypertension and dyslipidaemia, also known as risk factor management. Secondary prevention of macrovascular complications includes the use of aspirin.

4.2.3 Generate a general picture of HCP compliance to type 2 diabetes care guidelines and possible factors that could negatively impact such compliance.

The general picture of HCP compliance to type 2 diabetes care guidelines is generally suboptimal. The term used to define poor compliance is clinical inertia, which exists when healthcare providers fail to intensify or initiate therapy when indicated (Khunti et al., 2018:428; Khunti et al., 2013:3411; Phillips et al., 2001:825). Clinical inertia is a global concern affecting both developing and developed countries (Adedeji et al., 2015:1; Delavari et al., 2009: 494; Panatalone et al., 2018; Ratanawongsa et al., 2012:95; Reach, 2014: 241; Vinagre et al., 2012:774). There are various ways that clinical inertia can manifest, either as failure to intensify or initiate anti-diabetic drugs or insulin treatment, and therefore patients experience poor glycaemic control for an extended period of time (Khunti et al., 2015:66; Khunti & Millar-Jones, 2016:10). In some cases, newly diagnosed patients experience a lack of treatment intensification after a period of more than six months of metformin monotherapy failure (Panatalone et al., 2018). There are three barriers that contribute to clinical inertia. These barriers include physician-related barriers, system-related barriers and patient-related barriers (Zafar et al., 2014:407). Physician-related barriers can range from factors influencing implementation, adoption of these guidelines and overestimation of care (Khunti & Millar-Jones, 2016:7; Philips et al., 2001:827). System-related barriers are the practical challenges that form part of healthcare delivery systems that could include poor planning and communication between members of the healthcare team, inadequate access to supportive technologies and resources that aid in the proper management of patients. The last barrier is patient-related barriers that contribute to the poor physician-patient relationship and treatment adherence (Reach et al., 2017:506; Ross, 2013:s38). It can therefore be concluded that although there are different barriers to clinical inertia, it is still the responsibility of physicians to provide proper care according to the recommendation of the clinical care guidelines as Philips et al. (2001:827) stated that clinical inertia remains the responsibility of the HCPs.
4.2.4 Investigate the overall number of T2DM patient reaching therapeutic targets both nationally and globally.

In section 2.3, the goals of DM management were revealed to be the treatment of hyperglycaemia, hypertension and dyslipidaemia in order to prevent or delay the development of microvascular and macrovascular complications (ADA, 2017:s57; RSA, 2014:9.7; SEMDSA type 2 diabetes guidelines expert committee, 2017:s20; WHO, 2016:60). These guidelines are therefore aimed at reducing blood glucose, BP and blood lipid levels to the recommended therapeutic targets (for the therapeutic targets refer to Annexure A). Clinical inertia, as seen from the literature review in section 2.4, affects the quality of care leading to poor patient outcomes (Delavari et al., 2009:492; Braga et al., 2012:457; Reach et al., 2017:501). This was seen in studies conducted both nationally and internationally, which revealed that DM care is sub-optimal. Braga et al. (2012:457) revealed that only 19% of the study population reached the targeted blood glucose, BP and blood lipid levels. Stone et al. (2013:774) revealed that despite improvements in patient outcomes at primary healthcare facilities, the majority of patients had difficulty reaching the targeted blood glucose, BP and blood lipid levels in Catalonia. Some studies also revealed delayed or lack of treatment intensification despite HbA1c levels ≥7% (Pantalone et al., 2016:1529; Pantalone et al., 2018). Pinchevsky et al. (2015:81) performed an audit of the number of patients receiving care at a South African tertiary hospital reaching the targeted blood glucose, BP and blood lipid levels. This study also revealed that the majority of these patients did not achieve the specific target for these targets, as well as a downward trend in glycaemic control. It can therefore be concluded that clinical inertia poorly affects patient outcomes both nationally and internationally.

4.3 Conclusions: Empirical study

4.3.1 Manuscript one

Healthcare provider compliance with the PHC STG EML 2014 was sub-optimal regarding the monitoring of guideline-specific parameters monitored at baseline and annually. Compliance with the monitoring of blood glucose levels by means of a finger-prick blood glucose test and blood pressure at every visit was optimal. However, weight measurements were taken in the minority of patients, as seen at only one MOPD visit in 13 patients. Weight should have been measured at every MOPD visit. Patient waist circumference was not measure once, neither any of the albumin: creatinine ratios when urine dipstick tests were positive for proteinuria. The monitoring of eye function by means of an eye assessment was done in reaction to patient complaints to the presence of retinopathy, the same was true with regard to the monitoring of neuropathy by means of foot assessments. This indicated reactive care in order to treat microvascular complications rather than proactive care in order to prevent microvascular complications. This correlates with
existing evidence of research done on the same topic that concluded that one of the physician-related barriers that contributes to clinical inertia is reactive care rather than proactive care. The majority of patient records indicated that HCP compliance with the treatment practices was optimal as the majority of the prescribing actions that were taken by the HCPs were according the recommendations of the PHC STG EML 2014. The literature review showed evidence of clinical inertia in terms of pharmacologic treatment. This was not the case within the study population of this study as the results revealed optimal HCP compliance with the pharmacologic treatment recommendations of the PHC STG EML 2014. However, despite some areas of optimal compliance, which include finger-prick blood glucose testing and blood pressure measurement at every MOPD visit, the monitoring of specific parameters at baseline and annually was sub-optimal. Poor monitoring of these parameters could result in either over-estimation of care and delayed treatment when indicated; this further promotes the development of microvascular complications. These specific parameters such as HbA1c can give a better indication of glycaemic control (Selvin et al., 2010:800). Prolonged exposure to hyperglycaemia (also indicated by HbA1c of > 7%) is the main cause of microvascular complications in T2DM patients (Giacco & Brownlee, 2010:1059). Serum creatinine- and potassium, eGFR along with urine dipstick monitoring can be used to determine the presence or absence of nephropathy, as well as the severity of nephropathy (Satirapoj, 2012:110). Eye- and foot assessments can reveal the presence of retinopathy and neuropathy (ADA, 2017:s93; Altomare et al., 2018:s210; Hurley, 2017:s1). As stated in section 2.3, one of the goals of T2DM care is to prevent or delay the development of microvascular and macrovascular complications and to treat these complications accordingly (ADA, 2017:s57; RSA, 2014:9.7; SEMDSA type 2 diabetes guidelines expert committee, 2017:s20). By neglecting to monitor patients according to the recommendations of the PHC STG EML 2014, HCPs cannot adequately detect the presence of complications nor treat complications. The conclusion that HCP compliance was sub-optimal is based upon the poor monitoring of baseline and annual parameters. Inadequate monitoring of guideline-recommended parameters was also found in the literature review, and therefore it can be concluded that the performance of the HCPs at the study setting responsible for providing care to DM patients correlated with the literature review (Adedeji et al., 2015:1; Delavari et al., 2009:494; Panatalone et al., 2016:1527; Ratanawongsan et al., 2012:95; Reach, 2014:241; Vinagre et al., 2012:774).

4.3.2 Manucript two

Healthcare provider compliance with the PHC STG EML 2014 recommendations for the management of hyperglycaemia can be considered as optimal with improvement needed in monitoring of HbA1c. There was high compliance with the monitoring of blood glucose through finger-prick testing as well as with the pharmacological treatment. The literature review revealed
HCP compliance with the guideline recommendations for the treatment of hyperglycaemia is sub-optimal overall, with regard to both initiating treatment and/or treatment intensification. The results of this study showed that the majority of the prescriptions were prescribed according to the recommendations of the PHC STG EML 2014. There was evidence of treatment intensification as well as initiating insulin therapy when finger-prick blood glucose test results indicated hyperglycaemia. Sub-optimal compliance with the monitoring of glycaemic control especially by means of HbA1c was according to the literature review, which revealed that failure to monitor blood glucose according to the guidelines is a component of clinical inertia present globally. The final conclusion of this manuscript is that HCP compliance with the PHC STG EML 2014 recommendations for the management of hyperglycaemia was optimal; however, improvement is needed in order to better manage hyperglycaemia by means of HbA1c.

4.4 Limitations and strengths

During the empirical study, there were both limitations and strengths that might have influenced the outcomes of the study. The limitations to this study were as follows:

- A single study setting in the DKKD meant that the results of this study is specific to the DKKD and cannot be generalised to the whole of the North West Province or to South Africa.
- The use of hard copy patient records for data collection meant that all the patient records could not be reviewed within the data collection period.
- Data collection was performed by the researcher exclusively, which created room for mistakes such as a missing gender value. A bigger research team could have collected data from more patient files.
- The hard copy patient records contained data from both in-hospital treatment as well as treatment received in the MOPD. This meant that the data of MOPD visits had to sorted from in-hospital data. This could have led to data that were relevant to the research being left out during the data collection process.

The strengths of this study were as follows:

- The use of patient records in order to evaluate HCP compliance with the PHC STG EML 2014 gave an objective perspective of patient care. This proved as a strength as the use of questionnaires or structured interviews with the HCPs would have introduced a subjective perspective and possibly an over-estimation of care that contributes to clinical inertia.
- The study was based at a study setting that formed part of the public health sector, which was also a strength as the majority of the South African population receive care in the public health sector. Which is also true in the DKKD.
4.5 Recommendations

To further investigate HCP compliance with clinical care guidelines in the public sector of South African healthcare, it can be recommended that the perspective of both patients and HCPs be included by ways of questionnaires or interviews. This could give insight to contributing factors to the current state of patient care and possibly reveal the barriers to proper patient care according to the recommendations of clinical care guidelines present in the public health sector. A study with a longer study period could possibly reveal whether patient care has improved or worsened over time.

4.6 Chapter summary

The literature review revealed that T2DM is a progressive disease that needs good management in order to prevent the onset of diabetes-related complications. The management of hyperglycaemia is especially important. Hyperglycaemia does not only lead to the progressive decline in beta-cell function, but is also a major contributor to the development of microvascular complications and to a lesser extent macrovascular complications. Healthcare provider compliance with the management practices recommended by type 2 diabetes care guidelines is sub-optimal. This, in turn, causes a gap between the clinical guidelines and the clinical care that patients receive. This gap results in patients not being monitored as recommended leading to complications going unnoticed.

The empirical study revealed a relatively well-organised approach of healthcare providers to the monitoring and treatment of hyperglycaemia and hypertension, which can be translated to optimal compliance to these singular components of the PHC STG EML 2014. Nevertheless, there remains much room for improvement in compliance with the monitoring of patient weight, kidney function, eye function and neuropathy, as the majority of these recommended clinical tests and assessments were left out.
REFERENCES


Hasstedt, S.J., Ren, Q., Teng, K. & Elbein, S.C.  2001.  Effect of the peroxisome proliferator-activated receptor-γ2 pro ala variant on obesity, glucose homeostasis, and blood pressure in
members of familial type 2 diabetic kindreds. The journal of clinical endocrinology & metabolism, 86(2):536-541.


## ANNEXURE A: GUIDELINE-SPECIFIC PARAMETERS

<table>
<thead>
<tr>
<th>Assessment parameters</th>
<th>Monitoring frequency</th>
<th>Goals</th>
<th>Take action</th>
<th>Action to be taken</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td>At every visit</td>
<td>4 - 7 mmol/L</td>
<td>&gt; 8 mmol/L</td>
<td>Stepwise treatment according to the national diabetes guidelines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recommend changes in diet and lifestyle</td>
</tr>
<tr>
<td>2hr post prandial</td>
<td>At every visit</td>
<td>5 - 8 mmol/L</td>
<td>&gt; 10 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Glycosylated haemoglobin</td>
<td>Annually (every 3-6 months for patients whose medication changed until stable)</td>
<td>&lt; 7%</td>
<td>&gt; 8%</td>
<td></td>
</tr>
<tr>
<td><strong>Blood pressure:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>At every visit</td>
<td>&lt; 140 mmHg</td>
<td>&gt; 140 mmHg</td>
<td>Treat stepwise according to the national diabetes guidelines</td>
</tr>
<tr>
<td>Diastolic</td>
<td>At every visit</td>
<td>&lt; 90 mmHg</td>
<td>&gt; 90 mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>Blood lipids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting total cholesterol</td>
<td>Baseline measurement</td>
<td>&lt; 4.1 mmol/L</td>
<td>&gt; 5 mmol/L</td>
<td>Treatment according to the national diabetes guidelines</td>
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<td>Treatment recommended in all T2DM patients who:</td>
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<td>• Are older than 40 years</td>
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<td>• Had a history of cardiovascular disease</td>
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<td>• Have eGFR of &gt; 60 ml/min</td>
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<tr>
<td>Triglycerides</td>
<td>Baseline measurement</td>
<td>&lt; 1.7 mmol/L</td>
<td>&gt; 1.7 mmol/L</td>
<td></td>
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<tr>
<td>HDL</td>
<td>Baseline measurement</td>
<td>&gt; 1.5 mmol/L in both men and women</td>
<td>&lt; 1.0 mmol/L in men &lt; 1.3 mmol/L in women</td>
<td></td>
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<tr>
<td>LDL</td>
<td>Baseline measurement</td>
<td>&lt; 1.8 mmol/L</td>
<td>&gt; 3 mmol/L</td>
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<tr>
<td>Assessment parameters</td>
<td>Monitoring frequency</td>
<td>Goals</td>
<td>Take action</td>
<td>Action to be taken</td>
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<td><strong>Kidney function</strong></td>
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<tr>
<td>Serum creatinine</td>
<td>Baseline and annually</td>
<td></td>
<td>&lt; 30 ml/minute</td>
<td>Treatment according to the national diabetes guidelines</td>
</tr>
<tr>
<td>concentration and eGFR</td>
<td></td>
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<tr>
<td>Serum potassium</td>
<td>Baseline and annually</td>
<td></td>
<td>&lt; 30 ml/minute</td>
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<tr>
<td>concentration (in patients on ACE-inhibitor) estimate eGFR</td>
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<tr>
<td>Urine protein</td>
<td>Baseline and annually</td>
<td></td>
<td>positive</td>
<td></td>
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<tr>
<td>Albumin: creatinine</td>
<td>Baseline and annually</td>
<td></td>
<td>&gt; 3 mg/mmol</td>
<td></td>
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<tr>
<td>Abdominal circumference</td>
<td>Baseline</td>
<td></td>
<td>&gt; 94 cm in men</td>
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<td></td>
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<td>&gt; 80 cm in women</td>
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<tr>
<td>Eye assessment</td>
<td>Baseline and annually</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Refer to ophthalmologist</td>
</tr>
<tr>
<td>Foot assessment</td>
<td>Baseline and annually</td>
<td>Normal</td>
<td>Neuropathy Infection Ischaemia</td>
<td>Treatment according to the national diabetes guidelines</td>
</tr>
<tr>
<td>Weight</td>
<td>At every visit</td>
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</table>
## ANNEXURE B: DATA COLLECTION TOOL

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Date (DD/MM/YYYY)</th>
<th>Date of birth (DOB)</th>
<th>Age (Calculated)</th>
<th>Weight (kg)</th>
<th>Length (cm)</th>
<th>BMI (calculated)</th>
<th>Blood glucose (Y=1/N=0)</th>
<th>Blood glucose (mmol/L)</th>
<th>Blood glucose (Target) (Y=1/N=0)</th>
<th>Action taken (Y=1/N=0)</th>
<th>If yes: Indicate action</th>
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<thead>
<tr>
<th>Blood pressure (Y=1/N=0)</th>
<th>Blood pressure (mm/Hg)</th>
<th>Blood pressure (Target) (Y=1/N=0)</th>
<th>Action taken (Y=1/N=0)</th>
<th>If yes: Indicate action</th>
<th>Weight (Y=1/N=0)</th>
<th>Weight (Kg)</th>
<th>Weight (Target) (Y=1/N=0)</th>
<th>Action taken (Y=1/N=0)</th>
<th>If yes: Indicate action</th>
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<thead>
<tr>
<th>Annually HbA&lt;sub&gt;1&lt;/sub&gt;C (Y=1/N=0/N/A)</th>
<th>HbA&lt;sub&gt;1&lt;/sub&gt;C (%)</th>
<th>HbA&lt;sub&gt;1&lt;/sub&gt;C (Target) (Y=1/N=0)</th>
<th>Action taken (Y=1/N=0)</th>
<th>If yes: Indicate action</th>
<th>Baseline blood lipids (Y=1/N=0)</th>
<th>Total cholesterol (mmol/L)</th>
<th>Triglycerides (mmol/L)</th>
<th>HDL (mmol/L)</th>
<th>LDL (mmol/L)</th>
<th>Blood lipids (Target) (Y=1/N=0)</th>
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<tr>
<th>Action taken (Y=1/N=0)</th>
<th>If yes: Indicate action</th>
<th>Baseline serum creatinine (Y=1/N=0)</th>
<th>Annual serum creatinine (Y=1/N=0/N/A)</th>
<th>Serum creatinine (ml/min)</th>
<th>Baseline serum potassium (Y=1/N=0)</th>
<th>Annual serum potassium (Y=1/N=0/N/A)</th>
<th>Serum potassium (ml/min)</th>
<th>eGFR (Calculated) (ml/min)</th>
<th>eGFR (Target) (Y=1/N=0)</th>
<th>Action taken (Y=1/N=0)</th>
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<table>
<thead>
<tr>
<th>If yes: Indicate action</th>
<th>Baseline urine protein ((Y=1/N=0))</th>
<th>Annual Urine protein ((Y=1/N=0/N/A))</th>
<th>Urine protein (Target) ((Positive=1/ Negative=0))</th>
<th>Urine protein (Positive=1/ Negative=0)</th>
<th>Action taken ((Y=1/N=0))</th>
<th>If yes: Indicate action</th>
<th>Baseline albumin: creatinine ((Y=1/N=0))</th>
<th>Annual Albumin: creatinine ((Y=1/N=0/N/A))</th>
<th>Albumin: creatinine ((mg/mmol))</th>
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<tr>
<th>If yes: Indicate action</th>
<th>Action taken ((Y=1/N=0))</th>
<th>Abdominal circumference ((Y=1/N=0))</th>
<th>Abdominal circumference ((cm))</th>
<th>Baseline: Eye examination ((Y=1/N=0))</th>
<th>Annual: Eye examination ((Y=1/N=0/N/A))</th>
<th>Eye examination ((Normal/Abnormal))</th>
<th>Action taken ((Y=1/N=0))</th>
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<table>
<thead>
<tr>
<th>If yes: Indicate action</th>
<th>Baseline foot examination: (y=1/n=0)</th>
<th>Annual foot examination: (Y=1/N=0/N/A)</th>
<th>Foot examination (Normal/Abnormal)</th>
<th>Action taken (Y=1/N=0)</th>
<th>If yes: Indicate action</th>
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ANNEXURE C: MEETING AGENDA

Meeting to discuss proposed research

Guideline compliance in type 2 diabetes care: Regional hospital out-patient department in the Dr Kenneth Kaunda District

Meeting roles

Host: Selected regional hospital

Facilitator: D Venter

Meeting objectives:

1. Study outlines
2. Problem statement
3. Study objectives
4. Dissemination of results after completion of study

Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00</td>
<td>Welcome/introduction</td>
</tr>
<tr>
<td>09:15</td>
<td>Study outlines</td>
</tr>
<tr>
<td>10:15</td>
<td>Problem statement</td>
</tr>
<tr>
<td>10:45</td>
<td>Study objectives</td>
</tr>
<tr>
<td>11:00</td>
<td>Dissemination of results after completion of study</td>
</tr>
<tr>
<td>11:15</td>
<td>Questions</td>
</tr>
</tbody>
</table>
ANNEXURE D: APPROVAL: HEALTH RESEARCH ETHICS COMMITTEE OF THE NORTH-WEST UNIVERSITY

Dr JM du Plessis
Clinical Pharmacy
MUSA

9 September 2018

Dear Dr du Plessis

APPROVAL OF YOUR APPLICATION BY THE HEALTH RESEARCH ETHICS COMMITTEE (HREC) OF THE FACULTY OF HEALTH SCIENCES

Ethics number: NWU-00881-17-S1

Kindly use the ethics reference number provided above in all future correspondence or documents submitted to the administrative assistant of the Health Research Ethics Committee (HREC) secretariat.

Study title: Guideline compliance in type 2 diabetes care: Regional hospital outpatient department in the Dr Kenneth Kaunda District

Study leader: Dr JM du Plessis

Student: DE Venter-23509414

Application type: Single study

Risk level: Minimal (monitoring report required annually)

Expiry date: 30 September 2019 (monitoring report due at the end of September annually until completion)

You are kindly informed that after review by the HREC, Faculty of Health Sciences, North-West University, your ethics approval application has been successful and was determined to fulfill all requirements for approval. Your study is approved for a year and may commence from 09/09/2018. Continuation of the study is dependent on receipt of the annual (or as otherwise stipulated) monitoring report and the concomitant issuing of a letter of continuation. A monitoring report should be submitted two months prior to the reporting dates as indicated i.e. annually for minimal risk studies, six-monthly for medium risk studies and three-monthly for high risk studies, to ensure timely renewal of the study. A final report must be provided at completion of the study or the HREC. Faculty of Health Sciences must be notified if the study is temporarily suspended or terminated. The monitoring report template is obtainable from the Faculty of Health Sciences Ethics Office for Research, Training and Support at Ethics-HRECMonitoring@nwu.ac.za. Annually, a number of studies may be randomly selected for an internal audit.

The HREC, Faculty of Health Sciences requires immediate reporting of any aspects that warrants a change of ethical approval. Any amendments, extensions or other modifications to the proposal or other associated documentation must be submitted to the HREC, Faculty of Health Sciences prior to implementing these changes. These requests should be submitted to Ethics-HRECApply@nwu.ac.za with a cover letter with a specific subject title indicating, “Amendment request: NWU-XXXXXX-XX-XX”. The letter should include the title of the approved study, the names of the researchers involved, the nature of the amendment/s being made (indicating what changes have been made as well as where they have been made), which documents have been attached and any further explanation to clarify the amendment request being submitted. The amendments made should be indicated in yellow highlight in the amended documents. The e-mail, to which you attach the documents that you send, should have a specific subject line indicating that it is an amendment request e.g., “Amendment request: NWU-XXXXXX-XX-XX”. This e-mail should indicate the nature of the amendment. This submission will be handled via the expedited process.
Any adverse/unexpected/unforeseen events or incidents must be reported on either an adverse event report form or incident report form to Ethics-HRECincident-SAE@nwu.ac.za. The e-mail to which you attach the documents that you send, should have a specific subject line indicating that it is a notification of a serious adverse event or incident in a specific project e.g. “SAE/Incident notification: NWU-XXXXX-XX-XX”. Please note that the HREC, Faculty of Health Sciences has the prerogative and authority to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process.


We wish you the best as you conduct your research. If you have any questions or need further assistance, please contact the Faculty of Health Sciences Ethics Office for Research, Training and Support at Ethics-HRECEmail@nwu.ac.za.

Yours sincerely

Prof Wayne Towers  
HREC Chairperson

Prof Minnie Greeff  
Ethics Office Head
This letter serves to inform the Researcher that permission to undertake the above mentioned study has been granted by the North West Department of Health. The Researcher is expected to arrange in advance with the chosen facilities, and issue this letter as proof that permission has been granted by the Provincial office.

This letter of permission should be signed and a copy returned to the department. By signing, the Researcher agrees, binds him/herself and undertakes to furnish the Department with an electronic copy of the final research report. Alternatively, the Researcher can also provide the Department with electronic summary highlighting recommendations that will assist the Department in its planning to improve some of its services where possible. Through this the Researcher will not only contribute to the academic body of knowledge but also contributes towards the bettering of health care services and thus the overall health of citizens in the North West Province.

Kindest regards

Dr. F.R.M. Reichel

Director: PPRM&E

Date 30/07/2019

Researcher

Date 02/08/19
ANNEXURE F: GOODWILL PERMISSION FORM

OFFICE OF THE CLINICAL MANAGER

03 April 2018

TO: Ms D.E. Venter
North West University
Potchefstroom

FROM: Clinical Manager

REF NO: RS 18/03/2018 Guideline compliance in type two diabetes care Regional Hospital OPD Department in Dr. KK District

Dear Ms. Venter,

This is to inform you that the Hospital Patient Safety Group (PSG) that sat on 13/03/2018 has given you permission to proceed with your research titled:

Guideline compliance in type two diabetes care Regional Hospital OPD Department in Dr. KK District

We wish you all the best with your study and look forward to sharing in the results of your findings.

Sincerely,

[Signature]

Healthy Living for All
## ANNEXURE G: TREATMENT ALGORITHM FOR GLYCAEMIC CONTROL

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
</table>
| SEMDSA 2017 | Initiate one of the oral anti-diabetic drugs at diagnosis in conjunction with lifestyle modification.  
**Preferred therapy:** Metformin  
Starting dose of 500 mg once daily titrated to a maximum dose of 2550 mg daily in three divided doses.  
In patients with renal impairment:  
eGFR ≥ 60 ml/min  
Standard dosing while monitoring eGFR annually.  
eGFR 45 – 60 ml/min  
Standard dosing while monitoring eGFR every 3-6 months  
eGFR 30 – 45 ml/min  
Maximum dose of 1000 mg daily  
eGFR < 30 ml/min  
Metformin use contraindicated.  
Alternative therapies without motivation:  
Gliclazide MR  
DPP-4i  
Pioglitazone | Combine any two oral anti-diabetic drugs:  
**Preferred therapy:** Metformin and sulphonylurea  
**Gliclazide:**  
Starting dose of 40 mg once daily; maximum dose 320 mg daily in two divided doses.  
**Gliclazide modified-release:**  
Starting dose of 30 mg once daily to maximal dose of 120 mg once daily  
**OR**  
Metformin and DPP-4i  
**Saxagliptin:**  
5 mg daily.  
2.5 mg daily if eGFR < 50 ml/min.  
**Sitagliptin:**  
100 mg daily  
50 mg daily if eGFR 30 - 50 ml/min  
25 mg daily if eGFR < 30 ml/min  
**Vidagliptin:**  
50 mg twice daily  
50 mg daily if eGFR < 50 ml/min.  
**Preferred therapy:** Metformin combined with:  
DPP-4i  
Gliclazide MR  
Pioglitazone:  
Starting dose of 15 mg once daily increase to maximum dose of 45 mg daily if necessary.  
**Alternative therapy without motivation:**  
GLP1RA  
Basal insulin  
SGLT2i | Combine three drugs  
If HbA1c target is not reached with dual therapy consider adding a third oral anti-diabetic drug.  
**Preferred therapy:** Metformin combined with:  
DPP-4i  
**Saxagliptin:**  
5 mg daily.  
2.5 mg daily if eGFR < 50 ml/min.  
**Sitagliptin:**  
100 mg daily  
50 mg daily if eGFR 30 - 50 ml/min  
25 mg daily if eGFR < 30 ml/min  
**Vidagliptin:**  
50 mg twice daily  
50 mg daily if eGFR < 50 ml/min.  
**Alternative therapy without motivation:**  
GLP1RA  
Basal insulin  
SGLT2i | Triple therapy inadequate to maintain glycaemic control, complex therapy (combination injectable) will become necessary.  
**Preferred therapy:** Metformin and combination insulin:  
Premix insulin: Basal-plus prandial insulin  
**OR:** Combination injectable: Metformin and Basal insulin and GLP-1RA |
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<tr>
<th>Guideline</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
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<tbody>
<tr>
<td>CDA 2018</td>
<td><strong>HbA1c levels and symptomatic hyperglycaemia and/or metabolic decompensation.</strong>&lt;br&gt;&lt;br&gt;<strong>HbA1c &lt; 1.5% above target of 7.0% (in most cases):</strong>&lt;br&gt;Lifestyle modification. Start metformin if patient is not at target within 3 months.&lt;br&gt;&lt;br&gt;<strong>HbA1c ≥ 1.5% above target:</strong>&lt;br&gt;Start metformin immediately and consider dual therapy with oral anti-diabetic drugs:&lt;br&gt;Second oral anti-diabetic drug is dependent on whether or not clinical CVD is present:&lt;br&gt;- Yes:&lt;br&gt;Empagliflozin&lt;br&gt;Canagliflozin&lt;br&gt;Liraglutide&lt;br&gt;- No:&lt;br&gt;Add additional antihyperglycaemic drug best suited according to clinical considerations.&lt;br&gt;&lt;br&gt;<strong>Symptomatic hyperglycaemia and/or metabolic decompensation:</strong>&lt;br&gt;Initiate insulin treatment with or without metformin dependent on the individual patient.</td>
<td>Pioglitazone&lt;br&gt;SGLT2i</td>
<td><strong>HbA1c &lt; 1.5% above target:</strong>&lt;br&gt;In the presence of CVD:&lt;br&gt;Add:&lt;br&gt;Antihyperglycaemic agent with demonstrated CV benefit.&lt;br&gt;Empagliflozin&lt;br&gt;Canagliflozin&lt;br&gt;Liraglutide</td>
<td><strong>HbA1c &lt; 1.5% above target</strong>&lt;br&gt;Add another antihyperglycaemic agent from another class.&lt;br&gt;If CVD was present in previous step:&lt;br&gt;Add another antihyperglycaemic drug from another class best suited to the individual according to clinical considerations.&lt;br&gt;&lt;br&gt;<strong>Symptomatic hyperglycaemia and/or metabolic decompensation:</strong></td>
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<tr>
<td>Guideline</td>
<td>Step 1</td>
<td>Step 2</td>
<td>Step 3</td>
<td>Step 4</td>
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| **PHC STG EDL RSA 2014** | Entry to Step 1: Diagnosis  
Start with metformin and lifestyle modifications.  
Starting dose 500 mg titrated up to a maximum dose of 850 mg three times daily.  
In patients with renal impairment:  
eGFR of > 30 - 60mL/minute:  
Continue use at 50% with a maximum dose of 500 mg twelve hourly.  
eGFR of < 30 mL/minute:  
Stop metformin use | Entry to Step 2:  
Failure to reduce HbA1c or finger prick blood glucose levels to target.  
Add sulphonylurea:  
**Glimepiride:**  
Initial dose 1 mg daily adjusted in 1mg increments every 1 to 2 weeks to a maximum dose of 15 mg daily.  
(Daily dose of ≥7.5 mg, the dose should be divided 2/3 of dose in the morning and 1/3 of the dose in the evening)  
**Glibenclamide:**  
Initial dose of 2.5 mg daily, titrated up to a max dose of 15 mg daily.  
(Daily dose of ≥7.5 mg, the dose should be divided 2/3 of dose in the morning and 1/3 of the dose in the evening) | Entry to Step 3:  
Failure or oral combination to reduce blood glucose levels to targets  
Add Insulin, stop sulphonylurea.  
**Add on therapy**  
**Intermediate to long acting insulin.**  
Starting dose of 10 units in the evening, increases gradually to a maximum dose of 20 units in the evening.  
**Substitution therapy**  
**Biphasic insulin**  
Starting dose of 15 units daily divided in two doses:  
10 units in the morning before food  
5 units in the evening before food.  
Dose increases with 4 units weekly, the first increment added to morning dose and second increment added to evening dose. | Add on therapy:  
Intermediate to long acting insulin  
Start: 10 units in the evening before bedtime, not after 22h00.  
Adjust: If 10 units ineffective, increase gradually to 20 units by 2 - 4 unit increments each week).  
**Substitution therapy:**  
Start: 15 units daily in two divided doses.  
10 units, 30 minutes before breakfast.  
5 units, 30 minutes before supper.  
Adjust: Increase dose with 4 units weekly, first increment added to morning dose and second increment to evening dose. |
| **ADA 2018** | Monotherapy:  
Metformin in conjunction with lifestyle management.  
If HbA1c target is not reached within 3 - 6 months proceed to dual therapy | Dual therapy:  
Add to Metformin:  
Sulfonylureas or Thiazolidinedione  
DPP-4i or SGLT2-i or GLP-1 RA or | Triple therapy:  
Add to Metformin and Sulphonylurea:  
Thiazolidinedione or DPP-4i or SGLT2-i or GLP1RA or | Combination injectable therapy:  
Initiate basal insulin (usually with metformin or other oral anti-diabetic drug) |
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy is should not be considered if:</strong></td>
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<tr>
<td>HbA1c ≥ 9.0% (then dual therapy is to be considered).</td>
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<tr>
<td>HbA1c ≥ 10.0%, blood glucose levels ≥ 16.7mmol/L or patient is markedly symptomatic (Consider combination injectable therapy).</td>
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<td><strong>Step 2</strong></td>
<td>Basal insulin</td>
<td></td>
<td>Insulin</td>
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<tr>
<td>Adjust treatment to triple therapy if HbA1c target is not met within 3 months.</td>
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<td>OR</td>
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<tr>
<td>Add to Metformin and Thiazolidinedione: Sulphonylurea or DPP-4i or SGLT2-i or GLP1RA or Insulin</td>
<td></td>
<td></td>
<td>Add to Metformin and DPP4i: Sulphonylurea or Thiazolidinedione or DPP-4i or GLP1RA or Insulin</td>
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<tr>
<td>Add to Metformin and SGLT2-i: Sulphonylureas or Thiazolidinedione or DPP-4i or GLP1RA or Insulin</td>
<td></td>
<td></td>
<td>Add to Metformin and GLP1RA: Sulphonylureas or Thiazolidinedione or SGLT2i or</td>
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<tr>
<td>Hypoglycaemia: Determine and address the cause, if no cause found, down-titratedose by 4 units of 10 - 20%.</td>
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<td>If HbA1c not controlled, consider combination injectable therapy: Add 1 rapid-acting insulin injection before largest meal: Start: 4 units, 0.1 unit/kg or 10% basal dose. If HbA1c &lt; 8% consider to lower basal dose by same amount. Adjust: Increase dose by 1 - 2 units or 10 - 15% one or two times weekly until blood glucose target is reached. Hypoglycaemia: Determine and address cause, if no clear cause found; decrease dose by 2 - 4 units or 10 - 20%. OR Add GLP1RA: If the patient does not tolerate treatment adjust treatment to 2 injection insulin regimen.</td>
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<tr>
<td>Guideline</td>
<td>Step 1</td>
<td>Step 2</td>
<td>Insulin</td>
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<td>Add to Metformin and insulin; Thiazolidinedione or DPP-4i or SGLT2i or GLP1RA.</td>
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<td>OR</td>
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<td>Change to premixed insulin twice daily before meals:</td>
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<td>Start: Divide current basal dose into 2/3 in the morning and 1/3 in the evening or 1/2 in the morning and 1/2 in the evening.</td>
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<td></td>
<td>Adjust: Increase dose by 1 - 2 units or 10 - 15% basal dose one or two times weekly</td>
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<td></td>
<td>Hypoglycaemia: Determine and address the cause. If no cause is found decrease dose by 2 - 4 units or 10 - 20%.</td>
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<td>If HbA1c is not controlled:</td>
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<td>Consider either advancing to basal bolus or a third injection:</td>
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<td>≥ 2 rapid-acting insulin injections before meals.</td>
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<td></td>
<td></td>
<td>Start: 4 units, 0.1 unit/kg or basal dose or 10% basal dose/meal. If HbA1c &lt; 8% consider lowering basal dose by same amount.</td>
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<td></td>
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<td></td>
<td>Adjust: Increase dose by 1 - 2 units or 10 - 15% one to two times weekly to achieve blood glucose levels.</td>
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<td></td>
<td></td>
<td></td>
<td>Hypoglycaemia: Determine and address the cause and if</td>
<td></td>
</tr>
<tr>
<td>Guideline</td>
<td>Step 1</td>
<td>Step 2</td>
<td>Step 3</td>
<td>Step 4</td>
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<tr>
<td>no cause is found decrease dose by 2 - 4 units of 10 - 20%.</td>
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<tr>
<td>Change to premixed analogue insulin 3 times daily (breakfast, lunch, supper).</td>
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<td>Start: Add additional injection before lunch.</td>
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<tr>
<td>Adjust: Increase dose by 1 - 2 units or 10 - 15% one to two times weekly to achieve glucose target.</td>
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<tr>
<td>Hypoglycaemia: Determine and address cause and if no cause is found, decrease corresponding dose by 2 - 4 units or 10 - 20%.</td>
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</tbody>
</table>
## ANNEXURE H: MANAGEMENT OF MICROVASCULAR AND MACROVASCULAR COMPLICATIONS

<table>
<thead>
<tr>
<th>Complications</th>
<th>SEMDSA 2017</th>
<th>CDA 2018</th>
<th>ADA 2017</th>
<th>PHC STG EDL 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nephropathy</strong></td>
<td>Screening: Annual screening of: Random urine albumin:creatinine ratio and eGFR done annually. Urine dipstick annually</td>
<td>Screening Annual and baseline screening: Proteinuria Albumin:creatinine ratio and eGFR Serum potassium for patients using ACEi</td>
<td>Screening: Annual screening: Albumin:creatinine ratio and eGFR</td>
<td>Screening: Baseline and annual screening: Serum creatinine and eGFR Serum potassium and eGFR Urine dipstick</td>
</tr>
<tr>
<td></td>
<td>Treatment with ACEi or ARB in patients with established albuminuria</td>
<td>Treatment with an ACEi or ARB</td>
<td>Treatment with an ACEi.</td>
<td>Treatment with ACEi.</td>
</tr>
<tr>
<td><strong>Retinopathy</strong></td>
<td>Screening: Annual eye assessment</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Treatment: Maintain control of: Hyperglycaemia Hypertension Dyslipidaemia Refer to ophthalmologist</td>
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<tr>
<td><strong>Neuropathy</strong></td>
<td>Screening: Annual foot assessment</td>
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<td></td>
<td>Treatment: The use of anti-depressant (amitriptyline, duloxetine, venlafaxine) or anticonvulsants (pregabalin or gabapentin) may be used alone or in combination for pain relief.</td>
<td>Treatment: Pain relief for neuropathic pain with the use of anti-depressants such as amitriptyline, duloxetine and venlafaxine and anticonvulsants such as pregabalin, gabapentin or valproate are recommended. Opioids such as tramadol, morphine, oxycodone, tapentadol and</td>
<td>Treatment: Neuropathic pain can be relieved with the use of duloxetine and/or pregabalin. Further pain relieved with the use of tapentadol is also recommended.</td>
<td>Treatment: Neuropathic pain can be treated with the use of amitriptyline and/or paracetamol. Gastroparesis should be treated with metoclopramide.</td>
</tr>
<tr>
<td>Complications</td>
<td>SEMDSA 2017</td>
<td>CDA 2018</td>
<td>ADA 2017</td>
<td>PHC STG EDL 2014</td>
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<tr>
<td>Foot ulceration</td>
<td>Patients at risk of foot ulceration or amputation are to be referred to healthcare professionals trained in foot care.</td>
<td>dextromethorphan may be administered, however limited use is recommended due to the high risk of dependency and substance abuse. Further treatment also include referral to specialist HCPs trained in foot care. Foot ulceration should be treated with the use of antibiotics such as amoxicillin/clavulanic acid. also as wound care and education regarding footwear.</td>
<td>Gastroparesis can be treated with metoclopramide. Foot ulceration should be treated with antibiotics and wound care. Education regarding footwear should also be given. Referral to a podiatrist, orthopaedic or vascular surgeon is recommended.</td>
<td>Foot ulceration should be treated with amoxicillin/clavulanic acid. Referral to specialist care is recommended when the ulcer is associated with an abscess, cellulitis, crepitus or discoloration of the skin. Non-urgent referrals include ulcers that are associated with claudication or when ulcers are not responding to adequate treatment.</td>
</tr>
</tbody>
</table>

**Macrovascular complications**

- Treatment
- Aspirin
### ANNEXURE I: ANTI-DIABETIC DRUGS

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Glucose-lowering effects</th>
<th>Side effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Reduce hepatic and renal gluconeogenesis</td>
<td>Decreased endogenous glucose production</td>
<td>Gastrointestinal disturbances, Lactic acidosis</td>
<td>Renal and liver dysfunction, Irritable bowel syndrome, Hypersensitivity</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>Glipizide</td>
<td>Close K+ in beta cells increasing insulin release</td>
<td>Reduce circulating glucose, increase glycogen, fat and protein formation in patients with functioning beta-cells</td>
<td>Hypoglycaemia, Weight gain</td>
<td>History of severe hypoglycaemia, History of recurrent hypoglycaemia, Advanced liver disease</td>
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<tr>
<td></td>
<td>Glyburide</td>
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<td></td>
<td>Glimepiride</td>
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<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Acarbose</td>
<td>Inhibit alpha-glucosidases in the intestine</td>
<td>Reduction starch and disaccharides to monosaccharides and therefore lowers post prandial hyperglycaemia</td>
<td>Gastrointestinal symptoms</td>
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<td></td>
<td>Miglitol</td>
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<tr>
<td>Glucagon-like peptide-1 receptor agonist (GLP-1RA)</td>
<td>Liraglutide</td>
<td>Increase insulin secretion and suppression of glucagon by incretin effect.</td>
<td>Increased insulin secretion</td>
<td>Nausea and vomiting, Pancreatitis, Skin reactions</td>
<td>History of pancreatitis, History of pancreatic tumour, History of medullary thyroid cancer or multiple endocrine neoplasia</td>
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<tr>
<td></td>
<td>Exenatide</td>
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<tr>
<td>Glitinides</td>
<td>Repaglinide</td>
<td>Similar action to sulphonylureas, with</td>
<td></td>
<td>Hypoglycaemia</td>
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<td></td>
<td>Nateglinide</td>
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<tr>
<td>Class</td>
<td>Drug</td>
<td>Mechanism of action</td>
<td>Glucose-lowering effects</td>
<td>Side effects</td>
<td>Contraindications</td>
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<tr>
<td>Sodium-glucose co transporter (SGLT2-i) inhibitors</td>
<td>Canagliflozin</td>
<td>Reduction of renal glucose absorption by inhibiting the action of SGLT2</td>
<td>Increased urinary excretion of excess glucose and reducing plasma glucose levels in non-insulin dependent manner</td>
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<tr>
<td></td>
<td>Dapagliflozin</td>
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<td></td>
<td>Empagliflozin</td>
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<td></td>
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<td>some overlap in binding sites</td>
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<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
<td>Regulates gene expression by binding to PPAR</td>
<td>Reduces in insulin resistance.</td>
<td>Fluid retention</td>
<td>Age &gt;75 years</td>
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<tr>
<td></td>
<td>Rosiglitazone</td>
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<td></td>
<td>Mild anaemia</td>
<td>Congestive heart failure</td>
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<td>Increased risk of heart failure</td>
<td>Osteoporosis</td>
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<td>Dose related weight gain</td>
<td>History of bladder cancer or haematuria that has not been investigated</td>
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<td>Stage 4 or worse chronic kidney disease</td>
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<td>Insulin therapy</td>
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<tr>
<td>Glucagon-like polypeptidase-4 inhibitors (DPP-4i)</td>
<td>Sitagliptine</td>
<td>Blocks degradation of GLP</td>
<td>Reduces post meal glucose excursions by increasing glucose-</td>
<td>Rhinitis</td>
<td>History of pancreatitis or pancreatic tumour</td>
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<td></td>
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<td>Upper respiratory tract infections</td>
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<td>Headaches</td>
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<td></td>
<td>Pancreatitis,</td>
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<td>Allergic reactions</td>
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<tr>
<td>Amylin analogues</td>
<td>Pramlintide</td>
<td>Bind to amylin receptors</td>
<td>Reduces post-meal glucose excursions; lowering glucagon levels, slows gastric emptying and decreasing appetite</td>
<td>Nausea</td>
<td>History of pancreatitis or pancreatic tumour</td>
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<td></td>
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<td></td>
<td>Anorexia</td>
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<td>Hypoglycaemia</td>
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<td>Headache</td>
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</tbody>
</table>
### ANNEXURE J: SUMMARY OF STUDIES DONE ON CLINICAL INERTIA

<table>
<thead>
<tr>
<th>Title and author reference</th>
<th>Aim</th>
<th>Method</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical inertia in T2DM: Evidence from a large real-world dataset (Pantalone et al., 2018)</td>
<td>To evaluate for evidence of therapy intensification in patients with HbA1c levels exceeding treatment targets.</td>
<td>Electronic health records of patients who had HbA1c of ≥7% despite having been of a stable regimen of 2 oral anti-hyperglycaemic drugs for at least 6 months, were reviewed for 6 months following the index HbA1c%.</td>
<td>A total of 7389 patients’ records were reviewed. Of all patients, 62.9% did not receive treatment intensification. 4577 patients had HbA1c of 7 - 7.9 %, 71.6% did not receive treatment intensification. 1364 patients had HbA1c of 8 - 8.9%, 53.3% did not receive treatment intensification. 1448 patients had HbA1c of ≥9.0%, 44.4% did not receive treatment intensification.</td>
<td>Physicians are not responding quickly enough to evidence of poor glycaemic control in a high percentage of patients even in those with HbA1c levels far exceeding typical treatment targets. Therefore, these real-world findings confirm a high prevalence of clinical inertia with regard to T2DM management.</td>
</tr>
<tr>
<td>Therapeutic inertia in the treatment of hyperglycaemia in patients with type 2 diabetes: a systematic review (Khunti et al., 2017:427-437).</td>
<td>Identify how therapeutic inertia in glycaemic control was measured and to assess the extent of therapeutic inertia over the past decade.</td>
<td>Systematic review of articles published from 1 January 2004 to 1 August 2016.</td>
<td>In most of the studies the median time to treatment intensification after an HbA1c measurement above target for more than 1 year varied from 0.3 to 7.2 years. Therapeutic inertia further increased as the number of anti-hyperglycaemic drugs increased resulting in increased HbA1c levels. The majority of data came from Western countries, while studies in low-to-middle-income countries proved scarce.</td>
<td>Therapeutic inertia in glycaemic control in the management of T2DM is a major concern. The extent of therapeutic inertia is well documented in Western countries, corresponding data are urgently needed from low to middle income countries, with regard to the high prevalence of T2DM.</td>
</tr>
<tr>
<td>Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than</td>
<td>Determine the time to treatment intensification in patients with T2DM treated with one or</td>
<td>Retrospective cohort study based on 81753 patients with T2DM in the U.K. Clinical Practice Research Datalink for the period of Jan 2004 to</td>
<td>The median time for treatment intensification for patients with HbA1c above the cut-off point increased from 1.6 - 2.9 years in patients using 1 OAD to 6.9 – 7.2 years in patients taking 2</td>
<td>There are delays in treatment intensification in people with T2DM despite suboptimal glycaemia control. A substantial proportion of</td>
</tr>
<tr>
<td>Title and author reference</td>
<td>Aim</td>
<td>Method</td>
<td>Results</td>
<td>Conclusion</td>
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<td>----------------------------</td>
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<tr>
<td>80000 people (Khunti et al., 2013:3411-3417).</td>
<td>more oral antidiabetic drugs and the associated levels of glycaemic control</td>
<td>Dec 2006 with follow-up until April 2011</td>
<td>OAD. The median time to treatment intensification using insulin in patients using one, two or three OAD ranged from 6.0 – 7.1 years. The probability of treatment intensification in patients using OADs after follow-up ranged from 21.1 – 43.6% and intensification with insulin from 5.1 – 12.0%</td>
<td>people remain in poor glycaemic control several years.</td>
</tr>
<tr>
<td>Intensifications of diabetes therapy and time until A1C goals attainment among patients with newly diagnosed type 2 diabetes who fail metformin monotherapy within a large integrated health system (Pantalone et al., 2016: 1527-1534).</td>
<td>To evaluate the prevalence of clinical inertia, identify factors associated with clinical inertia and to quantify both the time until treatment intensification and the time until HbA1c control in newly diagnosed patients who did not achieve glycaemic targets after a period of at least 3 months of metformin monotherapy.</td>
<td>Retrospective review of patients with newly diagnosed T2DM in the period of 2005 to 2013 who failed to reach goal HbA1c after three months of metformin monotherapy. Using a time dependent survival analysis to compare the time until patients reach HbA1c goals in early intensification and late intensification (within 6 months of metformin failure). HbA1c goals were identified as 7%, 7.5% and 8.0%. Clinical inertia was defined as lack of intervention within 6 months after elevated HbA1c above baseline.</td>
<td>A total of 5239 patients met the inclusion and exclusion criteria. The time from baseline HbA1c measurement to time of intervention: For the overall cohort the median time until intervention was up to 14 months. The percentage of patients who experienced clinical inertia for HbA1c of &gt; 7%, &gt;7.5% and 8% were 38%, 31% and 28% respectively. The time until HbA1c was under control: Patients who underwent early intervention were more likely to have their HbA1c under control. Patients who underwent late intervention were more likely to not have their HbA1c under control.</td>
<td>A large number of newly diagnosed patients experienced clinical inertia (lack of intervention within 6 months of metformin monotherapy failure). Early intervention in patients when metformin monotherapy failed resulted in a higher probability of HbA1c goal attainment.</td>
</tr>
<tr>
<td>Primary care physician perspectives on basal insulin initiation and maintenance in</td>
<td>Describe perceptions of primary care physicians of patient reactions and concerns about insulin initiation and to identify</td>
<td>Cross-sectional, online survey of primary care physicians prescribing basal insulin to adults diagnosed with T2DM.</td>
<td>A total of 100 primary care physicians’ surveys were included: 85% of insulin initiation recommendations were originated by the primary care physicians.</td>
<td>The study identified opportunities for assisting patients in transitioning to insulin, which includes more frequent direct outreach to monitor insulin usage.</td>
</tr>
<tr>
<td>Title and author reference</td>
<td>Aim</td>
<td>Method</td>
<td>Results</td>
<td>Conclusion</td>
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<tr>
<td>patients with type 2 diabetes mellitus (Kalirai et al., 2018: 155-162).</td>
<td>opportunities for increased support.</td>
<td></td>
<td>96% offered both instructions on glucose monitoring and advice on lifestyle management. 35% provided insulin titration algorithms. 93% reported that their patients regularly took insulin within the first 3 months. 16% reported no outreach efforts to their patients 20% connected their patients with support groups.</td>
<td></td>
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<tr>
<td>Clinical inertia to insulin initiation and intensification in the UK: a focused literature review (Khunti &amp; Millar-Jones, 2016:3-12).</td>
<td>Review the evidence for clinical inertia and to identify the barriers and potential solutions.</td>
<td>Focused literature review of articles relating to clinical inertia in insulin initiation or intensification in T2DM patients using Pubmed, Scopus and Google Scholar.</td>
<td>Evidence for clinical inertia: Studies showed delayed insulin initiation and intensification associated with high HbA1c levels and longer disease duration and only 30% of primary care physicians personally initiated or intensified insulin. Barriers to guidelines adherence: Clinician level Limited awareness leads to overestimation of quality of care. Burden of management at primary care level leads to less specialised attention to address patient needs. Patient level Patient-level barriers include misconceptions, belief and fear of the use of insulin leading to non-compliance.</td>
<td>Clinical inertia with insulin intensification in diabetes is a global problem and even more so in the UK despite the availability of guidelines that outline the wide range of therapies.</td>
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<td>Title and author reference</td>
<td>Aim</td>
<td>Method</td>
<td>Results</td>
<td>Conclusion</td>
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<td>Awareness, agreement, adoption and adherence to type 2 diabetes mellitus guidelines: a survey of Indonesian primary care physicians (Widyahening et al., 2014)</td>
<td>Identify the degree of physicians’ awareness of agreement with adoption of and adherence to the T2DM guidelines in Indonesia.</td>
<td>Questionnaire survey among the general practitioners.</td>
<td>Of the total of 399 physicians who participated: 89% were aware of the existence of the guidelines. Awareness of each recommendation varied from 66 - 91%. 61% were aware of the recommendation to use a random glucose test for diagnostic purposes and 41% agreed with the recommendation. 48% adopted the recommendation of statin use and only 2% adhered to the recommendation.</td>
<td>High awareness of the Indonesian T2DM guidelines does not result to high levels of adoption or adherence to the guidelines important for outcomes and quality of care in T2DM management.</td>
</tr>
<tr>
<td>Type 2 diabetes control and complications in specialised diabetes care centres of six sub-Saharan African countries: The Diabcare Africa study (Sobngwi et al., 2012:30-36)</td>
<td>Collect standardised and comparable information for the evaluation of diabetes control, management and late complications in populations of patients diagnosed with DM at specialist clinics.</td>
<td>Cross-sectional descriptive study that included 2352 patients treated at specialist clinics for a minimum period of 12 months prior to the study.</td>
<td>Of the 2352 patients: 47% had HbA1c assessment in the past year. 29% achieved the goals HbA1c of 6.5%. 21% achieved BP within 130/80mmHG. 65% were treated for hypertension. 45% had fasting lipids assessment. 13% were treated for dyslipidaemia. 18% had retinopathy. 48% had neuropathy.</td>
<td>Only half of the patients received standard care, only a third had appropriated glycaemic control. This was, however, attributed to access to rather than quality of care.</td>
</tr>
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</table>
ANNEXURE K: AUTHOR GUIDELINES: PRIMARY CARE DIABETES

PRIMARY CARE DIABETES

Primary Care Diabetes is the official journal of Primary Care Diabetes Europe.

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DESCRIPTION

The journal publishes original research articles and high quality reviews in the fields of clinical care, diabetes education, nutrition, health services, psychosocial research and epidemiology and other areas as far as is relevant for diabetology in a primary-care setting. The purpose of the journal is to encourage interdisciplinary research and discussion between all those who are involved in primary diabetes care on an international level. The Journal also publishes news and articles concerning the policies and activities of Primary Care Diabetes Europe and reflects the society’s aim of improving the care for people with diabetes mellitus within the primary-care setting.

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AUDIENCE

General practitioners, nurses and other diabetes primary-care workers.

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4. Original Research Papers should be a maximum of 3000 words (not including up to 50 references and an abstract of up to 200 words structured according to Aims, Methods, Results, Conclusions and Keywords) with no more than five tables or illustrations. Papers should cover research or any other topics relevant to common diabetes conditions, chiefly clinical research with relevance to primary care and research in implementation of evidence-based guidelines. Copies of questionnaires used in the research should also be included. The text should be divided into sections headed Introduction, Methods, Results and Discussion. The Discussion should address the following issues:
   a) Difficulties encountered during this study;
   b) Alternative methodologies that would have been helpful in answering the research question;
   c) New questions arising from the study;
   d) Changes in your clinical practice as a result of the study.

5. Brief Reports should not exceed 1000 words, including a summary of no more than 50 words (but not including up to 20 references) and may be a preliminary report of work completed, a final report or an observation not requiring a lengthy write-up. A Brief Report may also be written in relation to a recent conference.

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