Prescribing patterns of hypoglycaemic drugs in the treatment of Type 2 Diabetes Mellitus in public institutions in Lesotho

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ABSTRACT

Title: Prescribing patterns of hypoglycaemic drugs in the treatment of Type 2 Diabetes Mellitus in public institutions in Maseru District of Lesotho

Keywords: Type 2 Diabetes Mellitus, antidiabetics, antihypertensives, prescribing patterns, Lesotho, prevalence, direct medicine treatment cost

The aim of the study was to evaluate type 2 diabetes mellitus (DM) medicine management in Government Clinics in Maseru, Lesotho. A two-dimensional research method was employed, consisting of a literature review and an empirical investigation. The objective of the literature review was to provide information on the pathophysiology, signs and symptoms, diagnosis, treatment and clinical management of DM. The empirical investigation consisted of a descriptive pharmacoepidemiological study, in which data for analysis was collected retrospectively from patients' medical records ("bukanas") at dispensing points, a using data collection tool. The selected study sites were Domiciliary Health Center, Mabote, Likotsi, and Qoaling filter clinics in Maseru district of Lesotho. Data on costs of antidiabetic agents was collected from purchase invoices provided by the pharmacy department of Domiciliary Health Center.

Results showed that the overall ratio of males to females was 1.3. There were no statistical difference in DM prevalence between males and females in the different clinics (p = 0.48). The mean age of males and females was 57.5 ± 14.2 years and 58.6 ± 11.3 years, respectively (Cohen's d = 0.07).

DM was more prevalent in patients 59 to 69 years for both males and females, with the exception of Mabote and Qoaling filter clinics, where DM was more prevalent in patients 49 to 59 years. These differences in prevalence were not statically significant. Overall, 20% (n = 69) of the study sample had DM alone, while 80.0% of patients had DM concurrently with hypertension. The odds ratio implicated that women were 1.7 times more likely to have hypertension concurrently with Type 2 Diabetes Mellitus.

The mean blood glucose level at 95% confidence interval for females and males were 10.1 ± 5.9 mmol/L (95% CI: 10.1–11.7) and 10.9 ± 6.2 mmol/L (95% CI: 11.0–14.0) respectively. The difference in the mean blood glucose levels of males *vs.* females was not statistically significant (p = 0.07). In both males and females there were outliers as high as 33.3 mmol/L.

Metformin 850 mg given three times, metformin 500 mg three times a day, glibenclamide 10 mg daily and glibenclamide 5 mg twice daily are oral hypoglycaemic agents that were first, second, third and fourth choice treatment of DM at all four study sites at a frequency of 54.2% (n = 160), 27.7% (n = 82), 4% (n = 12) and 2.7% (n = 27), respectively. Actraphane® 20 units in the morning and 10 units in the evening was prescribed at a frequency of 11.6% (n = 432) in comparison to other Actraphane®-containing regimens. The frequencies of prescribing metformin and Actraphane® as combination therapies represented 10.6% (n = 40), 7.1% (n = 27), and 6.6% (n = 25), respectively, for Actraphane® 20 units in the morning and 10 units in the evening, plus metformin 500 mg three times per day; Actraphane® 20 units in the morning and 10 units in the evening plus metformin 850 mg three times per day; and Actraphane® 30 units in the morning and 15 units in the evening plus metformin 850 mg three times per day.

The combination therapy of metformin and glibenclamide were prescribed at frequencies of 24.6% (n = 172), 22.9% (n = 160), and 13.4% (n = 94) respectively for glibenclamide 10 mg daily plus metformin 850 mg three times per day, glibenclamide 5 mg daily plus metformin 850 mg three times per day, and glibenclamide 5 mg once a day plus metformin 500 mg three times per day as first, second and third choice treatments at all study sites.

The total cost incurred for all the oral drugs prescribed alone within different regimens was M75.6 with the weighted average cost per patient of M0.81 ± 2.06 per day compared to the cost of Actraphane® which was M40 660.52 per month at a weighted average daily cost of M21.43 ± 6.23 per patient. The overall cost of Actraphane® and metformin combination therapy amounted to M50 676.50, at an average cost per patient of M21.77 ± 6.80 per day. The cost of combination therapy consisting of metformin and glibenclamide amounted to M377.10, at a weighted average cost amounting to M0.49 ± 0.16 per patient, per day.

Based on the results of this study some conclusions were reached on the prevalence of DM, prescribing patterns and the cost of antidiabetic agents. Recommendations pertaining to the clinics and further research were made.

OPSOMMING

Titel: Voorskryfpatrone van hipoglukemiese geneesmiddels in die behandeling van Tipe 2 Diabetes Mellitus in publieke instansies in Maseru Distrik van Lesotho

Trefwoorde: Tipe 2 Diabetes Mellitus, antidiabetiese middels, antihipertensiewe middels, voorskryfpatrone, Lesotho, voorkoms, direkte medisynebehandelingskoste

Die doel van die studie was om die bestuur van Tipe 2-Diabetes Mellitus (DM) medisyne in regeringsklinieke te Maseru, Lesotho, te evalueer. ‘n Twee-dimensionele navorsing metodologie is gebruik, wat bestaan uit 'n literatuuroorsig en 'n empiriese ondersoek. Die doel van die literatuuroorsig was om inligting oor die patofisiologie, tekens en simptome, diagnose, behandeling en kliniese bestuur van DM te voorsien. Die empiriese ondersoek het bestaan uit 'n beskrywende farmako-epidemiologiese studie, waarin data vir ontleding retrospektief versamel is uit pasiënte se mediese rekords (“bukanas”) by die resepteringspunte, met behulp van ’n data versamelingsinstrument. Die gekose studie-sentrums is Domiciliary Health Center, Mabote, Likotsi, en Qoaling filter klinieke in Maseru in Lesotho. Data oor die koste van antidiabetiese geneesmiddels is ingesamel vanaf aankoopfakture wat deur die apteek departement van Domiciliary Health Center verskaf is.

Resultate van die studie het getoon dat die totale verhouding van mans tot vroue 1.3 was. Daar was geen statistiese verskil tussen die aantal mans en vrouens in verskillende klinieke met betrekking tot DM voorkoms, nie (p = 0.48). Die gemiddelde ouderdom van mans en vroue was onderskeidelik 57.5 ± 14.2 jaar en 58.6 ±11.3 jaar (Cohen se d = 0.07).

DM was meer algemeen in pasiënte 59-69 jaar vir beide mans en vrouens, met die uitsondering van Mabote en Qoaling filter klinieke, waar DM meer algemeen in pasiënte 49-59 jaar was. Hierdie verskille in voorkoms was nie statisties beduidend nie. In totaal het 20% (n = 69) van die studiepopulasie slegs DM gehad, terwyl 80.8% van die pasiënte DM tesame met hipertensie gehad het. Die relatiewe kansverhouding impliseer dat vrouens 1.7 keer meer geneig was om hipertensie saam met tipe 2 Diabetes Mellitus te hê.

Die gemiddelde bloedglukosevlak met 95% vertrouensinterval vir vrouens en mans was onderskeidelik 10.1 ± 5.9 mmol/L (95% CI 10.1–11.7) en 10.9 ± 6.2 mmol/L (95% CI 11.0–14.0). Die verskil in die gemiddelde bloedglukosevlakke van mans en vroue was nie statisties beduidend nie (p = 0.07). In beide mans en vroue was daar uitskieters so hoog as 33.3 mmol/L.

Die orale hipoglisemiese geneesmiddels, metformin 850 mg gegee drie keer per dag, metformien 500 mg drie keer 'n dag, glibenklamied 10 mg daagliks en glibenklamied 5 mg drie maal per dag, was die eerste, tweede, derde en vierde keuse van behandeling vir DM in al vier studie-sentra teen 'n frekwensie van 54.2 % (n = 160), 27.7% (n = 82), 4% (n = 12) en 2.7% (n = 8), onderskeidelik. Actraphane® 20 eenhede in die oggend en 10 eenhede in die aand is voorgeskryf teen 'n frekwensie van 11.6% (n = 432) in vergelyking met ander Actraphane®-bevattende regimens. Die frekwensie vir die voorskryf van metformien en Actraphane® as kombinasie-terapie was onderskeidelik 10.6% (n = 40), 7.1% (n = 27) en 6.6% (n = 25) vir Actraphane® 20 eenhede in die oggend en 10 eenhede in die aand plus metformien 500 mg drie keer per dag; Actraphane® 20 eenhede in die oggend en 10 eenhede in die aand plus metformien 850 mg drie keer per dag; en Actraphane® 30 eenhede in die oggend en 15 eenhede in die aand plus metformien 850 mg drie keer per dag.

Die kombinasie terapie met metformien en glibenklamied is voorgeskryf teen frekwensies van 24.6% (n = 172), 22.9% (n = 160) en 13.4% (n = 94), onderskeidelik vir glibenklamied 10 mg per dag plus metformien 850 mg drie keer per dag; glibenklamied 5 mg plus metformien 850 mg per dag drie keer per dag; en glibenklamied 5 mg dagplus metformien 500 mg drie keer per dag, as eerste, tweede en derde keusebehandeling by al die studie-sentrums.

Die totale koste wat aangegaan is vir al die orale geneesmiddels wat alleen in verskillende regimens voorgeskryf is, het M75.6 beloop, teen ‘n gemiddelde koste van M0.81 ± 2.06 per pasiënt per dag, in vergeleke met die koste van Actraphane® wat M40 660.52 per maand beloop het met ‘n geweegde gemiddelde daaglikse koste van M21.43 ± 6.23 per pasiënt. Die totale koste van die Actraphane® en metformien kombinasie-terapie het M50 676.50 beloop teen 'n gemiddelde koste per pasiënt van M21.77 ± 6.80 per dag. Die koste van kombinasie-terapie met metformien en glibenklamied het M377.10 beloop, teen 'n geweegde gemiddelde koste van M0.49 ± 0.16 per pasiënt, per dag.

Gebaseer op die resultate van hierdie studie is 'n paar gevolgtrekkings bereik oor die voorkoms van DM, voorskryfpatrone en die koste van antidiabetiese middels. Aanbevelings met betrekking tot die klinieke en verdere navorsing is gemaak.

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LIST OF ABBREVIATIONS AND ACRONYMS

Acetyl Co-A:	Acetyl coenzyme A
ADA:	American Diabetes Association
ATP:	Adenosine triphosphate
CCF:	Congestive cardiac failure
CHAL:	Christian Health Association of Lesotho
CNS:	Central nervous system
DHC:	Domiciliary Health Center
DKA:	Diabetic ketoacidosis
DM:	Diabetes mellitus
DUR:	Drug utilisation review
END:	Endometriosis
FBG:	Fasting blood glucose
GDM:	Gestational diabetes mellitus
GFR:	Glomerular filtration rate
GIT:	Gastrointestinal tract
HbA1c:	Glycosylated haemoglobin
HLA:	Human leukocyte antigen
HTN:	Hypertension
ICA:	Islets cell antibodies
IDF:	International Diabetes Federation
IFG:	Impaired fasting glucose
LFC:	Likotsi Filter Clinic
LSTG:	Lesotho Standard Treatment Guidelines
MBT:	Mabote Filter Clinic
MHC:	Major histocompatibility complex
MNT:	Medical nutrition therapy
MOHSW:	Ministry of Health and Social Welfare, Lesotho
OGTT:	Oral glucose tolerance test
OHAs:	Oral hypoglycaemic agents
PPAR:	Peroxisome proliferator activated receptor gamma
PVD:	Peripheral vascular disease
QFC:	Qoaling Filter Clinic
SAS:	Statistical Analysis System

LIST OF ABBREVIATIONS AND ACRONYMS CONTINUED

SEMDSA:	Society of Endocrinology, Metabolism and Diabetes of South Africa
SUR1:	Sulfonylurea receptor1
HTN:	Hypertension

CHAPTER 1: INTRODUCTION AND STUDY OVERVIEW

The chapter gives an overall overview of the study. It provides the background information of the study problem with highlight of the situation in Lesotho. This chapter also states the problem statement and objectives.

1.1 BACKGROUND

Diabetes mellitus (DM) is one of the leading causes of death worldwide. By world ranking it is number 12 of diseases that cause death in humans. Its annual rate of diagnosis globally is reported to be on the ascendancy. As a result, the economic burden of diabetes on patients and governments are increasing (Kirigia *et al*., 2009:3). Kirigia *et al*. (2009:3) further pointed out that in Africa about seven million cases of DM in 2000 were reported of which Lesotho is included), resulted in a total economic loss of $25.51 billion. Kirigia and co-authors furthermore determined that this loss is not only due to treatment and other costs incurred by society in health system costs but also indirect costs from loss productivity because of disability and premature mortality, as well as intangible costs in terms of psychological pain to the family. By this computation, the disease appears to be exerting a heavy economic burden on society.

Lesotho has 10 national or government hospitals. These are distributed in all the ten districts of the country which are the Qacha's Nek, Quthing, Mohale's Hoek, Mafeteng, Maseru, Berea, Leribe, Botha Bothe, Mokhotlong and Thaba Tseka districts. In each national hospital there are surrounding clinics (Ministry of Health and Social Welfare (MOHSW), 2009:14). The Queen Elizabeth II hospital (herein referred to as Queen II) of Maseru district served as a referral hospital for the other nine district hospital. In 2012, the Government of Lesotho closed down Queen II and opened a referral hospital that is managed by Netcare and other private organisations. The referral hospital called "Queen 'Mamohato Memorial Hospital" has surrounding clinics namely Mabote, Qaoling and Likotsi filter clinics. There are still clinics in Maseru run by the government such as Domiciliary and Lesotho Defence Force clinics. There are other hospitals that are run by different missionaries under the administrative machinery of the Christian Health Association of Lesotho (CHAL), an association of mission hospitals in the country. These are found in many districts of the country. Like government hospitals, they have a number of clinics that serve the rural population surrounding them (MOHSW, 2009:14).

1.2 PROBLEM STATEMENT

Diabetes mellitus is defined by Porter *and Kaplan.* (2010) as an *"impaired insulin secretion and variable degrees of peripheral insulin resistance leading to hyperglycemia".* There are two main categories of DM, type 1 and type 2. Type 1 DM (also called juvenile-onset or insulin-dependent diabetes), is due to absolute insulin deficiency as a result of autoimmune pancreatic β-cell damage possibly triggered by an environmental exposure in genetically susceptible people. Type 2 DM (also called adult-onset or non-insulin-dependent diabetes), is mainly due to relative insulin deficiency, in the early stages of the disease, insulin levels are very high, as the disease progresses insulin resistance and increased production of glucose in the liver make insulin levels insuffient to regulate plasma glucose levels (Porter & Kaplan, 2010).

"The worldwide prevalence of diabetes for all age-groups was estimated to be 2.8% in 2000 and 4.4% in 2030" (Wild *et al.,* 2004:1047). "It is estimated that approximately 285 million people worldwide, or 6.6%, in the age group 20-79 years, will have diabetes in 2010, some 70% of whom live in low- and middle-income countries. The estimates for both 2010 and 2030 showed little gender difference in the number of people with diabetes. There are expected to be about one million more women than men with diabetes during 2010 (143 million women *vs*. 142 million men)" (Wild *et al.,* 2004:1047). The number of individuals with DM in Africa is also expected to double in the next 20 years from 12.1 to 23.6 million in 2030 (Bahendeka, 2010:2). According to Alqurashi *et al.* (2011:19) there are more women with diabetes than males because there is a high prevalence of obesity in females than in male with DM.

DM is a condition most Basotho men and women suffer from. It affects mostly women and is ranked among the top ten diseases causing death in Lesotho (MOHSW, 2007:1; MOHSW, 2006:1). In 2007 there were a total of 541 admissions of patients suffering from type 2 diabetes mellitus in the country, with a reported increase of 135 from 2006 (MOHSW, 2006:2; MOHSW, 2007:2). This number may double by the year 2030 according to results of the Bahendeka study (Bahendeka, 2010:2). With a current population of just over two million in Lesotho (World Health Organization, 2009:1), this is considered a significant number of people that will be suffering from the disease in the country. This will have a significant impact on prescribing patterns and use of antidiabetic medications as well as health budgets of the countries.

According to treatment guidelines of type 2 DM the first step in the management in its is a lifestyle intervention (Carter, 2008:284). International Diabetes Federation (IDF), 2005:35; Lesotho Standard Treatment Guidelines (LSTG), 2006:25). When lifestyle changes do not control the blood glucose to target levels, oral hypoglycaemic agents (OHAs) can be added. Metformin is the first drug of choice especially in obese patients with the option of adding a

second drug, often a sulfonylurea, when blood glucose target levels are still not met (LSTG, 2006:25). Two further options of drugs that can be considered are thiazolidinediones and α-glucosidase inhibitors (IDF, 2005:35). The patient can also be introduced to intensive insulin therapy. The rate of deterioration in such instances should be considered as it may warrant early use of insulin (Carter, 2008:284; LSTG, 2006:25). Comparing these guidelines with the 2009 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines and the stepped care approach by Kroon *et al.* (2008:50-62), they are similar with the above mentioned authors except that Kroon *et al*. and SEMDSA recommend early introduction of basal insulin, in the second stage with metformin.

A search of the literature yielded no publications with respect to studies done in Lesotho on the management of diabetes (MOH, 2010). One unpublished study has shown that at Queen II hospital patients with type 2 DM were often started on insulin even before they were prescribed OHAs (Marite, 2007:26). This mode of managing the disease was considered not to be in conformity with recommended treatment guidelines for the condition as outlined by Carter (2008:284) and LSTG (2006:82). Such mode of prescribing of the drugs as inferred from the author's (Carter, 2008:284; LSTG, 2006:82) indications may adversely impact on the effectiveness and costs of managing diabetes in Lesotho.

In view of the significant and increasing number of the Basotho population reported to be having or developing diabetes, it is speculated that costs of treating the disease will be high. Based on the study by Bahendeka (2010:2), these costs may actually triple within the next 20 years with a resultant deleterious effects on country's health budget. It is therefore essential to conduct a pharmacoepidemiological study to provide baseline information on the effectiveness and costs of antidiabetic agents in public health care sector in the country. Such information would be useful in making interventions required to ensure the cost effective use of these agents.

The research will try to answer the following questions:

- Is DM managed according to the Standard Treatment Guidelines of Lesotho at public clinics in Maseru Lesotho?
- Are diabetic treatment outcomes (blood glucose level) satisfactory as compared against the 2009 SEMDSA guidelines?
- What is the cost associated with the medicine management of patients with type 2 DM in Lesotho?

1.3 RESEARCH OBJECTIVES

The research objectives are divided into general and specific objectives**.**

1.3.1 General objective

The general objective aims to evaluate of Type 2 diabetes mellitus medicine management in Government Clinics in Maseru Lesotho.

1.3.2 Specific objectives

Both literature and empiric research was conducted within the confines of the specific objectives as indicated below.

1.3.2.1 Literature review objectives

The literature was searched with the specific objective of:

- Describing DM with respect to the classification, pathophysiology, diagnosis and signs, and symptoms.
- Discussing the clinical management guidelines of type 2 DM and expected clinical outcome.
- Discussing the pharmacological classifications of antidiabetic agents.
- Discussing the mechanism of action of antidiabetic agents.
- Documenting the side effects and interactions of the antidiabetic agents.
- Documenting interactions associated with of antidiabetic agents and other drugs.
- Comparing the clinical efficacy of antidiabetic agents.

1.3.2.2 Empirical research objectives

The specific research objectives of the empirical investigation were to:

- Determine the frequency of type 2 DM in government clinics in Maseru district of Lesotho, stratified by age and gender.
- Determine frequency of type 2 diabetes mellitus occuring with other chronic illnesses
- Determine the prescribing patterns and cost of antidiabetic agents used in the management of type 2 DM in government clinics in the Maseru district of Lesotho.
- Determine the average blood glucose levels achieved for both males and females, and compare these against the recommended guidelines by SEMDSA (2009), and

- Evaluate the treatment of type 2 DM in government clinics as against the recommended treatment guidelines of Lesotho.

1.4 RESEARCH DESIGN AND METHODOLOGY

1.4.1 Type and design of research

1.4.1.1 Study design

The study followed a descriptive pharmacoepidemiological design, in which data for analysis was collected retrospectively from the patients' medical records at dispensing points. Pharmacoepidemiology is the application of epidemiologic methods, measurements, analysis, and reasoning to the study and quality improvement of the uses and effects for drugs in a defined population, to optimise the benefit to risk balance in the medication usage and improve quality of health care (Waning & Montagne, 2000:47).

According to Sjoqvist and Birkett (2003:77), pharmacoepidemiology may be focused on drugs, with emphasis on the safety and effectiveness of individual drugs or groups of drugs, or utilisation-oriented aiming to improve the quality of drug therapy through pedagogic intervention. The two major approaches in conducting a pharmacoepidemiological research include observational and experimental studies (Waning & Montagne, 2000:44). Observational studies can be descriptive or analytic (Waning & Montagne, 2000:46). Observational studies provide details about the disease or patterns of drug usage by patients with different democraphic characterastics, place or time. The study designs in observational research include case control, case reports, cross-sectional and cohort studies, which can either be retrospective or prospective. This study followed a retrospective design as data were colleted from previously recorded bukanas.

According to Robert (2008:215), drug utilisation review (DUR) is defined as an "*authorized, structured, on-going review of prescribing, dispensing and use of medicatio*n". It comprises review of drug use against predetermined criteria that results in changes in drug therapy when these criteria are not met. Drug utilisation research is described as "*an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes"* (Wettermark *et al*., 2008:159).

According to Gama (2003:69) the aim of drug utilisation studies is "to evaluate factors related to the prescribing, dispensing, administering and taking of medication, and its associated events

(either beneficial or adverse)". DUR are classified into three main categories which include prospective, concurrent and retrospective studies (Robert, 2008:217). In this study retrospective drug utilisation research was applied to determine the use or frequency of prescribing the different antidiabetic agents and compare against the set standards such as LSTG and SEMDSA guidelines.

Retrospective DUR is assessment of treatment after the patient has received the medication (Robert, 2008:215). In retrospective design, the research question is conceived and studied using the data that were already collected or previous collected.

The advantages of using retrospective study design are use of historical data that have already been collected or recorded which becomes inexpensive to conduct. The benefit of the design is that the study can be conducted within a short period of time with easier access to a larger number of subjects (Waning & Montagne, 2000:48; WHO, 2003:2). "Retrospective DUR can also be used to detect the patterns of prescribing, dispensing, or administering drugs to prevent recurrence of inappropriate use or abuse and serves as a means for developing prospective standards and targets interventions" (Shalini *et al.*, 2010:806). However, the limitations include use of information and data that maybe less complete and accurate. In cases where subjects are interviewed, the subjects may not remember past information (Waning & Montagne, 2000:48).

1.4.1.2 Study site

A convenience sample of four filter clinics was chosen in the Maseru district of Lesotho. These included Mabote, Likotsi, Qoaling and Domiciliary filter clinics in Maseru district of Lesotho. They were chosen for the following reasons:

- They have the biggest patient population among all the clinics in the Maseru District.
- They are easily accessible to the researcher.

1.4.1.3 Research method

The study was divided into two main phases. Phase I was a literature review where all the relevant books, journals and publications were reviewed in line with specific objectives outlined in paragraph 1.3.2.

In the empirical investigation (phase two of the study), prescribing patterns of antidiabetic drugs and costs of medicine treatment were determined. Data were collected from the patients' files at dispensing points. Prescribed drugs and the blood glucose levels as measured during

patients' monthly clinic visits were recorded (refer to Appendix A1). Five research assistants were trained in the use of data collection tools used in collecting data for the study. The data collection process was supervised by the researcher to ensure the authenticity and quality of data collected. Data on costs of antidiabetic agents used at study sites were collected from purchase invoices of the drugs as provided by the pharmacies of the study sites. Drug costs per tablet were calculated and used to determine costs of courses of drug treatments (refer to Appendix A.2). The data collection process took one month starting from 1st to 31st July 2012. Data were analysed descriptively using the Statistical Analysis Systems (SAS) for Windows version 9.3 programme (SAS institute Inc., 2013). Results were presented using frequency tables, graphs, pie and bar charts.

1.5 ETHICAL CONSIDERATIONS

Permission was sought from the NWU Ethical committee (NWU-00004-12-S5) and from the Ministry of Health and Social Welfare Ethics Committee, Lesotho (refer to appendix A.4). The researcher obtained permission from Netcare management which runs the three government clinics (Mabote, Qoaling and Likotsi Clinics). The patients were given consent forms to complete before participating in the study (refer to Appendix A.3). Patient's codes were used in the data collection forms to maintain anonymity.

1.6 CHAPTER SUMMARY

This chapter gave a brief overview of the situation or background of Lesotho in terms of the problem under study. The chapter also outlined the research objective and also described the study methodology. The next chapter will provide the detailed information on DM through the search of relevant literature.

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CHAPTER 2: DIABETES MELLITUS PATHOPHYSIOLOGY, DIAGNOSIS, TREATMENT AND CLINICAL MANAGEMENT

2.1 INTRODUCTION

The previous chapter indicated the problem statement, together with the objectives. This chapter provides information as derived from the literature in line with the objectives of literature research and the research problem under study. Essentially the chapter presents the pathophysiology, signs and symptoms, diagnosis, treatment and clinical management of DM as reviewed from the literature. It also highlights the practices in the management of type 2 DM in Lesotho as recommended in the LSTG.

2.2 DIABETES MELLITUS

Under this section DM will be defined, its classification and pathophysiology will also be discussed.

2.2.1 Definition of diabetes mellitus

DM is defined as a chronic condition caused by a relative or an absolute lack of insulin. DM may be recognised with the symptoms such as thirst, polyuria, blurred vision and weight loss (Kroon *et al*., 2008:50-52). DM in its most severe form, as may be experienced particularly in type 1 DM, causes ketonemia and ultimately ketoacidosis. In type 1 DM, insulin production may become severely compromised or absent. The absence of insulin causes excessive mobilisation and accelerated conversion of free fatty acids into acetyl coenzyme A (Acetyl Co-A), a substrate for the production of ketone bodies, namely, acetone, and β-hydroxybutyrate increased production and accumulation of ketone bodies in the blood result in the ketonemia and the metabolic acidosis or ketoacidosis reportedly experienced in very severe forms of DM (Kumar & Clark, 1998:975). If DM is not treated; ketoacidosis may lead to stupor, coma and finally death (Kroon *et al.*, 2008:50-52).

2.2.2 Classification of diabetes mellitus

According to Amod *et al.* (2012:5), diabetes is classified based on both clinical stages and aetiology and types of hyperglycaemia. An elevated fasting glucose is divided into intermediate states which are impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) or type 2 DM. The aetiological types of diabetes are type 1, type 2 gestational diabetes and other

specific types of diabetes such as endocrinopathies and chemical or drug induced diabetes (Amod *et al.*, 2012:6).

Gestational diabetes mellitus (GDM) is glucose intolerance that occurs during pregnancy (Amod *et al*., 2012:6; Kroon *et al.*, 2008:50-52). Most patients with GDM have normal glucose levels within 6 weeks after delivery however, their risk of developing type 2 DM increases by 35-60% in 5 to 10 years period (National Diabetes Education Program, 2011:1). Pre-diabetes (impaired glucose tolerance (IGT) and/or IFG), is defined as "a condition in which individuals have a blood glucose level higher than normal but not high enough to be classified as diabetes" (Levitt *et al.,* 2005:30). According to the guidelines of the Society for Endocrine, Metabolism and Diabetes of South Africa (SEMDSA) (Levitt *et al*., 2009:1), IFG is a condition in which the fasting blood glucose (FBG) level is 5.6–6.9 mmol/L after an overnight fast. IGT is a condition in which the blood glucose level is 7.7–11.0 mmol/L after 2 hour oral glucose (Alberti, 2002:12). Patients with IGT and IFG have higher risk of developing DM of about 25-50% compared with normoglycaemic patients (Joshi *et al.*, 2008:22). The summary of the basic differences between type 1 and type 2 DM with regard to age of onset, pathogenesis, and clinical symptoms is shown in Table 2.1 (adapted from Kroon *et al*., 2008:50-55; Walker *et al.*, 2012:686).

Table 2.1: Basic differences between type 1 and type 2 diabetes mellitus based on age of onset, pathogenesis and clinical presentation

Characteristics	Type 1	Type 2
Synonyms for disease type	Insulin Dependent diabetes mellitus; juvenile onset diabetes mellitus	Non-insulin dependent diabetes mellitus; adult onset diabetes mellitus
Age of onset	Usually <30 years; peaks at 12-14 years; rare before 6 months	Usually >40 years, but increasing prevalence among the obese children
Pathogenesis	Associated with a certain human leukocyte antigen (HLA) type; presence of islets cell antibodies suggests autoimmune process	Defect in insulin secretion; tissue resistance to insulin; increased hepatic glucose output
Clinical presentation	Moderate to severe symptoms that generally progress relatively rapidly (days to weeks): polyuria, polydipsia, fatigue, weight loss, ketoacidosis	Rare, except in circumstances of unusual stress (e.g. infection. DM is often diagnosed on routine physical or dental examination
Onset of symptoms	Faster onset of symptoms	Slower onset of symptoms

2.3 PATHOPHYSIOLOGY OF DIABETES MELLITUS (DM)

Normal physiological effects of insulin form a basis of understanding the signs and symptoms of diabetes. Homeostatic mechanisms control the blood glucose levels in the ranges of 3.1 to 7.8 mmol/L. The central nervous system (CNS) uses glucose as a source of energy, of which a minimum of 2.2–3.3 mmol/L is required. When kidneys can no longer reabsorb glucose (concentration exceed 10.1 mmol/L), glucose spills into urine, resulting in frequent urination. Tissues such as muscles and fat, are dependent on insulin for glucose utilisation. In the absence of glucose, these tissues can not use as amino acids and fatty acids for energy (Smelter & Bare 2004:1151; Kroon *et al.*, 2008:50-54).

Glucose is a major stimulant of insulin release. The release is triggered by both nutrients intake and the release of gastro-intestinal hormones. In type 2 DM, insulin production decreases over a sustained period of time. Hyperinsulinaemia is able to maintain glucose levels for a certain period of time, but eventually the function of β-cells deteriorates and hyperglycaemia ensues (Walker & Whittlesea, 2012:686). The subsequent paragraph (paragraph 2.3.1) explains the effects of insulin on the metabolism of fat, carbohydrates and proteins.

2.3.1 Effects of insulin on fat, carbohydrates and protein metabolism

After food is ingested, blood-glucose concentration rise and stimulate insulin release. Once insulin is released it stimulates the utilisation of glucose, fatty acids, and amino acids and their change to storage forms in muscle and adipose tissue. The hormone also inhibits hepatic glucose production by suppressing glucagon and its effects on breakdown of fat and proteins (Rang *et al.*, 2003:385). In muscles, insulin promotes the uptake of glucose and its storage as glycogen. It also stimulates the uptake of amino acids and their conversion to proteins. In the adipose tissue, glucose is changed to free fatty acids and stored as triglycerides. Insulin prevents the metabolism of these triglycerides to free fatty acids, a form that may be transported to other tissues for utilisation (Kroon *et al.*, 2008:50-52; Rang *et al.,* 2003:382).

The effects of insulin on carbohydrates, fat and protein metabolism in liver, muscle and adipose tissue are summarised in Table 2.2 (adapted from Rang *et al*., 2003:382).

Table 2.2: Effects of insulin on fat, carbohydrates and protein metabolism

Type of metabolism	Liver cells	Fat cells	Muscle
Carbohydrate metabolism	• Increased gluconeogenesis • Decreased glycogenolysis • Increased glycolysis • Increased glycogenesis	• Increased glucose uptake • Increased glycerol synthesis	• Increased glucose uptake • Increased glycolysis • Increased glycogenesis
Fat metabolism	• Increased lipogenesis • Decreased lipolysis	• Increased synthesis of triglycerides • Increased fatty acids synthesis • Decreased lipolysis	-
Protein metabolism	• Decreased protein breakdown	-	• Increased amino acid uptake • Increased protein synthesis

2.4 PATHOGENESIS

This section entails a discussion on the origin of type 1 and type 2 DM.

2.4.1 Pathogenesis of type 1 diabetes mellitus

The pathogenesis of type 1 DM involve genetic and environmental factors that cause β-cell destruction, usually leading to absolute insulin deficiency (Inzucchi *et al.*, 2010:S62).

2.4.1.1 Genetics and environmental factors

Genes play an important role in the development of diabetes, particularly type 1DM (So *et al.,* 2000:69). Type 1 DM is closely associated with human leukocyte antigen (HLA) (also called major histocompatibility complex (MHC)), which are genes related to the immune system function. HLA regulates insulin production and processing, and confer risk of DM in together with MHC genes (Porter & Kaplan*,* 2010:3).

According to Porter and Kaplan (2010:3), the environmental factor that increases the risk of development of type 1 DM is congenital rubella infection. Up to 20% of children with this infection may develop diabetes later in life. Other viruses that have been linked to the onset of type 1 DM include the coxsackievirus, cytomegalovirus, Epstein-Barr virus and retroviruses (Porter & Kaplan, 2010:3).

2.4.2 Pathogenesis of type 2 diabetes mellitus

Type 2 DM is characterised by impaired insulin secretion and resistance to insulin action. In the presence of insulin resistance, glucose utilisation by tissues is impaired, hepatic glucose production is increased, and excess glucose accumulates in the circulation, causing hyperglycaemia (DeFronzo, 2004:791). This hyperglycaemia stimulates the pancreas to produce more insulin in an attempt to overcome insulin resistance causing more decline in the function of the pancreatic β-cells.

Genetic predisposition may play a role in development of type 2 DM. In spite of islets cell antibodies (ICA) being seen to be present, no association with HLA in the development of the condition has been established (Porter & Kaplan, 2010:3). Individuals with type 2 DM also show varying degrees of tissue resistance to insulin, insuffient insulin secretion, and increased basal hepatic glucose production. Environmental factors that highly play a role in insulin resistance include obesity and unhealthy lifestyles (Porter & Kaplan, 2010:3).

2.4.2.1 Causes of abnormal insulin secretion

Impaired insulin secretion is one of the factors that may lead to development of type 2 DM. According to Homsi and Lukic (1992:5), the causes of abnormal insulin secretion include the:

- Mutation in the gene for glucokinase. Glucokinase is a key enzyme in glucose metabolism in the β-cells and the liver. The mutation of glucokinase gene leads to the abnormal glucose sensing in the β-cells and impaired insulin secretion.
- Mutation in the transcription factors. Transcription factors regulate transcription of genes involved in β-cells metabolism.

2.4.2.2 Causes of insulin resistance

Insulin resistance is defined as “a condition in which insulin in the body does not exert sufficient action proportional to its blood concentration” (Kelley, 1997:2238). Insulin resistance is one of the factors that may lead to development of type 2 DM. According to Kelley (1997:2238), factors that may result in insulin resistance include preceptor defects, receptor defects, post-receptor defects and obesity. Both preceptor and receptor defects are rare abnormalities. In persons with pre-receptor defect, insulin, due to an abnormality in its molecular structure or certain antibodies is prevented from binding with a receptor. Receptor defect is an unusual autoimmune disorder in which antibodies directed against insulin receptors alter the affinity of the hormone and prevent its binding to the receptor. In patients with the defect, there is a decrease in available number of receptors. This results in such patients demonstrating syndromes of severe insulin

resistance. Post-receptor defects result from mutations in the insulin receptor genes that prevent the receptor from initiating the normal insulin signal transduction in the cell. The mutation causes abnormalities in the intracellular messenger mediating the effect of insulin and increased activity of protein tyrosine phosphatase which dephosphorylates the phosphorylated tyrosine needed for normal insulin receptor activation (Kelley, 1997:2244). Obesity causes insulin resistance as an environmental factor. Such resistances to insulin are more strongly linked to intra-abdominal fat, than fat in other depots such as liver and muscle (Flier & Maratos-Flier, 2008:608).

2.5 PREVALENCE AND EPIDEMIOLOGY OF DIABETES MELLITUS

In 1995 the WHO made estimates that 135 million people in the world were diabetic, with the expected increase of 154 million in 2000. A projection made by Wild *et al*. (2004:1047) indicates that there would be an increase in diabetic patients worldwide from 171 million in 2000 to 366 million in 2030. These estimations showed a rise of 2.8% in 2000 and 4% increase in 2030. Already in 2006, the IDF Atlas pointed to even higher current and future projections by estimating that in year (2006) 246 million (giving a percentage increase of 44%) people worldwide were diabetic, with an estimated increaseto 380 million by 2025 (more than 100% increase). Based on these estimates it is evident that diabetes prevalence is increasing in the world.

It was estimated in 2010 that about 285 million people worldwide, or 6.6%, in the range of 20-79 years had diabetes, 70% of of this people who live in developing countries (Sicree *et al*., 2004:7). In the same year Wild *et al.* (2004:1047) and Sicree *et al*. (2004:4) estimated “about one million more women than men with diabetes (143 million women *vs*. 142 million men) were expected”.

Diabetes was thought to be rare in sub-Saharan Africa (40 years ago), for instance, the reported prevalence in urban areas of countries such as Ethiopia, Ghana, Lesotho, Uganda and Malawi in the years 1960 and mid-1985, was below 1% (McLarty *et al.,* 1990:672). A recent study by Hall *et al.* (2011:13), however, indicates prevalence of type 2 DM rates of 0.6% and 12% in rural Uganda and urban Kenya, respectively. In these African countries, a low prevalence (0–7%) was established in Cameroon, Ghana, Guinea, Kenya, Nigeria, South Africa and Uganda and while Zimbabwe had the highest prevalence when compared with other countries (>10%). According to Sicree *et al*. (2004:4), between 2010 and 2030, there will be a 69% and 20% increase in numbers of adults with diabetes in developing countries and developed countries, respectively. It was reported in 2003 that developing countries worldwide accounted for 141 million people with diabetes (72.5% of the world total). With reference to Wild *et al.* (2004:1050)

between the years 2000 and 2030 the number of diabetic patients is estimated to double in Middle Eastern Crescent, sub-Saharan Africa, and India.

According to Rheeder (2006:20) increased prevalence worldwide is observed in the people older than 65 .Globally, comparison of males and females indicates that prevalence of diabetes is similar in men and women but there is a higher prevalence in men < 60 years of age and in women at older ages (Wild *et al.,* 2004:1047). In high income countries, DM is rated among the top ten leading causes of death (ranked number 8). The disease, however, is not one of the top ten causes of death in middle and low income countries (WHO, 2007). According to the IDF Diabetes Atlas (2011:3) the increase of diabetes in high income countries is associated economic development resulting in decrease physical activity and increased access to energy-rich diet.

It is estimated that from the prevalence of type 2 DM South Africa is between 3 and 28.7% (Rheeder, 2006:20), Durban and Cape Town had the highest prevalence 13% and 28.7% respectively.In 2003 IDF Diabetes Atlas reported a prevalence of 3.4% (24 million South Africans) in ages 20 to 79 (2003), with an expected increase of 3.9% by 2025 (Mbaya *et al*., 2006:2). Rheeder (2006:20) is of the opinion that this increase in diabetes is linked to the worldwide increase in obesity.

DM is a condition many Basotho suffer from. It affects mostly women and is ranked among the top ten diseases causing death in Lesotho (MOHSW, 2007:3; MOHSW, 2006:1). In 2007, there were a total of 541 admissions of patients suffering from type 2 DM in the country, with a reported increase of 135 from 2006 (MOHSW, 2006:2; MOHSW, 2007:2). With a current population of just over two million in Lesotho (WHO, 2009:1) this is considered a significant number of people suffering from the disease in Lesotho. Based on projections by the WHO (2008), 31 000 individuals in Lesotho had diabetes in 2000; by 2030 this number will increase to 42 000 (i.e. 7.2% increase).

2.6 SIGNS AND SYMPTOMS OF DIABETES MELLITUS

The signs and symptoms of type 1 and type 2 DM are similar, but they usually vary in intensity (Walker & Whittlesea 2012:688). The common clinical features of diabetes are increased thirst (secondary to increased plasma osmolality), increased urination (due to osmotic diuresis secondary to glucose in urine), glycosuria, tiredness and increased superficial infections such as genital candidiasis). The extent of severity of these signs and symptoms are outlined in Table 2.3 (adapted from Stephen *&* Papadakis*,* 2007:1223).

The symptoms are more pronounced in type 1 DM than in type 2 DM; however, the complications that occur over a long period of time, (such as peripheral neuropathy and recurrent blurred vision) are severe and common in type 2 DM than in type 1 DM (Stephen *&* Papadakis*,* 2007:1223).

Table 2.3: Clinical features of diabetes mellitus at diagnosis

Symptom	Type 1 diabetes mellitus	Type 2 diabetes mellitus
Polyuria and thirst	++	+
Weakness or fatigue	++	+
Polyphagia with weight loss	++	-
Recurrent blurred vision	+	++
Vulvovaginitis or pruritus	+	++
Peripheral neuropathy	+	++
Nocturnal enuresis	++	-
Often asymptomatic	-	++

A positive sign (+) indicate the presence of the symptoms. The more the number of + signs, the more intense is the symptoms. A negative sign (-) indicates the absence of a symptom.

2.7 DIAGNOSIS OF DIABETES MELLITUS

The aim of this section is to discuss DM diagnosis in line with signs and symptoms and blood glucose measurements associated with the condition. Clinical features of the disease and interpretations of blood glucose measurements in this aspect were reviewed and reported.

2.7.1 Clinical features of diabetes mellitus at diagnosis

The clinical features of DM at diagnosis and the extent to which these occur in the two types of diabetes, at the time of diagnosis are summarised in Table 2.3.

2.7.2 Methods of monitoring glycaemic control

This section entails the parameters used for monitoring blood glucose level.

2.7.2.1 Self-monitoring of blood glucose (SMBG)

Blood glucometers are used to measure fasting and random blood glucose levels. The recommended target of overall FBG and postprandial glucose is 4.0–7.0 mmol/L and 5.0–10.0 mmol/L, respectively (Amod *et al.,* 2012:S20). Blood capillary measurements are performed either by patients themselves or carried out in the health facilities using blood

meters. Most of the meters available in clinical settings are very precise; however, they differ in their speed, sample size and cost. (Masharani, 2012:1168). There are limitations associated with self-monitoring glucose system. These include:

- some meters requiring input of a code for each batch and with failures to enter such codes resulting in inaccurate readings,
- increased or decreased measured glucose levels due to corresponding increases or decreases in haematocrit concentrations, and
- limited ranges in glucose level calibrations due to accuracy of meters not being good for higher or lower glucose levels (the meter and test strips of some glucometers are calibrated over glucose concentrations ranging from 3.3 mmol/L to 8.9 mmol/L) (Masharani, 2012:1168).

2.7.2.2 Glycosylated haemoglobin (HbA_{1c})

Haemoglobin glycosylation occurs when haemoglobin is exposed to ambient glucose concentration in blood (Herfindal & Gourley, 2000:386). When the concentration of blood glucose increases, the percentage of HbA_{1c} increases because the red blood cells are freely permeable to glucose.

HbA_{1c} is "the weighted average of blood glucose levels during the preceding 120 days of the erythrocytes' life span, meaning that the glucose levels in the preceding 30 days contribute substantially more to the levels of HbA_{1c} than do glucose levels from 90–120 days earlier" (Amod *et al.,* 2012:S22). HbA_{1c} shows the average plasma concentration of glucose over the previous of 8 to 12 weeks (WHO, 2011).

HbA_{1c} assay is a well standardised test and useful measurement that can be used to assist in the choice of therapy and also predicting outcomes (Amod *et al*., 2012:S22). According to Herfindal and Gourley (2000:386), HbA_{1c} is an important measure of long term glycaemic control and is directly correlated to long term complications of diabetes.

Every patient should have a set HbA_{1c} target that should be in the ranges 6.5% and 7.5% based on their risk of developing macro- and micro-vascular complications (McIntosh *et al.,* 2005:23). According to Masharani (2012:1167), HbA_{1c} should be measured every 3 to 4 months so that adjustment of therapy can be made if HbA_{1c} is either subnormal or more than 2%. If the patients HbA_{1c} is at target and the treatment has not been altered, the HbA_{1c} can be checked every six months. If the HBA1c is above the target or the treatment has been altered or intensified, the HbA_{1c} can be checked after 3 months (Amod *et al.*, 2012:S21). There is direct relationship between HBA_{1c} and the average blood glucose levels determined from the continuous glucose

monitoring data (three months period) and from pre-prandial, post-prandial and bedtime glucose levels (Masharani, 2012:1167). In general a 1% increase in HbA_{1c} value correlates with the value of blood glucose increase by 1.8 mmol/L. For example a value of 6% HbA_{1c} would correlate with average blood glucose level of 6.7 mmol/L (Amod *et al.*, 2012:S22). Table 2.4 (adapted from Kroon *et al.,* 2009:50-56) shows the normal ranges of blood glucose concentrations in normal or non-diabetic patients, patients with impaired glucose tolerance, patients with IFG and diabetic patients. According to Kroon *et al.* (2009:50-56), a diagnosis of diabetes can be made when one of the following is present:

- Classic signs and symptoms of diabetes which help to classify as type 1 DM or type 2 DM (polyuria, polydipsia, ketonuria, and unexplained weight loss) combined with a random plasma glucose (RPG) ≥11.1 mmol/L.
- A fasting blood glucose (FBG) ≥7.0 mmol/L. Fasting means no caloric intake for at least 8 hours.
- After a standard oral glucose challenge (OGTT), the venous plasma glucose concentration is ≥11.1 mmol/L at 2 hours. The OGTT should be performed in patients with FBG ≥5.6 mmol/L and <7.0 mmol/L.

Table 2.4: Blood glucose concentrations of normal, impaired glucose tolerance, impaired fasting glucose and diabetic patients

	Fasting Plasma Glucose (FPG) (mmol/L)	**Random Plasma Glucose (RPG) (mmol/L)**	**Oral Glucose Tolerance Test (OGTT) 2hrs**	**2hr post OGTT**
Normal	<5.6	-	<11.1	<7.8
Impaired Glucose Tolerance	<7.0	-	<11.1	7.8-11.1
Impaired Fasting Glucose	5.6-6.9	-		
Diabetes	≥7.0	≥11.1	≥11.1	≥11.1

2.7.3 Diagnostic criteria: Oral glucose tolerance test (OGTT)

The diagnostic criteria for OGTTs as compiled by Kelley (1997:2238), includes the following processes: preparation, procedure and interpretation. The steps in performing OGTT are briefly described in subsequent paragraphs.

2.7.3.1 Dietary preparation for the oral glucose tolerance test

If the patient has not consumed a sufficient dietary carbohydrate diet (≥150 g) per day before the test, the insulin secretory response to the oral glucose test stimulus may not be as great as it should be, and the test results may be unreliable. Therefore a patient must consume a high carbohydrate diet (≥150 g) per day for a minimum of three full days before the testing. Other

factors for preparation include, 10–16 hour fasting, 10-hour abstinence from coffee, caffeine containing drinks, cigarettes, alcohol and vigorous exercise, and water consumption should be encouraged (Kelley, 1997:2238).

2.7.3.2 Oral glucose tolerance test procedure

Oral glucose is administered in a dose of 75 g (adults) or 1.75 g/kg body weight to a maximum of 75 g in children, consumed within 5 minutes. A fasting glucose baseline is obtained before glucose is consumed, thereafter blood samples are obtained at 30-, 60-, 90- and 120 minutes after glucose consumption is complete, for determination of plasma glucose (Haire-Joshua, 1996:276).

2.7.3.3 Interpretation of oral glucose tolerance test results

The interpretation of results from OGTT (Table 2.5, compiled from IDF, 2005; Kelley, 1997:2238) is classified into three categories: the normal glucose tolerance, impaired glucose tolerance, impaired glucose tolerance and the intermediate glucose tolerance.

Table 2.5: Interpretation of OGTT

Glucose level	Indication
2 Hour post glucose <7.8 mmol/L	Normal glucose tolerance
2 Hour post glucose between 7.8 and 11.1 mmol/l	Impaired glucose tolerance
2 Hours post glucose ≥ 11.1 mmol/L on repeated occasions	Diabetes mellitus
When the results of OGTT do not meet the criteria for normal, IGT or Diabetes	Intermediate glucose tolerance

OGTT; Oral Glucose Tolerance Test

2.8 COMPLICATIONS OF DIABETES MELLITUS

Uncontrolled blood glucose may lead to microvascular and macrovascular complications, or both (Porter & Kaplan, 2010:3). Short term complications, referred to as diabetic emergencies; include hyperglycaemia and ketoacidosis (Walker & Whittlesea, 2012:688). Microvascular and macrovascular complications and the combined effects of these complications as commonly encountered in diabetic patients are explained in sections 2.8.1, through 2.8.3.

2.8.1 Microvascular complications

According to Walker and Whittlesea (2012:692), microvascular complications are the three most common and devastating signs of DM, namely retinopathy, nephropathy and neuropathy.

Microvascular disease may also impair skin healing; this causes even minor breaks in skin to develop into deeper ulcers that are easily infected, particularly in the lower extremities such as feet. These complications will be briefly discussed in the following sections.

2.8.1.1 Diabetic retinopathy

Diabetic retinopathy is the most common cause of blindness in adult patients with diabetes. It is characterised initially by retinal capillary micro-aneurysms (a minute localised swelling of a capillary wall, which is found in the retina of patients with diabetic retinopathy) and later by macular oedema and neovascularization (abnormal or excessive formation of blood vessels as in some retinal disorders) (Barlow *et al.,* 1992:2384). The symptoms which vary from one person to another in terms of severity include focal blurring, vitreous or retinal detachment, and partial or total vision loss (Barlow *et al.,* 1992:2384). The primary effect of diabetes on the retina appears to be on its capillaries, with alterations in retinal blood flow and breakdown of blood retinal barrier (Haire-Joshua, 1996:240).

2.8.1.2 Diabetic nephropathy

Diabetic nephropathy is a leading cause of chronic renal failure. It is characterised by stiffening of the glomerular basement membrane, mesangial expansion, and glomerular sclerosis. These changes cause glomerular hypertension and progressive decline in glomerular filtration rate (GFR). Systemic hypertension may accelerate progression. Patients normally do not show symptoms until at a very late stage when they develop nephrotic syndrome or renal failure (Porter & Kaplan*,* 2010:3).

2.8.1.3 Diabetic neuropathy

Diabetic neuropathy is the result of “nerve ischemia due to microvascular disease, direct effects of hyperglycaemia on neurons and intracellular metabolic changes that impair nerve function” (Porter & Kaplan, 2010:5).The classifications of diabetic neuropathy which are based on its underlying pathophysiology (Porter & Kaplan, 2010:5) include the following:

- Symmetric polyneuropathy (with small- and large-fibre variants).
- Autonomic neuropathy.
- Radiculopathy.
- Cranial neuropathy and mono-neuropathy (Tripathi *et al.*, 2006:137; Porter & Kaplan*,* 2010:4).

These types of diabetic neuropathy are briefly discussed in subsequent paragraphs.

2.8.1.3.1 Symmetric polyneuropathy

Symmetric polyneuropathy is the most common type of neuropathy that affects the peripheral body parts such as the feet and hands; the symptoms among others include “dysesthesias, or a painless loss of sense of touch, vibration, proprioception, or temperature. In the lower extremities, these symptoms can lead to blunted perception of foot trauma due to ill-fitting shoes and abnormal weight bearing, which can in turn lead to foot ulceration and infection or to fractures, subluxation, and dislocation or destruction of normal foot architecture (Charcot's joint")” (Kumar & Clark,1998:982; Porter & Kaplan, 2010:4).

2.8.1.3.2 Autonomic neuropathy

Autonomic neuropathy can affect many systems of the body, including cardiovascular, gastrointestinal, genitourinary, and metabolic systems. its symptoms include “orthostatic hypotension, exercise intolerance, resting tachycardia, dysphagia, nausea and vomiting (due to gastroparesis), constipation, diarrhoea (including dumping syndrome), faecal incontinence, urinary retention and incontinence, erectile dysfunction and retrograde ejaculation, and decreased vaginal lubrication” (Tripathi *et al.*, 2006:137).

2.8.1.3.3 Radiculopathies

Radiculopathies presents with dermatomal pain and loss of cutaneous sensation. Although usually singular or unilateral, the syndrome may involve multiple dermatomal levels and may be bilateral in some cases. Radiculopathies is often associated with pain that is localised to the chest and also affects the abdominal wall (Haire-Joshua, 1996:270).

2.8.1.3.4 Mono-neuropathies

Mono-neuropathy is less common than poly-neuropathy and includes dysfunction of isolated cranial or peripheral nerves (Tripathi *et al.*, 2006:137). It causes finger weakness and numbness (median nerve) or foot drop (peroneal nerve). The carpal tunnel syndrome is the most common cause of sensory symptoms in the hands in diabetes, and appears to respond less well to decompression (Kumar & Clark, 1998:983).

2.8.2 Macrovascular diseases

The risk of macrovascular complications, including cardiovascular and peripheral vasculardiseases is 2–4 times higher for people with diabetes (Walker & Whittlesea, 2012:692).

The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of the arterial walls throughout the body (Fowler, 2008:79). These complications are briefly discussed in the subsequent sections.

2.8.2.1 Cardiovascular diseases

Cardiovascular diseases inclusive of hypertension, coronary heart disease and stroke are the most common cause of death in diabetic patients. They account for about 80% of deaths in patient groups (Walker & Whittlesea*,* 2012:692). Hypertension, a common cardiovascular disease manifesting in diabetic patients, is twice as common amongst the diabetic population as compared to the general population. It affects over 80% of those with type 2 DM and is a feature of the metabolic syndrome associated with insulin resistance (Walker & Whittlesea, 2012:692).

The most common heart diseases in patients of DM are due to arthrosclerosis (Masharani, 2012:1195). Patients with diabetes have a two- to four-fold higher risk of developing coronary heart diseases than individuals without diabetes (Ali *et al.*, 2010:584). Silent myocardial infarction is more common in patients with diabetes and may be due to cardiac autonomic neuropathy (Walker & Whittlesea, 2012:692).

2.8.2.2 Peripheral vascular disease (PVD)

Peripheral vascular disease affects the blood vessels in the periphery. In patients with diabetes, it often affects the arteries of the legs, giving rise to intermittent claudication and a cramping pain experienced on walking (Walker & Whittlesea*,* 2012:692). PVD is also responsible for much of the morbidity associated with diabetic foot ulcers.

2.8.3 Combined manifestations of macro and microvascular complications

Complications of DM can also manifest as combined effects of, malfunctioning micro- and microvascular systems. An infected diabetic foot ulcer is one such condition. Infected diabetic foot ulcers account for the largest number of diabetes-related hospitalisation and are non-trauma causes of amputation (Walker& Whittlesea*,* 2012:693). Foot problems develop as a result of combined effects of specific complications associated with diabetes. Complications of diabetes notably include the combined occurrence of sensory and autonomic neuropathy and peripheral vascular diseases in the presence of high blood glucose levels. The ulcers are prone to infection, with staphylococci and streptococci being the most commonly implicated pathogens (Walker & Whittlesea, 2010:694).

Neuropathic ulcers occur when the peripheral neuropathy causes loss of pain sensation. The ulcer can be deep but usually painless and are caused by trauma to the foot which is not noticed until after a significant damage has occurred. More than 80% of amputations occur after foot ulceration or injury resulting from diabetic neuropathy (Fowler, 2008:79). Ischemic ulcers on the other hand result from peripheral vascular diseases and poor blood supply causing a reduction in available nutrients and oxygen required for healing. Ischemic ulcers are painful and usually appear on the distal ends of the toe (Walker & Whittlesea, 2010:694).

2.9 DIABETIC EMERGENCIES

Hypoglycaemia and extreme hyperglycaemia causing ketoacidosis or a hyperosmolar hyperglycaemia state constitute the two acute emergencies associated with diabetes (Walker & Whittlesea, 2012:685). The symptoms and treatment of these two diabetic emergencies are discussed in paragraphs 2.9.1 and 2.9.2.

2.9.1 Hypoglycaemia

Hypoglycaemic symptoms are caused by release of counter-regulatory hormones predominantly adrenaline, noradrenaline, and glucagon, when the blood glucose is below 3.0 mmol/L (Walker & Whittlesea, 2012:689). According to Walker and Whittlesea (2012:689), the symptoms of hypoglycaemia occur in patients taking insulin or oral agents (in particular the long acting sulfonylureas).

2.9.1.1 Symptoms of hypoglycaemia

The symptoms of hypoglycaemia are normal physiological responses to a decrease in blood glucose and should alert the person to consume carbohydrates. These symptoms may be grouped into categories such as adrenergic, CNS and other symptoms. Adrenergic symptoms are associated with triggering of autonomic nervous system and release of adrenaline. They include sweating, trembling, tachycardia and palpitations. CNS symptoms on the other hand are those signs and symptoms associated with lack of glucose in the brain and its resultant cerebral dysfunction. They often manifest as faintness, loss of concentration, visual disturbance, confusion and coma. Other symptoms associated with hypoglycaemia are hunger, headache, and numbness (Berkow & Fletcher, 1992:1129).

2.9.1.2 Causes of hypoglycaemia

The most common causes of hypoglycaemia are either a decrease in carbohydrate

consumption, excess carbohydrate utilisation from unexpected exercise or an increase in circulating insulin and OHAs (Smelter & Bare, 2004:1178; Walker & Whittlesea, 2012:689).

2.9.1.3 Treatment of hypoglycaemia

If the patient is able to swallow safely without the risk of aspiration, then glucose should be given orally. In situations where the patient is unable to swallow, parenteral treatment with intravenous glucose (25 g) or intramuscular glucagon (1 mg) should be given (Walker & Whittlesea, 2012:685).

2.9.2 Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is characterised by uncontrolled hyperglycaemia, metabolic acidosis and increased total body ketones (Amod *et al*., 2012:S43). The liver metabolises non-esterified fatty acids to produce A (acetyl Co-A). As the capacity of the tricarboxylic acid cycle to metabolize acetyl Co-A is rapidly exceeded, ketone bodies, acetoacetate and hydroxybutyrate are formed in increased amounts and released into the circulation (Haire-Joshua, 1996:343; Walker & Whittlesea, 2012:690).

2.9.2.1 Signs and symptoms of diabetic ketoacidosis

The classic signs and symptoms of DKA include polyuria, polydipsia, hyperventilation and dehydration. Dehydration is usually apparent as a dry mucus membrane, absent tearing and poor perfusion. A fruity odour from the breath as results of exhaled ketones can often be detected. Extreme thirst, tachycardia, nausea, vomiting, hypotension, weakness and impaired consciousness can all be present in DKA (Haire-Joshua, 1996:345; Smelter & Bare, 2004:118).

2.9.2.2 Treatment of diabetic ketoacidosis

The therapeutic goals for DKA consist of improving circulatory volume and tissue perfusion, reducing blood glucose and serum osmolality toward normal levels, clearing ketones from serum and urine at a steady rate, correcting electrolyte imbalances and identifying precipitating factors (Haire-Joshua, 1996:346). The major procedures taken include:

- Fluid volume expansion or replacement using 0.9% sodium chloride to stabilise the circulation and maintain adequate urine production.
- Regular administration of insulin intravenously to correct hyperglycaemia, and
- Prevention of hypokalaemia and identification and treatment of any associated infection (Kitabchi *et al.,* 1999:3).

2.10 CLINICAL MANAGEMENT OF DIABETES MELLITUS

The aim of this section is to discuss the treatment guidelines and the goal of therapy for DM.

2.10.1 Overall goals of therapy

The major goal of therapy in the management of DM is to achieve normoglycaemia and alleviate patients of the signs and symptoms of the condition. (Amod *et al.*, 2012:S20; Levitt *et al*., 2009:507). For this purpose achieving targets of between 4.0 to 7.0 mmol/L for fasting or pre-prandial blood glucose levels, 5.0 to10.0 mmol/L for peak post-prandial glucose levels and an HbA_{1c} of ≤ 7 mg/dL have been recommended (Amod *et al.*, 2012:S20; Levitt *et al*., 2009:507).

2.10.2 Guidelines for management of type 2 diabetes mellitus

The treatment of DM disease must be individualised on the basis of the disease type and the specific needs of the individual patient. General principles of managing the condition as stated by Steven *et al*. (2007:1242) and Amod *et al*. (2012:S27) include:

- Beginning hypoglycaemic agents when lifestyle changes alone can not control the blood glucose at recommended levels.
- Initiating metformin therapy as an initial therapy of choice at the time of diagnosis in all patients, both overweight and of normal weight. Metformin reduces HbA_{1c} by 1–2%. It is recommended that the drug be continued even when other classes of drugs are added.
- Using sulfonylureas as a first line option in therapy when the HbA_{1c} is above target or when patients have normal weight or are intolerant to metformin or when they need rapid control of hyperglycaemic symptoms. Sulfonylureas reduce HbA_{1c} by 1–2%.
- Using α-glucosidase inhibitors as an alternative option in therapy when the patient is not responding to the first line regimen or in special circumstances, for example, when they are hypersensitive to metformin and the sulfonylureas.
- Increasing the doses and adding other hypoglycaemic agents, at frequent intervals (2–6 months) until the recommended blood glucose level is achieved.
- Insulin therapy may be added when the blood glucose control is not achieved using the above measures, however it may be added early despite the above recommendations.
- Using thiazolidinediones as an option when glucose control does not meet treatment targets and when the benefits outweigh the risks of its use. In such cases it is used in combination with to metformin as an alternative to sulfonylureas or as acombination therapy with

sulfonylurea where metformin is not tolerated or added to a combination of metformin and sulfonylurea.

A summary of guidelines for management of type 2 DM is outlined in Figure 2.1 (compiled from Amod *et al*., 2012:S38; Levitt *et al*., 2009:510; World Health Organization, 2006).

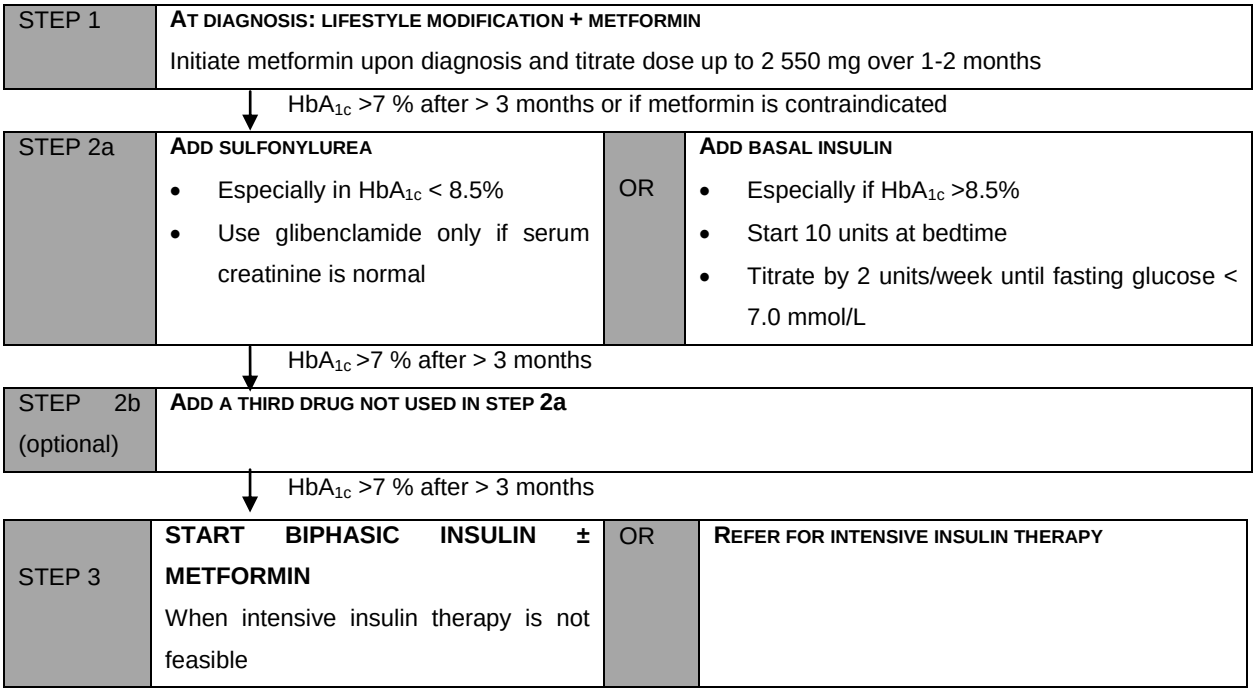


Figure 2.1: Guidelines in management of type 2 diabetes mellitus

In accordance with the Lesotho Standard Treatment (LSTG, 2006:88) diagnosis of DM must be based on FBG level. Patient management is started with non-pharmacological approaches such as weight reduction in obese patients and reduction in the intake of fatty foods. Non-pharmacological approaches are emphases at every stage of management of the disease. In the events of the patient not responding to this treatment option, metformin is initiated for obese patients and glibenclamide or gliclazide initiated for non-obese patients. Insulin injection is indicated for type 1 or uncontrolled type 2 DM, regardless the above measure (Standard Treatment Guidelines, 2006:89).

2.11 TREATMENT OF TYPE 2 DIABETES MELLITUS

Treatment strategies of DM include advice on nutrition, physical activity and drug therapy where necessary. These strategies will be discussed in paragraphs 2.11.1 and 2.11.2.

2.11.1 Diet

A well balanced, nutritious diet remains the fundamental element of therapy (Masharani, 2007:1230). According to Power (1996:36), medical nutrition therapy (MNT) plays a crucial role in therapy of individuals with diabetes. It embodies the following as its components:

- Assessing nutritional, medical, and social behaviours that influence food choices and medical conditions.
- Developing a nutrition prescription based on usual eating behaviours and medical needs.
- Providing self-care management training.
- Evaluating therapy outcomes.

For patients with type 2 DM, meal plans emphasises normalising plasma glucose and lipid levels as well as maintaining a normal blood pressure to prevent cardiovascular morbidity. The nutritional recommendations for diabetic patients (adapted from Masharani, 2007:1230; Power, 1996:38) are summarised in Table 2.6.

Table 2.6: The nutritional recommendations for people with diabetes

Nutrient	Recommendation
Carbohydrate	• The amount of dietary carbohydrate is the main determinant of insulin demand and is commonly used to determine the pre-meal insulin dose • The total amount of carbohydrate is more important than the source • Patients using fixed doses of insulin or hyperglycaemic medications (e.g. sulfonylureas) must eat meals containing consistent amount of carbohydrates to avoid hypoglycaemia
Sweeteners	• Non-nutritive sweeteners and sugar alcohols (e.g. mannitol, sorbitol) have been tested for safety in people with diabetes and are safe at approved daily intakes. • Nutritive sweeteners (fructose, sugar alcohols) have no advantage over sucrose
Fibre	• 25–35 g/day, same as general information
Sodium	• The American Diabetes Association (ADA) recommends a reduced sodium intake of <2 000 mg/day to help reduce the symptoms such as nephropathy and oedema.
Alcohol	• Moderate usage recommended, i.e. less than 2 alcoholic beverages daily for men and one drink per day for women. • Alcohol should always be taken with food to avoid its hypoglycaemic effect.
Proteins	• For adults without nephropathy, a protein intake of less than 1 g/kg of body weight, equivalent to about 10–20% of total energy intake is recommended. • For those with nephropathy, protein intake may need to be further restricted, but this requires a dietetic advice and supervision
Fat	• Cardiovascular disease is a major cause of morbidity and mortality in patients with diabetes. Therefore, a reduced fat diet (<30% of the total calories) with < 7% of calories from saturated fats is recommended. • The recommended cholesterol intake is less than 200 mg/day for patients with diabetes.

2.11.2 Physical activity

With reference to Herfindal and Gourley (2000:391), physical activity has many physical and psychological benefits and should be practiced in some form by diabetic patients. The benefits of physical activity in patients with type 2 DM are as follows:

- Improved glycaemic control.
- Decreased insulin resistance or improved insulin sensitivity.
- Increased cardiovascular fitness.
- Improved blood lipids.
- Improved blood pressure.
- Maintenance of weight loss.
- Reduced abdominal and overall fat percentage.
- Improved wellbeing.
- Decreased stress and anxiety (Amod *et al*., 2012:S18; Herfindal & Gourley, 2000:391).

According to Paul (2008:2), aerobic and resistance exercise over 6 months significantly improves HbA_{1c}. The patient should be advised to perform at least 150 minutes per week of moderate intensity aerobic physical activity. However patients should be educated on exercise induced hypoglycaemia (Paul, 2008:3).

2.11.3 Drug therapy

Under this section the medications used for treatment of type 2 DM are discussed under several categories which include biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones and insulin.

2.11.4 Oral hypoglycaemic agents (OHAs)

About 75% of people with type 2 DM, dietary and exercise alone do not produce adequate glycaemic control and oral hypoglycaemic therapy is required (Walker & Whittlesea., 2012:698). According to Herfindal and Gourley (2000:391) oral therapy is very efficacious in treating patients with type 2 DM. In this section, the different classes of OHAs, including their mechanisms of action and side effects, profile is discussed.

2.11.4.1 Biguanides

An example of a biguanide is metformin. Metformin is used either alone or in combination with other oral agents in treatment of patients with type 2 diabetes mellitus (Colin, 1999:M77).

2.11.4.1.1 Mechanism of action of metformin

Metformin (Glucophage®) is an antidiabetic agent reduces hyperglycaemia in patients with type

2 DM, by lowering both basal and postprandial plasma glucose. Metformin reduces the blood glucose by decreasing hepatic glucose production, decreasing glucose absorption from the gastrointestinal tract (GIT), and increasing glucose uptake and utilisation in the skeletal muscle (Brenner & Stevens 2010:396; Rang *et al*., 2003:388). Unlike the sulfonylureas, metformin does not cause hypoglycaemia in either patients with type 2 DM or normal subjects. Insulin secretion remains unchanged while fasting insulin levels and day long insulin response may actually decrease when a patient is managed with metformin (Kroon *et al*., 2009:50-10).

2.11.4.1.2 Side effects of metformin

The side effects associated with treatment with metformin are usually dose-related, affecting approximately one third of patients (Brenner & Stevens, 2010:396; Rang e*t al*., 2003:388). The most common of these which often transient and occur at the onset of therapy include a metallic taste in the mouth and gastrointestinal disturbances, including anorexia, nausea, vomiting, diarrhoea, abdominal discomfort. Vitamin B_{12} deficiency may occur in cases of prolonged use. Lactic acidosis is generally associated with the use of the biguanides but this is rather rare with metformin and may be experienced exclusively by patients with renal and hepatic failure (Katzung *et al.*, 2009:743; Porter & Kaplan., 2010:30).

2.11.4.1.3 Contra-indications of metformin

Metformin is contra-indicated in patients with renal disease or renal dysfunction, which may also result from other conditions such as cardiovascular collapse or shock, acute myocardial infarction, and septicaemia (Brunton *et al.*, 2008:1053). Patients with known hypersensitivity to metformin or, with conditions of metabolic acidosis, either acute or chronic, including DKA, should not be give metformin (Snyman, 2005:339). The drug should also be temporarily discontinued in patients undergoing radiologic studies involving intravenous administration of iodinated contrast materials as, the use of such products may result in acute alteration of renal function (Beers, 2005:814).

2.11.4.1.4 Drug-drug interactions associated with metformin

Metformin has been shown to cause hypoglycaemia in combination with cimetidine. Metformin is secreted through the kidneys, which is inhibited by cimetidine. (Snyman, 2005:339; Tatro, 2002:856). According to Tatro (2002:856), the interaction between metformin and cimetidine can occur within 24 hours of administering the two drugs. It is moderate but the effects can cause deteriorate the patients DM. A summary of metformin drug interactions are provided in Table 2.8.

2.11.4.1.5 Clinical dosages of metformin

According to Walker and Whittlesea (2012:699), the suggested regimen is to start with 500 mg daily for a week, followed by 500 mg twice daily for a week and then increasing the dose at weekly intervals until the desired hypoglycaemic response is achieved or intolerance occurs. The maximum recommended daily dose of metformin is 2.5 g divided into three doses with meals (Brunton *et al*., 2008:1053).

2.11.4.1.6 Clinical efficacy of metformin

The major clinical effect of metformin is to decrease fasting glucose levels, thereby reducing HbA_{1c} levels (Fowler, 2008:131). According to Dipiro *et al.* (2011:1278), metformin decrease of HbA_{1C} by 1.5% to 2%, a decrease in FBG by 3.5–4.4 mmol/L. Metformin retains the ability to reduce FBG levels when extremely high >16.8 mmol/L (Dipiro *et al.*, 2011:1278).

2.11.4.2 Sulfonylureas

The sulfonylureas are substituted aryl-sulfonylureas that differ by substitutions at the para-position on the benzene ring and at one nitrogen residue of the urea moiety (Brunton *et al*, 2008:1050). They are referred to as insulin secretagogues because of their ability to depolarise pancreatic β-cells, thereby opening voltage gated calcium channels, influx of calcium and the activation of secretory machinery that release insulin (Brunton *et al*., 2008:1039; Katzung *et al.*, 2009:738). They are classified into first and second generation drugs the latter are newer and more potent. Examples include:

- 1st Generation: tolbutamide, chlorpropamide, gliclazide.
- 2nd Generation: glimepiride, glipizide, glibenclamide (Porter & Kaplan, 2010:20).

With reference to Brenner and Stevens (2010:394) the second generation sulfonylureas are 100 times more potent than the first generation. The second generation drugs have fewer adverse effects and fewer drug interactions (Gutierrez, 2008:985).

2.11.4.2.1 Mechanism of action of sulfonylureas

Sulfonylureas stimulate insulin release from the pancreatic β-cells. These drugs bind to the sulfonylurea receptor-1 (SUR1) subunits and block β-cells inward rectifier adenosine triphosphate (ATP) sensitive potassium channels. The blockage prevents efflux of potassium and leads to β-cells depolarisation. The depolarisation opens voltage gated calcium channels, influx of calcium and the activation of secretory mechanisms that release insulin. Acting this

way, the drugs resemble physiological secretagogues as exemplified by glucose (Brunton *et al*., 2008:1039).

2.11.4.2.2 Side effects of sulfonylureas

The most common side effect of the sulfonylureas is hypoglycaemia. It is more common with the first generation than the second generation products. Other side effects commonly seen with the use of the drugs include nausea, vomiting, abdominal pain, diarrhoea, hypoglycaemia and weight gain. Less commonly, blood dyscrasias, demonstrating as agranulocytosis, haemolytic anaemia and thrombocytopenia, cholestatic obstructive jaundice, muscle weakness, headache and vertigo may also be encountered as side effects with the use of the sulfonylureas. Mild dermatitis may also occur with their use in some patients (Brenner & Stevens, 2010:394).

2.11.4.2.3 Contra-indications of sulfonylureas

Sulfonylureas are potentially harmful to the foetus; they cause severe hypoglycaemia at birth through stimulation of the foetal β-cells to release insulin. The drugs for this reason are contraindicated in pregnancy or in patients who may become pregnant (glibenclamide is an exception in this regard) (Rang *et al*., 2003:389). Long acting sulfonylureas (chlorpropamide and glibenclamide) should be avoided in elderly patients and those with impairment of liver or kidney function, as they increase the risk of hypoglycaemia (Battista, 2012:105).

2.11.4.2.4 Drug interactions of sulfonylureas

Several drugs can interfere with efficacy of sulfonylureas by influencing either their pharmacokinetics or pharmacodynamics, or both (Walker & Whittlesea, 2012:701). Loop and thiazide diuretics can for examples cause decreases in the effects of sulfonylureas. Other drugs that may enhance the action of sulfonylureas by causing hypoglycaemia include ethanol, androgens, β-blockers, chloramphenicol, fluconazole, histamine H_2-receptor antagonists and phenytoin (Brunton *et al*., 2008:1052; Tatro, 2002:1184). The interactions of sulfonylureas are summarised in Table 2.8.

2.11.4.2.5 Clinical dosages of sulfonylureas

The dosage of sulfonylureas should be individualised. In principle, the lowest possible dose required to attain the desired levels of blood glucose, without producing hypoglycaemia should be used (Walker & Whittlesea, 2012:701). The minimum and maximum doses of different sulfonylureas are presented in Table 2.7 (compiled from Walker & Whittlesea, 2012:701).

Table 2.7: Minimum and maximum daily doses of sulfonylureas

Drug	Minimum dose	Maximum dose
Tolbutamide	500 mg	3000 mg
Chlorpropamide	100 mg	500 mg
Glipizide	2.5 mg	40 mg
Gliclazide	40 mg	320 mg
Glimepiride	1 mg	6 mg
Glibenclamide	2.5 mg	15 mg

2.11.4.2.6 Clinical efficacy of sulfonylureas

The sulfonylureas reduce FBG by 3.3 to 3.9 mmol/L, with greatest reduction observed in patients with the highest FBG concentration on initiation of therapy (Luna & Feinglos, 2001:1750). Although the sulfonylureas vary in their potencies, they tend to lower HbA_{1C} to similar extends (approximately 1.5% points) as metformin (Fowler, 2007:132).

2.11.4.3 Thiazolidinediones (Glitazones)

Examples of thiazolidinediones include pioglitazone (Actos ®), rosiglitazone and troglitazone. According to Walker and Whittlesea (2012:703), rosiglitazone was withdrawn from United Kingdom market in 2010 because its use was associated with increased risks of cardiovascular disorders, including heart attacks and heart failure. Troglitazone similarly was withdrawn in 1997 because of the linkage of liver failure to a toxic metabolite of the drug. The only glitazone still available in the market is pioglitazone. Even with this glitazone an increased risk of bladder cancer has been associated with its use. Its use is recommended only when benefits of its use outweigh associated risks (Panikar, 2012:72).

2.11.4.3.1 Mechanism of action

Pioglitazone depends on the presence of insulin for its action as an antidiabetic agent. “It decreases insulin resistance in the periphery and in the liver, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output” (Gutierrez, 2008:983). Unlike the sulfonylureas, pioglitazone is not an insulin secretagogue. It is a potent agonist for peroxisome proliferator-activated receptor-gamma (PPARGγ). PPARG receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver, their activation modulates the transcription insulin responsive genes involved in the control of glucose and lipid metabolism (Porter & Kaplan, 2010:18). Stimulation of these receptors caused increased insulin sensitivity, reduced hepatic glucose production and increased peripheral

glucose usage (Grahame-Smith & Aronson, 2006:324).

2.11.4.3.2 Side effects of thiazolidinediones

The most common side effects of pioglitazone are oedema, increased plasma volume and weight gain particularly in patients with hypertension and cardiac failure (Brenner & Stevens., 2010:396; Porter & Kaplan, 2010:18).

2.11.4.3.3 Contra-indications of thiazolidinediones

Pioglitazone have been associated with development of heart and hepatic failure, they should therefore be used with caution in this group of patients (Brenner & Stevens, 2010:397).

2.11.4.3.4 Drug interactions of pioglitazone

Pioglitazone is metabolised by the cytochrome-P450 (CYP3A4) system and drugs that induce or inhibit this enzyme will therefore interact with pioglitazone. Ketoconazole, erythromycin, and fluconazole are cytochrome-P450 inhibitors and may increase the serum pioglitazone concentrations. Rifampicin and phenytoin on the other hand are cytochrome-P450 inducers and may decrease serum levels of pioglitazone in situations of concurrent administration of the drugs (Walker & Whittlesea, 2012:704). A summary of these drug-drug interactions are provided in Table 2.8.

2.11.4.3.5 Clinical dosages of pioglitazone

Pioglitazone is started at dosages of 15 mg daily (Brunton *et al.*, 2008:1054). According to Panikar (2012:73) the major link between pioglitazone and bladder cancer is when the drug is given for a duration of therapy >24 months and cumulative dose of >28 000 mg, giving a calculated average daily dose of 40 mg/day for this side effect to manifest.

2.11.4.3.6 Clinical efficacy of pioglitazone

Given for a period of about six months, pioglitazone decreases glucose levels by about 3.4–3.9 mmol/L and HbA_{1C} by up to 1.5% (Dipiro *et al.,* 2011:1279).

2.11.4.4 Alpha-glucosidase inhibitors

Acarbose is the first α-glucosidase inhibitor to be used therapeutically in regulating intestinal carbohydrate digestion and absorption (Colin, 1999:A7). Another α-glycosidase inhibitor in clinical use is miglitol. Acarbose is an oligosaccharide of microbial origin and miglitol is a desoxynojirimycin derivative (Kumar, 1998:7).

2.11.4.4.1 Mechanism of action of alpha-glucosidase inhibitors

In contrast to the sulfonylureas (refer to paragraph 2.10.2.2.1), glucosidase inhibitors do not promote insulin secretion. The α-glucosidase inhibitors act as competitive, reversible inhibitors of pancreatic alpha-amylase and membrane-bound intestinal α -glucosidase enzymes (Tripathi & Srivastava, 2006:142). Pancreatic alpha-amylase catalyses the conversion of starches to oligosaccharides in the lumen of the small intestine, while membrane-bound intestinal α-glucosidase hydrolyses oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharaides in the brush border of the small intestine. In diabetic patients, this enzyme inhibition results in a delayed glucose absorption and a reduced postprandial hyperglycemia (Brenner & Stevens, 2010:397).

2.11.4.4.2 Side effects of alpha-glucosidase inhibitors

The most common side effects associated with acarbose include flatulence, abdominal bloating and diarrhoea (Walker & Whittlesea, 2012:704). The side effects of α-glucosidase inhibitors reduce compliance in treated patients (Lorenzetti *et al.,* 2010:3014). These side effects are the result of the delivery of greater amounts of carbohydrate to the lower intestinal tract. According to Brenner and Stevens (2010:397), the α-glucosidase inhibitors exert an osmotic attraction for water in the lower intestinal tract, with subsequent metabolism by bacteria.

2.11.4.4.3 Contraindications of alpha-glucosidase inhibitors

Acarbose is contraindicated in patients with known hypersensitivity to the drug and in patients with the conditions such as DKA, cirrhosis inflammatory bowel disease, colonic ulceration, and partial intestinal obstruction or in patients predisposed to intestinal obstruction (Gutierrez, 2008:989). In addition, acarbose should not be used in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine (Katzung *et al*., 2009:680).

2.11.4.4.4 Drug-drug interactions of alpha-glucosidase inhibitors

Acarbose can increase the oral bioavailability of metformin by delaying absorption the gastrointestinal of this drug (Tatro, 2002:855). Miglitol similarly can decrease the absorption of ranitidine and propranolol. Intestinal absorbents (e.g. charcoal) may reduce the effect of acarbose and should therefore not be given concurrently (Gutierrez, 2008:999).

2.11.4.4.5 Clinical dosages of alpha-glucosidase inhibitors

Acarbose is given as a 25 mg dose with meals, three times a day (Asperheim & Favaro, 2012:170).

2.11.4.4.6 Clinical efficacy of alpha-glucosidase inhibitors

The efficay of α-glucosidase inhibitors is lesser when compared with other classes of OHAs. Compared to placebo, the drugs lower HbA_{1c} to extents of about 0.5% to1.0% (Fowler, 2007:133). With a reduction of FBG levels by 1.9 to 2.2 mmol/L, the α-glucosidase inhibitors have been documented to improve postprandial plasma glucose levels more than fasting glucose levels (Luna & Feinglos, 2001:1751).

2.11.4.5 Meglitinides

Meglitinides are benzoic acid derivatives with insulin releasing properties. They are referred to as post prandial glucose regulators, are useful for control of postprandial hyperglycaemia (Sattur, 2010:222). Examples of the agents are repaglinide and nateglinide. Repaglinide was the first member of the class. Nateglinide, a derivative of amino acid d-phenylalanine, was later introduced (Walker & Whittlesea, 2012:702).

2.11.4.5.1 Mechanism of action of meglitinides

The meglitinides act by stimulating the release of insulin from the pancreas, in the mechanism of action is the same as sulfonylureas (Brenner & Steven, 2010:394) (refer to paragraph 2.11.2.2.1).

2.11.4.5.2 Side effects of meglitinides

The primary side effect of meglitinides is hypoglycaemia. This can be serious enough to warrant a discontinuation of the drug (Brenner & Stevens, 2010:396). Other side effects include nausea

and vomiting, diarrhoea, constipation and dyspepsia (Brunton *et al.*, 2008:1053).

2.11.4.5.3 Contraindications of meglitinides

Both repaglinide and nateglinide should not be used in patients who are hypersensitive to the drugs and in patients with DKA with or without coma (Gutierrez, 2008:988).

2.11.4.5.4 Drug-drug interactions of meglitinides

According to Gutierrez (2008:988), there is an increased risk of hypoglycaemia when repaglinide is given together with azole antifungal drugs and antibacterials such as fluconazole.

2.11.4.5.5 Clinical dosage of meglitinides

Repaglinide is given as 0.5 to 4 mg daily doses before meals and in combination with other hypoglycaemic agents. Nateglinide on the other hand is given as monotherapy doses of 60 to 120 mg in divided doses (Gutierrez, 2008:986).

2.11.4.5.6 Clinical efficacy of meglitinides

The efficacy of repaglinide is of the same as that of the sulfonylureas. Nateglinide reduces HbA_{1c} concentrations by 0.5%–1.0% indicating a lesser effect when compared with sulfonylureas (Guiteirrez *et al*., 2008:988) (refer to Table 2.9).

Summaries of the interactions of different hypoglycaemic agents with other drugs and their severities and management procedures as well as the clinical efficacies of OHAs in reducing HbA_{1c} and FBG levels are provided in Table 2.8 (compiled from Baxter, 2011; Beers, 2005:815; Gutierrez *et al*., 2008:982;Tatro, 2002:856) and Table 2.9 (Luna & Feinglos, 2001:1749; Nathan *et al*., 2008:3)

Table 2.8: Interactions of oral hypoglycaemic agents with other drugs

Drug-drug interaction	Onset	Severity	Mechanism	Effect	Management
Metformin-cimetidine	Rapid	Moderate	Cimetidine reduces the renal clearance of metformin by inhibiting tubular secretion	Hypoglycaemia	Decrease or increase the dose of metformin when cimetidine is started or stopped respectively
Metformin-Acarbose	Rapid	Minor	Acarbose delays the intestinal absorption of metformin	Onset of metformin delayed after initial dose	No special precautions needed
Metformin-iodated contrast material	Rapid	Major	Iodated contrast materials induced renal failure can interfere with renal elimination of metformin	Increased risk of lactic acidosis	Co-administration of parenteral iodated contrast materials and metformin is contraindicated
Sulfonylureas-anticoagulants	Delayed	Moderate	Slowed metabolic degradation of chlorpropamide	Hypoglycaemia	Monitor the blood glucose and adjust the dosages accordingly
Sulfonylureas-Beta blockers	Delayed	Minor	Beta blockers especially propranolol increase the hypoglycaemic effects of sulfonylureas and also musk the symptoms of hypoglycaemia	Hypoglycaemia	Monitor blood glucose and observe for the clinical signs of hypoglycaemia
Sulfonylureas-cimetidine	Delayed	Moderate	Cimetidine inhibits metabolic degradation of sulfonylureas	Hypoglycaemia	Monitor blood glucose and observe the clinical signs of hypoglycaemia after initiation of metformin
Sulfonylureas-furosemide	Delayed	Minor	May decrease glucose tolerance	Hyperglycaemia	No special precautions needed
Sulfonylureas-phenytoin	Delayed	Minor	Phenytoin may cause an increase in blood glucose	Hyperglycaemia	Dosage adjustment may be required if hyperglycaemia develops
Sulfonylureas-ethanol	Rapid	Moderate	Ethanol prolongs glipizide activity by delaying glipizide absorption and elimination. Ethanol causes a **Disulfiram**-like reaction when given together with chlorpropamide	Hypoglycaemia **Disulfiram**-like reaction characteristics: facial flushing, headache, nausea and tachycardia	Counsel patients to avoid use ethanol together with sulfonylureas

Table 2.8: Interactions of oral hypoglycaemic agents with other drugs continued

Drug-drug interaction	Onset	Severity	Mechanism	Effect	Management
Sulfonylureas-magnesium salts	Rapid	Minor	Magnesium salts cause an increase absorption of sulfonylureas	Hypoglycaemia	If interaction is suspected adjust the dose accordingly
Sulfonylureas-methyldopa	Delayed	Rapid	Methyldopa may impair metabolic degradation of sulfonylureas	Hypoglycaemia	Monitor blood glucose. Adjust dose if necessary
Sulfonylureas-thiazide diuretics	Delayed	Moderate	Thiazide diuretics may decrease insulin tissue sensitivity and decrease insulin secretion	Hyperglycaemia	Monitor blood glucose and increase the dose of sulfonylureas
Sulfonylureas-tricyclic antidepressants	Delayed	Moderate	Pharmacological effects of sulfonylureas is increase	Hypoglycaemia	Monitor blood glucose if interaction is suspected and than adjust the dose accordingly
Acarbose-charcoal	Delayed	Moderate	Charcoal reduces the gastrointestinal absorption of acarbose	Hyperglycaemia	Avoid concurrent use
Insulin-selective beta blockers	Rapid	Minor	Inhibition of hepatic glycogenolysis	Hypoglycaemia	No clinical intervention require
Insulin- non selective beta blockers	Rapid	Moderate	Beta blockers mask clinical signs of hypoglycaemia	Prolonged hypoglycaemia with masked effects	Avoid use of non-selective beta blockers with insulin or monitor closely for signs of hypoglycaemia
Insulin-ethanol	Rapid	Major	Enhanced release of glucose and inhibition of gluconeogenesis	Hypoglycaemia	Advice moderate intake of ethanol with meals
Insulin-tetracyclines	Delayed	Moderate	Increased extra pancreatic response to insulin	Hypoglycaemia	Monitor blood glucose or adjust insulin dosage accordingly

Table 2.9: Clinical efficacy of oral hypoglycaemic agents

Class of OHAs	Reduction in HbA_{1c}%	Reduction in FBG (mg/dl [mmol/L])
Sulfonylureas	0.8-2.0	60-70 [3.3-3.9]
Meglitinides	0.5-2.0	65-75 [3.6-4.2]
Biguanides	1.5-2.0	50-70 [2.8-3.9]
Thiazolidinediones	0.5-1.5	25-50 [1.4-2.8]
Alpha-glucosidase inhibitors	0.7-1.0	35-40 [1.9-2.2]

2.11.5 Comparison of pharmacological groups of hypoglycaemic agents

Sulfonylureas tend to cause a more pronounced decrease in blood glucose levels than the biguanides. Patients on sulfonylureas should be cautioned regarding the signs and symptoms of hypoglycaemia (Fowler, 2007:132). Compared to the sulfonylureas, the meglitinides drugs appear to possess a lower propensity for hypoglycaemia (Fowler, 2007:132). Given the relatively poor efficacy of α-glucosidase inhibitors in comparison with other OHAs, α-glucosidase inhibitors are rarely used alone and are not recommended for use as first choice therapy for moderate to severe hyperglycemia. The α-glucosidase inhibitors are most useful when used with other OHAs (Luna & Feinglos, 2001:5).

2.11.6 Insulin

Insulin is a “51-amino-acid peptide made up of an α- and a β chain linked to a disulphide bond” (Battista, 2012:102). Synthesis of insulin occurs in the β-cells of the islets of Langerhans, produced as a high molecular weight precursor called pre-proinsulin (Kaplan & Pesie, 2010:737). Pre-proinsulin is transported to the Golgi apparatus where it undergoes proteolytic cleavage to produce insulin (Rang *et al.*, 2003:380).

2.11.6.1 Insulin preparations

Insulin for clinical use was made from pork (porcine) and beef (bovine) pancreas. Currently, it is almost entirely produced from human sources using recombinant DNA technology (Walker & Whittlesea, 2012:695). Insulin preparations are classified into rapid acting, short acting, intermediate and long acting, the classification is based on the onset and duration of action (Brenner & Stephens, 2010:392; Walker & Whittlesea, 2012:695). The preparations are summarised in Table 2.10 (Brenner & Stephens, 2010:393; Porter & Kaplan, 2010:20), with regard to onset, peak and duration of action.

Table 2.10: Onset, peak, and duration of action of human insulin preparations

Insulin preparation	Onset of action	Peak action	Duration of action
Rapid-acting			
Lispro, aspart, glulisine	5–15 min	45–75 min	3–5 h
Short-acting			
Regular	30–60 min	2–4 h	6–8 h
Intermediate-acting			
Isophane	About 2 h	4–12 h	18–26 h
Long-acting			
Glargine	4–8 h	10–16 h	16–20 h
Detemir	1–2 h	No peak	24 h
Premixed	1–2 h	No peak	14–24 h

2.11.6.2 Side effects of insulin preparations

Hypoglycaemia is a side effect of insulin therapy. The blood glucose levels at which patients develop symptoms of hypoglycaemia differ for individuals. Lipohypertrophy or the thickening of the subcutaneous tissue as a result of recurrent injection at the same site can also occur at the site of injection. Redness, swelling, or itching at injection sites is also common. Systemic allergic reactions rarely occur with the current universal use of highly purified insulin (Brunton *et al.,* 2008:1049; Walker & Whittlesea, 2012:698).

2.11.6.3 Drug-drug interactions of insulin

According to Brunton *et al*. (2008:1050), apart from oral hypoglycaemic drugs, other drugs that potentiate the hypoglycaemic effect of insulin are ethanol, β-blockers, tetracyclines and salicylates. The insulin drug interactions are summarised in Table 2.8.

2.11.6.4 Clinical dosages of insulin

Insulin requirement per day is often less than 20 units daily. Insulin therapy is usually started with a single daily dose of a long acting analogue of the preparation, giving a single dose at bedtime may be adequate for patients with early morning hyperglycaemia. Some patients benefit from using rapid acting insulin analogue after meals to control postprandial glycaemia (Walker & Whittlesea, 2012:697). The most common regimens include the following:

- Single injection regimen in which intermediate or long acting preparations are used.
- Two injection regimens in which again intermediate acting only, rapid or fast acting mixed with intermediate or premixed formulations are used.
- Three injection regimens in which also rapid or fast acting and intermediate acting preparations are given before breakfast or rapid or fast acting preparations given alone

before evening meal, and intermediate preparations given alone before bedtime, and

- Four injection regimens which involves giving rapid or fast acting preparations before every meal and long acting formulations once a day (Gutierrez, 2008:981).

2.11.6.5 Clinical efficacy of insulin

According to the United Kingdom Prospective Study (UKPDS, 1998:837), insulin induces lower FBG than OHAs but the response to HbA_{1c} is similar to OHAs.

2.12 CHAPTER SUMMARY

In this chapter, DM was defined, indicating the different types, with distinct emphasis on the difference between type 1 and type 2 DM. The pathogenesis, pathophysiology, diagnosis and complications of DM were discussed in detail.

The current and the past statistics of DM worldwide, sub-Saharan region and locally were also deliberated to indicate the prevalence and epidemiology of the disease. Further details were given on the clinical management of type 1 and type 2 DM putting emphasis on diet, physical activity and drug therapy. Chapter three will discuss the details of empiric investigation of the study.

CHAPTER 3: EMPIRICAL INVESTIGATION

3.1 INTRODUCTION

In chapter 2, the search of relevant literature to give a background overview of the problem under study and the objectives were described. The methodology used in the conduct of the empirical investigation phase of the research is outlined and described in detail in this chapter.

3.2 EMPIRICAL RESEARCH OBJECTIVES

The specific research objectives of the empirical investigation were to:

- Determine the frequency of type 2 DM in government clinics in Maseru district of Lesotho, stratified by age and gender.
- Determine the prescribing patterns and cost of antidiabetic agents used in the management of type 2 DM in government clinics in the Maseru district of Lesotho.
- Determine the average blood glucose of both males and females, and measure against the recommended guidelines by SEMDSA 2009.
- Evaluate the treatment of type 2 DM in government clinics as against the recommended treatment guidelines of Lesotho.

3.3 STUDY DESIGN

This study followed a **descriptive, retrospective cross-sectional study** design because the study evaluates the effects of hypoglycaemic agents on diabetic patient and also the prescribing patterns of hypoglycaemic agents. Waning and Montagne, (2000:44) describes a cross-sectional study as “a prevalence study that examines the relationships between a disease or drug use problem and other characteristics of people in a population at one point in time”. A retrospective DUR was conducted in this study to determine and compare the prescribing patterns against the LSTG to assess compliance.

3.4 DATA SOURCE

Data were obtained from patients’ treatment booklets or “bukanas”. Bukana is a patient personal booklet that is used for keeping medical records for outpatients. The doctor writes all medical information about the patient in this booklet Bukana remains in the care of the patients, who come with it during every hospital visit.

Data on the cost of hypoglycaemic agents were obtained from purchase invoices in the pharmacy department of Domiciliary Health Center (refer to Appendix A.2).

3.5 STUDY POPULATION

This section explains the rationale for the selection of the study population, and the processes used to select it. The subsequent paragraphs also explain the inclusion and exclusion criteria used in the study.

3.5.1 Rationale for selection of study population

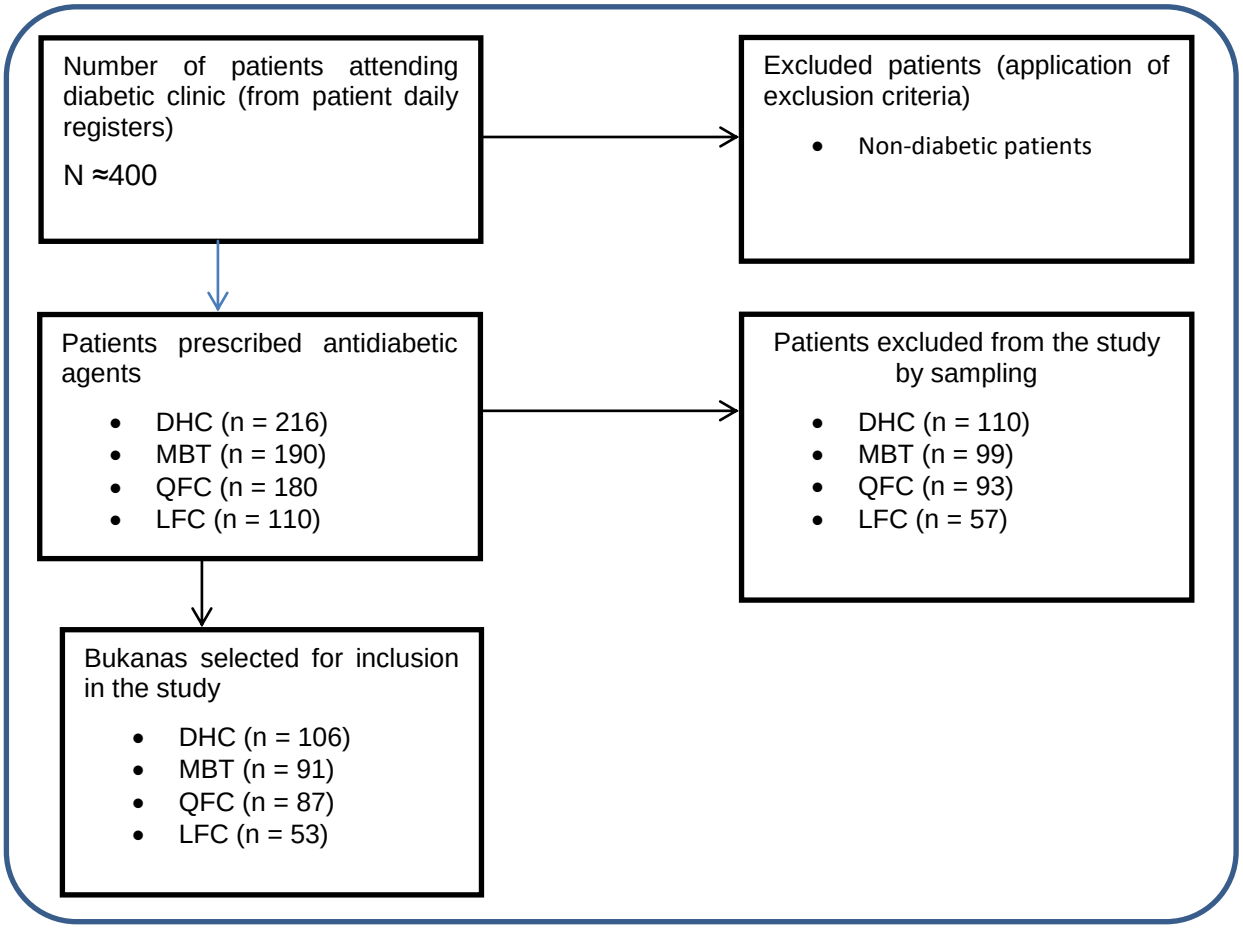
The study population included all diabetic patients attending diabetic clinic at Mabote, Likotsi, Qoaling and Domiciliary Filter clinics in the Maseru district of Lesotho. These clinics were selected as sites for the study for the reason that they have the largest patient attendance among all clinics in Lesotho.

3.5.2 Selection process of the study population

About 400 patients were estimated to attend diabetic clinics at Likotsi, Mabote, Qoaling and Domiciliary Clinics in a month. Of this number a sample size of about 200 study subjects was determined using the Stoker table (Strydom *et al*., 2005:196). This table indicates sample sizes expressed as percentages of study populations that can be used in studies involving given population sizes as the table indicates (Strydom *et al*., 2005:196). Selection of the study subjects was done in an alternating manner. By this arrangement, patients in odd number positions as they queue for their treatments were selected. As the patients' bukanas were taken by pharmacy personnel for refill during clinic visits, the researcher screened them to choose the ones that meet the selection criteria.

3.5.3 Inclusion and exclusion criteria

All type 2 DM patients that visited the diabetic clinics from 1st December 2011 to 1st June 2012 were included in the study. All patients who were not prescribed antidiabetic agents in the bukana were categorised as not having DM therefore were excluded in the study. Figure 3.1 shows a flow diagram illustrating the selection process of the study population.



DHC = Domiciliary Health Center; MBT = Mabote Filter Clinic; QFC = Qoaling Filter Clinic; LFC = Likotsi Filter Clinic, n = number of patients

Figure 3.1: Flow chart selection process of study subjects

3.6 DATA COLLECTION PROCEDURE

A stepwise approach using pre-designed data collection tools or questionnaires where appropriate (Strydom *et al.*, 2005:166) was adopted in procedures employed in collecting data. Data on patients' demography (gender, age and period of disease contraction) as well as prescribed hypoglycaemic drugs, other drugs concurrently prescribed and blood-glucose levels as recorded on patients' clinic visit dates were specifically collected. Patient treatment data were collected retrospectively from patient treatment booklets at pharmacies of study sites over a one month period starting from 11 June to 11 July 2012. A data collection tool (Appendix A.1) developed for the purpose was used. Data collected on drug treatments in the case of each individual patient expanded from the date of clinic attendance to a date marking a one year period of patient's clinic attendance in retrospect. To ensure that data was captured correctly, data collection was done consistently and systematically throughout the data collection process. According to Strydom *et al*. (2005:165), reliability of a measurement procedure is the stability or consistency of the measurement.

Data on costs of hypoglycaemic drugs used at study sites were collected from purchase

invoices provided by the pharmacies (2012 invoices) of the study sites using an appropriately designed data collection tool (Appendix A.2).

3.7 STUDY VARIABLES

The variables selected for analysis are outlined in the paragraphs that follow.

3.7.1 Age

Patient's ages were determined on the date of treatment, by subtracting the treatment date from the date of birth as indicated in the bukanas. Patients were categorised into the following age groups:

- Age group 1: ≥20, ≤ 29
- Age group 2: > 29,≤ 39
- Age group 3: > 39, ≤ 49
- Age group 4: > 49, ≤ 59
- Age group 5: > 59, ≤ 69
- Age group 6: > 69, ≤ 79
- Age group 7: > 79, ≤ 89

3.7.2 Gender

The number of males and females with DM in each clinic was identified.

3.7.3 Medicine cost

The cost of hypoglycaemic agents was calculated using data collected on costs of the agents used at the different study sites (refer to paragraph 3.6).

3.7.4 Blood Glucose

Fasting and random blood glucose levels were captured as recorded from the patients' bukana.

3.7.5 Blood Pressure

The systolic and diastolic pressures were captured as they appeared in the bukana.

3.7.6 Active ingredient

The active ingredients were used to identify the prescribed medications. The active ingredients in this study were metformin, glibenclamide, chlorpropamide and insulin. They were used to identify the antidiabetic agents prescribed.

3.8 PILOT STUDY

A pilot study was conducted at the Queen Elizabeth II Hospital to test the appropriateness of tool developed for collecting data from patients' bukanas. A total of thirty data records were in all collected from patients "bukanas". These were analysed and deficiencies in the use of the tool noted. The tool was then revised to address all noted shortcomings.

3.9 TRAINING OF RESEARCH ASSISTANTS

Research assistants who were final year students of Diploma in Pharmacy Technology at National Health Training College were trained in the use of both the data collection tools and the processes of screening patients' "bukanas" for relevant information to be collected from them.

3.10 DATA ANALYSIS

Data were captured using Microsoft excel 2010 and analysed using the Statistical Analysis System (SAS) version 9.3. Data were analysed using a descriptive statistics. Inferential statistics was used to establish practical significances of differences in blood glucose levels of patient groups treated with different types of antidiabetic drug treatment regimens.

3.10.1 Application of statistical tests/measures

The measurements used in this the study for data analyses are described in this section.

3.10.1.1 Mean

The mean is the most commonly used descriptive measure, all the values in the data are added and then the sum is divided by the total number of the individuals in the sample (Waning & Montage, 2000:83):

$$\mu = \frac{\sum x_i}{n}$$

Where μ= mean, $\sum$ = sum of, x_i = individual value, n = sample size

The mean was used in analysis of the blood glucose level.

3.10.1.2 Percentage

It is the proportion in relation to a whole which is usually the amount per hundred.

3.10.1.3 Ratios

A ratio shows the relative sizes of two or more values. The ratio was used in this study to compare the number of males to females in relation to DM and occurrence of other chronic illnesses.

3.10.1.4 Cramer's V

It is the correlation coefficient measuring the strength of association or dependency between two variables. The following scales were used for the interpretation:
0 - 0.30 = no relationship to weak relationship.
0.31 - 0.70 = moderate relationship.
0.71 - 1.0 = strong relationship.

Cramer's V was used to compare statistical significance between the numbers of males and females, different age groups and mean blood glucose for males and females in the study sites.

3.10.1.5 Cohen's *d*

It is a measure of effect size that is often used to compare the mean of one sample to another. It is defined as

$$d = \frac{\mu 1 - \mu 2}{\sigma}$$

Were μ1 = mean of the first population; μ2 = mean of the second population; σ = population standard deviation that is assumed to be common across both populations Cohen (1988:25).

The standard interpretation offered by Steyn (2012):
0.8 = large effect size
0.5 = moderate effect size
0.2 = small effect size

Effect size was used to compare the practical significance between diabetic males and females, age groups and the mean blood glucose for males and females

3.10.1.6 Odds ratios

Odds ratios (OR) are used to compare the relative odds of occurrence of the outcome of interest (in the case of this study is DM) (Szumilas, 2010:227).

$$\text{odds females} = \frac{\text{females with diabetes mellitus + hypertension}}{\text{females with diabetes mellitus only}}$$

$$\text{odds males} = \frac{\text{males with diabetes mellitus + hypertension}}{\text{males with diabetes mellitus only}}$$

$$\text{odds ratio} = \frac{\text{odds females}}{\text{odds males}}$$

Interpretation of the odds ratio:
OR = 1 Exposure does not affect odds of outcome
OR > 1 Exposure associated with higher odds of outcome
OR < 1 Exposure associated with lower odds of outcome

The odds ratio was used to analyse the occurrence of DM in males and females.

3.10.1.7 Weighted average

Petrie and Sabin (2005:16) describe the weighted average as “similar to an arithmetic mean; where instead of each of the data points contributing equally to the final average”, certain values of the variable of interest, ẋ, are more important or larger than others. The weighted average was calculated using Microsoft® Office Excel 2010. The following formula (Microsoft®, 2011a) was used:

Weighted average = SUMPRODUCT(Xi:Xn,Yi:Yn)/SUM(Yi:Yn)

where:
Xi = average of first observation
Xn = average of the last observation
Yi =frequency of the first observation
Yn = frequency of the last observation

The weighted average was used to analyse the cost of antidiabetic agents per patient.

3.10.1.8 Weighted standard deviation

The weighted standard deviation is calculated as the positive square root of the variance, though, employing the weighted variance of the weighted average (Kozak *et al*., 2008:27). The weighted standard deviation was calculated using Microsoft® Office Excel 2010 with the formula (Microsoft®, 2011b):

Weighted standard deviation = SQRT(SUMPRODUCT((Xi:Xn-Z)^2,Yi:Yn)/(SUM(Yi:Yn)-1))

where:
Xi = average of first observation
Xn = average of the last observation
Yi =frequency of the first observation
Yn = frequency of the last observation
Z = weighted average

3.11.2 Drug utilisation review (DUR) measurements

Under this section, the drug utilization measurements used in data analysis are explained.

3.11.2.1 Determining prescribing patterns of hypoglycaemic agents

Patterns of Antidiabetic agent prescribing stratified by age group, gender and study site were determined through descriptive statistical data analysis. A frequency table for the general prescribing of hypoglycaemic agents was constructed to display the frequencies of prescribing of respective hypoglycaemic agents either singly or in combination (refer to Tables 4.4–4.17).

3.11.2.2 Determining costs of treatments of diabetes

The cost of single and combination therapies of antidiabetic drugs were determined and tabulated (refer to Tables 4.18–4.21). Costs of antidiabetic agents as used in cost of treatment regimen determinations were based on costs of individual agents. Costs of individual agents were taken to be the same for all study sites since all these procure drug from a central store, the National Drug Service Organization (NDSO). The currency of Lesotho is Maloti (M). The Maloti is rated at a 1:1 basis with the South African Rand and both currencies are legally used within Lesotho (International Monetary Fund, 2008: 11). The drug utilisation review

measurements used include cost per tablet and cost per regimen. The calculations used to deduce the costs are as follows:

- $$\text{cost per tablet} = \frac{\text{cost of unit pack}}{\text{unit pack}}$$
- $$\text{cost per unit} = \frac{\text{cost of vial}}{\text{total number of uints (100IU)}}$$
- $$\text{cost per daily dosage regimen} = \text{cost per tablet} * \text{dosing interval}$$
- $$\text{monthly cost of treating with regimen (M)} = \text{Frequency of prescribing} * \text{cost per daily dosage regimen} * 30\text{days}$$
- $$\text{cost \%} = \frac{\text{cost of individual antidiabetic}}{\text{total cost of all antidiabetics}}$$

In this study the equations were used to calculate the cost of antidiabetic agents used by study sites.

3.11.2.3 Number of prescriptions

Counting of prescriptions is a measure in this study that is used to determine the frequency of prescribing. The prescriptions were further used to determine the prevalence of DM and other chronic illnesses.

3.11.2.4 Evaluation of the blood glucose level

The mean, standard deviation, median, minimum and maximum value of patients' blood glucose levels were determined using ANOVA. A boxplot graph was used to portray the distribution of blood glucose among males and females in the study (refer to Figure 4.7 and Table 4.3).

3.11.2.5 The prevalence of chronic illnesses

The percentages of individuals who have DM concurrently with other chronic illnesses such as asthma, congestive cardiac failure, and hypertension were calculated. The association of males and females with respect to having other chronic illnesses was described using odds ratios (refer to Figures 4.5 and 4.6).

3.11.2.6 Evaluation of prescribers' adherence to diabetic treatment guidelines

LSTG were used as an instrument in deciding on the conformity of prescriptions to recommendations in the treatment guidelines. The percentage of prescriptions compliant with STG recommendations was determined and interpreted as the degree of health care providers' adherence to treatment guidelines.

3.12 ETHICAL CONSIDERATIONS

Permission was sought from the NWU Ethical committee (NWU-00004-12-S5) and from the Ministry of Health and Social Welfare Ethics Committee Lesotho (Appendix A.4).

The researcher obtained permission from Netcare management which runs three of the government clinics, namely Mabote, Qoaling and Likotsi Clinics from which data was collected. Patients who took part in the study were given consent forms to fill prior to their participation in the study (refer to Appendix A.3). In addition to these codes were used for patient records in the data collection forms to maintain anonymity of participants in the study.

3.13 CHAPTER SUMMARY

In this chapter, the methodology used in the conduct of this research was described in detail and the procedural steps followed in the study explained. The other topics dealt with in this chapter included, the study design, the study population, data sources, reliability and validity of the data collection tools and the statistical methods of data analysis. Ethical considerations for the conduct of the research have also been covered. The results of the study and discussions thereof are presented in the chapter that follows.

CHAPTER 4: RESULTS AND DISCUSSIONS

4.1 INTRODUCTION

Chapter 3 reviewed the methods used in the empirical investigation phase of the study. This chapter provides a presentation of study results and ensuing discussions. This will be done with a focus on the following topic outlines embodying the specific objectives of the study:

- General characterisation of the study population
- Antidiabetic drug prescribing patterns
- Evaluations of antidiabetic drug treatment costs
- Blood glucose associations with age and gender
- Type 2 DM treatment evaluations in government clinics in Lesotho.

4.1.1 Notations on terms used in data analysis

Cost: in this study, cost excludes indirect costs.

Study site: the study site in this research refers to the clinics from which data had been collected for analysis. In this case they include Mabote Filter Clinic (MBT), Qoaling Filter Clinic (QTC), Likotsi Filter Clinic (LFC) and Domiciliary Health Center (DHC)

Single therapy: the term “single therapy” is used to designate treatment for patients given only one antidiabetic drug to control the blood glucose levels.

Combination therapy: the term “combination therapy” is used to designate treatment of patients using two or more antidiabetic agents The combinations started from drug one up to drug 12 (including both antidiabetic agents and non-hypoglycaemic agents); for this reason a single patient can fall under different combinations and this resulted in drug being counted more than once. This accounts for why there are more frequencies of prescribing than there are in the actual number of patients (refer to Table 4.1).

4.1.2 General outlay of the results presentation

Figure 4.1 shows a flow chart of the results presentation. Data will first be analysed according to patients’ demographic characteristics which includes age and gender. The second presentation of data will include the analysis of prescribing patterns with special focus on the frequency of prescribing antidiabetic drugs as single agents or in combination with other hypoglycaemic

agents. The prescribing patterns will also be analysed in relation to frequency of prescribing in different age groups and gender. Data will also be analysed according to the cost of each regimen used in treating diabetic patients in different study sites, with emphasis on the cost per daily dose and cost per combination.

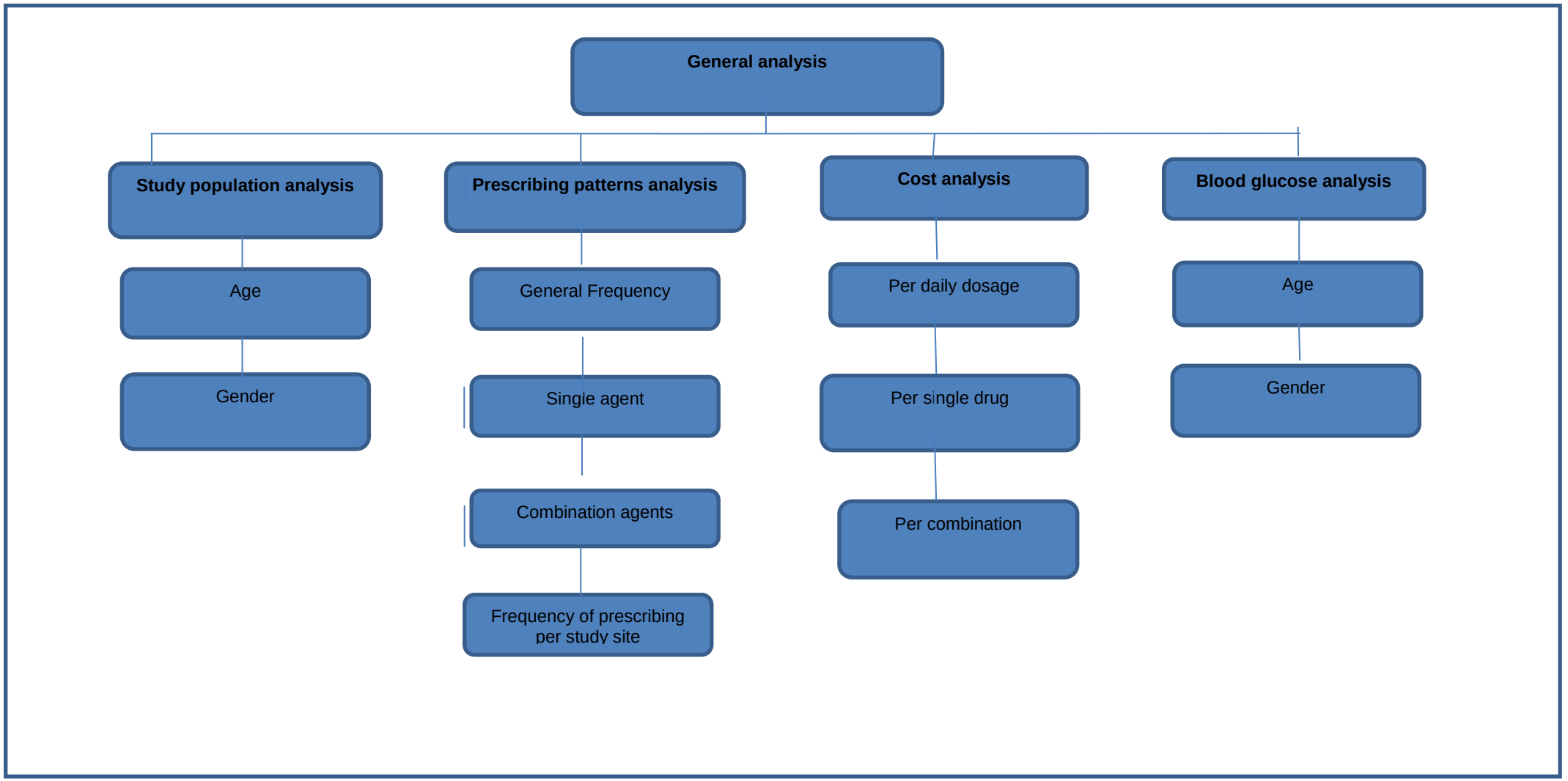


Figure 4.1: Flow chart of results presentation

4.2 ASSOCIATIONS BETWEEN PATIENT DEMOGRAPHIC FACTORS AND THE DEVELOPMENT OF DIABETES MELLITUS

The results of data analysis to establish prevalence of DM among patients with defined demographic characteristics are presented and discussed under this subsection of the chapter.

4.2.1 Results

Table 4.1 indicates the demographic characteristics of patients at different study sites. A total number of 337 patients altogether were entered into the study. From these patients, 31.5% (n = 106) were seen at the Domiciliary Health Centre, 15.7% (n = 53) from Likotsi Filter Clinic, 27% (n = 91) from Mabote Filter Clinic and 25.8% (n = 87) from the Qoaling Filter Clinic. Overall, 89 were males and 248 were females giving an overall ratio of 1:3 of males to females with DM (N = 337).

The percentage distribution of diabetic patients according to gender and age groups across all four sites of study are shown in Figures 4.2 through 4.4. Figure 4.5 similarly shows the percentage distribution of patients according to chronic diseases they were having concurrently with DM. Observed as essential findings were that:

- The mean age of males and females were 57.5 ± 14.2 years and 58.6 ± 11.3 years respectively (Figure 4.2).
- The highest prevalence of 30.2% (n = 248) and 34.8% (n = 89) of DM in that order occurred among women in the age group of >49 ≤ 59 years and among men in the age of >59 ≤ 69 years (Table 4.1).
- In the exception of age group 1 (> 20 ≤ 29) which has more male than female patients with diabetics, a higher number of female than male patients were observed to develop diabetes in all age groups (Table 4.2).
- Seventeen per cent (n =57) of total number of patients studied had diabetes without any concurrent chronic disease while up to 83% (n = 281) had the disease occurring concurrently with hypertension (Figure 4.5).
- Small percentages of 2.1% (n = 7), 0.9% (n = 3) and 0.3% (n= 1) had the disease occurring concurrently with asthma, epilepsy and congestive failure or endometriosis, respectively (Figure 4.5).
- More females (82.2% (n = 248 females with DM)) than males (73% (n= 89 males with DM)) have type 2 DM concurrent with hypertension (Figure 4.6).

Table 4.1 indicates the distribution of patients with in the study sites according to demographic characteristics.

Table 4.1: Distribution of patients' characteristics per study site

GENDER	AGE-GROUP (years)	SITE									
		DHC (n = 83)		LFC (n = 37)		MBT (n = 58)		QFC (n = 70)		Total (N = 248)	
		N	%	N	%	N	%	n	%	N	%
F	> 20, ≤ 29	1	1.2	0	0.0	0	0.0	1	1.4	2	0.8
	> 29, ≤ 39	2	2.4	1	2.7	4	6.9	4	5.7	11	4.4
	> 39, ≤ 49	15	18.1	8	21.6	9	15.5	12	17.1	44	17.7
	> 49, ≤ 59	22	26.5	11	29.7	20	34.5	22	31.4	75	30.2
	> 59, ≤ 69	23	27.7	14	37.8	15	25.9	13	18.6	65	26.2
	> 69, ≤ 79	17	20.5	3	8.1	8	13.8	14	20.0	42	16.9
	> 79, ≤ 89	0	0.0	0	0.0	2	3.4	4	5.7	6	2.4
	Unknown age	3	3.6	0	0.0	0	0.0	0	0.0	3	1.2
F Total		**83**	**100.0**	**37**	**100.0**	**58**	**23.4**	**70**	**100.0**	**248**	**100.0**
		DHC (n = 23)		**LFC (n = 16)**		**MBT (n = 33)**		**QFC (n = 17)**		**Total (N = 89)**	
		N	**%**	**N**	**%**	**N**	**%**	**n**	**%**	**N**	**%**
M	>20, ≤ 29	2	8.7	0	0.0	2	6.1	0	0.0	4	4.5
	>29, ≤ 39	2	8.7	0	0.0	3	9.1	3	17.6	8	0.9
	>39, ≤ 49	5	21.7	0	0.0	4	12.1	0	0.0	9	10.1
	>49, ≤ 59	3	13.0	6	37.5	8	24.2	4	23.5	21	23.6
	>59, ≤ 69	6	26.1	7	43.8	11	33.3	7	41.2	31	34.8
	>69, ≤ 79	4	17.4	3	18.8	5	15.2	1	5.9	13	14.6
	>79, ≤ 89	0	0.0	0	0.0	0	0.0	2	11.8	2	2.2
	>89, ≤ 99	1	4.3	0	0.0	0	0.0	0	0.0	1	1.1
M Total		**23**	**100.0**	**16**	**100.0**	**33**	**100.0**	**17**	**100.0**	**89**	**100.0**
Total		**106**		**53**		**91**		**87**		**337**	

DHC = Domiciliary Health Center; MBT = Mabote Filter Clinic; LFC = Likotsi Filter Clinic; QFC = Qoaling Filter Clinic; F = Females, M = Males, n = number of patients.

Figure 4.2 indicates the percentage of diabetes mellitus in four study sites, comparing males and females.

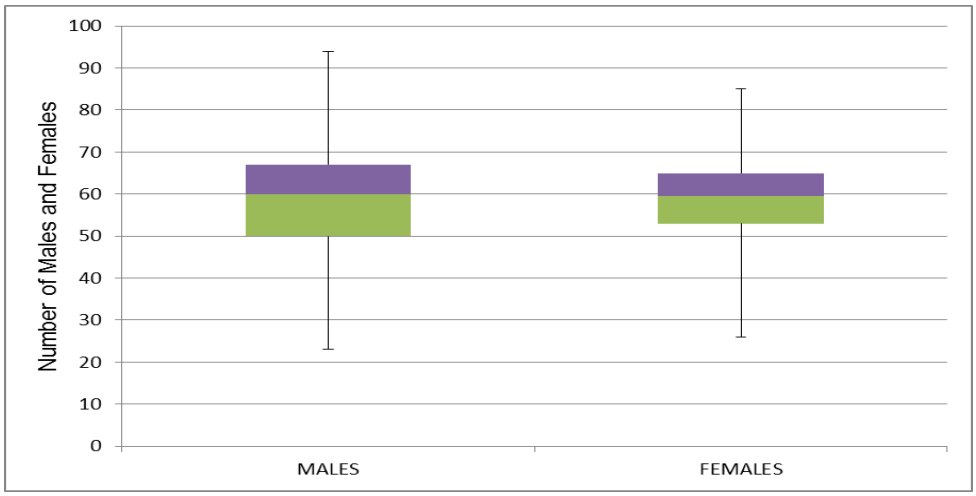


Figure 4.2: Box plot of mean age of patients by gender

Figure 4.3 and 4.4 portrays the distribution of gender across the age groups.

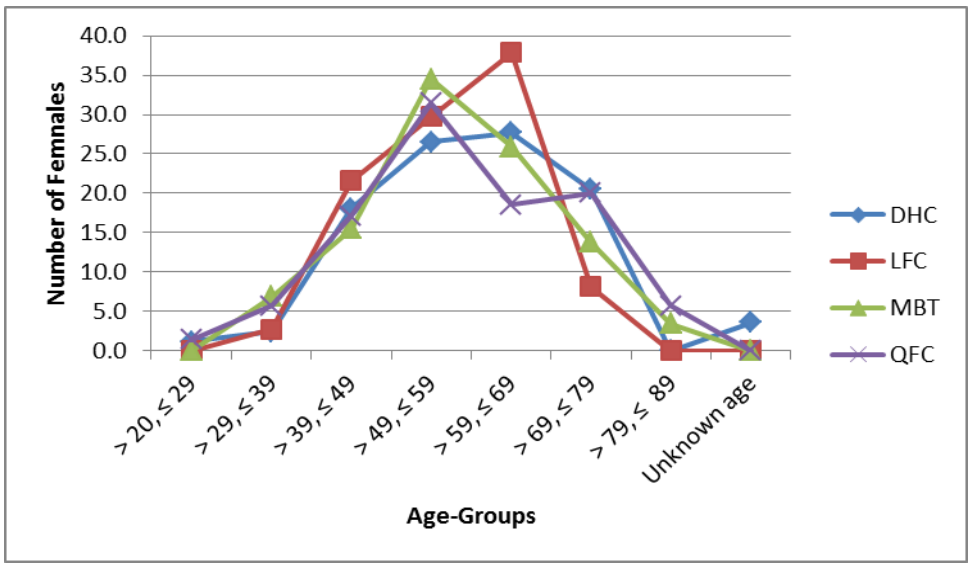


Figure 4.3: Distribution of females, according to age

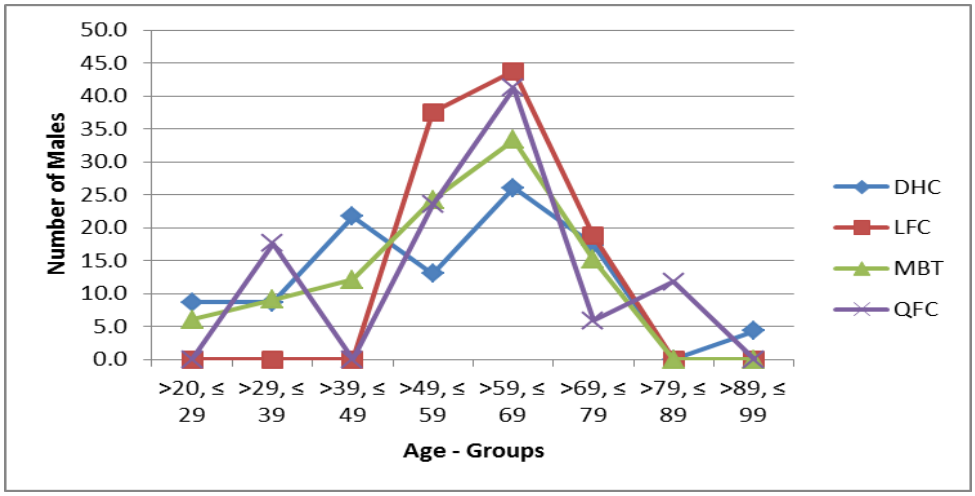


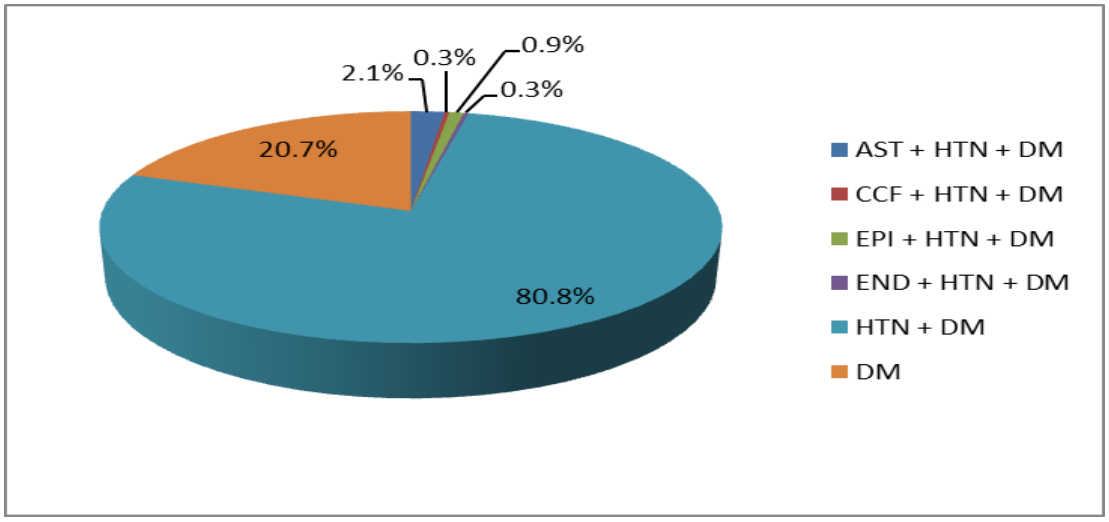
Figure 4.4: Distribution of males, according to age

The ratios of male to female in different age groups are indicated in Table 4.2.

Table 4.2: Ratio of males to females across the age groups

Age Group	Ratio of males to females
> 20, ≤ 29	2:1
> 29, ≤ 39	1:3
> 39, ≤ 49	1:5
> 49, ≤ 59	1:4
> 59, ≤ 69	1:2
> 69, ≤ 79	1:4
> 79, ≤ 89	1:3

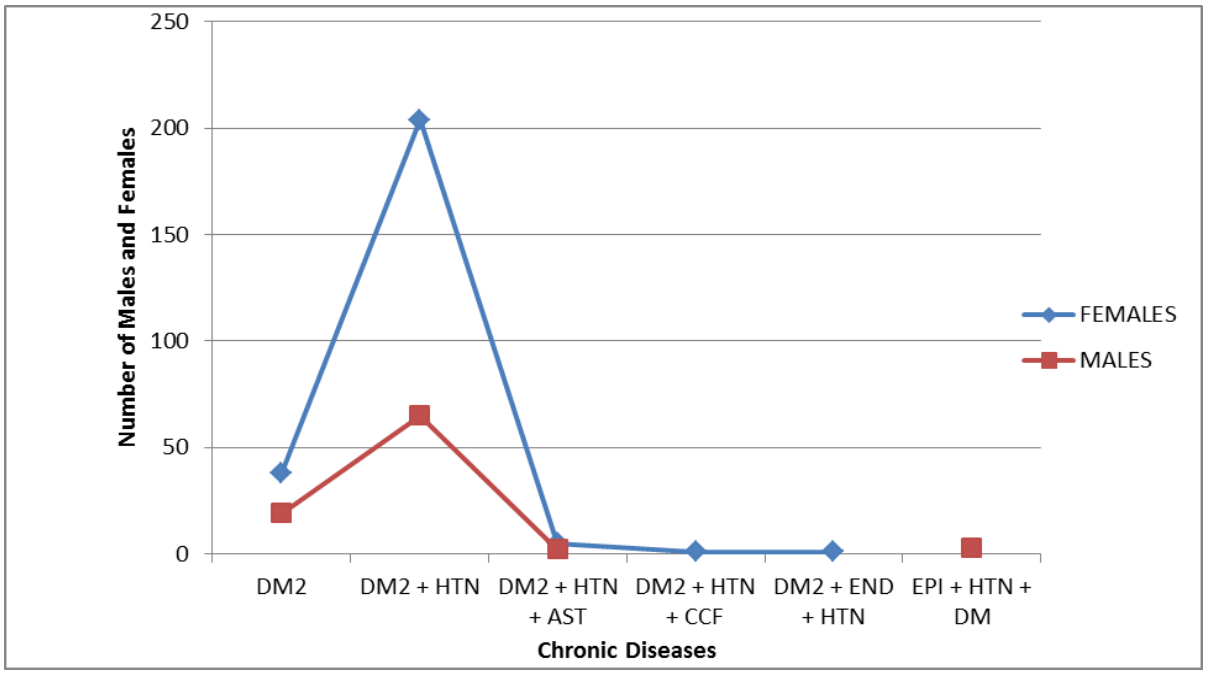
Figure 4.5 indicates the prevalence of diabetes mellitus occurring with other chronic illnesses.



CCF = Congestive Cardiac Failure; HTN = Hypertension; DM = Diabetes Mellitus; AST = Asthma, END = endometriosis; EPILEPSY = epilepsy.

Figure 4.5: Distribution of prevalence of diabetes mellitus occurring with other chronic illnesses

Figure 4.6 illustrates the percentage of males and females with DM alone or DM concurrently with other chronic illnesses.



DM2 = type 2 diabetes mellitus; HTN = hypertension; END = endometriosis; EPI = epilepsy; AST = asthma; CCF = congestive cardiac failure; F = Females; M = Males

Figure 4.6: The percentage of males and females with other chronic diseases

4.2.2 Discussion

Diabetes mellitus as study results have shown, appear to be more prevalent in females than in males except in age group 1 (> 20, ≥29 years) where more males than females had the disease (Table 4.2). This observed difference between the number of males and females with diabetes were not seen to be of statistical significance. Wild *et al*. (2004:1047) reported that there is a high prevalence of diabetes in men than women, but there are more women with diabetes than men which agree with the results of this study as there were more females with DM than males.

As outlined in the results diabetes mellitus is more prevalent in patients within age group 49 to 59 years in the case of women and 59 to 69 years in the case of men. If gender is disregarded, the disease would be seen to be most prevalent in the age groups >49 ≤ 59 and >59 ≤69 of the studied population (Table 1). Evaristo-Neto *et al.* (2010:3) in a similar study they carried out in Angola, found out that diabetes mellitus was most prevalent in patients within the age group of 60 to 69 years. Mbaya and Ramiaya (2006:1) furthermore noted that in Sub-Sahara Africa more than 46% per cent of the diabetic populations are 40 to 59 years old. Reporting on the global prevalence of diabetes, Wild *et al*. (2004:1047) also remarked that the most important diabetes prevalence across the world seems to be increased in people greater than 65 years of age. The findings or remarks of the above mentioned authors to a large extent validate the results of this study which can be interpreted to indicate that the Lesotho population has the same trends in the development of diabetes mellitus as the rest of the world. Inspite of these findings, it is

important to mention here that statistical evidence for diabetes mellitus being more prevalent in males and females in the age group 59 to 69 years is weak (*p*-value = 0.19), Cramer's V determinations showed weak correlations between the age groups 2, 4, and 5 and prevalence of diabetes (Cramer's V = 0.19, 0.18 and 0.19 respectively for the groups), moderately strong correlations between age group 3 and the disease (Cramer's V = 0.22 for the age group) and a very strong correlation between age group 6 and the disease (Cramer's V = 0.41). In contrast, the study by Ekpenyong *et al.* (2012:20) on the study titled "gender and age specific prevalence and associated risk factors of type 2 diabetes mellitus in Uyo Metropolis (South Easten Nigeria)", reported that there is a practical significant difference in the age group 36 to 60 years in patients with diabetes mellitus.

More females than males have been observed to have type 2 DM concurrently with hypertension. Duggiral *et al*. (2005:418) reported that poor control of blood pressure especially the systolic blood pressure was observed in women than men, supporting the observed prevalence of occurrence of hypertension and DM in this study. The odds of females and males being both diabetic and hypertensive were determined and found to be 4.6 and 2.7, respectively. A calculated odds ratio of 1.7 indicates that women are 1.7 times more likely than men to have hypertension when they have type 2 DM (paragraph 3.10.1.6).

The results that a smaller percentage of patients had diabetes mellitus concurrently with other chronic diseases like asthma, epilepsy, congestive cardiac failure, or endometriosis in comparison with hypertension concur with the findings of studies carried out by Long and Dagogo-Jack (2011:244). These authors reported that up to 75% of diabetic patients have it concurrently with hypertension, and that patients with hypertension alone often show evidence of insulin resistance. They further stated that, hypertension and diabetes are commonly linked conditions that share a significant overlap in underlying risk factors (e.g. ethnicity and familial, and lifestyle determinants) and complications. According to Cheung and Li (2012:161) hypertension and diabetes mellitus have common metabolic pathways such as obesity, inflammation, oxidative stress, and insulin resistance, therefore this finding may be considered as an explanation of why hypertension and DM occur concurrently as observed in this study.

4.3 ANALYSIS OF BLOOD GLUCOSE LEVELS

4.3.1 Results

An analysis of blood glucose level data showed that:

- Half of all women and men had blood glucose levels above 9 mmol/L, and 12 mmol/L, respectively (Figure 4.7).

- Of the total number of patients studied, 25% (n = 84) had their blood glucose levels controlled within the range of 4.4 to 9.7mmol/L for both FBG and random blood glucose (RBS). Up to 62.4% (n = 209) on the other hand had their blood glucose levels above 7.1 mmol/L for both FBS and RBS (Table 4.3).
- The mean blood glucose levels for females and males were 10.1 ± 5.9 (95% CI: 10.1–11.7) and 10.9 ± 6.2 (95% CI: 11.0 – 14.0) respectively.
- The overall mean blood glucose level for the study population was 10.6 ± 5.6 mmol/L. In both males and females there were outliers with blood glucose levels as high as 33.3 mmol/L.
- Blood glucose levels were not recorded in the bukana for 12.7% of patients (Table 4.3).

Figure 4.7 illustrate a box-plot of blood glucose levels in the study population, based on gender.

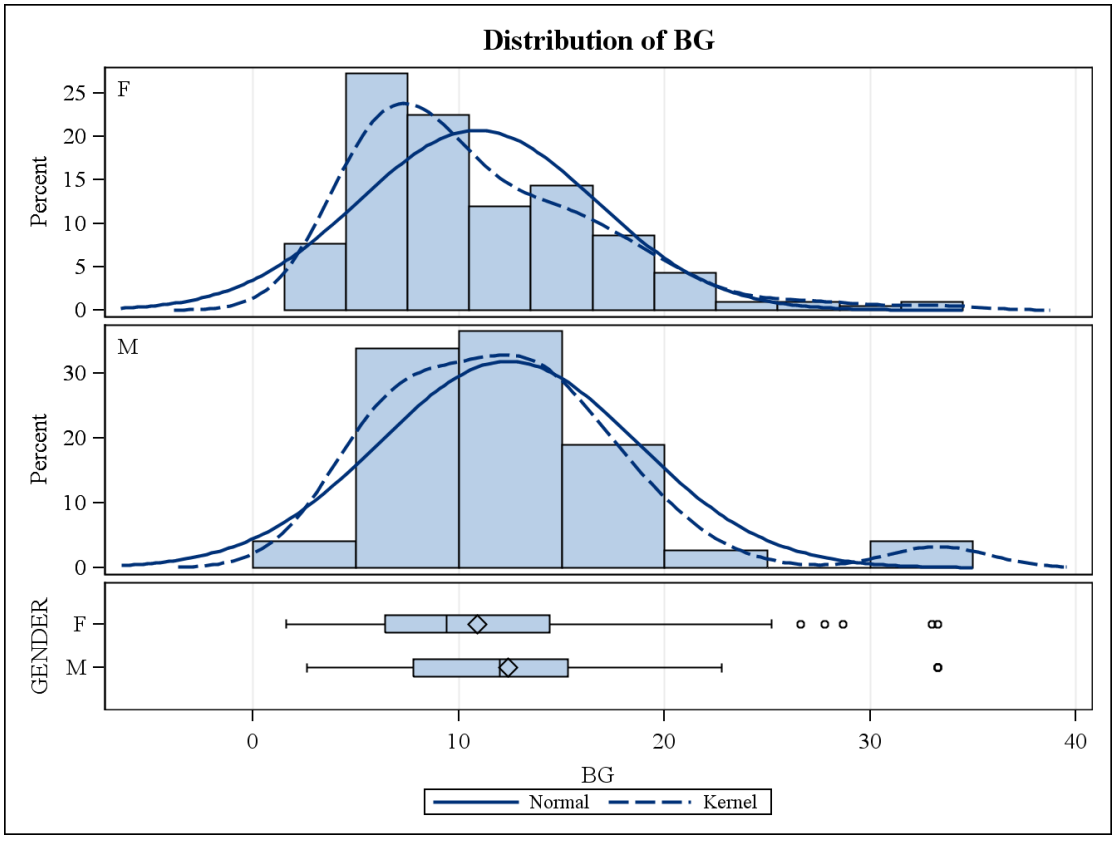


Figure 4.7: Box plot of mean blood glucose levels by gender

Table 4.3 shows the blood glucose types that were recorded.

Table 4.3: Percentage distribution of patients with blood glucose within and outside target ranges

Type	Out		Within		Unknown		Total
	N	%	N	%	N	%	
FBS	137	40.7	70	20.8			207 (61)
RBS	73	21.7	16	4.7			89 (26.4)
Unknown					42	12.5	42 (12.5)
Grand Total	210	62.4	85	25.5	42	12.5	337 (100)

FBS = Fasting blood glucose; RBS = Random blood glucose; Out = Out of target; Within = within target; Unknown = no information obtained on the blood glucose

4.3.2 Discussion

Female patients had lower mean blood glucose levels than their male counterparts. These differences between males and females however were not seen to be of any practical importance (*d*-values = 0.12). Among both males and females there were outliers with as high as 33.3 mmol/L. This indicated complete failures to control blood glucose levels in some patients using current hypoglycaemic agents available at study sites either in mono- or combination therapies.

Only 25% of the patients in the study were within the recommended targets for blood glucose level in diabetic patients of fasting or pre-prandial target of between 4.0-7.0 mmol/L and a peak post-prandial glucose 5.0-10.0 mmol/L (Amod *et al.*, 2012:S20; Levitt *et al*., 2009:507). According to Stratton *et al.* (2010:405) the risk of developing diabetic complications is strongly linked with previously uncontrolled blood glucose among patients with type 2 diabetes mellitus. This indicates that majority of patients in this study who are not within the recommended targets are at risk of developing diabetic complication. Blood glucose levels were not recorded in the bukana for 12.7% of patients (Table 4.3). This could be attributed to the unavailability of standard operating procedures that indicate that the patient's blood glucose should be tested before a refill or consultation.

4.4 PRESCRIBING PATTERNS OF ANTIDIABETIC DRUGS

Results and discussions of data analysis to establish types and prescribing frequencies of antidiabetic agents as mono- or combination therapies are discussed in this subsection.

4.4.1 Results

4.4.1.1 Antidiabetic drug prescribing as monotherapy

Frequencies of prescribing respective antidiabetic agents as monotherapy are shown in Tables 4.4 and 4.5. Tables 4.4 and 4.5 depict that:

- Prescribed at a relative frequencies of 54.2% (n = 160), 27.7% (n = 82), 4% (n = 12) and 2.7% (n = 8), metformin 850 mg given three times a day; metformin 500 mg three times a day; glibenclamide 10 mg daily and glibenclamide 5 mg twice daily are OHAs were first, second, third and 4th choices treatment of diabetes at all four study sites.
- High doses of 1000 mg of metformin three times daily was also used at the same prescribing frequency as glibenclamide 5 mg daily in treating diabetic mellitus as monotherapy (2.7%, = 295).
- Prescribed at much lower frequencies (i.e. 0.3% to 1.3%), the following oral hypoglycaemic drug treatment regimens were also seen to be used as single therapies. They include metformin 500 mg twice daily (1.3%), metformin 500 mg daily (0.7%), and 0.3% rates of prescribing each of glibenclamide 5 mg twice daily, glibenclamide 10 mg twice daily and chlorpropamide 500 mg twice daily.
- Actraphane® injection in dosage regimens of 10–40 units at night was prescribed as single therapy, at percentages of 0.3% to 1% in treatment of diabetes mellitus at all four study sites.
- Prescribed at a higher frequency was Actraphane® 20 units in the morning and 10 units in the evening at a rate of 11.6% (n = 50 patients). The second choices were Actraphane® 30 units in the morning and 15 units in the evening (6.3%) and Actraphane® 40 units in the morning and 20 units in the evening (4.4%).
- The third choice treatments of Actraphane® based on frequencies, were Actraphane® 28 units in the morning and 14 units in the evening; Actraphane® 32 units in the morning and 16 units in the evening at both at 3.9% (n = 17).
- There were other regimens that were still prescribed at low percentages from 0.3% to 3.2 which include chlorpropamide 500 mg twice per day, chlorpropamide 500 mg once a day, glibenclamide 10 mg in the morning and 5 mg in the evening, and metformin 500 mg once a day (1.0%, 0.3%, 0.3%, and 1.4% respectively).

In respect to prescribing of antidiabetic agents as single therapies at respective study sites, it was observed that:

- Metformin 850 mg three times daily was prescribed at all four sites of study at 67% (n = 91) for Mabote Filter Clinic, 56.9% (n = 65) for Likotsi Clinic and 53.7% (n = 69) for the Qoaling

Filter Clinic. The lowest frequency of use of metformin 850 mg three times daily as a single therapy was recorded for the Domiciliary Health Centre where the regimen was used in35.7% (n = 70).

- Prescribed at a relative frequency of 40.0% (n = 70), metformin 500 mg three times daily was used the most at the Domiciliary Health Centre as a monotherapy in the treatment of DM. The regimen was also used at Likotsi, Qoaling and Mabote Filter clinics at prescribing frequencies of 33.8% (n = 65), 24.6% (n = 69) and 16.5% (n = 91) in that order for the three study sites respectively.
- Use of Actraphane® as a single agent was most common at all the study sites where the highest rate of 12.8% (n = 153), 20.0% (n = 152) and 26.1% (n = 33) was recorded for Actraphane® 20 units in the morning and 10 units in the evening for Domiciliary Health center, Qoaling and Likotsi Filter clinics, respectively.
- On the other hand Mabote Filter clinic had the highest prescribing frequency of 10.0% (n = 121 patients)- for Actraphane® 27 units in the morning and 18 units in the evening instead of Actraphane® 20 units in the morning and 10 units in the evening like other study sites.

Table 4.4 portrays the regimens used for single agents.

Table 4.4: Prescribing frequencies of oral antidiabetic agents as single agents

Agent/Regimen	Number of prescriptions/patients									
	DHC		MBT		QFC		LFC		Total	
	N	n%	N	n%	N	n%	N	n%	n	n%
Chlorpropamide 500 mg bd	3	4.3							3	1
Chlorpropamide 500 mg OD					1	1.4			1	0.3
Glibenclamide' 10 mg mane, 5 mg nocte			1	1.1					1	0.3
Glibenclamide 10 mg OD	3	4.3	8	8.8	1	1.4			12	4
Glibenclamide 5 mg BD					1	1.4			1	0.3
Glibenclamide 5 mg OD	1	1.4	3	3.3	3	4.3	1	1.5	8	2.7
Metformin 1000 mg TDS	1	1.4			7	10.1			8	2.7
Metformin 500 mg BD	2	2.8					2	3.1	4	1.4
Metformin 500 mg OD					2	2.9			2	0.7
Metformin 500 mg TDS	28	40.0	15	16.5	17	24.6	22	33.8	82	27.7
Metformin 850 mg BD	7	10.0	3	3.2					10	3.3
Metformin 850 mg TDS	25	35.7	61	67.0	37	53.6	37	56.9	160	54.2
Total	**70**		**91**		**69**		**65**		**295**	**100**

DHC = Domiciliary Health Center; MBT = Mabote Filter Clinic; QFC = Qoaling Filter Clinic; LFC = Likotsi Filter Clinic; OD = once a day; BD = two times a day; TDS = three times a day; nocte = at night; mane = in the morning

Table 4.5 indicates the different regimens of Actraphane® used at in the study sites.

Table 4.5: Frequency of prescribing different dosage regimens of Actraphane® in the study sites

Agent/Regimen (units)	Number of prescriptions/ patient n (%)				Totals
	DHC (n = 149)	MBT (n = 119)	QFC (n = 148)	LFC (n =33)	N (%)
Actraphane® 10 units nocte			1 (0.7)	1 (4.3)	2 (0.5)
Actraphane® 16 units nocte			3 (2.0)	3 (13.0)	6 (1.4)
Actraphane® 20 units nocte	1 (0.7)			1 (4.3)	2 (0.5)
Actraphane® 26 units nocte		2 (1.7)		2 (8.7)	4 (0.9)
Actraphane® 40 units nocte	3 (2.0)			3 (13.0)	6 (1.4)
Actraphane 25 units mane, 15 units nocte			1 (0.7)		1 (0.2)
Actraphane® 10 units mane, 5 units nocte	6 (4.0)				6 (1.4)
Actraphane® 10 units mane, 8 units nocte		5 (4.2)			5 (1.2)
Actraphane® 12 units mane, 6 units nocte		6 (5.0)		3 (13.0)	9 (2.1)
Actraphane® 14 units mane, 12 units nocte		7 (5.9)			7 (1.6)
Actraphane® 15 units mane, 12 units nocte		5 (4.2)			5 (1.2)
Actraphane® 16 units mane, 10 units nocte	9 (6.0)	2 (1.7)			11 (2.5)
Actraphane® 16 units mane, 12 units nocte		4 (3.4)			4 (0.9)
Actraphane® 16 units mane, 8 units nocte	1 (0.7)	6 (5.0)			7 (1.6)
Actraphane® 18 units mane, 10 units nocte	1 (0.7)	6 (5.0)	5 (3.4)		12 (2.8)
Actraphane® 18 units mane, 12 units nocte		4 (3.4)	1 (0.7)		5 (1.2)
Actraphane® 18 units mane, 15 units nocte		2 (1.7)	6 (4.1)		8 (1.9)
Actraphane® 18 units mane, units nocte	3 (2.0)		1 (0.7)		4 (0.9)
Actraphane® 20 units mane, 10 units nocte	19 (12.8)		25 (20)	6 (26.1)	50 (11.6)
Actraphane® 20 units mane, 12 units nocte			6 (4.1)		6 (1.4)
Actraphane® 22 units mane, 12 units nocte		5 (4.2)			5 (1.2)
Actraphane® 22 units mane, 15 units nocte		1 (0.8)			1 (0.2)
Actraphane® 23 units mane, 13 units nocte			2 (1.4)		2 (0.5)
Actraphane® 24 units mane, 10 units nocte	2 (1.3)				2 (0.5)
Actraphane® 24 units mane, 12 units nocte	2 (1.3)	6 (5.0)	2 (1.4)		10 (2.3)
Actraphane® 24 units mane, 14 units nocte		6 (5.0)	6 (4.1)		12 (2.8)
Actraphane® 25 units mane, 15 units nocte			4 (2.7)		4 (0.9)
Actraphane® 25 units mane, 20 units nocte		2 (1.7)			2 (0.5)
Actraphane® 26 units mane, 12 units nocte		5 (4.2)	6 (4.1)		11 (2.5)
Actraphane® 26 units mane, 13 units nocte				6 (26.1)	6 (1.4)
Actraphane® 26 units mane, 14 units nocte	6 (4.0)	2 (1.7)	6 (4.1)		14 (3.2)
Actraphane® 26 units mane, 16 units nocte	6 (4.0)				6 (1.4)
Actraphane® 26 units mane, 18 units nocte	6 (4.0)				6 (1.4)
Actraphane® 27 units mane, 18 units nocte		12 (10.1)			12 (2.8)
Actraphane® 28 units mane, 14 units nocte	7 (4.7)		10 (6.8)		17 (3.9)
Actraphane® 28 units mane, 17 units nocte		6 (5.0)			6 (1.4)
Actraphane® 28 units mane, 22 units nocte		6 (5.0)			6 (1.4)
Actraphane® 29 units mane, 14 units nocte	5 (3.4)				5 (1.2)

Table 4.5: Frequency of prescribing different dosage regimens of Actraphane® in the study sites continued

Agent/Regimen (units)	Number of prescriptions/ patient n (%)				Totals
	DHC (n = 149)	MBT (n = 119)	QFC (n = 148)	LFC (n =33)	N (%)
Actraphane® 30 units mane, 10 units nocte		3 (2.5)	6 (4.1)		9 (2.1)
Actraphane® 30 units mane, 12 units nocte	2 (1.3)				2 (0.5)
Actraphane® 30 units mane, 14 units nocte	6 (4.0)				6 (1.4)
Actraphane® 30 units mane, 15 units nocte	10 (6.7)		17 (11.5)		27 (6.3)
Actraphane® 30 units mane, 16 units nocte				1 (4.3)	1 (0.2)
Actraphane® 30 units mane, 20 units nocte	4 (2.7)		4 (2.7)		8 (1.9)
Actraphane® 32 units mane, 16 units nocte	6 (4.0)		6 (4.1)	5 (21.7)	17 (3.9)
Actraphane® 34 units mane, 17 units nocte	6 (4.0)				6 (1.4)
Actraphane® 35 units mane, 12 units nocte	2 (1.3)				2 (0.5)
Actraphane® 35 units mane, 15 units nocte				2 (8.7)	2 (0.5)
Actraphane® 35 units mane, 20 units nocte		6 (5.0)			6 (1.4)
Actraphane® 36 units mane, 16 units nocte	1 (0.7)		6 (4.1)		7 (1.6)
Actraphane® 36 units mane, 18 units nocte	2 (1.3)		5 (3.4)		7 (1.6)
Actraphane® 38 units mane, 16 units nocte	6 (4.0)				6 (1.4)
Actraphane® 38 units mane, 18 units nocte			8 (5.4)		8 (1.9)
Actraphane® 40 units mane, 11 units nocte			6 (4.1)		6 (1.4)
Actraphane® 40 units mane, 15 units nocte	1 (0.7)				1 (0.2)
Actraphane® 40 units mane, 16 units nocte	2 (1.3)	6 (5.0)			8 (1.9)
Actraphane® 40 units mane, 18 units nocte	5 (3.4)				5 (1.1)
Actraphane® 40 units mane, 20 units nocte	17 (11.4)		2 (1.4)		19 (4.4)
Actraphane® 40 units mane, 24 units nocte	3 (2.0)				3 (0.7)
Actraphane® 42 units mane, 16 units nocte			1 (.07)		1 (0.5)
Actraphane® 42 units mane, 20 units nocte	1 (0.7)				1 (0.5)
Actraphane® 44 units mane, 22 units nocte	2 (1.3)	6 (5.0)	3 (2.0)		11 (2.5)
Actraphane® 44 units mane, 26 units nocte			1 (0.7)		1 (0.2)
Actraphane® 46 units mane, 16 units nocte			2 (1.4)		2 (0.5)
TOTAL	153	121	152	833	432(100)

DHC = Domiciliary Health Center; MBT = Mabote Filter Clinic; QFC = Qoaling Filter clinic; LFC = Likotsi Filter Clinic; mane = in the morning; nocte = in the evening

4.4.1.2 Antidiabetic drug prescribing as combination therapies

Tables 4.6 to 4.10 show frequency distributions of prescribed combination therapies of antidiabetic agents according to study sites and patient demographic characteristics. Information as shown in these tables indicates that:

- The relative frequencies of prescribing metformin and Actraphane® as combination therapies of Actraphane® 20 units in the morning and 10 units in the evening plus metformin 500 mg three times per day; Actraphane® 20 units in the morning and 10 units in the evening plus metformin 850 mg three times per day; and Actraphane® 30 units in the

morning and 15 units in the evening plus metformin 850 mg three times per day were 10.6% (n = 40), 7.1% (n = 27), and 6.6% (n = 25), respectively.

- The combination therapy of antidiabetic agents that had the lowest frequency of prescribing was insulin and glibenclamide (as outlined in Table 4.7) with the relative frequency of prescribing of Actraphane® 40 units in the morning, 20 units in the evening in the evening plus glibenclamide 5 mg daily at 25% (n = 12).
- Triple therapy was used at a very low prescribing frequency for the three study sites being Domiciliary health center, Qoaling and Likotsi Filter clinics. Regimens representing 31.0% (n = 16) of prescriptions consisted of Actraphane® 48 units in the morning, 12 units in the evening in the evening plus glibenclamide 10 mg daily and metformin 1000 mg three times per day.
- The combination therapy of metformin and glibenclamide was prescribed at relative frequencies of 24.6% (n = 172), 22.9% (n = 160), and 13.4% (n = 94) for glibenclamide 10 mg daily plus metformin 850 mg three times per day; glibenclamide 5 mg daily plus metformin 850 mg three times per day; and glibenclamide 5 mg daily plus metformin 500 mg three times per day as first, second and third choices treatments for all the study sites.

In respect to prescribing of antidiabetic agents as combination therapy at respective study sites, it was observed that:

- Specific regimens per study sites indicated that highly prescribed Actraphane® and metformin combination therapies for both Domiciliary Health Center and Qoaling filter clinic consisted of Actraphane® 20 units in the morning, and 10 units in the evening plus metformin 500 mg three times a day at a frequency of 13.9% (n = of 137) and 17.4% (n = 121), respectively. On the other hand, Likotsi Health Center used a regimen of Actraphane® 30 units in the morning in the morning and 15 units in the evening plus metformin 850 mg three times a day at a frequency of 19.6% (n = 46).
- The regimens of Actraphane® and metformin that were highly used at Mabote filter clinic at 8% (n = 75), included Actraphane® 28 units in the morning, 12 units in the evening plus metformin 500 mg three times per day; Actraphane® 30 units in the morning, 15 units in the evening plus metformin 500 mg three times per day; Actraphane® 35 units in the morning, 15 units in the evening plus metformin 500 mg three times per day; and Actraphane® 36 units in the morning, 22 units in the evening plus metformin 500 mg three times per day.
- At specific study sites Actraphane® 28 units in the morning and 14 units in the evening plus glibenclamide 10 mg daily plus glibenclamide 10 mg immediately was prescribed at Domiciliary Health Center (40%, n =10), Actraphane® 30 units in the morning, 15 units in the evening plus glibenclamide 5 mg daily at Likotsi filter clinic and lastly Atrapid® 10 units immediately plus glibenclamide 5 mg daily at Qoaling filter clinic.

- Metformin and glibenclamide combination regimens that were specifically prescribed, at different study sites were glibenclamide 5 mg per day and metformin 850 mg three times per day (Mabote Filter clinic 37.1% (n = 221), and Likotsi filter clinic 27.7% (n = 83)); glibenclamide 10 mg daily plus metformin 850 mg three times daily at Qoaling filter clinic 44.3% (n = 185) and glibenclamide 5 mg per day plus metformin 500 mg three times a day (Domiciliary Health Clinic — 21.4%, n = 210).
- The second combination therapy that was prescribed was glibenclamide 10 mg once a day plus metformin 850 mg three times daily, representing 27.1% (n = 221) of prescriptions and 13.3% (n = 83) for Mabote and Qoaling filter clinics, respectively. Glibenclamide 5 mg once a day plus metformin 500 mg three times daily 12.9% (n = 210) and 15.1% (n=185) were prescribed at Domiciliary Health Center and Qoaling filter clinics, respectively.
- Very few patients were put on a combination of three drugs at Domiciliary Health Center, Qoaling and Likotsi filter clinic, with the highest relative frequency ranging from 31.0% to 6.3% (n = 16) for all the three study sites. Mabote Filter clinic was an exception which had no patients managed with a combination of three drugs.
- With reference to Table 4.9; the three drug combination therapy used most commonly at Domiciliary Health center was Actraphane® 40 units in the morning, 20 units in the evening plus glibenclamide 5 mg per day plus metformin 500 mg three times daily, representing 57.1% (n = 7) of prescriptions. At Qoaling filter clinic, the regimen most frequently prescribed included Actraphane® 48 units in the morning, 12 units in the evening plus glibenclamide 10 mg per day plus metformin 1000 mg three times per day. This regimen was prescribed for 83.3% (n = 6) of prescriptions.
- The three drug regimen mostly prescribed at Likotsi filter clinic consisted of Actraphane® 30 units in the morning, 15 units in the evening, glibenclamide 5 mg daily plus metformin 850 mg three times daily.

Table 4.6 indicates the different regimens of Actraphane and metformin that were employed in the study site.

Table 4.6: Regimens prescribed for a combination therapy of Actraphane® plus metformin

Agent/regimen	Number of prescriptions/patient n (%)				Totals
	DHC (n = 137)	MBT (n = 75)	QFC (n = 121)	LFC (n= 46)	
Actraphane® 10 units mane, 5 units nocte plus metformin 1000 mg tds			6 (5.0)		6 (1.6)
Actraphane® 10 units mane, 20 units nocte plus metformin 500 tds	1 (0.7)				1 (0.3)
Actraphane® 12 units mane, 6 units nocte plus metformin 850 tds				3 (6.5)	3 0.8)
Actraphane® 14 units mane, 10 units nocte plus metformin 500 tds		6 (8.0)			6 (1.3)
Actraphane® 14 units mane, 12 units nocte plus metformin 850 tds		4 (5.3)			4 (1.1)
Actraphane® 14 units nocte, metformin 850 tds		6 (8.0)		1 (2.2)	7 (1.8)
Actraphane® 15 units mane, 12 units nocte plus metformin 1000 tds		1 (1.3)			1 (0.3)
Actraphane® 15 units mane, 5 units nocte plus metformin 850 tds				3 (6.5)	3 (0.79)
Actraphane® 16 units mane, 12 units nocte plus metformin 850 tds		2 (2.7)			2 (0.5)
Actraphane® 18 units mane, 12 units nocte plus metformin 500 tds		6 (8.0)			6 (1.6)
Actraphane® 18 units mane, 12 units nocte plus metformin 850 tds			6 (5.0)		6 (1.6)
Actraphane® 18 units mane, 14 units nocte plus metformin 500 tds		3 (4.0)			3 (0.8)
Actraphane® 18 units mane, 14 units nocte plus metformin 850 tds		1 (1.3)			1 (0.3)
Actraphane® 20 units mane, 10 units nocte plus metformin 1000 tds			4 (3.3)	1 (2.2)	5 (1.3)
Actraphane® 20 units mane, 10 units nocte plus metformin 500 tds	19 (13.9)		21 (17.4)		40 (10.6)
Actraphane® 20 units mane, 10 units nocte plus metformin 850 bd	5 (3.6)				5 (1.3)
Actraphane® 20 units mane, 10 units nocte plus metformin 850 tds	5 (3.6)	5 (6.7)	17 (14.0)		27 (7.1)
Actraphane® 20 units mane, 12 units nocte plus metformin 500 tds		2 (2.7)	1 (0.8)		3 (0.8)
Actraphane® 20 units mane, 12 units nocte plus metformin 850 tds		1 (1.3)			1 (0.3)
Actraphane® 20 units mane, 15 units nocte plus metformin 500 tds		2 (2.7)			2 (0.5)
Actraphane® 20 units mane, 15 units nocte plus metformin 850 tds	4 (2.9)				4 (1.1)
Actraphane® 24 units mane, 10 units nocte plus metformin 500 tds	2 (1.5)				2 (0.5)
Actraphane® 24 units mane, 12 units nocte plus metformin 500 tds	2 (1.5)		4 (3.3)		6 (1.6)
Actraphane® 24 units mane, 12 units nocte plus metformin 850 tds			2 (1.7)		6 (1.6)
Actraphane® 24 units mane, 18 units nocte plus metformin 500 tds			4 (3.3)		2 (0.5)
Actraphane® 24 units nocte, metformin 850 mg bd	2 (1.5)				4 (1.1)

Table 4.6: Regimens prescribed for a combination therapy of Actraphane® plus metformin continued

Agent/regimen	Number of prescriptions/patient n (%)				
	DHC (n = 137)	MBT (n = 75)	QFC (n = 121)	LFC (n= 46)	
Actraphane® 25 units mane, 15 units nocte plus metformin 500 mg tds	5 (3.6)				5 (1.3)
Actraphane® 25 units mane, 18 units nocte plus metformin 850 mg tds	1 (0.7)				1 (0.3)
Actraphane® 26 units mane, 12 units nocte plus metformin 850 mg bd	1 (0.7)				1 (0.3)
Actraphane® 26 units mane, 12 units nocte plus metformin 850 mg tds	4 (2.9)				4 (1.1)
Actraphane® 26 units mane, 14 units nocte plus metformin 500 mg tds			7 (5.8)		7 (1.8)
Actraphane® 26 units mane, 14 units nocte plus metformin 850 mg tds	2 (1.5)				2 (0.5)
Actraphane® 26 units mane, 24 units nocte plus metformin 850 mg tds		2 (2.7)			2 (0.5)
Actraphane® 28 units mane, 12 units nocte plus metformin 500 mg tds		6 (8.0)			6 (1.6)
Actraphane® 28 units mane, 14 units nocte plus metformin 500 mg tds			7 (5.8)		7 (1.8)
Actraphane® 28 units mane, 14 units nocte plus metformin 850 mg tds	6 (4.4)		5 (4.1)		11 (2.9)
Actraphane® 28 units mane, 17 units nocte plus metformin 500 mg tds				1 (2.2)	1 (0.3)
Actraphane® 28 units mane, 20 units nocte plus metformin 850 mg tds		5 (6.7)			5 (1.3)
Actraphane® 29 units mane, 14 units nocte plus metformin 850 mg tds	1 (0.7)				1 (0.3)
Actraphane® 30 units mane, 10 units nocte plus metformin 500 mg tds				3 (6.5)	3 (0.8)
Actraphane® 30 units mane, 10 units nocte plus metformin 850 mg tds				4 (8.7)	4 (1.1)
Actraphane® 30 units mane, 12 units nocte plus metformin 850 mg bd	1 (0.7)				1 (0.3)
Actraphane® 30 units mane, 12 units nocte plus metformin 850 mg tds			4 (3.3)		4 (1.1)
Actraphane® 30 units mane, 15 units nocte plus metformin 5 mg od	1 (0.7)				1 (0.3)
Actraphane® 30 units mane, 15 units nocte plus metformin 500 mg tds	2 (1.5)	6 (8.0)			8 (2.1)
Actraphane® 30 units mane, 15 units nocte plus metformin 850 mg tds	16 (11.7)			9 (19.6)	25 (6.6)
Actraphane® 30 units mane, 16 units nocte metformin 850 mg tds	1 (0.7)				1 (0.3)
Actraphane® 30 units mane, 16 units nocte plus metformin 1000 mg tds			6 (5.0)		6 (1.6)
Actraphane® 30 units mane, 20 units nocte plus metformin 850 mg tds				5 (10.9)	5 (1.3)
Actraphane® 30 units mane, 60 units nocte plus metformin 500 mg tds			1 (0.8)		1 (0.3)
Actraphane® 32 units mane, 10 units nocte plus metformin 500 mg tds	3 (2.2)				3 (0.8)
Actraphane® 32 units mane, 12 units nocte plus metformin 500 mg tds	3 (2.2)				3 (0.8)

Table 4.6: Regimens prescribed for a combination therapy of Actraphane® plus metformin continued

Agent/regimen	Number of prescriptions/patient n (%)				
	DHC (n = 137)	MBT (n = 75)	QFC (n = 121)	LFC (n= 46)	
Actraphane® 32 units mane, 16 units nocte plus metformin 500 mg tds	10 (7.3)				10 (2.6)
Actraphane® 32 units mane, 16 units nocte plus metformin 850 mg tds	2 (1.5)				2 (0.5)
Actraphane® 34 units mane, 14 units nocte plus metformin 850 mg tds				3 (6.5)	3 (0.8)
Actraphane® 34 units mane, 15 units nocte plus metformin 850 mg tds	3 (2.2)			3 (6.5)	6 (1.6)
Actraphane® 34 units mane, 18 units nocte plus metformin 850 mg tds				3 (6.5)	3 (0.8)
Actraphane® 34 units mane, 20 units nocte plus metformin 850 mg od	2 (1.5)				2 (0.5)
Actraphane® 34 units mane, 20 units nocte plus metformin 850 mg tds	1 (0.7)				1 (0.3)
Actraphane® 35 units mane, 10 units nocte plus metformin 850 mg tds	1 (0.7)				1 (0.3)
Actraphane® 35 units mane, 12 units nocte plus metformin 500 mg tds	9 (6.6)				9 (2.3)
Actraphane® 35 units mane, 15 units nocte plus metformin 500 mg tds		6 (8.0)			6 (1.6)
Actraphane® 36 units mane, 18 units nocte plus metformin 500 mg tds			5 (4.1)		5 (1.3)
Actraphane® 36 units mane, 22 units nocte plus metformin 500 mg tds		6 (8.0)			6 (1.6)
Actraphane® 40 units mane, 20 units nocte plus metformin 500 mg tds	4 (2.9)		6 (5.0)		10 (2.6)
Actraphane® 40 units mane, 20 units nocte plus metformin 850 mg tds	8 (5.8)	5 (6.7)	3 (2.5)	3 (6.5)	19 (5.0)
Actraphane® 40 units mane, 24 units nocte plus metformin 850 mg tds	3 (2.2)				3 (0.8)
Actraphane® 42 units mane, 20 units nocte plus metformin 850 mg tds	1 (0.7)				1 (0.3)
Actraphane® 44 units mane, 14 units nocte plus metformin 850 mg tds				2 (4.3)	2 (0.5)
Actraphane® 44 units mane, 26 units nocte plus metformin 500 mg tds			5 (4.1)		5 (1.3)
Actraphane® 46 units mane, 16 units nocte plus metformin 500 mg tds	3 (2.2)				3 (0.8)
Actraphane® 46 units mane, 16 units nocte plus metformin 850 mg tds	3 (2.2)				3 (0.8)
Actraphane® 48 units mane, 12 units nocte plus metformin 1000 mg tds			1 (0.8)		1 (0.3)
Actraphane® 50 units mane, 16 units nocte plus metformin 500 mg tds				2 (4.3)	2 (0.5)
Actraphane® 60 units mane, 30 units nocte plus metformin 1000 mg tds			6 (5.0)		6 (1.6)
TOTALs	137	75	121	46	379 (100)

DHC = Domiciliary Health Center; MBT = Mabote Filter clinic; QFC = Qoaling Filter Clinic; LFC = Likotsi Filter Clinic; Mane = in the morning; nocte = in the evening; od = once a day; bd = twice a day; tds = three times a day

Table 4.7 shows the prescribing frequencies different regimens of Actraphane® and glibenclamide combination therapy.

Table 4.7: Frequency of prescribing Actraphane® with glibenclamide

Agent/regimen	Number of prescriptions/patient n (%)			Totals
	DHC (n = 10)	QFC (n = 1)	LFC (n = 1)	
Actraphane® 15 units mane, glibenclamide 10 mg od	1 (10.0)			1 (8.3)
Actraphane® 28 units mane, 14 units nocte plus glibenclamide 10 mg od	1 (10.0)			1 (8.3)
Actraphane® 28 units mane, 14 units nocte plus glibenclamide 10 mg od plus glibenclamide 10 mg stat	4 (40.0)			4 (33.3)
Actraphane® 30 units mane, 15 units nocte plus glibenclamide 5 mg od			1 (100.0)	1 (8.3)
Actraphane® 40 units mane, 20 units nocte plus glibenclamide 5 mg od	3 (30.0)			3(25.0)
Actrapid® 20 units STAT plus Glibenclamide 5 mg od	1 (10.0)			1 (8.3)
Atrapid 10 units STAT plus glibenclamide 5 mg od		1 (100.0)		1 (8.3)
TOTAL	10	1	1	12 (100)

OD = once a day; mane = in the morning; nocte = in the evening; Stat = immediately

Table 4.8 indicates the regimens of oral antidiabetic agents' combination therapies at the different study sites.

Table 4.8: Prescribing pattern of prescribing oral hypoglycaemic agents as a combination therapy

Agent/regimen	Number of prescriptions/patient n (%)				Totals
	DHC (n = 210)	MBT (n = 221)	QFC (n = 185)	LFC (n =83)	
Chlorpropamide 250 mg od plus glibenclamide 5 mg od	1 (0.5)				1 (0.1)
Chlorpropamide 250 mg tds plus metformin 1000 mg tds	3 (1.4)				3 (0.4)
Chlorpropamide 500 mg od plus metformin 850 mg tds			5 (2.7)		5 (0.7)
Glibenclamide 10 mg bd plus metformin 1000 mg tds	1 (0.5)	12 (5.4)		6 (7.2)	19 (2.7)
Glibenclamide 10 mg bd plus metformin 1000 mg tds					
Glibenclamide 10 mg bd plus metformin 500 mg tds	4 (1.9)			2 (2.4)	6 (0.9)
Glibenclamide 10 mg bd plus metformin 850 mg bd	4 (1.9)			1 (1.2)	5 (0.7)
Glibenclamide 10 mg bd plus metformin 850 mg tds	15 (7.1)	9 (4.1)		7 (8.4)	31 (4.4)
Glibenclamide 10 mg mane, 5 mg nocte					
Glibenclamide 10 mg mane, 5 mg nocte plus metformin 1000 mg tds	10 (4.8)				10 (1.4)
Glibenclamide 10 mg mane, 5 mg nocte plus metformin 500 mg tds	2 (1.0)		3 (1.6)		5 (0.7)
Glibenclamide 10 mg mane, 5 mg nocte plus metformin 850 mg tds	7 (3.3)	5 (2.3)		2 (2.4)	14 (2.0)
Glibenclamide 10 mg od plus metformin 1000 mg tds	1 (0.5)	12 (5.4)	17 (9.2)	4 (4.8)	34 (4.9)
Glibenclamide 10 mg od plus metformin 500 mg tds	9 (4.3)	5 (2.3)	10 (5.4)	4 (4.8)	28 (4.0)
Glibenclamide 10 mg od plus metformin 850 mg bd	13 (6.2)				13 (1.9)
Glibenclamide 10 mg od plus metformin 850 mg tds	19 (9.0)	60 (27.1)	82 (44.3)	11 (13.3)	172 (24.6)
Glibenclamide 10 mg tds plus metformin 850 mg tds	6 (2.9)				6 (0.9)
Glibenclamide 15 mg mane, 10 mg nocte plus metformin 1000 mg tds	1 (0.5)				1 (0.1)
Glibenclamide 2.5 mg od plus metformin 850 mg bd	1 (0.5)				1 (0.1)
Glibenclamide 5 mg bd plus metformin 1000 mg tds			4 (2.2)	1 (1.2)	5 (0.7)
Glibenclamide 5 mg bd plus metformin 500 mg tds	9 (4.3)		13 (7.0)	4 (4.8)	26 (3.7)
Glibenclamide 5 mg bd plus metformin 850 mg bd	2 (1.0)				2 (0.3)
Glibenclamide 5 mg bd plus metformin 850 mg tds	15 (7.1)		5 (2.7)	8 (9.6)	28 (4.0)
Glibenclamide 5 mg od plus metformin 1000 mg tds		5 (2.3)	5 (2.7)	1 (1.2)	11 (1.6)
Glibenclamide 5 mg od plus metformin 500 mg bd					
Glibenclamide 5 mg od plus metformin 500 mg od			3 (1.6)		3 (0.4)

Table 4.8: Prescribing pattern of prescribing oral hypoglycaemic agents as a combination therapy continued

Agent/regimen	Number of prescriptions/patient n (%)				Total
	DHC (n = 210)	MBT (n = 221)	QFC (n = 185)	LFC (n =83)	
Glibenclamide 5 mg od plus metformin 500 mg tds	45 (21.4)	31 (14.0)	9 (4.9)	9 (10.8)	94 (13.4)
Glibenclamide 5 mg od plus metformin 850 mg bd	14 (6.7)				14 (2.0)
Glibenclamide 5 mg od plus metformin 850 mg od	1 (0.5)		1 (0.5)		1 (0.1)
Glibenclamide 5 mg od plus metformin 850 mg tds	27 (12.9)	82 (37.1)	28 (15.1)	23 (27.7)	160 (22.9)
TOTALs	210	221	185	83	699 (100)

Od = once a day; bd = twice a day; tds = three times a day; mane = in the morning; nocte = in the evening

The antidiabetic agents used together as three agents are indicated in Table 4.9.

Table 4.9: Percentage frequency distribution prescribed triple therapies of antidiabetic drug regimens according to study sites

Agent/regimen	Number of prescriptions n (%)				Totals
	DHC (n = 7)	MBT (n = 0)	QFC (n = 6)	LFC (n = 3)	N (%)
Actraphane® 40 units mane, 20 units nocte plus glibenclamide 5 mg od plus metformin 500 mg tds	4 (57.1%)	-	-	-	4 (25)
Actrapid® 20 units STAT plus glibenclamide 5 mg od plus metformin 850 mg tds	1 (14.3%)	-	-	3 (100%)	4 (25)
Actraphane® 30 units mane, 15 units nocte plus glibenclamide 5 mg od plus metformin 850 mg tds	1 (14.3)	-	-	-	1 (6.3)
Actraphane® 48 units mane, 12 units nocte plus glibenclamide 10 mg od plus metformin 1000 mg tds	-	-	5 (83.3%)	-	5 (310.)
Actrapid® 20 units STAT plus glibenclamide 10 mg mane, 5 mg nocte plus metformin 850 mg tds	1 (14.3%)	-	-	-	1 (6.3)
Actraphane® 24 units mane, 18 units nocte plus glibenclamide 5 mg od plus metformin 500 mg tds	-	-	1 (1.7%)	-	1 (6.3)
TOTAL	7	0	6	3	16 (100.0)

Mane = in the morning; nocte = in the evening; od = once a day; tds = three times a day; stat = immediately

Table 4.10 illustrates the different regimens of insulin and glibenclamide combination therapy.

Table 4.10: The frequency of prescribing insulin and glibenclamide combination therapy

Agent/regimen	Number of prescriptions/patient n (%)	
	DHC (n = 11)	QFC (n = 2)
Actraphane 15 units mane, glibenclamide 10 mg od	1 (9.1)	
Actraphane 28 units mane, 14 units nocte plus glibenclamide 10 mg od	1 (9.1)	
Actraphane 28 units mane, 14 units nocte plus glibenclamide 10 mg od plus glibenclamide 10 mg STAT	4 (36.4)	
Actraphane 30 units mane, 15 units nocte plus glibenclamide 5 mg od		
Actraphane 40 units mane, 20 units nocte plus glibenclamide 5 mg od	3 (27.3)	
Actrapid 20 units STAT plus Glibenclamide 5 mg od	2 (18.2)	
Atrapid 10 STAT plus glibenclamide 5 od		2 (100.0)

Mane = in the morning; nocte = in the evening; od = once per day; STAT = immediately

4.4.2 Discussion

The results of the study indicated a high frequency of using metformin as a single agent, the regimen that was mostly used being metformin 500 mg three times per day followed by

metformin 850 mg three times per day. In combination antidiabetic drug treatments, metformin 850 mg times per day combined with glibenclamide 10 mg times a day was found to be most prescribed combination therapy. These findings indicate that the healthcare providers prescribe antidiabetic agents largely according to recommendations of the standard treatment guidelines of Lesotho (LSTG, 2005:117). The guidelines recommend that metformin should be used as a drug of first choice especially in obese patients, then addition of a second drug, sulfonylureas or basal insulin (refer to Figure 2.1), can be considered if target is still not met and *vice versa*. According to Turner *et al.* (1999:2005), insulin and metformin as monotherapy would reduce the progression of diabetes mellitus for about three years, but after about 9 years the disease progression would increase and the majority of patients would need multiple therapies to attain glycaemic targets in the long term. The findings of Turner *et al*. coincide with this study, as insulin was a drug that was also prescribed quite frequently as a single agent (refer to Table 4.5). The type of insulin that was mostly used at the study sites was Actraphane®.

Chlorpropamide does not appear under the LSTG (refer to Figure 2.1) but was prescribed at Domiciliary Health Center and Qoaling filter clinic (refer to Table 4.8). This indicates non-compliance to the standard treatment guidelines.

The study also revealed that the combination therapy consisting of metformin and Actraphane® were prescribed in 0.3% to 10.6% of prescriptions at the respective clinics (refer to Table 4.6). The regimens that were specifically mostly prescribed in this study were Actraphane® 20 units in the morning, and 10 units in the evening plus metformin 500 mg three times a day and Actraphane® 30 units in the morning in the morning and 15 units in the evening plus metformin 850 mg three times a day. The use of combination therapies of metformin and Actraphane® is considered a good clinical choice (Strowig *et al*., 2002:1691). According to Strowig and colleagues (2002:1691), the combination of these two drugs results in significantly improvement in glycaemic control in type 2 diabetes patients comparable to those achieved by insulin as monotherapy.

Combination regimens of glibenclamide and metformin that were frequently prescribed, at different study sites were glibenclamide 5 mg per day and metformin 850 mg three times per day (refer to Table 4.8); glibenclamide 10 mg daily plus metformin 850 mg three times daily at Qoaling filter clinic and glibenclamide 5 mg per day plus metformin 500 mg three times a day at Domiciliary Health Centre. The choice of using glibenclamide and metformin combination are supported by Garber *et al*. (2003:3603), who indicated that the combination of glibenclamide and metformin provides a higher efficacy as initial therapy in patients with different blood glucose levels, therefore the safest and effective choice for patients with type 2 DM.

The antidiabetic agents were also used as triple therapies for a few patients (n = 13) as shown by the combinations used of Actraphane, metformin and glibenclamide (Actraphane® 40 units in the morning, 20 units in the evening plus glibenclamide 5 mg daily plus metformin 500 mg three times per day; Actraphane® 48 units in the morning, 12 units in the evening plus glibenclamide 10 mg daily plus metformin 1000 mg three times per day; and Actrapid® 20 units immediately plus glibenclamide 5 mg daily plus metformin 850 mg three times per day at Domiciliary Health Center, Qoaling and the Likotsi filter clinic. According to the Lesotho standard treatment guidelines (LSTG, 2005:118), a combination of glibenclamide, metformin and Actraphane® is a third line regimen in the management of diabetes mellitus. Since there are very few patients managed by the use of this third line recommended regimen of three drugs it can be speculated diabetic patients generally are well managed according to the LSTG.

In conclusion, all of the above mentioned regimens were in line with the treatment guidelines of Lesotho except chlorpropamide. The same however, cannot be said about the appropriateness of drug dosages used in treating patients as patients body weights were not recorded in their bukanas for use in cross-checking the correctness of prescribed drug doses. It can also not be claimed that choices of antidiabetic agents were based on patients' body weight.

4.5 POTENTIAL DRUG-DRUG INTERACTIONS

In this section, the potential drug-drug interactions that were observed in the study are reported and discussed.

4.5.1 Results

Potential drug-drug interactions observed in the study included possible interactions between metformin and cimetidine; glibenclamide and furosemide; and glibenclamide and hydrochlorothiazide. Only 5 (N = 337) patients studied were prescribed metformin with cimetidine, and 6 (N = 337) were given glibenclamide in combination with furosemide.

4.5.2 Discussions

Potential drug-drug interactions established in this study may have moderate effects on blood glucose levels according to Tatro (2002:856). Such patients needed to be monitored for their blood glucose level to avoid hypoglycaemia. The patients should be made aware of some of the familiar warning signs of hypoglycaemia like tachycardia, tremor, and sweating (paragraph 2.9.1.1).

4.6 ANALYSIS OF COST OF ANTIDIABETIC DRUGS ACCORDING TO TREATMENT REGIMENS

In this section, results of costs of antidiabetic drug usage determinations based on costs of treatment regimens as used at study sites have been presented and discussed. The costs of the different regimens are shown in Tables 4.11 to 4.15.

4.6.1 Results

The cost of antidiabetic agents was analysed and the following data was obtained:

- Table 4.11 portrays the cost of regimens consisting of single prescribed drugs. The total cost incurred for all the oral agents prescribed alone with different regimens was M75.6. The weighted average cost per patient was M0.81 ± 2.06 per day. The regimen that was most expensive when compared with others in the category of single drug prescription (Table 4.11) was metformin 850 mg three times per day, accounting for M20.1 or 26.6% of the total costs incurred.
- Table 4.12 portray the cost of regimens containing Actraphane® only. The total cost incurred on Actraphane® in a month was M40 660.52, indicating that it was the most expensive antidiabetic agent. The most costly Actraphane® regimen that was prescribed was Actraphane® 44 units in the morning and 22 units in the evening (M1 099.77). The weighted average cost per patient was M21.43 ± 6.23 per day.
- The overall cost of Actraphane® and metformin combination therapy amounted to M62 313.00, at an average cost per patient of M21.77 ± 6.80 per day Table 4.13). The specific regimen which was more costly than others was Actraphane® 60 units in the morning, 30 units in the evening plus metformin 1000 mg three times a day, amounting to M19 062.00 per month.
- The second combination therapies that were expensive include Actraphane® 40 units in the morning, 24 units in the evening plus metformin 850 mg three times per day and Actraphane® 42 units in the morning, 20 units in the evening plus metformin 850 mg three times per day three times per day at a cost of M1 021.8 per regimen.
- The cost of combination therapy consisting of metformin and glibenclamide (Table 4.14) amounted to M377.10, with the most costly regimen being glibenclamide 10 mg three times daily plus metformin 850 mg three times daily (total cost per month = M22.2). The weighted average cost per patient amounted to M0.49 ± 0.16 per day.

Table 4.11 indicates the cost of regimes used as single agents, whereas Table 4.12 shows the cost incurred per regimen of Actraphane®.

Table 4.11: Cost of regimens containing single agents

Single drug regimen (unit pack)	Cost/ unit pack (M)	Cost/ tablet (M)	Cost/ day (M)	Cost/ month (M)
Chlorpropamide 500 mg BD (1000)	94.22	0.09	0.19	5.7
Chlorpropamide 500 mg OD (1000)	94.22	0.09	0.09	2.7
Glibenclamide 10 mg mane, 5 mg nocte (1000 mg)	39.05	0.04	0.12	3.6
Glibenclamide 10 mg OD (1000)	39.05	0.04	0.08	2.4
Glibenclamide 5 mg BD (1000)	39.05	0.04	0.08	2.4
Glibenclamide 5 mg OD (1000)	39.05	0.04	0.04	1.2
Metformin 1000 mg TDS	66.67	0.07	0.40	12
Metformin 500 mg BD (1000)	66.67	0.07	0.13	3.9
Metformin 500 mg OD (100)	66.67	0.07	0.07	2.1
Metformin 500 mg TDS (1000)	66.67	0.07	0.20	6
Metformin 850 mg BD (1000)	224.44	0.22	0.45	13.5
Metformin 850 mg TDS (1000)	224.44	0.22	0.67	20.1
Total	**1 060.20**	**1.06**	**2.52**	**75.6**

Od = once per day; bd = twice per day; tds = three times per day; mane = in the morning; nocte = in the evening; FOP = Frequency of prescribing

Table 4.12: Cost of regimens containing Actraphane® only

Agent/ regimen	Total units/day	cost/ unit (M)	cost/day (M)	Cost/ month (M)
Actraphane® 10 units nocte	10	0.5237	5.24	157.20
Actraphane® 16 units nocte	16	0.5237	8.38	251.40
Actraphane® 20 units nocte	20	0.5237	10.47	314.41
Actraphane® 26 units nocte	26	0.5237	13.62	408.60
Actraphane® 40 units nocte	40	0.5237	20.95	628.5
Actraphane® 10 units mane, 5 units nocte	15	0.5237	7.86	235.665
Actraphane® 10 units mane, 8 units nocte	18	0.5237	9.43	282.798
Actraphane® 12 units mane, 6 units nocte	18	0.5237	9.43	282.798
Actraphane® 14 units mane, 12 units nocte	26	0.5237	13.62	408.486
Actraphane® 15 units mane, 12 units nocte	27	0.5237	14.14	424.197
Actraphane® 16 units mane, 10 units nocte	26	0.5237	13.62	408.486
Actraphane® 16 units mane, 12 units nocte	38	0.5237	19.90	597.018
Actraphane® 16 units mane, 8 units nocte	24	0.5237	12.57	377.064
Actraphane® 18 units mane, 10 units nocte	28	0.5237	14.66	439.908
Actraphane® 18 units mane, 12 units nocte	30	0.5237	15.71	471.33
Actraphane® 18 units mane, 15 units nocte	33	0.5237	17.28	518.463
Actraphane® 18 units mane, 8 units nocte	26	0.5237	13.62	408.486
Actraphane® 20 units mane, 10 units nocte	30	0.5237	15.71	471.33
Actraphane® 20 units mane, 12 units nocte	32	0.5237	16.76	502.752

Table 4.12: Cost of regimens containing Actraphane® only continued

Agent/ regimen	Total units/day	cost/ unit (M)	cost/day (M)	Cost/ month (M)
Actraphane® 22 units mane, 12 units nocte	34	0.5237	17.81	534.174
Actraphane® 22 units mane, 15 units nocte	37	0.5237	19.38	581.307
Actraphane® 23 units mane, 13 units nocte	36	0.5237	18.85	565.596
Actraphane® 24 units mane, 10 units nocte	34	0.5237	17.81	534.174
Actraphane® 24 units mane, 12 units nocte	36	0.5237	18.85	565.596
Actraphane® 24 units mane, 14 units nocte	38	0.5237	19.90	597.018
Actraphane® 25 units mane, 15 units nocte	40	0.5237	20.95	628.44
Actraphane® 25 units mane, 20 units nocte	45	0.5237	23.57	706.995
Actraphane® 26 units mane, 12 units nocte	38	0.5237	19.90	597.018
Actraphane® 26 units mane, 13 units nocte	39	0.5237	20.42	612.729
Actraphane® 26 units mane, 14 units nocte	40	0.5237	20.95	628.44
Actraphane® 26 units mane, 16 units nocte	42	0.5237	22.00	659.862
Actraphane® 26 units mane, 18 units nocte	44	0.5237	23.04	691.284
Actraphane® 27 units mane, 18 units nocte	45	0.5237	23.57	706.995
Actraphane® 28 units mane, 14 units nocte	42	0.5237	22.00	659.862
Actraphane® 28 units mane, 17 units nocte	45	0.5237	23.57	706.995
Actraphane® 28 units mane, 22 units nocte	50	0.5237	26.19	785.55
Actraphane® 29 units mane, 14 units nocte	33	0.5237	17.28	518.463
Actraphane® 30 units mane, 10 unit nocte	40	0.5237	20.95	628.44
Actraphane® 30 units mane, 12 units nocte	42	0.5237	22.00	659.862
Actraphane® 30 units mane, 14 units nocte	44	0.5237	23.04	691.284
Actraphane® 30 units mane, 15 units nocte	45	0.5237	23.57	706.995
Actraphane® 30 units mane, 16 units nocte	43	0.5237	22.52	675.573
Actraphane® 30 units mane, 20 units nocte	50	0.5237	26.19	785.55
Actraphane® 32 units mane, 16 units nocte	48	0.5237	25.14	754.128
Actraphane® 34 units mane, 17 unit nocte	51	0.5237	26.71	801.261
Actraphane® 35 units mane, 12 units nocte	47	0.5237	24.61	738.417
Actraphane® 35 units mane, 15 units nocte	50	0.5237	26.19	785.55
Actraphane® 35 units mane, 20 units nocte	55	0.5237	28.80	864.105
Actraphane® 36 units mane, 16 units nocte	52	0.5237	27.23	816.972
Actraphane® 36 units mane, 18 units nocte	54	0.5237	28.28	848.394
Actraphane® 38 units mane, 16 units nocte	54	0.5237	28.28	848.394
Actraphane® 38 units mane, 18 units nocte	56	0.5237	29.33	879.816
Actraphane® 40 units mane, 11 units nocte	51	0.5237	26.71	801.261
Actraphane® 40 units mane, 15 units nocte	55	0.5237	28.80	864.105
Actraphane® 40 units mane, 16 units nocte	56	0.5237	29.33	879.816
Actraphane® 40 units mane, 18 units nocte	58	0.5237	30.37	911.238
Actraphane® 40 units mane, 20 units nocte	60	0.5237	31.42	942.66

Table 4.12: Cost of regimens containing Actraphane® only continued

Agent/ regimen	Total units/day	cost/ unit (M)	cost/day (M)	Cost/ month (M)
Actraphane® 42 units mane, 16 units nocte	68	0.5237	35.61	1068.348
Actraphane® 42 units mane, 20 units nocte	62	0.5237	32.47	974.082
Actraphane® 44 units mane, 22 units nocte	66	0.5237	34.56	1036.926
Actraphane® 44 units mane, 26 units nocte	70	0.5237	36.66	1099.77
Actraphane® 46 units mane, 16 units nocte	62	0.5237	32.47	974.082
Total	**2604**	**32.99**	**1363.75**	**40 660.52**

mane = in the morning' nocte = in the evening;

Table 4.13 and 4.14 indicate the cost of different regimens of metformin plus Actraphane® and metformin and glibenclamide combination therapy respectively.

Table 4.13: The cost of regimens used in Actraphane® and metformin combination therapy

Agent/regimen	c/u (M)	total u/d (M)	units c/d (M)	Cost/ tab (M)	tabs/day (n)	tabs c/d (M)	TC/Day (M)	TC/ month (M)
Actraphane® 10 units mane, 5 units nocte plus metformin 1000 mg tds	0.52	15.00	7.86	0.06	6.00	0.35	8.20	246
Actraphane® 10 units mane, 20 units nocte plus metformin 500 mg tds	0.52	30.00	15.71	0.06	3.00	0.17	15.89	246
Actraphane® 12 units mane, 6 units nocte plus metformin 850 mg tds	0.52	18.00	9.43	0.18	3.00	0.54	9.97	299.1
Actraphane® 14 units mane, 10 units nocte plus metformin 500 mg tds	0.52	34.00	17.81	0.18	3.00	0.54	18.35	299.1
Actraphane® 14 units mane, 12 units nocte plus metformin 850 mg tds	0.52	36.00	18.85	0.18	3.00	0.54	19.39	581.7
Actraphane® 14 units nocte, metformin 850 mg tds	0.52	14.00	7.33	0.18	3.00	0.54	7.87	581.7
Actraphane® 15 units mane, 12 units nocte plus metformin 1000 mg tds	0.52	27.00	14.14	0.06	6.00	0.35	14.49	434.7
Actraphane® 15 units mane, 5 units nocte plus metformin 850 mg tds	0.52	20.00	10.47	0.18	3.00	0.54	11.01	434.7
Actraphane® 16 units mane, 12 units nocte plus metformin 850 mg tds	0.52	28.00	14.66	0.18	3.00	0.54	15.20	456
Actraphane® 18 units mane, 12 units nocte plus metformin 500 mg tds	0.52	30.00	15.71	0.06	3.00	0.17	15.89	456
Actraphane® 18 units mane, 12 units nocte plus metformin 850 mg tds	0.52	30.00	15.71	0.18	3.00	0.54	16.25	487.5
Actraphane® 18 units mane, 14 units nocte plus metformin 500 mg tds	0.52	32.00	16.76	0.06	3.00	0.17	16.93	487.5
Actraphane® 18 units mane, 14 units nocte plus metformin 850 mg tds	0.52	32.00	16.76	0.18	3.00	0.54	17.30	519
Actraphane® 20 units mane, 10 units nocte plus metformin 1000 mg tds	0.52	30.00	15.71	0.06	6.00	0.35	16.06	519
Actraphane® 20 units mane, 10 units nocte plus metformin 500 mg tds	0.52	30.00	15.71	0.06	3.00	0.17	15.89	476.7
Actraphane® 20 units mane, 10 units nocte plus metformin 850 mg bd	0.52	30.00	15.71	0.18	2.00	0.36	16.07	476.7
Actraphane® 20 units mane, 10 units nocte plus metformin 850 mg tds	0.52	30.00	15.71	0.18	3.00	0.54	16.25	487.5
Actraphane® 20 units mane, 12 units nocte plus metformin 500 mg tds	0.52	32.00	16.76	0.06	3.00	0.17	16.93	487.5
Actraphane® 20 units mane, 12 units nocte plus metformin 850 mg tds	0.52	32.00	16.76	0.18	3.00	0.54	17.30	519

Table 4.13: The cost of regimens used in Actraphane® and metformin combination therapy continued

Agent/regimen	c/u (M)	total u/d (M)	units c/d (M)	Cost/ tab (M)	tabs/day (n)	tabs c/d (M)	TC/Day (M)	TC/ month (M)
Actraphane® 20 units mane, 15 units nocte plus metformin 500 mg tds	0.52	35.00	18.33	0.06	3.00	0.17	18.50	519
Actraphane® 20 units mane, 15 units nocte plus metformin 850 mg tds	0.52	35.00	18.33	0.18	3.00	0.54	18.87	566.1
Actraphane® 24 units mane, 10 units nocte plus metformin 500 mg tds	0.52	35.00	18.33	0.06	3.00	0.17	18.50	566.1
Actraphane® 24 units mane, 12 units nocte plus metformin 500 mg tds	0.52	36.00	18.85	0.06	3.00	0.17	19.03	570.9
Actraphane® 24 units mane, 12 units nocte plus metformin 850 mg tds	0.52	36.00	18.85	0.18	3.00	0.54	19.39	570.9
Actraphane® 24 units mane, 18 units nocte plus metformin 500 mg tds	0.52	42.00	22.00	0.06	3.00	0.17	22.17	665.1
Actraphane® 24 units nocte, metformin 850 mg bd	0.52	24.00	12.57	0.18	2.00	0.36	12.93	665.1
Actraphane® 25 units mane, 15 units nocte plus metformin 500 mg tds	0.52	40.00	20.95	0.06	3.00	0.17	21.12	633.6
Actraphane® 25 units mane, 18 units nocte plus metformin 850 mg tds	0.52	43.00	22.52	0.18	3.00	0.54	23.06	633.6
Actraphane® 26 units mane, 12 units nocte plus metformin 850 mg bd	0.52	38.00	19.90	0.18	2.00	0.36	20.26	607.8
Actraphane® 26 units mane, 12 units nocte plus metformin 850 mg tds	0.52	38.00	19.90	0.18	3.00	0.54	20.44	607.8
Actraphane® 26 units mane, 14 units nocte plus metformin 500 mg tds	0.52	40.00	20.95	0.06	3.00	0.17	21.12	633.6
Actraphane® 26 units mane, 14 units nocte plus metformin 850 mg tds	0.52	40.00	20.95	0.18	3.00	0.54	21.49	633.6
Actraphane® 26 units mane, 24 units nocte plus metformin 850 mg tds	0.52	50.00	26.19	0.18	3.00	0.54	26.73	801.9
Actraphane® 28 units mane, 12 units nocte plus metformin 500 mg tds	0.52	40.00	20.95	0.06	3.00	0.17	21.12	801.9
Actraphane® 28 units mane, 14 units nocte plus metformin 500 mg tds	0.52	42.00	22.00	0.06	3.00	0.17	22.17	665.1
Actraphane® 20 units mane, 10 units nocte plus metformin 850 mg tds	0.52	30.00	15.71	0.18	3.00	0.54	16.25	487.5
Actraphane® 20 units mane, 12 units nocte plus metformin 500 mg tds	0.52	32.00	16.76	0.06	3.00	0.17	16.93	487.5
Actraphane® 20 units mane, 12 units nocte plus metformin 850 mg tds	0.52	32.00	16.76	0.18	3.00	0.54	17.30	519

Table 4.13: The cost of regimens used in Actraphane® and metformin combination therapy continued

Agent/regimen	c/u (M)	total u/d (M)	units c/d (M)	Cost/ tab (M)	tabs/day (n)	tabs c/d (M)	TC/Day (M)	TC/ month (M)
Actraphane® 20 units mane, 15 units nocte plus metformin 500 mg tds	0.52	35.00	18.33	0.06	3.00	0.17	18.50	519
Actraphane® 20 units mane, 15 units nocte plus metformin 850 mg tds	0.52	35.00	18.33	0.18	3.00	0.54	18.87	566.1
Actraphane® 24 units mane, 10 units nocte plus metformin 500 mg tds	0.52	35.00	18.33	0.06	3.00	0.17	18.50	566.1
Actraphane® 24 units mane, 12 units nocte plus metformin 500 mg tds	0.52	36.00	18.85	0.06	3.00	0.17	19.03	570.9
Actraphane® 24 units mane, 12 units nocte plus metformin 850 mg tds	0.52	36.00	18.85	0.18	3.00	0.54	19.39	570.9
Actraphane® 24 units mane, 18 units nocte plus metformin 500 mg tds	0.52	42.00	22.00	0.06	3.00	0.17	22.17	665.1
Actraphane® 24 units nocte, metformin 850 mg bd	0.52	24.00	12.57	0.18	2.00	0.36	12.93	665.1
Actraphane® 25 units mane, 15 units nocte plus metformin 500 mg tds	0.52	40.00	20.95	0.06	3.00	0.17	21.12	633.6
Actraphane® 25 units mane, 18 units nocte plus metformin 850 mg tds	0.52	43.00	22.52	0.18	3.00	0.54	23.06	633.6
Actraphane® 26 units mane, 12 units nocte plus metformin 850 mg bd	0.52	38.00	19.90	0.18	2.00	0.36	20.26	607.8
Actraphane® 26 units mane, 12 units nocte plus metformin 850 mg tds	0.52	38.00	19.90	0.18	3.00	0.54	20.44	607.8
Actraphane® 26 units mane, 14 units nocte plus metformin 500 mg tds	0.52	40.00	20.95	0.06	3.00	0.17	21.12	633.6
Actraphane® 26 units mane, 14 units nocte plus metformin 850 mg tds	0.52	40.00	20.95	0.18	3.00	0.54	21.49	633.6
Actraphane® 26 units mane, 24 units nocte plus metformin 850 mg tds	0.52	50.00	26.19	0.18	3.00	0.54	26.73	801.9
Actraphane® 28 units mane, 12 units nocte plus metformin 500 mg tds	0.52	40.00	20.95	0.06	3.00	0.17	21.12	801.9
Actraphane® 28 units mane, 14 units nocte plus metformin 500 mg tds	0.52	42.00	22.00	0.06	3.00	0.17	22.17	665.1
Actraphane® 28 units mane, 14 units nocte plus metformin 850 mg tds	0.52	42.00	22.00	0.18	3.00	0.54	22.54	665.1
Actraphane® 28 units mane, 17 units nocte plus metformin 500 mg tds	0.52	45.00	23.57	0.06	3.00	0.17	23.74	712.2
Actraphane® 28 units mane, 20 units nocte plus metformin 850 mg tds	0.52	48.00	25.14	0.18	3.00	0.54	25.68	712.2

Table 4.13: The cost of regimens used in Actraphane® and metformin combination therapy continued

Agent/regimen	c/u (M)	total u/d (M)	units c/d (M)	Cost/ tab (M)	tabs/day (n)	tabs c/d (M)	TC/Day (M)	TC/ month (M)
Actraphane® 29 units mane, 14 units nocte plus metformin 850 mg tds	0.52	43.00	22.52	0.18	3.00	0.54	23.06	691.8
Actraphane® 30 units mane, 10 units nocte plus metformin 500 mg tds	0.52	40.00	20.95	0.06	3.00	0.17	21.12	691.8
Actraphane® 30 units mane, 10 units nocte plus metformin 850 mg tds	0.52	40.00	20.95	0.18	3.00	0.54	21.49	644.7
Actraphane® 30 units mane, 12 units nocte plus metformin 850 mg bd	0.52	42.00	22.00	0.18	2.00	0.36	22.36	644.7
Actraphane® 30 units mane, 12 units nocte plus metformin 850 mg tds	0.52	42.00	22.00	0.18	3.00	0.54	22.54	676.2
Actraphane® 30 units mane, 15 units nocte plus metformin 500 mg od	0.52	35.00	18.33	0.06	1.00	0.06	18.39	676.2
Actraphane® 30 units mane, 15 units nocte plus metformin 500 mg tds	0.52	35.00	18.33	0.06	3.00	0.17	18.50	555
Actraphane® 30 units mane, 15 units nocte plus metformin 850 mg tds	0.52	35.00	18.33	0.18	3.00	0.54	18.87	555
Actraphane® 30 units mane, 16 units nocte metformin 850 mg tds	0.52	36.00	18.85	0.18	3.00	0.54	19.39	581.7
Actraphane® 30 units mane, 16 units nocte plus metformin 1000 mg tds	0.52	36.00	18.85	0.06	6.00	0.35	19.20	581.7
Actraphane® 30 units mane, 20 units nocte plus metformin 850 mg tds	0.52	50.00	26.19	0.18	3.00	0.54	26.73	801.9
Actraphane® 30 units mane, 60 units nocte plus metformin 500 mg tds	0.52	90.00	47.13	0.06	3.00	0.17	47.31	801.9
Actraphane® 32 units mane, 10 units nocte plus metformin 500 mg tds	0.52	42.00	22.00	0.06	3.00	0.17	22.17	665.1
Actraphane® 32 units mane, 12 units nocte plus metformin 500 mg tds	0.52	42.00	22.00	0.06	3.00	0.17	22.17	665.1
Actraphane® 32 units mane, 16 units nocte plus metformin 500 mg tds	0.52	48.00	25.14	0.06	3.00	0.17	25.31	759.3
Actraphane® 32 units mane, 16 units nocte plus metformin 850 mg tds	0.52	48.00	25.14	0.18	3.00	0.54	25.68	759.3
Actraphane® 34 units mane, 14 units nocte plus metformin 850 mg tds	0.52	48.00	25.14	0.18	3.00	0.54	25.68	770.4
Actraphane® 34 units mane, 15 units nocte plus metformin 850 mg tds	0.52	49.00	25.66	0.18	3.00	0.54	26.20	770.4
Actraphane® 34 units mane, 18 units nocte plus metformin 850 mg tds	0.52	52.00	27.23	0.18	3.00	0.54	27.77	833.1

Table 4.13: The cost of regimens used in Actraphane® and metformin combination therapy continued

Agent/regimen	c/u (M)	total u/d (M)	units c/d (M)	Cost/ tab (M)	tabs/day (n)	tabs c/d (M)	TC/Day (M)	TC/ month (M)
Actraphane® 34 units mane, 20 units nocte plus metformin 850 mg od	0.52	54.00	28.28	0.18	1.00	0.18	28.46	833.1
Actraphane® 34 units mane, 20 units nocte plus metformin 850 mg tds	0.52	54.00	28.28	0.18	3.00	0.54	28.82	864.6
Actraphane® 35 units mane, 10 units nocte plus metformin 850 mg tds	0.52	45.00	23.57	0.18	3.00	0.54	24.11	864.6
Actraphane® 35 units mane, 12 units nocte plus metformin 500 mg tds	0.52	47.00	24.61	0.06	3.00	0.17	24.79	743.7
Actraphane® 35 units mane, 15 units nocte plus metformin 500 mg tds	0.52	50.00	26.19	0.06	3.00	0.17	26.36	743.7
Actraphane® 36 units mane, 18 units nocte plus metformin 500 mg tds	0.52	54.00	28.28	0.06	3.00	0.17	28.45	853.5
Actraphane® 36 units mane, 22 units nocte plus metformin 500 mg tds	0.52	58.00	30.37	0.06	3.00	0.17	30.55	853.5
Actraphane® 40 units mane, 20 units nocte plus metformin 500 mg tds	0.52	60.00	31.42	0.06	3.00	0.17	31.60	948
Actraphane® 40 units mane, 20 units nocte plus metformin 850 mg tds	0.52	60.00	31.42	0.18	3.00	0.54	31.96	948
Actraphane® 40 units mane, 24 units nocte plus metformin 850 mg tds	0.52	64.00	33.52	0.18	3.00	0.54	34.06	1021.8
Actraphane® 42 units mane, 20 units nocte plus metformin 850 mg tds	0.52	62.00	32.47	0.18	3.00	0.54	33.01	1021.8
Actraphane® 44 units mane, 14 units nocte plus metformin 850 mg tds	0.52	58.00	30.37	0.18	3.00	0.54	30.91	927.3
Actraphane® 44 units mane, 26 units nocte plus metformin 500 mg tds	0.52	70.00	36.66	0.06	3.00	0.17	36.83	927.3
Actraphane® 46 units mane, 16 units nocte plus metformin 500 mg tds	0.52	62.00	32.47	0.06	3.00	0.17	32.64	979.2
Actraphane® 46 units mane, 16 units nocte plus metformin 850 mg tds	0.52	62.00	32.47	0.18	3.00	0.54	33.01	979.2
Actraphane® 48 units mane, 12 units nocte plus metformin 1000 mg tds	0.52	60.00	31.42	0.06	3.00	0.17	31.60	948
Actraphane® 50 units mane, 16 units nocte plus metformin 500 mg tds	0.52	66.00	34.56	0.06	3.00	0.17	34.74	948
Actraphane® 60 units mane, 30 units nocte plus metformin 1000 mg tds	0.52	90.00	47.13	0.06	3.00	0.17	47.31	1419.3
Total	**48.88**	**3916.00**	**2050.87**	**11.64**	**284.00**	**33.65**	**2084.63**	**62131.00**

Cost per unit; u/d = unit per day; c/u = cost per unit; tabs/day = tablets per day; tabs c/d = tablets cost per day; TC/Day = total cost per day, TC/month = total cost per month

Table 4.14: The cost of different regimens employed in combination therapy of glibenclamide and metformin

Agent/regimen	c/tab (glib)	tot tabs/ day	C/D	c/tab (met)	tot tabs/ day	C/D	TC/day	TC/Month
Chlorpropamide 250 mg od plus glibenclamide 5 mg od	0.08	1	0.08	0.34	1	0.34	0.42	12.6
Chlorpropamide 250 mg tds plus metformin 1000 mg tds	0.08	3	0.24	0.06	6	0.35	0.59	17.7
Chlorpropamide 500 mg od plus metformin 850 mg tds	0.08	2	0.16	0.18	3	0.54	0.7	21
Glibenclamide 10 mg bd plus metformin 1000 mg tds	0.03	4	0.14	0.06	6	0.35	0.49	14.7
Glibenclamide 10 mg bd plus metformin 1000 mg tds	0.03	4	0.14	0.06	6	0.35	0.49	14.7
Glibenclamide 10 mg bd plus metformin 500 mg tds	0.03	4	0.14	0.06	3	0.17	0.31	9.3
Glibenclamide 10 mg bd plus metformin 850 mg bd	0.03	4	0.14	0.18	2	0.36	0.5	15
Glibenclamide 10 mg bd plus metformin 850 mg tds	0.03	4	0.14	0.18	3	0.54	0.68	20.4
Glibenclamide 10 mg mane, 5 mg nocte plus metformin 1000 mg tds	0.03	3	0.1	0.06	6	0.35	0.45	13.5
Glibenclamide 10 mg mane, 5 mg nocte plus metformin 500 mg tds	0.03	3	0.1	0.06	3	0.17	0.27	8.1
Glibenclamide 10 mg mane, 5 mg nocte plus metformin 850 mg tds	0.03	3	0.1	0.18	3	0.54	0.64	19.2
Glibenclamide 10 mg od plus metformin 1000 mg tds	0.03	2	0.07	0.06	6	0.35	0.42	12.6
Glibenclamide 10 mg od plus metformin 500 mg tds	0.03	2	0.07	0.06	3	0.17	0.24	7.2
Glibenclamide 10 mg od plus metformin 850 mg bd	0.03	2	0.07	0.18	2	0.36	0.43	12.9
Glibenclamide 10 mg od plus metformin 850 mg tds	0.03	2	0.07	0.18	3	0.54	0.61	18.3
Glibenclamide 10 mg tds plus metformin 850 mg tds	0.03	6	0.2	0.18	3	0.54	0.74	22.2
Glibenclamide 15 mg mane, 10 nocte plus metformin 1000 mg tds	0.03	5	0.17	0.06	6	0.35	0.52	15.6
Glibenclamide 2.5 mg od plus metformin 850 mg bd	0.03	0.5	0.02	0.18	2	0.36	0.38	11.4
Glibenclamide 5 mg bd plus metformin 1000 mg tds	0.03	2	0.07	0.06	6	0.35	0.42	12.6
Glibenclamide 5 mg bd plus metformin 500 mg tds	0.03	2	0.07	0.06	3	0.17	0.24	7.2
Glibenclamide 5 bd mg plus metformin 850 mg bd	0.03	2	0.07	0.18	2	0.36	0.43	12.9

Table 4.14: The cost of different regimens employed in combination therapy of glibenclamide and metformin continued

Agent/regimen	c/tab (glib)	tot tabs/ day	C/D	c/tab (met)	tot tabs/ day	C/D	TC/day	TC/Month
Glibenclamide 5 mg bd plus metformin 850 mg tds	0.03	2	0.07	0.18	3	0.54	0.61	18.3
Glibenclamide 5 mg od plus metformin 1000 mg tds	0.03	1	0.03	0.06	6	0.35	0.38	11.4
Glibenclamide 5 mg od plus metformin 500 mg bd	0.03	1	0.03	0.06	2	0.12	0.15	4.5
Glibenclamide 5 mg od plus metformin 500 mg od	0.03	1	0.03	0.06	1	0.06	0.09	2.7
Glibenclamide 5 mg od plus metformin 500 mg tds	0.03	1	0.03	0.06	3	0.17	0.2	6
Glibenclamide 5 mg od plus metformin 850 mg bd	0.03	1	0.03	0.18	2	0.36	0.39	11.7
Glibenclamide 5 mg od plus metformin 850 mg od	0.03	1	0.03	0.18	1	0.18	0.21	6.3
Glibenclamide 5 mg od plus metformin 850 mg tds	0.03	1	0.03	0.18	3	0.54	0.57	17.1
Total	**1.12**	**69.5**	**2.64**	**3.55**	**99**	**9.93**	**12.57**	**377.10**

Od = once per day; bd = twice per day; tds = three times per day; mane = in the morning; nocte = in the evening; c/tab (glib) = cost per tablet of glibenclamide; tot.tabs/day = total number of tablets per day; C/D = cost per day; c/tab (met) = cost per tablet of metformin; TC/month = total cost per month

Table 4.15 indicates the Cohen's *d*-values for the different combination therapies.

Table 4.15: Cohen's *d*-values for the difference in cost of the antidiabetic combination therapies

Regimen	1a	1b	1c	1d
1a				
1b	**0.93**			
1c	0.05	**0.98**		
1d	0.06	**0.99**	0.01	
1e	**2.82**	**1.05**	**1.00**	**1.45**

1a = Single agents regimens; 1b = Actraphane® BD regimens; 1c = Actraphane® plus metformin combination therapy; 1d = metformin plus glibenclamide combination therapy; 1e = Actraphane® plus metformin plus glibenclamide combination therapy.

4.6.2 Discussion

The study revealed that the most expensive antidiabetic agent was Actraphane® and the combination therapies containing Actraphane®. The overall cost of insulin therapy will be expected to increase as more patients are moved to insulin therapy or insulin added to the drug therapy to maintain glycaemic control (Theodorou *et al*., 2011:5), this is the case in this study, as higher percentage of patients are on insulin. According to Gill *et al*. (2011:20) developing countries are usually financially challenged in the healthcare systems, as a result insulin is an expensive drug for these countries , and provision of insulin in such countries may require an increase of 10% of the total national healthcare budget, Lesotho included as a developing country. This indicates that Lesotho may be challenged financially as the percentage of patients put on Actraphane® or Actrapid® increases. There was a practical significant difference between the costs of regimen 1a and 1b, 1a and 1e, 1b and 1c, 1b and 1d, 1b and 1e, 1c and 1e, and 1d and 1e ($d < 0.8$). The combination therapies that were of practical significance consisted of Actraphane®, supporting that the cost of different regimens increases when insulin is added. It can therefore be speculated that delay of initiating insulin therapy will reduce the direct cost of antidiabetic agents.

4.7 CHAPTER SUMMARY

In this chapter the results obtained from the empirical investigation were presented and discussed with reference to relevant literature. The last chapter includes the conclusions and recommendations made from the study, and limitations encountered during the study.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

5.1 INTRODUCTION

In this chapter, the conclusions are drawn based on the main and specific objective of this study as outline in paragraph 1.3. The challenges encountered during the study and the recommendations will also be outlined.

5.2 THE CONCLUSIONS FROM THE LITERATURE REVIEW

These specific research objectives of the literature study were attained in chapter 2.

The first objective was to describe diabetes mellitus with respect to the classification, pathophysiology, diagnosis and signs, and symptoms

The search of literature indicated that diabetes mellitus (DM) is defined as a chronic condition caused by a relative or an absolute lack of insulin. Diabetes classification encompasses both clinical stages and aetiological types of diabetes, and other categories of hyperglycaemia. An elevated fasting glucose is divided into intermediate states which are IFG and IGT or type 2 diabetes mellitus. The aetiology types of diabetes are type 1, type 2, gestational diabetes and other specific types such as endocrinopathies and chemical or drug induced diabetes (paragraphs 2.2.1 and 2.2.2).

The evidence from literature indicates that the pathogenesis of type 1 diabetes mellitus involves genetic and environmental factors that cause to β-cell damage, usually leading to absolute insulin deficiency. The environmental factor that increases the risk of development of type 1 diabetes mellitus is congenital rubella infection, where up to 20% of such children later in life develop diabetes (paragraph 2.4.1). Genetic predisposition may play a role in development of type 2 diabetes mellitus. In spite of ICA being seen to be present, no association with HLA types in the development of the condition has been established. Individuals with type 2 diabetes mellitus also exhibit varying degrees of tissue resistance to insulin, impaired insulin secretion, and increased basal hepatic glucose production. Environmental factors such as obesity and sedentary lifestyle also contribute significantly to the development of insulin resistance (paragraph 2.4.1).

Based on the literature it is concluded that the signs and symptoms of type 1 and type 2 diabetes mellitus are similar, but they usually vary in intensity. The common clinical features of

diabetes are increased thirst (secondary to increased plasma osmolality), increased urination (due to osmotic diuresis secondary to glucose in urine), glycosuria, tiredness and increased superficial infections such as genital candidiasis) (paragraph 2.6). A diagnosis of diabetes can be made when one of the following is present: classic signs and symptoms of diabetes which help to classify as type 1 DM or type 2 DM (polyuria, polydipsia, ketonuria, and unexplained weight loss) combined with a random plasma glucose (RPG) ≥ 11.1 mmol/L; A FBG ≥ 7.0 mmol/L and after a standard OGTT, the venous plasma glucose concentration is ≥ 11.1 mmol/L at 2 hours. The OGTT should be performed in patients with FBG ≥ 5.6 mmol/L and <7.0 mmol/L (paragraph 2.7).

The second objective was to discuss the clinical management guidelines of type 2 diabetes mellitus and expected clinical outcome:

With reference to paragraph 2.10.2, treatment must be individualised on the basis of the type of diabetes and the specific needs of individual patient. However, certain general principles of management can be outlined for hyperglycaemic states of different types of patients. It is recommended that the first line of management is to start hypoglycaemic agents when lifestyle interventions alone are unable to maintain blood glucose control at target levels. Metformin is a first choice at the time of diagnosis in all patients (especially for obese patients). It is recommended that metformin be continued even when other classes of drugs are added. Metformin reduces HbA_{1c} by 1–2%. Sulfonylureas as a first line option in therapy when the HbA_{1c} is above target, in patients with normal weight and in patients who are metformin intolerant. The α-glucosidase inhibitors is an alternative option in therapy when the patient is not responding to the first line regimen or in special circumstances (e.g. when hypersensitive to metformin and sulfonylureas) is recommended.

Doses should be stepped up and other hypoglycaemic agents added, at frequent intervals (2–6 months) until blood glucose control is at target levels. Insulin therapy may be needed at any stage considering the deterioration of the disease. The thiazolidinediones is an option when glucose control does not meet the target, only when the benefits outweigh the risks, and adding to the combinations therapies already initiated. The recommended targets for glycaemic control are; overall fasting or pre-prandial target of between 4.0–7.0 mmol/L and a peak post-prandial glucose 5.0–10.0 mmol/L; HbA_{1c} is ≤ 7 mg/dL (paragraph 2.10.1).

The third objective was to discuss the pharmacological classifications of antidiabetic agents:

The literature review showed that there are five pharmacological classifications of antidiabetic

agents being biguanide (e.g. metformin), sulphonylureas (e.g. glibenclamide), thiazolidinediones (e.g. pioglitazone), α-glucosidase inhibitors (e.g. acarbose) and meglitinides (e.g. nateglinide). Insulin preparations (short acting and long acting) are also antidiabetic agents.

The fourth objective was to discuss the mechanism of action of antidiabetic agents:

Based on the search of literature metformin reduces the blood glucose by decreasing hepatic glucose production, glucose absorption from the GIT, and increasing glucose uptake and utilisation in the skeletal. Sulfonylureas and meglitinides stimulate insulin release from the pancreatic β-cells by binding to the sulfonylurea receptor1 (SUR1) subunits and block beta cells inward rectifier ATP sensitive potassium channels with a resultant decreae in the blood glucose. The blockage prevents efflux of potassium and leads to β-cells depolarisation. The depolarisation opens voltage gated calcium channels, influx of calcium and the activation of secretory machinery that release insulin.

Pioglitazone acts by binding to peroxisome proliferator-activated receptor-gamma (PPARγ) as an agonist. Stimulation of PPARγ nuclear receptors promotes the transcription of insulin responsive genes involved in the control of glucose and lipid metabolism, these results in increased insulin sensitivity, reduced hepatic glucose output and increased peripheral glucose disposal.

Alpha-glycosidase inhibitors act as competitive, reversible inhibitors of pancreatic alpha-amylase and membrane-bound intestinal alpha-glucosidase enzymes. Pancreatic alpha-amylase catalyses the conversion of complex starches to oligosaccharides while the membrane-bound intestinal α-glucosidases hydrolyse oligosaccharides, trisaccharides, and disaccharides to glucose. In diabetic patients, this enzyme inhibition results in a delayed glucose absorption and therefore a lowering of after meals hyperglycaemia.

The fifth objective was to discuss the side effects of the antidiabetic agents:

A conclusion is made on the common side effects that may develop when using the different antidiabetic agents (paragraph 2.11.4.1.2). The side effects associated with treatment with metformin are usually dose-related, affecting approximately one third of patients and include metallic taste in the mouth and gastrointestinal disturbances, including anorexia, nausea, vomiting, diarrhoea, abdominal discomfort. The most common side effect of the sulfonylureas is hypoglycaemia. It is more common with the first generation than the second generation products. The side effects of pioglitazone are oedema, increased plasma volume and weight gain particularly in patients with hypertension and cardiac failure. The most common side

effects associated with acarbose include flatulence, abdominal bloating and diarrhoea. The primary side effect of meglitinides is hypoglycaemia, which can result in discontinuation of the drug (paragraph 2.11.4.1 to 2.11.4.5).

The sixth objective was to discuss interactions of antidiabetic agents with other drugs:

It is concluded that rrug interactions that are common among the antidiabetic agents are minor to moderate in terms of severity. The majority of the interactions are minor and require dose to be adjusted if interaction is suspected. The drug-drug interactions that enhance the degradation of antidiabetics are sulphonylureas and biguanides when concurrent administered with cimetidine and sulphonylureas when administered with anticoagulants. Thiazide diuretics decrease the sensitivity of insulin, thereby reducing the effects of sulphonylureas when given together. For all of the mentioned interactions the intervention required is to monitor the blood glucose closely and make dosage adjustments when necessary.

There is also an interaction between sulphonylureas and ethanol, especially chlorpropamide, which causes disulfiram-like effects therefore consumption of ethanol while using chlorpropamide is highly discouraged. Insulin interacts with propranolol which results in prolonged hypoglycaemia and masks symptoms of hypoglycaemia, it is recommended that the selective β-adrenoceptors should be used or blood glucose level should be closely monitored (Table 2.8 and paragraph 2.11.4).

The seventh objective was to compare the clinical efficacy of antidiabetic agents:

The literature review indicated that metformin decrease of HbA_{1C} by 1.5% to 2%, a decrease in FBG by 3.5–4.4 mmol/L. The sulfonylureas reduce the FBG by 3.3 to 3.9 mmol/L, with greatest reduction observed in patients with the highest FBG concentration on initiation of therapy. Although the sulfonylureas vary in their potencies, they tend to lower HbA_{1C} to similar extends as (approximately 1.5% points) as metformin. The efficacy of repaglinide is similar to that of sulfonylureas, whereas nateglinide reduces HbA_{1c} concentrations by 0.5%–1.0% which is a lesser effect when compared to sulfonylureas. Pioglitazone decreases glucose levels by about 3.4–3.9 mmol/L and HbA_{1C} by up to 1.5% when given for a period of six months. Alpha-glucosidase inhibitors have a leeser efficacy than other classes of OHAs, (FBG levels by 1.9 to 2.2 mmol/L and an average haemoglobin A_{1c} lowering effect of about 0.5%–1.0%). Insulin induces lower FBG than OHAs but the response to HbA_{1c} is similar to OHAs.

5.3 THE CONCLUSIONS FROM THE EMPIRICAL INVESTIGATION

The specific research objectives for the empirical investigation (refer to paragraph 1.5.2) were attained in chapter 4.

The first objective was to compare the number of type 2 diabetes mellitus patients in government clinics in Maseru district of Lesotho, stratified by age and gender:

There were 248 females and 89 males in this study (ratio 1.3). There were no statistical difference between the number of males and females in different study sites with regard to having diabetes mellitus (p = 0.48). The results of the present study showed that diabetes mellitus was more prevalent in patients from age group five (i.e. for both males and females). It is therefore concluded that there is higher prevalence of type 2 diabetes mellitus in females than males in the age group five (i.e. patients aged 59 to 69 years).

The second objective was to determine frequency of type 2 diabetes mellitus occuring with other chronic illnesses:

Analysis of data on the prevalence of diabetes occurring with other chronic illnesses indicated that only 20% of the study sample had diabetes mellitus alone as compared to nearly 81% of patients who had diabetes mellitus concurrently with hypertension. It is therefore concluded that the diabetes mellitus occurs most concurrently with hypertension.

The third objective was to determining the prescribing patterns of antidiabetic agents used in the management of type 2 diabetes mellitus in public clinics in Maseru district of Lesotho:

The regimen that was highly used among all the clinics in this study was metformin 850 mg three times per day, and 500 mg three times a day. Based on these results, it is concluded that metformin 850 mg three times per day and metformin 500 mg three times per day indicate the prescribing pattern of metformin when used as single agent.

Actraphane® was used commonly as a single agent at different dosage regimens with the highest usage at Mabote filter clinic. Established from the results, it is concluded that the prescribing pattern of Actraphane® was in the range 20 to 30 units in the morning and 10 to 15 units in the evening.

It is concluded that the use of chlorpropamide indicates that there is non-compliance to LSTG

as analysis of the results indicate that chlorpropamide was another drug used in management of diabetes at Domiciliary Health Center and Qoaling filter clinic. Combination therapies of metformin and Actraphane® used were metformin 500 mg three times daily plus Actraphane® 20 units in the morning, 10 units in the evening and metformin 850 mg three times daily and Actraphane® 30 units in the morning, 15 units in the evening. The conclusion made on these results concurs with the above conclusion on metformin and Actraphane® as single agents.

The investigation on the combination therapies of glibenclamide and metformin established that combination regimens that were mostly used at different study sites were glibenclamide 5 mg once daily or 10 mg once daily and metformin 500 mg or 850 mg three times a day.

A combination therapy of the three drugs was prescribed at different study sites at a lesser frequency. A conclusion is therefore made that very few patients are not responding to the second line regimen according to the LSTG, hence a very small number of patients are on the third line regimen in management of diabetes mellitus.

The fourth objective was to determining the cost of antidiabetic agents used in the management of type 2 diabetes mellitus in public clinics in Maseru district of Lesotho:

The most expensive single agent was Actraphane® which amounted to M40 660.52 in a month, with the average cost per patient of M21.43 ± 6.23 per day. The total cost of single drug therapy of oral antidiabetic agents amounted to M10 833.73 with a weighted average cost per patients of M0.81 ± 2.06. It is therefore concluded that oral antidiabetic agents are far cheaper than Actraphane®. The overall cost of Actraphane® and metformin combination therapy was M50 676.50, at an average cost per patient is M21.77 ± 6.80 compared to the cost of glibenclamide and metformin of M377.10 (weighted average cost per patient M0.49 ± 0.16 per day). Based on these results it is concluded that the combination therapy of metformin and Actraphane® is more expensive than the combination therapy of glibenclamide and metformin.

This brings to a conclusion that the combination therapies that contain Actraphane® are more expensive than combination therapies of oral antidiabetic agents.

The fifth objective was to determine the average blood glucose of both males and females, and measure against the recommended guidelines by SEMDSA 2009:

The mean blood glucose level at 95% confidence interval for females and males were 10.1 ± 5.9 (95% CI: 10.1–11.7) and 10.9 ± 6.2 (95% CI: 11.0–14.0) respectively. The difference

in the mean blood glucose of males and females was not statistically significant (p = 0.07). It is therefore concluded that diabetes mellitus is well controlled in all study sites as the blood glucose levels concur with the recommended 2009 SEMDSA guidelines. Blood glucose levels were not recorded in the bukana for 12.7% of patients. It is concluded that there are no clear SOPs that are followed in diabetes mellitus care and management.

The sixth objective was to evaluate the treatment of type 2 diabetes mellitus in government clinics as against the recommended treatment guidelines of Lesotho based on the pattern of prescribing:

It is concluded that public institutions in Maseru Lesotho comply with the recommended treatment guidelines of Lesotho with exception of very few patients prescribed chlorpropamide which does not appear in the LSTG (paragraph 5.3.2).

5.4 RECOMMENDATIONS

The following recommendations are made based on the findings:

- Computerised systems should be available to simplify accessibility of the patients' information.
- Other monitoring tools should be employed in management of DM such as the documentation of HbA_{1c} levels.
- Standard operating procedures should be developed to indicate the type of blood glucose to be tested during diagnosis and refills to make easy analysis of effectiveness of the different antidiabetic regimens.
- Further studies should be conducted to establish the clinical effectiveness of the different regimens used at the study sites.
- The LSTG should be reviewed to indicate the recommended doses of insulin and target goals for treatment.
- Patients should only be started on Actraphane® when they are not responding to oral antidiabetic agents as it is the most expensive antidiabetic drug.
- Intensive education programs should be done to help patient control the blood glucose within the recommended levels.

5.5 LIMITATIONS OF THE STUDY

Due to data being collected from patients' bukana some information was missing. Some bukanas was new and the previous booklet was not attached. Indirect cost of management of

diabetes mellitus was not included in the study. The study type (retrospective) used could not determine the effectiveness of the treatment regimens used in the study sites

5.6 CHAPTER SUMMARY

In this chapter, the conclusions based on the objectives were drawn. The recommendations for further studies were made, and the limitations encountered were outlined.

ANNEXURES A

This section provides the figures and tables that form part of Chapter 3.

Appendix A.1: data collection survey form # 1

Data collection survey form # 1: Patient demography and disease profile

study site Date of data collection

patient code Sex DOB Height

Date of clinic vis.	Prescribed drug				Date of diagnosis	Other c/illness	Blood glucose level			Body weight		B/P (mmHg)		Comments
	Drug	Dosage	Dosage interval	Nr of tabs/day			Date	Reading	Type	Date	Reading	Date	Reading	

Appendix A.2: data collection form on cost

Data collection survey form #2: Commonly prescribed antidiabetic agents, monthly consumption and cost

Study site:……. Date of data collection:……/……/2011

Prescribed antidiabetic agent (active ingredients)	Average Amount ordered Monthly	Price (M) per unit pack

Appendix A.3: Patient consent form

PATIENT CONSENT

Introduction

I am 'Motseng Alice Marite registered for M. Pharm under MUSA. I am conducting a research project aimed at evaluating Type 2 diabetes mellitus medicine management in public institutions in Maseru Lesotho

The information obtained in this study would be useful in making interventions required to ensure the cost effective use of the antihyperglyacemic agents.

Part of this research project involves a data collector who will be collecting data on my behalf.

Confidentiality

Any information about you that is obtained during the study will remain confidential. Such information will be disclosed only with your permission.

Participation and withdrawal

You can choose whether or not you wish to participate in the study. If you agree to participate, you may withdraw at any time without penalty. The investigator may withdraw you from this research project if circumstances arise which warrant doing so.

By signing this consent form and participating in this research project, you are not waiving any legal claims, rights or remedies to which you are entitled.

Consent form

Study number_____ **Date**_____

Investigator Name_____

Title of project

Prescribing patterns of hypoglycaemic drugs in the treatment of Type 2 Diabetes Mellitus in public institutions in Maseru District of Lesotho

1.	I confirm that I have read and understood the information sheet for the above study and have the opportunity to ask questions	*
2.	I confirm that I have had sufficient time to consider whether or not I want to be included in the study	*

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. *

4. I agree to take part in the above study. *

Name of Patient	Date	Signature
Name of Person taking consent (data collector)	Date	Signature
Researcher	Date	Signature

Comments or concerns during the study:

If you have any comments or concern you may discuss these with the investigator (data collector). If you which to complain about any aspect of the way you have been approached or treated during the course of the study, feel free to contact the project leader: Mrs M. A. Marite on +266(58786543)

LESOTHO

Ministry of Health and
Social Welfare
P.O. Box 514
Maseru 100

06th March, 2012

Motseng A. Marite
Master of Pharmacy Candidate
North West University
P.O. Box 1207
Maseru 100,
Lesotho

Dear M. A. Marite

Re: A pharmaco-epidemiological evaluation of type II diabetes mellitus medicine management in Domiciliary, Mabote and Qoaling clinics in Maseru in Lesotho

Thank you for re-submitting the above mentioned protocol. The ministry of Health and Social Welfare Research and Ethics Committee having reviewed your protocol hereby authorizes you to conduct this study among specified population. The study is authorised with the understanding that the protocol will be followed as stated. Departure from the stipulated protocol will constitute a beach of permission.

We are looking forward to have a progress report regularly and final report at the end of your study.

Best Regards,

Dr. M. M. Moteetee
Chairperson Research and Ethics Committee
Director General Health Services

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