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A critical review of whether goals for treatment in type 2 diabetes mellitus as set out by the 2012 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines are being achieved in patients attending the diabetic clinic at Helen Joseph Hospital

Bulbulia, Saajidah

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A CRITICAL REVIEW OF WHETHER GOALS FOR TREATMENT IN TYPE 2 DIABETES MELLITUS AS SET OUT BY THE 2012 SOCIETY FOR ENDOCRINOLOGY, METABOLISM AND DIABETES OF SOUTH AFRICA (SEMDSA) GUIDELINES ARE BEING ACHIEVED IN PATIENTS ATTENDING THE DIABETIC CLINIC AT HELEN JOSEPH HOSPITAL

Dr. Saajidah Bulbulia

A dissertation submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in fulfilment for the requirements of the degree of Master of Medicine

Johannesburg, 2018

DECLARATION

I, Saajidah Bulbulia, declare that this research report is my own work which is being submitted for the degree Master of Medicine (in the submissable format with my protocol and an extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

_____ _____

Dr. Saajidah Bulbulia Date

MBBCh (Wits 2008)

FCP (SA) 2016

PRESENTATION AND PUBLICATION ARISING FROM THIS STUDY

Poster Presentation at the 51st Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) Congress, Johannesburg, South Africa, May 2017.

DEDICATION

To my family

For your never ending love, faith and support.

ETHICS COMMITTEE APPROVAL

This research was approved by the Ethics Department of the Helen Joseph Hospital as well as the Ethics Committee for Research on Human Subjects, University of the Witwatersrand (Clearance Certificate number: M151193)

ABSTRACT

Background

The risk of complications from T2DM is high. Complications reduce quality of life and place a large burden on our health system and economy. Achieving targets in our diabetic patients significantly reduces the morbidity and mortality of the disease. This study aims to assess whether patients at the Helen Joseph Academic Hospital Diabetic Clinic are meeting the 2012 SEMDSA targets for diabetes with the current hospital treatment protocols.

Methods

A Retrospective Clinical Audit was carried out at the Helen Joseph Hospital Diabetic Clinic. The files of 321 patients with T2DM for a duration of longer than five years and who were on insulin were reviewed. The following information was assessed: Glycated haemoglobin (HbA1c), Blood pressure, abdominal circumference and lipograms.

Results

The study population of 321 patients compromised majority black (44.6%) and coloured (34%) patients. The mean age amongst these patients was 59.4 years. This sample was predominantly female (62.3%). A large proportion of patients had concomitant Hypertension (89.1%) and dyslipidaemia (82.2%); with 91.2% fulfilling criteria for the diagnosis of metabolic syndrome. The majority of patients 56.3% did not exercise. A small amount partook in recreational activities that increase cardiovascular risk (smoking 12.5% and alcohol use 10.6%). Target HbA1c used for the purpose of this study was 7% or lower. The mean HbA1c in this study population was 9.5% (range 3.9 – 16.9%). Only 15.3% achieved the 7% target. The number of patients who achieved the target Blood Pressure of <140/90 was 72 (25%) (95% CI 20.2-30.5). LDL target was achieved in 22.6% and abdominal circumference 11%.

Conclusions

Despite adequate protocols and access to tertiary medical care, only a very small percentage of patients at the diabetic clinic are achieving proposed targets. Other audits have revealed a range of reasons for poor control in their patients. More comprehensive analysis is required to assess the reasons in this clinic if we are to address the problem with the urgency it requires. Ultimately, the goal is to offer the best treatment and quality of life to our ever increasing diabetic population.

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LIST OF ABBREVIATIONS

ACCORD – Action to Control Cardiovascular Risk in Diabetes

ACE-I – Angiotensin Converting Enzyme Inhibitor

ADA – American Diabetes Association

ADVANCE – Action in Diabetes and Vascular Disease: Preterix and Diamicron Modified Release and Controlled Evaluation

ARB – Angiotensin Receptor Blocker

BMI – Body mass Index

CAD – Coronary Artery Disease

CARDS – Collaborative Atorvastatin Diabetes Study

CCB – Calcium Channel Blocker

CVD – Cerebrovascular Disease

DCCT – Diabetes Control and Complications Trial

DKA – Diabetic Ketoacidosis

DM – Diabetes mellitus

DN – Diabetic Nephropathy

DR – Diabetic Retinopathy

EDIC – Epidemiology of Diabetes Interventions and Complications

GAD – Glutamic Acid Decarboxylase

GUIDANCE – European Guideline Adherence to Enhance Care Study

HbA1c – Glycated Haemoglobin

HDL – High Density Lipoprotein

HHS - Hyperosmolar Hyperketotic Syndrome

HIV – Human Immune Virus

HOT – Hypertension Optimum Treatment Trial

IDF – International Diabetes Federation

IFG – Impaired fasting Glucose

IGT – Impaired Glucose Tolerance

IMPROVE-IT – IMProved Reduction of outcomes Vytorin Efficacy International Trial

IRO – Insulin Resistant Obese

LDL – Low Density Lipoprotein

MBO – Metabolically Benign Obese

MI – Myocardial Infarction

NCD – Non-communicable Diseases

NDDG – national Diabetes Data Group

NHANES – National health and Nutrition Survey

NHLS – National Health Laboratory Services

OGGT – Oral Glucose Tolerance Test

PVD – Peripheral Vascular Disease

RedCap – Research Electronic Data Capture

SEMDSA – Society for Endocrinology, Diabetes and Metabolism South Africa

T1DM – Type 1 Diabetes Mellitus

T2DM – Type 2 Diabetes mellitus

TB – Tuberculosis

TG – Triglycerides

UKPDS – United Kingdom Prospective Diabetes Study

UN – United Nations

VADT – Veterans Affairs Diabetes Trial

WHO – World Health Organisation

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CHAPTER ONE

Literature Review and Protocol

1. LITERATURE REVIEW

The global burden of non-communicable diseases (NCD) is rapidly escalating.[1] More than 63% of annual global deaths (approximately 36 million people) can be attributed to NCD's with the large majority (86%) occurring in low to middle income countries.[2] The impact on society, the economy and the health sector is immense and could be crippling if not attended to with utmost urgency.[2–6] The World Health Organisation (WHO) and the United Nations (UN) have listed the following four NCD's as areas for intervention over the next few decades: cardiovascular diseases, cancers, chronic respiratory diseases and Diabetes Mellitus (DM).[1, 2, 5] The main focus of this work is DM.

1.1 A Brief History of Diabetes

DM is first described within the Ebers Papyrus, a document of ancient Egyptian medicine written in approximately 1500B.C.[7] Here it is described as a disease of "too great emptying of the urine". The first complete description of DM is credited to Aretaeus of Cappadocia who coined the term "Diabetes" in the 1st century A.D.[7] Ancient Indian physicians also describe a disease as known as "Madhumeha" (sweet urine) in their 5th century texts and document cases of patients with excessive urination, excessive thirst and emaciation occurring more commonly in rich people who consumed large amounts of rice, cereals and sweets.[8]

The various clinical features and complications of DM were described by various physicians over the following centuries and during this time was widely thought to be a disease that originated in the kidneys.[8] Swiss physician Paracelsus in the 16th century A.D. was the first to describe the disease as a process originating outside the kidneys.[9] The term Mellitus was coined by John Rollo in 1798 in order to distinguish between polyuria with glycosuria and polyuria of other origins.[7]

During the late 18th and early 19th centuries, patients with DM were shown to have glucose in the blood and urine and tests to identify these abnormalities were

refined.[8] In the late 19th century the islets of Langerhans were identified and the causal relationship between lesions in the pancreas and the development of DM was described.[8,9] Large strides were made in the 20th century, with the identification of insulin and its use in treatment; development of diagnostic and monitoring tools and a multitude of oral and injectable drugs for treatment.[7–9]

1.2 Definition and Classification

Prior to the 1970's the nomenclature and diagnostic criteria for DM varied. In 1979 the WHO and the American National Diabetes Data Group (NDDG) published diagnostic criteria and classification systems for DM.[3] In 1995 an international expert committee was put together to revise the classification systems and diagnostic criteria defined in 1979.[10] The current definition of DM is "a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both".[11–13]

The different types of DM are classified according to aetiology.[10] They are:

1.2.1 Type 1 Diabetes Mellitus (T1DM)

Immune Mediated

T1DM constitutes 5-10% of diabetes cases.[14] It occurs as a results of pancreatic β - cell destruction through cell-mediated autoimmune processes. [10,15] Autoantibodies to insulin, Glutamic acid decarboxylase (GAD), islet cells and tyrosine phosphates can be demonstrated in 85-90% of patients.[16] A combination of genetic predisposition and environmental factors (such as autoimmune activation of antibodies by viral infections) are responsible for β-cell destruction. β-cell destruction rate is variable and can be slowly or rapidly progressive.[14, 1] This type of DM is common in children. When it occurs in adults a slow onset of insulin dependency related to the presence of insulin cell antibodies is noted. Here it is called latent autoimmune diabetes in adults (LADA).[18,19] The hallmark of this disease is little or no insulin secretion with low to undetectable c-peptide level and a predisposition to ketoacidosis.[10, 16, 19]

Idiopathic

This form predominantly affects people of African and Asian descent, is strongly inherited and has no known aetiology or demonstrable autoantibodies. Individuals present with varying degrees of insulin deficiency interspersed with episodes of ketoacidosis.[16]

1.2.2 Type 2 Diabetes Mellitus (T2DM)

(This will be the focus of further sections in this document)

This type accounts for 90-95% of cases worldwide.[16] Though exact aetiology is unknown, a strong familial (most likely genetic) link has been demonstrated.[11, 15] Factors that increase the risk of developing T2DM have been identified. These include: obesity, lack of physical activity, increasing age and a history of gestational DM amongst others.[16] The disease in these patients is attributable to disorders of insulin action (insulin resistance) and secretory defects causing relative insulin deficiency.[10,11,18]The onset of T2DM is, in most cases, insidious and asymptomatic due to low levels of hyperglycaemia and many patients remain undiagnosed for long periods.[11,21] Nevertheless, the risk of developing complications during this period remain high.[16]

1.2.3 Gestational DM

This is defined as any degree of glucose intolerance which begins in or is first recognised during pregnancy and which does not fit criteria for overt diabetes. This form of glucose intolerance usually resolves after delivery. [11,22]

1.2.4 Other Specific Types of DM

These are relatively uncommon forms of DM in which a specific defect or disease process can be identified as the cause.[11] These include DM associated with other diseases or drugs and specific genetically defined types.[18]

Table 1.1: Other Specific Types of DM [11,18,22]

Genetic defects of beta-cell function Chromosome 20, HNF4a (*MODY1) Chromosome 7, glucokinase (*MODY2) Chromosome 12, HNF1a (*MODY3) Chromosome 13, IPF-1 (*MODY4) Mitochondrial DNA 3243 mutation Others	**Genetic defects in insulin action** Type A insulin resistance Leprechaunism Rabson-Mendenhall syndrome Lipoatrophic diabetes Others
Diseases of the exocrine pancreas Fibrocalculous pancreatopathy Pancreatitis Trauma / pancreatectomy Neoplasia Cystic fibrosis Haemochromatosis Others	**Endocrinopathies** Cushing's syndrome Acromegaly Phaeochromocytoma Glucagonoma Hyperthyroidism Somatostatinoma Others
Drug- or chemical-induced Nicotinic acid Glucocorticoids Thyroid hormone Alpha-adrenergic agonists Beta-adrenergic agonists Thiazides Dilantin	**Other genetic syndromes** Down's syndrome Friedreich's ataxia Huntington's chorea Klinefelter's syndrome Lawrence-Moon-Biedel syndrome Myotonic dystrophy Porphyria

Pentamidine Vacor Interferon-alpha therapy Others	Prader-Willi syndrome Turner's syndrome Wolfram's syndrome Others
Infections Congenital rubella Cytomegalovirus Others	**Uncommon forms of immune-mediated diabetes** Insulin autoimmune syndrome (antibodies to insulin) Anti-insulin receptor antibodies "Stiff Man" syndrome Others

**MODY – Mature onset diabetes of the young*

1.3 Epidemiology and Socioeconomic Impact

In 2015 the International Diabetes Federation (IDF), estimated that 415 million people worldwide or 8.8% of people aged 20-79 years are living with DM and this number is estimated to rise to 642 million people by 2040.[21] Approximately 75% of these people live in low to middle income countries.[21] The scarcity of nationwide data for the majority of African countries makes the estimates for Africa uncertain. Nevertheless, from available data the IDF estimates that the prevalence of diabetes in Africa was 3.2% in 2015 (between 9.5 and 29.5 million people). In addition, an estimated 66.7% of these people are undiagnosed, the largest proportion in any IDF region.[21] The IDF estimated prevalence of diabetes in the South African population is 7% (1.2-4.6 million adults aged 20-79).[21] Of the 2.3 million South Africans with diabetes, 61.1% (1.4 million) were undiagnosed. The 2010 estimate for South Africa was 4.5%.[23] That is a greater than 60% increase in just 5 years.

This rapid increase in the number of people with DM is a worldwide phenomenon. This is concerning when one considers the impact that DM has on every level of society, from the individual suffering with the disease, family members, nationwide health systems and economics and the world at large.[3, 20] Individuals suffering from DM have been noted to spend more on health care compared to their contemporaries without DM and health systems require increased budgets to facilitate care of the disease and its complications.[24,25] The IDF estimates that 11.6% of global health expenditure is spent on diabetes, three quarters of which occurs in middle and low income countries.[21] In 2015, the cost per person annum for people with DM in South Africa was R 26 743.69.[21]

Additionally, families, employees and economy suffer because of loss of productivity/income that occur as a result of disabilities caused by DM complications and deaths.[26] DM is one of the leading causes of death worldwide and is projected to be the 7th leading cause of death in 2030.[21] The IDF reported 5 million deaths from DM worldwide in 2015. In 2016, DM was reported as the cause of death for 5% of cases in South Africa.[27]

The reasons for the global increase in DM are multiple. These include:

1.3.1 Increasing age of the world's population

The incidence of DM increases with age.[16] As the number of people in older age groups increase, so too does the prevalence of DM increase; and the proportion of older individuals worldwide has increased substantially in last few decades.[28] According to the 2015 UN World Population Prospects report, 1 in every 8 individuals (904 million people) is 60 years old or older. With the expected increase of 56% in the next 45 years. This means, that by 2050 there will be 1.4 billion people aged 60 years and older.[28]

Moreover, the rate of increase in population ageing over the next few decades in developing countries is expected to be much faster than what has previously

occurred in developed countries, forcing them to adapt to these changes much more rapidly and likely with lower national incomes than the developed countries.[28]

1.3.2 Urbanisation

More than 50% of the world's population currently resides in cities.[29] With the change from rural to urban living comes the problem of unbalanced and often unhealthy diet, sedentary lifestyle, increase in obesity rates and easier access to smoking, alcohol and other drugs. These increase the risks and thus the rates of all NCD.[29–31]

1.3.3 Overweight and Obesity

The WHO defines overweight as Body Mass Index (BMI) >25-29.9kg/m^2 and obese as BMI >30kg/m^2.[1] The prevalence of both overweight and obese individuals is rising globally. Worldwide prevalence of overweight adults is 39%, while prevalence rates for obesity in males and females are 11% and 15% respectively. Obese individuals can be divided into two groups: the metabolically healthy obese (MBO) and the insulin resistant obese (IRO).[32] Evidence for the increased risk of NCD and mortality in the IRO is overwhelming.[33,34] In the MBO individual, there is conflicting evidence with regard to risk of NCD and mortality.[34] Most interventional programmes do not distinguish between the two types. As there is some evidence that the individual with MBO is also at higher risk for cardiovascular disease and complications, it may be sensible to continue to encourage weight loss in all individuals. In keeping with this notion, the WHO recommends that target individual BMI be 18.5-24.9kg/m^2 and median BMI for adult populations be 21-23kg/m^2.[1]

1.3.4 The Metabolic Syndrome

The Metabolic Syndrome refers to a cluster of interrelated risk factors that confer an increased risk of CVD and DM.[35] CVD is doubled and the risk of DM is increased 5-fold.(36) Many definitions and diagnostic criteria for the Metabolic Syndrome exist.[36]

The harmonised criteria (which is the most commonly used internationally) are as follows:[11,18,35,36]

Table 1.2: The Harmonised Criteria for the clinical diagnosis of the Metabolic Syndrome

Elevated Waist Circumference	Population and country specific definitions *Sub-Saharan Africa: ≥ 94 cm in men ≥ 80 cm in women
Elevated triglycerides	≥ 1.7 mmol/L
Reduced HDL cholesterol **	< 1.0 mmol/L in men < 1.3 mmol/L in women
Elevated Blood Pressure (BP)	Systolic ≥ 130 mm Hg Diastolic ≥ 85 mm Hg
Elevated Blood sugar	≥ 5.6 mmol/L

**In Sub-Saharan Africa the IDF/Europid definition for elevated waist circumference is used.*

***HDL – high density lipoprotein*

****Drug treatment for elevated triglyceride, blood pressure or glucose or for reduced HDL cholesterol is an alternate indicator*

1.4 Diagnosis and Screening for T2DM

The WHO, ADA and Society for Endocrinology Metabolism Diabetes of South Africa (SEMDSA) give the following recommendations for diagnosing diabetes.[11, 18, 22, 37]

Table 1.3: Criteria for diagnosis of DM

Fasting* Plasma Glucose (FPG)	>7.0 mmol/l
2hour Plasma Glucose (2h PG) in an OGTT**	> 11.1 mmol/l
Glycated Haemoglobin (HbA1c)	>6.5%
Random Plasma Glucose (RPG)	>11.1 mmol/l in presence of classic symptoms of diabetes or hyperglycaemic crisis.

**Fasting – no caloric intake for eight hours*

***OGTT – performed according to the WHO guidelines*

Metabolic states of impaired glucose regulation (previously referred to as prediabetic states) have also been identified. These, increase the individuals risk of progression to DM and developing cardiovascular disease.[11, 20, 21] They are:

1 Impaired fasting glucose (IFG) - fasting plasma glucose of 5.6mmol/l - 6.1mmol/l (according to the WHO) and 6.9 mmol/l (according to the American Diabetes Association (ADA)).

2 Impaired glucose tolerance (IGT) – 2hour plasma glucose in an oral glucose tolerance test (OGGT) of >7.8mmo/l but <11.0mmol/l.

Values for diagnosing diabetes are given in table 1.3 above. The guidelines all recommend that:[11,18,22,37]

I. Diagnosis be based on formal laboratory tests and not point of care bedside instruments.

II. Confirmatory tests done on a separate day (using the same modality) should be used to establish a diagnosis. The exception being the patient with obvious symptoms of polyuria, polydipsia and weight loss or in the case of a person presenting with hyperglycaemic crisis (Diabetic ketoacidosis (DKA) and hyperosmolar hyperketotic state (HHS)).

III. If HbA1c is being used the test method must conform to certain quality assurance criteria. Namely: the assay must be standardised to international reference values as per the National Glycohaemoglobin Standardisation Programme (NGSP) and must also be standardised to the Diabetes Control and Complications Trial (DCCT). Additionally, no conditions that preclude using the assay must be present (these will be discussed later (section 1.1.8)).

IV. Should results be unequivocal or discrepant results obtained after performing two different tests, then a 75g OGTT should be performed.

Screening for T2DM should occur only within health care settings so that appropriate follow up can be organised should tests conducted be diagnostic of DM. Random screening is recommended for adults over the age of 45 years. Opportunistic screening during visits for other conditions and targeted screening of individuals identified as high risk should be performed in individuals with any of the indications stated in table 1.4 below.[11, 18]

Screening should be performed at 3 yearly intervals if the original test is normal and annually should there be multiple risk factors present or if the individual has been diagnosed with IFG or IGT.

Table 1.4: Indications for DM screening/High Risk Individuals

All adults (any age) with body mass index (BMI) ≥ 25 kg/m2 (overweight or obese), plus one or more additional risk factors
Additional Risk factors: - Physical inactivity - Hypertension [blood pressure (BP) ≥ 140/90 mmHg] - Family history of diabetes (first degree) - Dyslipidaemia - Polycystic ovarian syndrome - High-risk ethnic group e.g. those of South Asian descent - Cardiovascular disease history - Gestational diabetes or baby weighing > 4 kg - Previous IFG or IGT - Other conditions associated with insulin resistance

1.5 Complications

The long term consequences of diabetes result from chronic hyperglycaemia.[17,20,38,39] Complications include damage to both vascular and nonvascular structures leading to dysfunction of multiple organ systems.[17] Non-vascular complications comprise mainly of emergencies related to diabetes such as DKA, HHS, hypoglycaemia and recurrent infections.[20] Vascular disease is common and a major cause of morbidity and mortality of DM.[3] The vascular complications of DM can be further classified according to microvascular and macrovascular complications.[38,39] In the CODE-2 study which collated data from eight European studies and involving a total of 7000 people with diabetes, found that 72% of individuals had at least one complication and 24% had both microvascular and macrovascular complications.[40]

1.5.1 Microvascular disease

Diabetic Nephropathy (DN)

Chronic hyperglycaemia results in a complex series of events that cause destruction of the kidneys.[39] The structural and haemodynamic changes within the kidneys leads to a progression of events beginning with hyperfiltration and hypertrophy of the kidneys and ending in end stage renal failure with eventual need for dialysis (and possible renal transplant) if no steps are taken to intervene.[20] DN can be detected by screening for microalbuminuria/proteinuria at diagnosis and during follow-up.(38) The mainstay of treatment for the proteinuria of DN is Angiotensin Converting Enzyme inhibitors (ACE-I) and Angiotensin Receptor Blockers (ARB).[18, 22, 39]

Diabetic Eye Disease

This comprises Diabetic Retinopathy (DR) and cataracts. These are some of the leading causes of visual loss and blindness in both the developing and developed world.[18, 35]

DR can be divided into non-proliferative DR with changes in retinal blood vessel integrity and permeability (microaneurysms and haemorrhages seen on fundoscopy) and proliferative DR with neovascularisation of the retina.[20] Treatments that reduce visual loss include laser photocoagulation, vascular endothelial growth factor antagonists and vitrectomy.[39]

Diabetic Neuropathy

Approximately 50% of patients with DM will develop neuropathy.[39] DM affects both the somatic and autonomic divisions of the peripheral nervous system.[38,39] Individuals with somatic involvement, may present with distal symmetrical polyneuropathy, mononeuropathies or polyradiculopathies which may be further complicated by ulceration and injuries.[19, 35]

The manifestations of the autonomic neuropathy of DM are:[37–39]

- Cardiovascular – resting tachycardia, orthostatic hypotension
- Gastrointestinal – oesophageal dysmotility, gastroparesis, nausea, bloating, diarrhoea, faecal incontinence
- Genitourinary – sexual dysfunction (males: erectile dysfunction, retrograde ejaculation; females: decreased libido, decreased lubrication, dyspareunia), urinary incontinence and bladder dysfunction
- Recurrent infections

No cure currently exists for diabetic neuropathy. Treatment consists of optimizing glucose control and the management of neuropathic pain and other symptoms.[20]

1.5.2 Macrovascular disease

Atherosclerosis is thought to be the main pathological mechanism by which DM causes macrovascular disease.[38]

Coronary artery disease (CAD)

Diabetes is an individual risk factor for CAD.[38] In the Framingham Heart Study, diabetes was associated with a 3-fold higher risk of myocardial infarction (MI) as well as substantially increased risk of hypertensive heart disease and heart failure.[41, 42]

The increased risk of CAD can be attributed to the increased prevalence of traditional risk factors (such as hypertension, obesity and dyslipidaemia) in the diabetic population, as well as the presence of non-traditional risk factors.[43,46] Insulin resistance, hyperinsulinaemia, post-prandial hyperglycaemia and glucose variability, microalbuminuria, platelet hyperactivity, hypercoagullibility and chronic low grade inflammation are just some of the non-traditional risk factors recognised in DM.[46] The best outcomes are achieved by addressing all of the risk factors present and the

need to find the simplest and safest way to do this has become the target of many studies. Drugs such as Empaglifozin, a selective inhibitor of the sodium glucose cotransporter 2, have proven to be promising in this regard.[47]

Cerebrovascular disease (CVD)

There is a 150-400% increase in the risk of stroke and stroke related complications are also increased in DM.[38]

Peripheral vascular disease (PVD)

Furthermore, in addition to chronic hyperglycaemia, there are other factors that increase the risk of complications. Diseases such as Hypertension (HT) and dyslipidaemia often occur concurrently with Type 2 Diabetes Mellitus. These conditions may accelerate complications through a compounding effect.[18, 37, 39] In order to prevent complications, early diagnosis; good glycaemic control and control of concomitant risk factors is recommended. A number of different parameters can be used to assess severity of disease and disease control.[18, 37]

1.6 Treatment of T2DM

1.6.1 Lifestyle intervention

Lifestyle modification is arguable the most important intervention in the treatment of DM. It should target glycaemic control, modification of cardiovascular risk factors and weight reduction.[41, 42] These can be achieved through:

Medical Nutrition Therapy

With the assistance of a dietician and in some cases behavioural modification therapy, individualized diets that take into account patients nutritional requirements, weight loss goals, budget, personal choice and cultural /religious practices can be designed.[49]

Exercise

To ensure optimal results, exercise too should be approached using a multidisciplinary team. A tailor-made exercise program that fits the patient's lifestyle, preference and physical limitations is most likely get better results.[48] SEMDSA has adopted the WHO recommendation of 150 minutes per week of moderate intensity exercise.[2]

Smoking Cessation

Smoking is an independent risk factor for cardiovascular disease.[50] In smokers with diabetes the cardiovascular disease risk is cumulative. Smoking cessation has been proven to improve control of DM and co-morbidities such as Hypertension; and also to decrease incidence of complications.[51–53] Many patients find it very difficult to quit alone. Assistance with counselling, pharmacological and non-pharmacological aids may be required.[54]

Alcohol Consumption

The harmful effects of excessive alcohol use are well known.[2] Moderate alcohol use has no adverse effects on DM control and has even been demonstrated to be cardioprotective.[55, 56] Identifying patients with excessive alcohol use/abuse and assisting them with appropriate assistance is thus an important aspect of management. SEMDSA recommendations for alcohol consumption is one unit a day for females and two units a day for males. Avoidance of alcohol should be encouraged in persons who are obese and those with hypertriglyceridaemia.[22]

1.6.2 Pharmacological Treatment

A number of different oral and injectable medications and insulins are available for the treatment of DM. Most guidelines advocate a stepwise approach to the treatment of DM beginning with one oral medication and progressing to combination oral treatment and eventually insulin based treatments.[18, 21, 50]

Metformin is the mainstay of treatment, and should be used in the majority of patients, the only exceptions being severe renal failure and intolerable side effects.[37,57,58] Metformin is recommended as the first step in many guidelines for the treatment of T2DM including the 2017 SEMDSA guideline and the 2017 American Diabetes Association Guidelines.[22,37] Metformin has also proven useful in individuals with insulin resistance in preventing the progression to DM.[59] Patient monitoring should occur at three monthly intervals and treatment regimen should be intensified until target Glycated Haemoglobin (HbA1c) has been achieved.[22]

Dual, triple and complex treatment regimens involve the addition of one or more of the following: sulphonylurea, pioglitazone, DDP-4 (dipeptidyl peptidase-4) inhibitor, SGLT-2 (sodium-glucose linked transporter 2) inhibitor, GLP-1 (glucagon-like-peptide-1) agonist and various insulin preparations. The choice of additional agent should be individualized according to patient requirements and patient preference, as while all drugs have been proven to be efficacious with regard to lowering blood glucose they differ in side effect profiles and additional benefits such as weight loss and cardiovascular protection.[22, 57]

Certain presentations may require starting with combination therapy (HbA1c >9% without severe decompensation) or even with insulin (severe decompensation: ketoacidosis, HbA1c >11%, fasting plasma glucose >15mmol/l, weight loss >5% and severe polyuria and polydipsia).[18]

Treatment of concomitant medical conditions such as hypertension and dyslipidaemia is important in the patients with DM and will be discussed elsewhere in this text. Additionally, the use of aspirin is not advocated for primary prevention of cardiovascular disease in patients with T2DM but strongly recommended (dose of 75mg to 162mg per day) for secondary prevention in patients with established cardiovascular disease.[22,37] Alternate platelet aggregator inhibitors can be offered to patients with established cardiovascular disease who cannot tolerate aspirin.[22]

1.6.3 Surgery

Gastric and bariatric surgeries have proven to have beneficial effects in the control of obese diabetics and in the prevention of complications.[21, 53] However, surgery is costly and comes with the possibility of serious complications. The SEMDSA guidelines therefore only recommends surgery in carefully chosen individuals: those with a BMI ≥ 35kg/m^2 and in those patients with BMI between ≥ 30 kg/m2 who fail to achieve control of glucose with adequate medication and lifestyle modification. Bariatric surgery should only be carried out under the supervision of a multidisciplinary team.[22]

1.7 Targets for Treatment and Guidelines

Proper organisation and management of resources ensure that people get the best treatment possible. To this effect, most diabetic societies have proposed guidelines to assist clinicians. The 2012 SEMDSA guidelines were in use when this study was proposed. Newer guidelines have subsequently been published in 2017.[18, 22] The following targets for treatment have been identified in the SEMDSA guidelines.

1.7.1 Glycated haemoglobin (HbA1c) levels

HbA1c is a stable haemoglobin variant which is formed through the irreversible non-enzymatic glycation of one or both N-terminal valines of the β=chains during exposure of haemoglobin to plasma glucose.[61] It is a measure of the average blood glucose over the preceding 10-12 weeks (lifespan of a red blood cell).[62] The fraction of

glycated haemoglobin increases in a predictable manner with the increase in blood glucose and an estimated average glucose level can thus be ascertained.[41]

The reliability of the HbA1c test can be affected by a number of factors that affect the haemoglobin compound, the red blood cell, the glycation process and the assay used to perform the test.[63] The factors are tabulated below.

Table 1.5: Factors Affecting HbA1c:

Aspect Affected	Decrease HbA1c	Increase HbA1c	Variable Effect on HbA1c
Haemoglobin			Methaemoglobin Haemoglobinopathies Foetal Haemoglobin
Erythropoiesis	Iron, Vitamin B12 or erythropoietin administration, Chronic Liver Disease Reticulocytosis	Decreased erythropoiesis Iron deficiency Vitamin B12 deficiency	
Erythrocyte	Decreased erythrocyte lifespan Splenomegaly Rheumatoid Arthritis Haemoglobinopathies Drugs (Antiretrovirals/ Dapsone/ Ribavarin)	Increased erythrocyte lifespan Splenectomy	

Glycation	Increased erythrocyte pH Certain haemoglobinopathies Ingestion of Aspirin, Vitamin C and Vitamin E	Decreased erythrocyte pH Chronic renal failure Alcoholism	Genetic Determinants
Assay	Hypertriglyceridaemia	Carbamylated haemoglobin Alcoholism Hyperbilirubinaemia Chronic opiate use Large doses of Aspirin	Haemoglobinopathies

*Adapted from Gallagher ET. Al

The use of targeted HbA1c levels to reduce the level of complications of diabetes has been evaluated in a number of studies. The following landmark studies are important to take note of:

Diabetes Control and Complications Trial (DCCT)

Performed in the late 1980's and early 1990's, this trial aimed to assess the effects of intensive glucose control in T1DM as measured by reduction in HbA1c to a level comparable to the non-diabetic population on micro and macrovascular complications. The study consisted of 1441 people with T1DM and randomized them to the control (continuation of regular treatment) and intervention arm (intensive increase in treatment to achieve near normal HbA1c). The mean HbA1c achieved was 7% in the intervention group and 9% in the control group. The DCCT demonstrated that tighter glycaemic control resulted in a 35-76% decrease in early microvascular complications of DM. The two major adverse events noted was increased frequency of hypoglycaemia and weight gain in the intervention arm. A review of the same cohort of patients 30 years later in the Epidemiology of Diabetes Interventions and complications study (EDIC) revealed that though average HbA1c had become comparable in the control and intervention arms of the DCCT, the intervention arm had lower rates of both microvascular and microvascular complications. This sustained

response to early intensive glucose control was attributed to “molecular memory” also known as legacy effect or metabolic memory.[44]

United Kingdom Prospective Diabetes Study (UKPDS)

The main aim of the UKPDS was to assess the impact of intensive glycaemic control on the incidence of complications. The cohort comprised of 5102 subjects in 23 centers throughout the United Kingdom (UK). Individuals were randomized to either, intensive therapy (with target fasting glucose of 6.0mmol/l) and a conventional treatment arm (target fasting glucose <15mmol/l and keeping patients asymptomatic). Subjects were followed for a duration of 10years. Composite end points which included any microvascular events, macrovascular events and diabetes related deaths were assessed. On conclusion of the study the UKPDS demonstrated a 25% reduction in microvascular complications and a trend towards a reduction in macrovascular complications. However the latter was not statistically significant.[64]

Action to Control Cardiovascular Risk in Diabetes (ACCORD)

The ACCORD trial undertook to specifically address the question of whether intensive glycaemic control with target HbA1c <6.0% as compared to standard control HbA1c of 7.0-7.9%, would improve cardiovascular outcomes in middle-aged or older people with T2DM. They recruited more than 10000 participants and were meant to follow them up for a period of five years. The study was however, terminated after three and a half years due to increase in all-cause mortality in the intensive arm group.[65]

Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release and Controlled Evaluation (ADVANCE)

The ADVANCE trial was structured in a similar manner to the UKPDS trial and looked at similar outcomes. HbA1c levels of <6.5% were achieved in the intensive treatment group in contrast to the DCCT and UKPDS study and without the increase in mortality seen in the ACCORD trial. ADVANCE concluded that intensive glucose control to

<6.5% had no impact on macrovascular disease. However, there was a statistically significant effect on microvascular disease, particularly nephropathy.[45]

Veterans Affairs Diabetes Trial (VADT)

This trial had the same objectives as the trials discussed above. The study assessed intense glucose control in an older population. Mean HbA1c in the intensive group after 5.6 years of treatment was 6.9% in comparison to 8.4% achieved in the control group. The VADT trial demonstrated a reduction in cardiovascular events of 17% but at the risk of increase in frequency of severe hypoglycaemic events. There was no impact on overall mortality.

10 year follow of these participants revealed a sustained decrease in cardiovascular events with 8.6 fewer events per thousand when compared to the control group. This finding is similar to that seen in the follow up of DCCT (Epidemiology of Diabetes Interventions and Complications (EDIC)).[66]

Informal review of these studies and with formal meta-analysis which include the above and other trials it is evident that early, intensive glycaemic control reduces the risk of major complications.[65, 67] Although the ACCORD trial was stopped prematurely due to increase in mortality in the intensively controlled group (HbA1c <6.5%), this has not been noted in any of the other studies. What must also be kept in mind is that the majority of studies show this benefit couple with increases in severe though non-fatal hypoglycaemic events and weight gain.[67] In the real world treatment of people with DM it is thus imperative that the clinician take into consideration all of these facts and individualizes the HbA1c target to balance optimal benefit with lowest risk.[67] This approach is also advocated by both the ADA and SEMDSA guidelines.[18, 21]

The 2012 and 2017 SEMDSA guidelines recommends that HbA1c levels be tested 3 months after any initiation of or change in medication, and after 6 months if the last measured HbA1c was within target range.[18, 22]

Table 1.6: Glycated Haemoglobin Target:

Young Low risk Newly diagnosed No cardiovascular disease	<6.5%
Majority of patients	<7%
Elderly High risk/ Established CVD Hypoglycaemic unaware Poor short term prognosis	<7.5%

1.7.2 Blood Pressure (BP)

Blood pressure measurement is a critical aspect in the care of patients with Diabetes Mellitus. Elevated blood pressures have been demonstrated to be an increased risk factor for both microvascular and macrovascular disease.[67] In the general population, blood pressures of >115/75mmHg have been shown to confer a higher risk for cardiovascular events and mortality. This doubles for every 20mmHg increase in systolic blood pressure and 10mmHg increase in diastolic blood pressure.[68] A number of trials have evaluated the importance of blood pressure control in DM.

I. The ACCORD trial monitored blood pressure lowering in patients with T2DM. ACCORD did not demonstrate any significant reduction in overall morbidity and mortality with intensive BP control. However, it did show reduction in stroke occurrence and an increase in adverse events in the patients with systolic blood pressure lower than 120mmHg caused by hypotension, syncope and bradycardia.[69]

II. The UKPDS study randomized patients to a goal blood pressure of <150/85mmHg (tight group) and <180/105mmHg (less tight group). Follow –up of participants after 8-9 years revealed a 24% reduction in all diabetes related end points. Notably, there was a 44% reduction in stroke rate and 32% reduction in deaths related to diabetes in the lower blood pressure group. Of mention is a 34% decrease in occurrence of retinopathy in the higher blood pressure group.[64]

III. The ADVANCE trial also showed significant risk reduction for microvascular and macrovascular complications; cardiovascular deaths and all-cause mortality in the group with intensive BP monitoring.[45]

IV. The Hypertension Optimum Treatment (HOT) trial demonstrated that a diastolic blood pressure of <80mmHg is cardio-protective and reduces risk of other diabetic complications as well.[70]

Antihypertensive drugs such as ACE-I, ARBs, thiazide diuretics, calcium channel blockers (CCB) and beta-blockers have been shown in studies to reduce microvascular and cardiovascular complications.[71] Though all of these drugs have proven to be effective through their effects on lowering BP, some have proven to have additional benefits.[72] ACE-I and ARB's have shown to have advantages effects in the treatment of proteinuria, DN, heart failure and myocardial infarctions.[37, 66–68] Multiple trials have demonstrated the benefit of diuretics and beta blockers in cardiac failure, myocardial infarctions and stroke.[71,72] CCB have additional benefit in preventing stroke and its complications.[71]

BP in DM individuals is usually difficult to control and multiple agents may be required.[71] The 2017 SEMDSA guidelines recommend initiation of treatment for hypertension if BP >140/90.[22] The following are recommended:

- In patients without albuminuria: monotherapy with either thiazide-like diuretic, ACE-I, ARB or CCB is suitable.
- Diuretics and CCB are recommended as first line treatment in the black population
- The preferred diuretic is Indapamide (thiazide like diuretic)
- Compelling indications such as diabetic kidney disease, stroke, heart failure and ischaemic heart disease necessitate the use and avoidance of specific anti-hypertensive drugs.

	2012	2017
Systolic BP	120 - 140 mmHg	130 – 140 mmHg
Diastolic BP	70 – 80 mmHg	80 – 90 mmHg

Table 1.7: Blood Pressure Targets:[18,22]

*In patients with a high risk of stroke, a Systolic Blood Pressure of <130 mmHg should be targeted if this can be achieved without undue treatment burden

1.7.3 Lipids

T2DM leads to altered lipid metabolism with mainly increases in triglycerides (TG) and decreases in HDL-cholesterol.[74] In addition, increased circulating lipid cause elevations in blood glucose. Lipid abnormalities contribute to accelerated atherosclerosis and cardiovascular risk, thereby increasing the morbidity and mortality of T2DM.[75–77] The Heart Protection Study (HPS) and the Collaborative Atorvastatin Diabetes Study (CARDS) were two of the largest trials that demonstrated reductions in of cardiovascular disease with reduction LDL- cholesterol.[76] LDL-cholesterol lowering drugs (such as Statins) have been shown to reduce the risk of major coronary

events 15-40%.[78,79] Controversy exists with regards to the use of fibrates, however, in clinical practice these drugs have proven useful in some individuals.[80]

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) demonstrated the efficacy of combination Ezetimibe and statin therapy in improving cardiovascular outcomes.[76,79] Other drugs, PSCK-9 inhibitors, microsomal triglyceride transport protein inhibitor, apolipoprotein A1 mimetics, and antisense oligonucleotide against Apolipoprotein B have also proven useful in the treatment of dyslipidaemia. However, these are still in trial phase and long term efficacy is uncertain.[79]

The 2017 SEMDSA guidelines recommend measurement of lipids at diagnosis with treatment targeted at the abnormalities identified. During initial titration of treatment, lipid measurements should be performed every three months. Once targets have been achieved, monitoring should occur on a yearly basis.[18]

Table1.8: Lipid Targets:

Total Cholesterol	< 4.5 mmol/l
Triglycerides:	< 1.7 mmo/l
HDL cholesterol:	> 1.2 mmol/l for women > 1.0 mmol/l for men
LDL cholesterol:	< 1.8 mmol/l

1.7.4 Obesity

The concept of obesity as a heterogeneous entity has already been discussed. IRO individuals have been proven to have significantly increased cardiovascular risks. Though the MBO individual seems to have little to no risk in short term studies, long term follow-up suggests that these individuals do subsequently develop features of insulin resistance/DM as well as other complications.[81] Furthermore, it is not just increased weight, but weight distribution that is important. Increase in visceral rather than subcutaneous fat has proven to be a metabolic and cardiovascular risk factor.[82, 83]

Thus, as stated earlier, intervention to reduce complication, should target all obese individuals. Interventions may include nutritional and exercise programs, behavioural therapy, pharmacotherapy and bariatric surgery.

Table1.9: Obesity Target:

Waist Circumference	
Women	<80cm
Asian men	<90cm
Other men	<94cm
BMI target of <25 kg/m2	

1.8 Diabetes and Infectious Diseases

Infectious diseases comprise the majority of the health care burden in Africa.[84] With the rise in NCD in this region the interaction between the two cannot be ignored. Of note, Human Immune Virus (HIV) and its treatment has been implicated as a cause of DM.[85–87] The postulated mechanisms through which this occurs is:[85,88]

1.8.1. Changes in glucose homeostasis through:

- Insulin resistance is the main pathogenic factor
- Concomitant infection with Hepatitis C increases hepatic steatosis and TNF-α
- Visceral adipose tissue accumulation
- Longer duration of HIV, low-CD4 count and high HIV viral load

1.8.2 Changes caused by Antiretroviral Drugs

- Protease Inhibitors interfere with GLUT-4 mediated glucose transport causing insulin resistance and reduction in insulin secretion.
- Protease inhibitors also inhibits peroxisomal proliferator activator γ through interaction with cellular retinoic acid-binding protein type 1 release of free fatty acids and insulin resistance.
- Nucleoside reverse transcriptase inhibitors cause mitochondrial dysfunction, lipodystrophy and insulin resistance.

Like HIV, DM increases the risk of infections such as tuberculosis (TB). In turn, TB treatment and outcomes may be adversely impacted by the presence of DM.[87,89,90] Furthermore, both HIV and TB treatment may make control of DM difficult.[83, 84, 86] There are currently no local studies assessing the incidence and prevalence of diabetes in patients who are HIV positive and on treatment.

1.9 Review of literature pertaining to achievement of targets in DM

1.9.1 South African Studies

Sub-Optimal Management of Type 2 Diabetes Mellitus – A Local Audit.[92]

This study conducted in 2009 reviewed 150 patients from the three academic hospitals in Johannesburg and assessed control of glucose, blood pressure, lipids and weight in patients with T2DM on both oral hypoglycaemic agents and insulin.

The mean HbA1c in this population was 8.7% with only 30.7% of patients reaching target HbA1c of <7%. Of the 150 patients, 21.3% reached target SBP <130mmHg, 40.2% reached target DBP <80mmHg, 50.7% of patients achieved target LDL-cholesterol of <2mmol/l and 70.2% of patients were classified as overweight and obese with the majority having abdominal circumferences greater than the recommended values.

The achievement of glycaemic, blood pressure and LDL cholesterol targets in patients with type 2 diabetes attending a South African tertiary hospital outpatient clinic.[93]

In 2013, Pinchevsky et al reviewed clinic records of 261 patients attending the diabetic clinic at Charlotte Maxeke Johannesburg Academic Hospital. These patient records had also been audited in 2009 and a comparison of glycaemic control, BP and LDL-cholesterol levels between the two audits was carried out. The cohort consisted of mainly females (55%) and African patients (42.9%). Mean HbA1c was 8.5% in 2009 and 8.7% in 2013 with target HbA1c of <7% achieved in 25.4% of the cohort in 2009 and 15.5% in 2013. BP target of <140/90mmHg was achieved by 35.9% in 2009 and 49.6% in 2013. LDL-cholesterol targets were achieved in 72.7% in 2013 as compared to 47.7% in 2009.

Diabetes guidelines and clinical practice: is there a gap? The South African cohort of the International Diabetes Management Practices Study.[58]

This article reviewed the South African cohort of an international, multicentre cross-sectional review of control in DM patients in private care settings. The population of this cohort was mainly Caucasian males in contrast to the studies conducted in public health care centres. Target achievement assessment was only carried out for HbA1c levels. However, means were reported for BP (132.9/80) and waist circumference (108.3 for males and 101.7 for females). Mean HbA1c for T2DM was 8.1% with patients on insulin-only having a higher mean HbA1c than those on oral agents alone (9.02% vs 7.62%).

1.9.2 Studies Conducted in Other Countries

Prevalence of Type 2 Diabetic Patients Within the Targets of Care Guidelines in Daily Clinical Practice: A Multi-Centre Study in Brazil.[94]

Over the period of May 2000 to May 2001 a multi-centre, cross sectional study was conducted in Brazil. The study involved thirteen public endocrine clinics in urban areas which served a mainly low income population. Clinic records of 2233 patients was analysed to assess weight, BMI, HbA1c, BP and cholesterol. Mean age of patients was 59.2% and the sample population was predominantly female (60%). One third of patients were obese and 42.1% were overweight. 46% of patients achieved glycaemic targets. However, it is important to note that the rate of glycaemic target achievement was higher in patients receiving dietary or oral treatment than in patients on insulin alone or insulin-oral combination (67% & 56% vs 35% and 39%). Targets for SBP, DBP and LDL-Cholesterol were met by 28.5%, 19.3% and 20.6% of patients respectively.

Glycemic control in diabetic patients in King Khalid University Hospital (KKUH) – Riyadh – Saudi Arabia.[95]

Medical records of patients collecting treatment from the King Khalid university hospital pharmacy were reviewed over a one year period. Subjects included in the study numbered 1520. Majority were female, over the age of 40 (90%) and obese (90%). Glycaemic control (HbA1c <7%) was achieved in 40% of patients, target LDL-cholesterol in 24.6% of patients and SBP BP targets in 50% and DBP target in 72%.

Glucose, Lipid, and Blood Pressure Control in Australian Adults With Type 2 Diabetes. The 1999-2000 AusDiab. [96]

The baseline data collection for the Australian Diabetes, Obesity and Lifestyle study also showed very poor achievement of targets for glycaemic control, BP and lipids in the large population based survey. Over the twelve year follow-up, there was little improvement in target HbA1c and BP achievement. However there was marked improvement in the achievement of LDL-cholesterol targets.[97]

Review of the American National health and nutrition surveys (NHANES) data and the European Guideline Adherence to Enhance Care Study (GUIDANCE) also reveal poor levels of achieving DM targets.[98, 99]

Other significant points to note from review of these and other studies are:

1. Individuals with poorer control include younger patients, women and patients on insulin based regimens.[100–102]

2. Reasons cited for poor achievement of targets include: non-compliance to lifestyle intervention and prescribed treatment, low income with poor access to healthcare and monitoring and inertia in escalating treatment.[95,103,104]

In summary, DM is one of the NCD that is increasing exponentially worldwide and has been recognised by national and international institutions as an area of concern. Uncontrolled hyperglycaemia leads to significant morbidity and mortality and has far-reaching social and economic consequences. Comorbidities such as hypertension, dyslipidaemia and obesity further increases the risk of complications. In South Africa, as in many other regions, guidelines have been developed to assist with screening and treatment. Still, in most places, achievement of targets set out within guidelines is low. The purpose of this study is to assess whether the patients at the Helen Joseph Diabetic Clinic are achieving said targets.

2 PROTOCOL

2.1 Study Objectives

2.1.1 Primary Objectives

To evaluate the degree to which target HbA1c levels are achieved in accordance with The 2012 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines.

2.1.2 Secondary Objectives

a. To determine if targets for Blood Pressure in patients attending the Diabetic Clinic are achieved.

b. To determine if goals for serum lipids in patients attending the Diabetic Clinic are achieved.

c. To determine the prevalence of obesity of patients attending the Diabetic Clinic based on the World Health Organization definition of obesity.

d. To determine the prevalence of metabolic syndrome of patients attending the Diabetic Clinic based on the Harmonized definition of the metabolic syndrome.

e. To assess whether patients attending the Diabetic Clinic adhere to lifestyle modification. The following factors will be looked at: smoking, alcohol consumption and exercise

2.2 Methods

2.2.1 Study Design

Retrospective Cross-Sectional Clinical Audit for the defined date range 1st March 2013 to 30 April 2015.

2.2.2 Study population

a. All established type 2 diabetic patients attending the diabetic clinic

b. Exclusion Criteria

    i. Less than 5 years since diagnosis

    ii. Patients on oral hypoglycaemic agents other than Metformin

2.2.3 Setting

The Diabetic Clinic Helen Joseph Academic Hospital

2.2.4 Patient recruitment

a. Sample size : 30 patients

b. Sample selection: 300 consecutive patients who attended the Diabetic Clinic at the Helen Joseph Hospital during the period 1st March 2015 to 30th April 2015

2.2.5 Data being collected

All data being collected are done routinely at the clinic visit.

a. Demographic – age, race and gender

b. Year of diagnosis of diabetes

c. Year at which insulin was started

d. Smoking history. This is recorded in yes/no format in the patient files and is not quantified

e. Alcohol use- This is recorded in yes/no format in the patient files and is not quantified

f. Exercise- This is recorded in yes/no format in the patient files and is not quantified

g. List of medications used by patient as recorded at last clinic visit

h. Height in meters(assumed to have been collected using a standardize height meter)

i. Weight in kilograms using a standard scale placed on the floor. Patients are weighed standing barefoot without any support.

j. Body mass index was calculated as a function of the measured height and weight using Quetelet's formula = weight (kg)/height(m) x height(m)

k. Abdominal circumference recorded with the use of the IDF measuring tape

l. Blood Pressure was measured with an automated sphygmomanometer. An average of the blood pressures from the last 3 visits were assessed in order to compensate for white coat hypertension

m. Latest HbA1c recorded

n. Last Serum lipogram recorded

2.2.6 *Data confidentiality*

No patient names or hospital number will be recorded on data sheets. Data sheets (see Appendix A) will be assigned a study number only. Any links between the study numbers, patient initials and identity of patients will be kept separate. Data will then be accessible to the supervisor, statistician and myself.

2.2.7 Endpoints

Endpoint of the study will be marked by selection of 300 patients

2.2.8 Sources of Bias

a. Sampling: As consecutive patients will be included in the study, it is purely chance that determines inclusion. Thus the audited sample is rarely fully representative of the general population.

b. Selection Bias: The Specialist Diabetic Clinic is a referral clinic that accepts patients who are poorly controlled with or without established target organ damage. This will result in higher average HbA1c analysis.

c. Measurement Bias: Reliability of observations/measurements taken by nursing sister as well as poor record keeping by doctors

2.2.9 Confounding variables/Limitations

a. Patient's non-compliance with regards to medication will not be assessed in this retrospective audit.

b. Patient's non-compliance with regards to exercise and other lifestyle modifications will not be assessed in this retrospective audit.

c. Smoking and drinking of alcohol will not be quantified.

d. Duration and frequency of exercise will not be assessed.

e. Patient's adherence to diet will not be assessed in this retrospective audit.

2.2.10 Study Strengths

a. All the necessary information captured should be available as part of standardised care

b. The blood results are standardised and performed by the same laboratory (National Health and Laboratory Service based at Helen Joseph Academic Hospital)

c. Using the data sheet, a single researcher will collect the data from the patient records ensuring standardisation and reliability.

2.3 Data Analysis

- Data will be captured on physical paper and then captured electronically on (the program that you using)
- Date from (the program that you using will be exported to Excel where the following Basic Data analysis will be done
- Descriptive analysis of the demographics
- Male and female breakdown as a percentage of study population
- Age will be shown as median and range
- Duration of treatment will be shown as median and range
- HbA1c, Blood pressures and waist circumference will be shown as range and median
- Prevalence of metabolic syndrome will be reported as percentage

2.4 Approval / Ethics

Approval will be obtained from the relevant governing committees: Ethics Committee Helen Joseph Hospital and University of the Witwatersrand Ethics Committee.

2.5 Funding

The study was self-funded. No cost will be imposed on the hospital or the patient. The results will be obtained from clinical and hematological records, the patients will be seen at their routine visits and will not be required to come in for a second visit. Any funds required for paperwork (data sheet) will be provided by the doctor conducting the audit.

2.6 Timing

The study will commence once approval is received. The expected duration of the audit is 10-12 months. This will be subject to the clinical commitments of the primary investigator, hence the time frame maybe shortened or lengthened.

The following Gantt chart outlines the audits timeline:

	Mar -15	Apr-15	May -15	Jun-15	Jul-15	Aug -15	Sep -15	Oct-15	Nov -15	Dec -15	Jan-16	Feb -16
Literature Review												
Protocol Preparation												
Protocol Assessment												
Ethics Application												
Data Collection And Write Up												

2.7 Consent Form

The audit is retrospective and all information that will be recorded audit is done at a routine follow up visit.

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CHAPTER TWO

Submissable Article

TITLE

A Critical review of whether goals for treatment in Type 2 Diabetes Mellitus as set out by the 2012 Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) guidelines are being achieved in patients attending the Diabetic clinic at Helen Joseph Hospital.

AUTHORS

1. Saajidah Bulbulia
2. Firdous Variava
3. Zaheer Bayat

AFFILIATIONS

1. Division of Diabetes, Endocrinology and Metabolism, Helen Joseph Academic Hospital
2. University of the Witwatersrand, Johannesburg, South Africa

SHORT TITLE

Are Goals for Type 2 Diabetes Mellitus being met at Helen Joseph Academic Hospital?

CONFLICT OF INTEREST

Nil

KEYWORDS

Diabetes, targets, Helen Joseph, SEMDSA guidelines

CORRESPONDING AUTHOR

Saajidah Bulbulia

E-mail: sjdh_blbl@yahoo.com

Mobile: 082 573 5909

WORD COUNT: 3173

ABSTRACT WORD COUNT: 207

ABSTRACT

Background:

The risk of complications from Type 2 Diabetes Mellitus (T2DM) is high. Achieving targets reduces the morbidity and mortality. This study aims to assess whether patients at the Helen Joseph Hospital's Diabetic Clinic are meeting the 2012 SEMDSA targets for diabetes.

Methods:

A Retrospective Clinical Audit was carried out. The files of 321 patients with T2DM were reviewed. Glycated haemoglobin (HbA1c), Blood pressure, abdominal circumference and lipograms were assessed.

Results:

The study population compromised majority black (n=143; 44.6%) and coloured (n=109; 34%) patients and was predominantly female (n=200; 62.3%).The mean age was 59.4 years (SD 9.9y). 89.1% (n=286) had Hypertension; and 82.2% (n=264) dyslipidaemia. The metabolic syndrome criteria was fulfilled by 266 (91.2%) patients. The majority did not exercise (n=174; 56.3%). A small amount smoked (n=39; 12.5%) and used alcohol (n=33; 10.6%). Mean HbA1c was 9.5% (SD 2.4; range 3.9 – 16.9%). Only 49 (15.3%) achieved the target HbA1c. Target Blood Pressure was achieved by 72 patients (25%). LDL target was achieved by 71 (22.6%) and abdominal circumference by 32 (11%) patients.

Conclusions:

Despite adequate protocols and access to tertiary medical care, a very small percentage of patients are achieving proposed targets. The reasons for this is likely multi-fold and further analysis is required to assess these.

INTRODUCTION

The global burden of non-communicable diseases (NCD) is rapidly escalating.[1] More than 63% of annual global deaths can be attributed to NCD's with the majority occurring in low to middle income countries.[2] The impact on society, the economy and the health sector is immense and could be crippling if not attended to.[2–6] Diabetes Mellitus (DM) is one of the four areas listed for intervention by the World Health Organisation (WHO) and the United Nations (UN).[1, 2, 5]

The 2015 International Diabetes Federation (IDF), worldwide estimated prevalence of adults DM is 415 million (8.8%) and this number is estimated to rise to 642 million by the year 2040.[7] Approximately 75% of these people live in middle to low income countries.[7] The scarcity of nationwide data for the majority of African countries makes the estimates for Africa uncertain.

Nevertheless, from available data the 2015 IDF estimated prevalence of DM in Africa is 3.2%. In addition, an estimated 66.7% of these people remain undiagnosed, the largest proportion in any IDF region.[7] In South Africa, the IDF estimated prevalence of DM is 7% (2.3 million South Africans) and 61.1% remain undiagnosed. When compared to the 2010 IDF estimate for DM in South Africa (4.5%)[8] , this equates to a greater than 60% increase in the prevalence of DM in just 5 years.

This rapid increase in the number of people with DM is a worldwide phenomenon with multiple underlying causes, including: rapid urbanisation, increasing age of the world's population and the rapid rise of obesity and the metabolic syndrome. The great concern over this rapid rise stems from the widespread impact of this disease on individuals, families, communities and nations.[3,7] According to IDF estimates, 11.6% of global health expenditure is used for DM.[7] DM is also one of the leading causes of death worldwide and in South Africa was reported as the cause of death, in 5% of deaths in 2016.[9]

Early recognition, diagnosis and implementation of treatment, continuous access to appropriate medications, treatment of concomitant medical problems and vigilant screening and recognition of complications is imperative in the management of DM. For this reason, Diabetic Societies worldwide have proposed guidelines to assist clinicians.[10, 11] Still, in most places, achievement of targets set out within guidelines is low. The purpose of this study is to assess whether the patients at the Helen Joseph Diabetic Clinic are achieving said targets.

AIMS

The primary aim of this study was to evaluate if target HbA1c levels are achieved among patients attending the Diabetic Clinic. Secondary objectives were to determine if targets for Blood Pressure, waist circumference and serum lipids were being achieved in these patients. Lastly, to determine the prevalence of obesity based on the WHO definition and the prevalence of the metabolic syndrome based on the Harmonized definition of the metabolic syndrome.

METHODS

Study Design

A Retrospective Cross-Sectional Clinical Audit of the Helen Joseph Academic Hospital Diabetic Clinic for the defined date range of the 1st March 2015 to 30 April 2015 was conducted. Records of all patients attending the diabetic clinic assessed. Records of patients with type 1 diabetes (T1DM) were excluded. T2DM patients not on insulin metformin were excluded from the study as these patients are usually followed up at the hospital medical out patients (MOPD) clinic and only referred to the Diabetic Clinic when insulin initiation is required. Records of patients with established T2DM (greater than 5 years duration) and who were on insulin-only therapy or insulin-metformin combination therapy were included in the study. The records of 321 patients fulfilled inclusion criteria and were entered into the data collection set. Each file was given a study number.

Data Collection

Demographics and other descriptive characteristics were obtained from institutional records. The list of medications prescribed at the last clinic visit was used. As per records, information on exercise, smoking and alcohol use are noted in a yes/no format without being quantified and was thus recorded as such.

Clinical parameters are measured by nursing staff on duty at every visit and inter-observer variability is possible. Height is measured using a standardised height meter. Weight using a standardised scale is measured with patients standing barefoot without support. Body mass index (BMI) is calculated from the patients weight and height using Quetelet's formula (weight (kg)/Height (m) x Height (m)). Abdominal circumference is measured using the International Diabetes Federation (IDF) measuring tape placed at 2cm above the anterior superior iliac crest with the patient standing. Blood Pressure (BP) is measured using the Mindray vs-800 calibrated automatic sphygmomanometer. An average of the last three measurements was used in order to compensate for the phenomenon of white coat hypertension.

As Helen Joseph Hospital is a public sector hospital, blood samples are processed by the National Health Laboratory Services (NHLS). The last recorded glycated haemoglobin (HbA1c) value and random serum Lipograms were used for analysis.

Data was recorded on data sheets and the inputted into the Research Electronic Data Capture (RedCap) web based application. Once all data was recorded, a data report formed in RedCap was transferred to Microsoft Office Excel for analysis.

Statistical and Data Analysis

Descriptive analysis of the data was carried out as follows. Categorical variables were summarised by frequency and percentage tabulation, and illustrated by means of bar

charts. Continuous variables were summarised by the mean, standard deviation, median and interquartile range, and their distribution illustrated by means of histograms. The prevalence of patients who met each of the treatment goals was estimated, together with 95% confidence intervals. The association between target achievement and insulin regimen was analysed by means of a chi-squared test. Data analysis was carried out using SAS version 9.4 for Windows. The 5% significance level was used throughout.

RESULTS

Demographics

The study population comprised 321 patients aged 30 to 88 years old, with a mean age of 59.4 years (SD 9.9). Complete demographic data can be seen in Table 1. The cohort compromised majority black (n=143; 44.6%) and coloured (n=109; 34%) patients. This sample was predominantly female (n=200, 62.3%). The year of diagnosis ranged between 1973 and 2010. The majority of patients had a sedentary lifestyle: 174 patients (56.3%) did not exercise. In addition, a small amount of patients in this study population smoked (n=39; 12.5%) and used alcohol (n=33; 10.6%).

A large proportion of patients had concomitant Hypertension (n=286; 89.1%) and dyslipidaemia (n=264; 82.2%). More than half of the patients were classified as obese according to the WHO classification. A staggering, 91.2% (n=266) fulfilled the criteria for diagnosis of the metabolic syndrome.

The following insulin regimens were used: Protophane only 11.2% (n=36), bi-daily Actraphane 73.2% (n=235), combination of Protophane and Actrapid 4.6% (n=47) and Actraphane/Actrapid combination 0.9% (n=3). Analysis of the small number of patients in the Actraphane/Actrapid group, would not have revealed any significant results. This group was thus excluded from further analysis.

Metformin was used in 72.5% (n=228) of patients. Of note, the majority of patients were being treated with statins, aspirin and Angiotensin Converting Enzyme Inhibitors. A complete list of medications used can be found in table 2.

Achievement of targets:

Table 3 shows detailed analysis of each variable. Figure 1 and table 4 depicts percentage of patients achieving targets.

Anthropometric measurements

The mean average Systolic BP was 144 mmHg (sd 20; range 98-245 mmHg) and the mean average Diastolic BP was 81 mmHg (sd 20; range 98-245 mmHg). Only 72 patients achieved the target BP of <140/90mmHg (25.1%; 95% CI=20.2-30.5). Target waist circumference was taken to be <80cm for females and ≤ 94cm for males. Mean waist circumference was found to be 109cm for females (sd 16 cm; range 72-160 cm) and 106cm for male (sd 15 cm; range 55-157 cm) and only 32 patients (11%; 955 CI 7.9-15.1) had ideal waist circumference .

Blood results

Target HbA1c used for the purpose of this study was 7% or lower which is the SEMDSA recommended guideline for the majority of patients.[12] The reason for this was that though the SEMDSA guidelines for target HbA1c differs according to age, prevalence of cardiovascular risk factors, hypoglycaemic unawareness and general overall prognosis; no clear outline of age range and prognosis is given.[12] Additionally, data collected during this study did not include incidence of hypoglycaemic events, patient's awareness of hypoglycaemia and presence of target organ damage. In addition, factors affecting the HbA1c analysis (example anaemia) was not assessed. The mean HbA1c in this study population was 9.5% (SD 2.4; range 3.9-16.2%). Only 49 (15.3%; 95% CI 11.5-19.7) achieved the target HbA1c of 7% or less. Figure 2 depicts the range of HbA1c.

Data has demonstrated that the number of daily insulin injections is inversely proportional to compliance.[13] Thus greater injection numbers equal higher HbA1c levels. Table 5 illustrates the relationship between insulin regimen and HbA1c. There was no significant association between patients with HbA1c at target and insulin regimen used (p=0.85). There was however, a higher mean HbA1c level amongst patients on basal bolus than those using other regimens, even when controlling for co-morbidities.

Analysis of lipograms revealed unequally distributed data with: Median total cholesterol of 4.4mmol/l (IQR 3.6-5.2), median triglyceride level of 1.6mmol/l (IQR 1.1-2.2), median LDL-cholesterol of 2.4mmol/l (IQR 1.9-3.0) and median HDL-cholesterol level of 1.0mmol/l (IQR 0.9-1.2) for males and 1.1mmol/l (IQR 0.9-1.4) for females. Target LDL-cholesterol was taken to be <1.8mmol as recommended by the current SEMDSA guidelines.[10, 12] Only 71 patients (22.6%; 95% CI 18.1-27.6%) had LDL-cholesterol levels below the target. 61.3% (n=192) and 46.6% (n=146) of patients had low HDL-cholesterol and high triglyceride levels respectively. The only statin available at the time was Simvastatin. The relationship to dose was not assessed.

DISCUSSION

The rapid rise in prevalence of DM in the last few decades has generated concern globally. [2,7] The socio-economic concerns stemming from this disease and its complications are extensive, affecting all levels of society.[5,14] As a result, healthcare organisations worldwide have produced evidenced based guidelines to assist clinicians with the screening, diagnosis and management of DM.[10, 11, 14]

The establishment of specialised Diabetic clinics is an attempt to improve access to healthcare and a continuous supply of medication for all individuals.[10] At hospital level, diabetic clinics are referral centres for the complicated and often difficult to treat

patients. Regular audits of these institutions allows management to assess systems and protocols and address areas of concern.[10]

Audits of diabetic clinics, in South Africa and internationally reveal that even with evidenced based guidelines, only small numbers of patients are able to achieve set targets.[15, 16] South African studies have revealed glycaemic target achievement in ≤30% of patients in both the public and private health care sectors. Achievement of target BP and LDL-cholesterol was only slightly better.[18–21] Moreover, Pinchevsky et al. demonstrated a decline in percentage of patients achieving targets between the years 2009 and 2013 in their audit of the Charlotte Maxeke Johannesburg Academic Hospital diabetic clinic.[21] International studies reveal only slightly better results with the greatest level of target achievement in resource-rich developed countries.[21–25]

Our cohort of 321 patients consisted mainly of black and coloured patients consistent with the South African demographic, the drainage area of the hospital and the individuals that reported using public health care facilities in the last South African Household Survey.[26] Female predominance is consistent with findings from Hilawe et.al and cohorts noted in other studies.[16,27] Similarly the mean age of 59.4 years is in keeping with other cohorts.[23–25]

Rates of smoking in this study population was found to be lower than the reported South African national average.[28] Use of alcohol was also noted in only a small percentage of patients. Though these rates are low; considering the fact that both smoking and excessive alcohol use confer additional risk in terms of cardiovascular disease and other complications; it is imperative that patients who require assistance with cessation of these risk activities be identified and helped.

The low numbers of patients with HIV/AIDS in this cohort is surprising, considering the high prevalence of HIV/AIDS in South Africa.[9] This is most likely due to a combination of underreporting by patients and under-screening by clinicians. Another

reason may be that these patients are not being referred to the Diabetic Clinic (due to limited capacity) and are being treated at either the MOPD Clinic or the HIV Clinic. The interactions between HIV/AIDS and NCD's as well as their treatments have been well documented.[29–32] It is thus evident that further measures need to be taken within this diabetic clinic to ensure adequate screening and treatment for HIV/AIDS.

The high prevalence of obesity, hypertension and dyslipidaemia is reflective of the global rise in the Metabolic Syndrome.[33] Considering the higher risk of cardiovascular disease and other complications in patients diagnosed with the metabolic syndrome, this is disquieting. Even more perturbing is the very low rates of achievement of HbA1c, BP and lipid targets set by the SEMDSA diabetes guidelines.[12]

On cursory comparison with other studies, both national and international, it seems that the Helen Joseph Diabetes Clinic is achieving much lower rates than other clinics. This can be seen in the meta-analysis done by Pinchevsky et el. in 2015.[16] However, it must be noted that formal comparison with these studies cannot be done as all the sample populations and settings are heterogeneous to the one in this study. That is, the study populations in most similar studies comprise of either a mix of patients with both T1DM and T2DM or all patients with T2DM, regardless of treatment regimen. Additionally, the majority of studies looking at similar outcomes have been carried out in primary health care settings as opposed to specialised diabetic clinics like the one at Helen Joseph Hospital. Still, the trend in many of these studies is lower levels of target achievement in individuals with T2DM who are on insulin based therapy, as opposed to those receiving oral hypoglycaemic agents.[16]

The reasons for low rates of target achievement are multifactorial and some have been noted in large multicentre studies such as the Diabetes Attitudes, Wishes, and Needs (DAWN) Program conducted across 11 countries in America, Europe, Asia and Australia.[34] These reasons encompass patient, care-giver and system factors that influence outcomes. The most pertinent factors will be discussed.

Education is the cornerstone of any good management plan. Education of both patients and doctors have been proven to improve outcomes in diabetic patients.[35–37] Education with regards to illness and treatment, amongst South African patients in the public sector has been demonstrated to be poor.[38] The implementation of structured education programmes with a focus on diabetes self-management is encouraged. Additionally, diabetic educators and physicians require continuous training in order to offer the best possible patient care.

With the high rates of obesity noted in this study it is imperative that intervention be directed toward maintaining an adequate weight loss program as this can has been demonstrated to have many advantages including better control and even reversal of concomitant diseases and prevention of complications.[39,40] Weight management can also significantly impact psychosocial well- being and quality of life.[41]

At the Helen Joseph diabetic clinic, patients have access to a dietician and receive group education on diet and exercise. Exercise is recorded in clinic notes in a yes/no manner and <50% of patients were recorded as exercising. Compliance to diet was not assessed in this audit. There is thus a clear need to further analyse patients understanding, perceptions and compliance to diet and exercise regimens. Other barriers toward lifestyle changes that have been noted are the perceived high costs of healthy food[42] and risk of exercise associated complications (example: hypoglycaemia). SEMDSA recommends individualised medical nutrition therapy and exercise programmes.[12] Collaboration with community based diet and exercise programmes could be a feasible and useful option. Consideration of appropriate patients for medical management of weight loss and bariatric surgery and ensuring access to these treatments in the public sector would also assist with improving outcomes.

Open and easy channels of communication and appropriate glucose monitoring ensures that adequate and timely changes to treatment, diet and exercise

programmes can be implemented.[42, 43] Thus target levels can be achieved quickly and sustained for long periods. Glucose monitoring was not assessed in this study and may be an area that needs further evaluation in future. As communication in our technology driven age becomes easier, the implementation of online forums and support groups may enhance treatment.

Another area that poses a large obstacle to the ability of patients in the public sector achieving targets is the lack of access to appropriate medications, as well as the lack of consistency in obtaining medications. As compared to the 2012 Guidelines, the latest 2017 SEMDSA guidelines advocates the use of Glicazide as the only sulphonylurea, however it is not available in the state sector. [12] Other drugs used as first line oral additions to Metformin are also unavailable. The 2017 Guidelines also advocates the use of Indapamide as the diuretic of choice for the treatment of hypertension.[12] Again, this medication is not available in the public sector.

Other notable reasons for poor target achieving that have been widely recognised is patient and doctor inertia to increase current treatments despite poor control and fears surrounding starting insulin therapy.[45] Psychosocial factors also contribute considerably to patient outcomes. Patients' perceived burden of illness, fears of complications and treatment, as well as depression affect health related quality of life and adherence to treatment and follow-ups. These factors have a major impact on control of disease and outcomes.[39, 40] Early recognition of anxiety and depression as well as ensuring adequate access to support groups and counselling is essential.

Further analysis of the patients at the Helen Joseph Hospital Diabetic clinic is imperative in order to assess which of these barriers is prevalent and where intervention is most needed. In the interim, some universal steps to intensify treatment, monitoring and education can be undertaken to ensure that greater targets can be achieved. A multi-disciplinary approach involving the patient, the patients support network and the health care team together with individualisation of treatment will ensure better treatment outcomes and quality of life.

The Diabetic Clinic at Helen Joseph Hospital is a referral clinic for the MOPD, the Polyclinic (a primary health care clinic based at the hospital), as well as the regional and district level clinics. Due to its nature as being a tertiary referral centre, most patients referred are either poorly controlled or have significant complications. Once patients have achieved and maintained a good level of control, they are often stepped down back to their respective referral clinics. These factors could also play a major role into understanding why a higher level of HbA1c was found in this study group of patients.

CONCLUSION

Despite adequate protocols and access to tertiary medical care, only a very small percentage of patients at the diabetic clinic are achieving proposed targets. Potential barriers identified include: lack of education, inertia in increasing medication and lack of access to newer agents to treat diabetes. Prospective evaluation of these and other factors needs to be conducted in order to advise on appropriate cost effective resource allocation for our ever increasing diabetic population.

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TABLES:

Table 1: Demographic Data			
Variable	**Category**	**Number**	**%**
		N=321	
Gender	Female	200	62.3
	Male	121	37.7
Ethnicity	Black	143	44.6
	Coloured	109	34.0
	Indian	44	13.7
	White	25	7.8
Comorbidities	Hypertension	286	89.1
	Dyslipidaemia	264	82.2
	HIV	15	4.7
	Thyroid disease	14	4.4
	None	8	2.5
Exercise	Yes	174	56.3
	No	135	43.7
	Unknown	12	3.7
Smoking	Yes	39	12.5
	Never	220	70.7
	Ex-smoker	52	16.7
	Unknown	10	3.1
Alcohol use	Yes	33	10.6
	No	277	89.4
	Unknown	11	3.4
Medication	Actraphane	235	73.2
	Protophane+Actrapid	47	14.6
	Protophane	36	11.2
	Actraphane+Actrapid	3	0.9
BMI (kg/m^2)	<30	127	42.3
	30-34.9	84	28.0
	35-39.9	56	18.7
	>=40	33	11.0
	Unknown	21	6.5
Metabolic syndrome	>=3 criteria	266	90.2
	0-2 criteria	29	9.8
	Unknown	26	8.1

BMI = Body Mass Index. Metabolic syndrome as per International Harmonised Criteria.

Table 2: Medications Used		
Medication	**Number of Patients**	**Percentage of Patients**
Statin (Simvastatin)	294	91.6
ASA	280	87.2
ACE-I/ARB	258	80.4
Metformin	228	71.0
Diuretic	216	67.3
CCB	191	59.5
B-blocker	82	25.5
Tryptanol	75	23.4
PPI	75	23.4
Alpha blocker	50	15.6
ARVs	28	8.7
Tegretol	21	6.5
Fibrate	7	2.2
Allopurinol	7	2.2
Colchicine	3	0.9
Thyroxine	3	0.9
Other	15	4.7

Table 3: Analysis of Variables								
Variable	**N**	**Mean**	**Std Dev**	**Median**	**Interquartile range**		**Minimum**	**Maximum**
Age (y)	321	59.4	9.9	60.0	53.0	66.0	30.0	88.0
BMI (kg/m^2)	300	32.1	8.8	3103	26.6	36.0	16.8	103.8
WC (male) (cm)	111	106	16	105	94	114	72	160
WC (female) (cm)	181	109	15	108	101	117	55	157
SBP (average) (mmHg)	287	144	20	143	129	157	98	245
DBP (average) (mmHg)	287	81	11	82	73	88	53	122
HbA1c (%)	321	9.5	2.4	9.4	7.8	11.1	3.9	16.2
Total cholesterol (mmol/l)	315	4.46	1,09	4.35	3.62	5.16	2.05	9.28
Triglycerides (mmol/l)	313	1.89	1,27	1.61	1.09	2.20	0.43	11.70
HDL cholesterol (male) (mmol/l)	116	1.07	0,29	1.03	0.90	1.17	0.57	2.77
HDL cholesterol (female) (mmol/l)	197	1.16	0,34	1.10	0.91	1.38	0.60	2.52
LDL cholesterol (mmol/l)	301	2.49	0,91	2.36	1.89	3.01	0.29	6.03

BMI = Body Mass Index; WC = Waist Circumference; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure, HbA1c = Glycated Haemoglobin; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein

Table 4: Patients who meet targets				
Measurement	**n**	**%**	**95% CI (%)**	
SBP (n=287)	131	45,6	40,0	51,6
DBP(n=287)	131	45,6	40,0	51,6
BP (<=140/80 mm Hg) (n=287)	72	25,1	20,2	30,5
Waist circumference (n=292)	32	11,0	7,9	15,1
BMI (n=300)	127	42,3	36,7	48,1
HbA1c (n=321)	49	15,3	11,5	19,7
Total cholesterol (n=315)	169	53,7	48,0	59,3
Triglycerides (n=313)	167	53,4	47,7	59,0
HDL cholesterol (n=313)	135	43,1	37,6	48,8
LDL cholesterol (n=314)	71	22,6	18,1	27,6

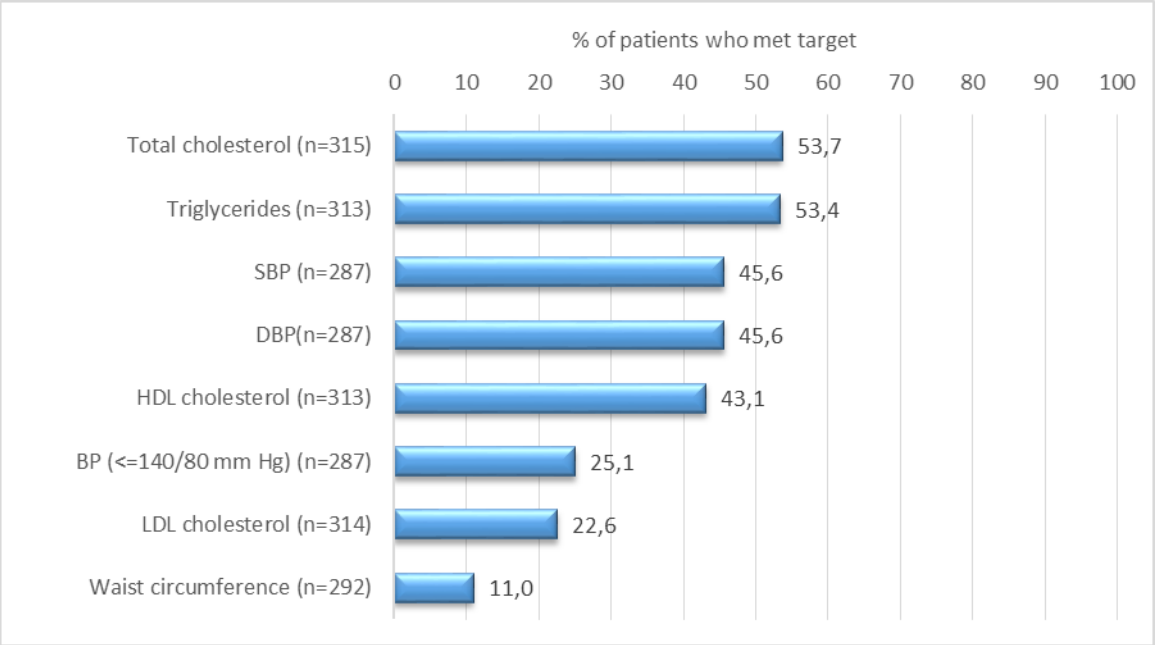
BMI = Body Mass Index;; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure, BP = Blood Pressure; HbA1c = Glycated Haemoglobin; HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein

Table 5: Relationship between Insulin Regimen and HbA1c								
Insulin Type	**n**	**%**	**Mean**	**STD Dev**	**Minimum**	**Maximum**	**HbA1c < 7%**	**HbA1c ≥ 7%**
Actraphane	235	73.2	9.4	2.4	3.9	14.8	15.7	84.3
Protophane+Actrapid (basal bolus)	47	14.6	10.4	2.5	4.7	16.2	12.8	87.2
Protophane	36	11.2	9.4	2.4	5.7	15.0	16.7	83.3

HbA1c = Glycated haemoglobin

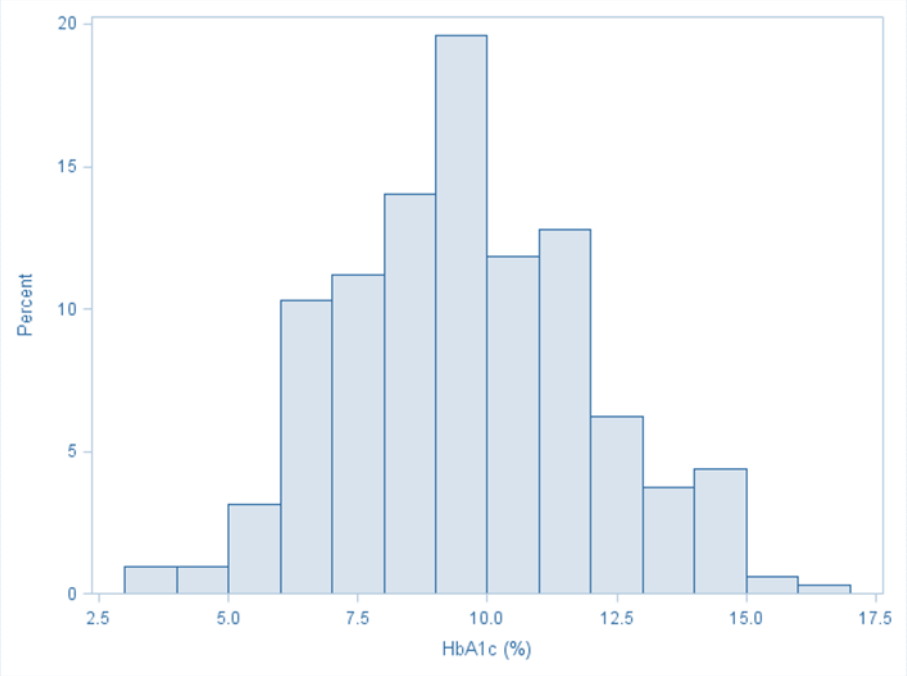
FIGURES:

Figure 1: Percentage of patients who met targets



SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure, HDL = High Density Lipoprotein; LDL = Low Density Lipoprotein

Figure 2: HbA1c Range



APPENDICES

Study No: | | | | **Appendix A**

1. Demographics:

Race: | Black | White | Indian | Coloured | Other |

Sex: | Male | Female |

Age: _____

2. History:

Year of diagnosis _____

Year Insulin started: _____

3.Treatment:

	Dose		*Dose*
Actraphane		Protophane	
Actrapid		Metformin	
Diuretic		CCB	
ACE/ARB		Beta-blocker	
Alpha-blocker		Statin	
Fibrate		Tryptanol	
Allopurinol		Tegretol	
Colchcine		Aspirin	
Other			

Study No: | | | | **Appendix A**

4. Clinical Parameters:

Height		cm
Weight		kg
Systolic Blood Pressure		mm Hg
Diastolic Blood Pressure		mm Hg
Abdominal Circumference		cm

5. Laboratory findings:

Glycated Haemaglobin (HbA1c)		%
Total cholesterol		mmol/l
Triglyceride		mmol/l
HDL cholesterol		mmol/l
LDL cholesterol		mmol/l
TSH		mmol/l