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The Prevalence of Renal Dysfunction in Insulin-Requiring Type 2 Diabetic Patients being followed up at a Specialist Diabetic Clinic at a Tertiary Academic Hospital

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

Johannesburg, 2018

Declaration

I, Zareena Angamia, declare that this report is of my own work.

It is being submitted for the Degree of Master of Medicine in the Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand.

It has not been presented for any other degree at any other University.

_____ _____

Dr Zareena Angamia Date

MBBCh (Wits), FCP (SA)

Dedication

For the unrelenting stoicism of my mother.

For the unwavering love and support of my husband.

For the perspective my children bring.

I am truly blessed.

Ethics Committee Approval

This research was approved by the Ethics Committee for Research on Human Subjects, University of the Witwatersrand (Clearance Certificate number: M151188).

Abstract

Background

Diabetes Mellitus (DM), particularly Type 2 DM, with its high prevalence, continuous growth and numerous complications, places a significant burden on health care systems. Much of the morbidity and mortality is due to Diabetic Nephropathy (DN); a frequent cause of chronic kidney disease (CKD) and a leading cause of end stage renal disease. As such, early diagnosis and appropriate management is essential in alleviating the strain of DN on health care.

Limited information about the prevalence of DN and the evaluation of screening and treatment protocols in our, South African, healthcare facilities is available. This study aims to assess the prevalence and stage of renal dysfunction in type 2 diabetic patients, measured as chronic kidney disease, attending a specialist diabetic clinic at a tertiary academic hospital. Furthermore, the study attempts to review the association of certain parameters (such as demographics, co-morbidities, HbA1c, BMI and proteinuria) with DN.

Patients and Methods

This study is a retrospective clinical audit and descriptive study of patients attending the Helen Joseph Academic Hospital (HJAH) Diabetic Clinic. The files of 321 insulin-requiring type 2 diabetic patents, who had been diagnosed more than five years previously, were reviewed between the 01/03/2015 and 21/04/2015. In order to determine the prevalence of renal dysfunction, the patient profile and associated factors the following parameters were assessed: demographics, co-morbidities, HbA1c, BMI, renal function, urine dipstick and urine PCR.

Results and Discussion

The study population of 321 patients yielded a mean age of 59.4 years, a female predominance of 62% and comprised 44.6% black and 34% coloured patients. Hypertension and dyslipidaemia were the most common co-morbid diseases (89.1% and 82.2% respectively); while 54% of the sample were classified as obese. Over half of the sample population (56.3%) did not engage in exercise and almost a third (29.2%) had tobacco exposure. The mean HBA1c was 9.5%.

66.8% of the study group showed evidence of CKD, a large proportion of which were classified as Stage 2 CKD. It was demonstrated that Glomerular Filtration Rates (GFRs) did not worsen in general with time, but rather tended to oscillate between the defined CKD stages and there were no significant differences in the time between the transitions between the stages. Urine dipstick results noted proteinuria in 16.8% and glycosuria in 37.7%. The association of time period from diagnosis, co-morbid disease, HbA1c and BMI yielded no significant difference between the groups with normal renal function and renal dysfunction. Limited information regarding urine PCR was available.

Conclusion

The prevalence of DN, as defined by CKD, is significant in this study population. Glycaemic control is considerably poorer than target levels; there are high levels of co-morbid diseases and poor lifestyle choices. The screening for DN (micro-albuminuria measurement) is under-utilised, possibly contributing to delay in diagnosis, treatment and poor outcome. Appropriate amendments in screening and management is essential to improve DN-associated morbidity.

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Table of Contents

Declaration ii
Dedication iii
Ethics Committee Approval iv
Abstract v
Background v
Patients and Methods v
Results and Discussion vi
Conclusion vi
Acknowledgements vii
Table of Contents viii
List of Figures x
List of Tables xi
List of Study Abbreviations xii
List of Abbreviations xiii
1. Chapter 1: Literature Review 1
1.1. Introduction 1
1.2. Aetiology and Classification 1
1.3. Complications 3
1.4. Stages of DN 4
1.5. Risk Factors 5
1.6. Management 7
1.7. Challenges in Management 14
1.8. Therapies for the Future 16
1.9. Conclusion 19
2. Chapter 2: Patients and Methods 20
2.1. Aims and Objectives 20
2.2. Methodology 21
3. Chapter 3: Results 27
3.1. Demographics 27
3.2. Year of Diagnosis 28
3.3. Co-morbidities 29
3.4. Lifestyle 29
3.5. BMI 30
3.6. Medication 31

3.7. Time period 32
3.8. HbA1c 34
3.9. GFR 35
3.10. Urine Dipstick 36
3.11. Urine PCR 37
3.12. Prevalence of CKD 38
3.13. Time from Diagnosis to CKD Stage 38
3.14. Time between changes in CKD stage 41
3.15. HbA1c and Insulin 43
3.16. Renal Function 44
4. Chapter 4: Discussion 47
4.1. Analysis 47
4.2. Strengths and Limitations of the Study 57
4.3. Future considerations 59
4.4. Future Studies 60
4.5. Conclusion 61
5. Chapter 5: Bibliography 62
Appendix A - Sample Size Calculation 71
Appendix B - Data Collection Sheet 72
Page 1 72
Page 2 73
Appendix C - Ethics Approval Letters 74
1. Wits HREC 74
2. HJAH Ethics Committee 76
Appendix D - Turnitin Letter from Supervisor 76

List of Figures

Figure 1: Age Demographics 27
Figure 2: Year of Diagnosis 28
Figure 3: Prevalence of Co-morbidities 29
Figure 4: BMI of Study Patients 30
Figure 5: Distribution of time period between Diagnosis and Baseline Measurement (Time in years) 33
Figure 6: Distribution of time period between Baseline and Second result set. 33
Figure 7: Distribution of time period between Second and Recent result set. 34
Figure 8: Measured HbA1c levels 35
Figure 9: Categorised GFR Levels 36
Figure 10: Abnormalities detected on urine dipstick 37
(NAD - No Abnormalities Detected) 37
Figure 11: The GFR profile of five patients (time in months) 38
Figure 12: The CKD profile of five patients (time in months) 39
Figure 13: The GFR profile of each patient from time of diagnosis to each measurement point (Baseline, Second and Recent) 39
Figure 14: The CKD stage profile 40
Figure 15: Median time from diagnosis to each CKD stage 41
Figure 16: Median time for stage transition 42

List of Tables

Table 3.1: Patient Ethnicity 28
Table 3.2: BMI of study patients 30
The data shows that 66% of females are classified as overweight/obese, in comparison to 42% of males. 30
Table 3.3: Concurrent Medication 31
Table 3.4: Time Period between Measurements 32
Table 3.5: Distribution of Calculated GFR measurements 36
Table 3.6: Urine PCR Outcome 37
Table 3.7: Prevalence of CKD in the study group (categorised by stage) 38
Table 3.8: Time from diagnosis to CKD Stage 2-4 40
Table 3.9: Time between changes in CKD stage 41
Table 3.10: HbA1c Level according to Insulin regimen 43
Table 3.11: Association between the most recent HbA1c and renal function. 44
Table 3.12: Association of BMI and Kidney function 44
Table 3.13: Association of Urine dipstick and CKD Stage 45

List of Study Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release and Controlled Evaluation
ALICE-PROTECT	Analyse Longitudinale Informatisée de Cohorte Evaluant la PROtéinurie, la Tension et les Evènements Cardiovasculaires et rénaux chez les diabétiques de Type 2
CARDS	Collaborative Atorvastatin Diabetes Study
CCB	Calcium Channel Blocker
COSMIC	Comparative Outcome Study on Metformin Intervention versus Convention)
DCCT	The Diabetes Control and Complications Trial
DCCT-EDIC	The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications
DETAIL	Diabetics Exposed to Telmisartan and Enalapril
EMPA-REG	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
GREACE	Greek Atorvastatin and Coronary Heart Disease Evaluation
HPS	Heart Protection Study
IDNT	Irbesartan Diabetic Nephropathy Trial
MARVAL	Micro-Albuminuria Reduction with Valsartan
MDRD	Modification of Diet in Renal Disease
NHANES	National Health and Nutritional Examination Survey
ONTARGET	Ongoing Telmisartan Along and in Combination with Ramipril Global Endpoint Trial
RENAAL	Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan
SAVOR-TIMI	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction
SHARP	Study of Heart and Renal Protection
TNT	Treating to New Target
UKPDS	United Kingdom Prospective Diabetes Study
VA-NEPHRON-D	Veterans Affairs Nephropathy in Diabetes

List of Abbreviations

ACE-I	Angiotensin-converting-enzyme inhibitor
ACR	Albumin Creatinine Ratio
ADA	American Diabetes Association
BMI	Body Mass Index
BP	Blood Pressure
Cr	Creatinine
DM	Diabetes Mellitus
DN	Diabetic Nephropathy
DPP4-I	dipeptidyl peptidase 4 inhibitor
eGFR	estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
g/24hr	gram per 24 hours
GA	Glycated albumin
GAGs	Glycosaminoglycans
GFR	Glomerular Filtration Rate
GLM	General Linear Model
GLP-1	glucagon-like peptide-1
HbA1c	Glycosylated Haemoglobin
HDL-C	high density lipoprotein
HIV	human immunodeficiency virus
HJAH	Helen Jospeh Academic Hospital
IgA	immunoglobulin A
IQR	the interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	kilogram
LDL-C	low density lipoprotein
LPL	lipoprotein lipase
mcg/min	micrograms per minute
ml/min	millilitre per minutes
ml/min/1.73m^2	millilitre per minute per 1.73 square meters

mmHg	millimetre of mercury
n	number
NAD	No abnormalities detected
NAG	N-Acetyl-B-D-glucosaminidase
NDRD	non-diabetic renal disease
NGAL	neutrophil gelatinase-associated lipocalin
NHLS	National Health Laboratory Service
NIDDM	non-insulin-dependent diabetes mellitus
p	p value
PGs	Proteoglycans
PUFAs	polyunsaturated fatty acids
RAAS	Renin-Angiotensin-Aldosterone System
Scr	serum creatinine
sd	standard deviation
SEMDSA	Society for Endocrinology, Metabolism and Diabetes of South Africa
SGLT2	Sodium/Glucose Cotransporter 2
SNS	Sympathetic Nervous System
TG	triglyceride
U-PCR	Urine Protein Creatinine Ratio)
U&E	urea and electrolytes
UANG	Urinary angiotensinogen to creatine ratio
UCCR	Urinary cystitis-C to creatinine ratio
UKIM-1	Urinary KIM-1 to creatinine ratio
UNGAL	Urinary NGAL to creatinine ratio
US FDA	United States Food and Drug Administration
VLDL-C	very low density lipoprotein
WHO	World Health Organisation

1. Chapter 1: Literature Review

1.1. Introduction

Health care systems, worldwide, are facing a major challenge in management of chronic non-communicable diseases due to their high prevalence and continuous growth. Diabetes Mellitus (DM) is a prime example of such a disease, in both industrialised and developing countries. Without adequate preventative and management strategies in place, the numbers of people affected by the condition and the complications associated with DM will expand at an unparalleled rate[1].

1.2. Aetiology and Classification

DM is a metabolic disorder with multiple aetiologies. Defective insulin secretion, insulin action or both, result in chronic hyperglycaemia and disturbances in carbohydrate, fat and protein metabolism. Diabetes can be classified into type 1, type 2, gestational diabetes and other secondary forms ([2],[3],[4]).

Type 1 DM, which accounts for less than 10% of cases, occurs as a result of beta cell destruction and hence, absolute deficiency of insulin. Type 2 DM is the most common type of diabetes (approximately 90% of cases) and is due to insulin resistance as well as an inadequate insulin secretory response. Gestational diabetes involves hyperglycaemia in pregnancy. Secondary forms of DM occur as a result of:

I. Genetic defects of beta cell function or insulin action.
II. Diseases of the exocrine pancreas such as pancreatitis.
III. Endocrinopathies like Acromegaly and Cushing's syndrome.
IV. Infections (cytomegalovirus and congenital rubella).

V. Drug or chemical induced i.e. glucocorticoids.

VI. Some genetic syndromes associated with DM (Down's, Klinefelter's, Turner's).

VII. Other uncommon forms of immune-mediated DM (anti-insulin receptor antibodies).

Pre-diabetes is also considered a separate entity and encompasses Impaired Glucose Tolerance and Impaired Fasting Glycaemia ([3],[4],[5]).

In 2015, the prevalence of DM was estimated to be 415 million and was expected to increase to 642 million by the year 2040 [6]. This amounts to 8-10% of the global population and is primarily attributable to the rapid increase in type 2 DM worldwide ([7], [8]). The extent of this "silent epidemic", as it has been described by the World Health Organisation (WHO), is appreciable when one considers that the annual diabetes health care expenditure amounts to a staggering 12% of total global expenditure on health ([6], [9]). The entity called the Metabolic Syndrome is on the rise, contributing to the prevalence of DM. This syndrome is characterised by an elevated waist circumference, blood-pressure, blood glucose, triglycerides and reduced high density lipoprotein cholesterol.

It is the scale of the epidemic as well as the chronicity and morbidity associated with DM that contributes to the escalating cost of managing this disease. The complications associated with DM occur as a result of chronic hyperglycaemia, damaging both vascular and non-vascular structures, causing dysfunction in multiple organ systems.

1.3. Complications

Non-vascular complications are mainly acute in nature and includes diabetic ketoacidosis, hyperosmolar hyperglycaemic non-ketotic syndrome, hypoglycaemia and recurrent infections. The vascular complications develop over time and can be further classified as microvascular or macrovascular (due to atherosclerosis) ([3],[5]).

Microvascular disease

- Nephropathy - renal failure
- Retinopathy - decreasing visual acuity, blindness
- Peripheral Neuropathy - foot ulcers, infection, amputations
- Autonomic Neuropathy - gastrointestinal, genitourinary and cardiovascular dysfunction

Macrovascular disease

- Coronary Artery Disease - angina, myocardial infarction
- Cerebrovascular Disease - stroke
- Peripheral Vascular Disease - claudication, gangrene ([3],[5]).

These complications have a significant impact on DM morbidity and mortality. A massive 673 billion US Dollars is being spent globally to treat DM and manage its complications, while an estimated 5 million DM associated deaths occur annually. The complication of Diabetic Nephropathy (DN) occurs in 20-40% of patients with DM, placing a significant burden on health care expenditure ([6], [10]).

1.4. Stages of DN

DN is a frequent cause of chronic kidney disease and has been recognised as the leading cause of end stage renal disease (ESRD) globally, sometimes requiring renal replacement therapy or kidney transplantation [7]. The DN syndrome is characterised by progressive, pathological albuminuria associated with podocyte loss, glomerulosclerosis and tubulointerstitial fibrosis and, ultimately, a decrease in Glomerular Filtration Rate (GFR) and renal failure [11].

The onset of DN is insidious in nature with five different stages of the glomerular disease identified ([12],[13],[11]):

- Stage 1 - Glomerular hyper-filtration, associated with renal hyper-function and hypertrophy. Blood pressure (BP) is normal, there is no micro-albuminuria and as the GFR increases, the serum creatinine decreases.
- Stage 2 - Develops over years and is characterised by morphologic lesions without clinical disease. The changes on renal biopsy are an increased basement membrane thickness and mesangial expansion. Serum creatinine is stable, there is no proteinuria and GFR is normal.
- Stage 3 - Incipient DN, manifests predominantly as elevated urinary albumin excretion, higher than in normal individuals but lower than in clinical disease states (15-300 mcg/min). BP is elevated, the GFR deteriorates and glomerulosclerosis can be seen.
- Stage 4 - Overt DN, manifests as persistent proteinuria (>0,5g/24hr) and associated hypertension. Kimmelsteil-Wilson nodules (classic lesions of nodular glomerulosclerosis) are present on renal biopsy.
- Stage 5 - ESRD, with uraemia, severe reduction in GFR (<15ml/min) and other associated complications. This stage often requires renal replacement therapy or renal transplant.

It is generally accepted that many factors contribute to the development of DN, some modifiable and others not.

1.5. Risk Factors

The unmodifiable risk factors to consider are:

- Age - with which there is a progressive decline in renal function in type 2 DM.
- Ethnic group - a black patient is at greater risk of developing DN and renal failure compared to a white patient.
- Gender - DN is more frequently observed in males.
- Family history - there is evidence of familial clustering of DN in type 2 DM.
- Genetic profile - Probable genes to consider are those involved in the renin-angiotensin system, nitric oxide pathway, aldose reductase pathway and lipoproteins metabolism. Although this topic is currently more theoretical, as gene therapy research forges ahead, it may soon cross into modifiable territory ([7], [12], [10]).

The modifiable risk factors to consider are as follows:

- Arterial Hypertension - In DM, hypertension is twice as common as in the general population. In type 2 DM it often exists prior to the nephropathy, as part of the complex Metabolic Syndrome. Uncontrolled hypertension causes progression of renal disease in as much as worsening renal function leads to elevated BP. There are numerous mechanisms of hypertension in DN (such as the activation of the Renin-Angiotensin-Aldosterone System (RAAS), increased body sodium, increased sympathetic nervous system (SNS) activity, endothelial cell dysfunction, oxidative stress and abnormal nitric oxide metabolism) that collude to cause volume expansion

and peripheral vasoconstriction thus exacerbating hypertension, DN and, subsequently, cardiovascular disease ([12], [14]).

- Poor glycaemic control - DN is more likely to develop in patients with worse glycaemic control. The proposed mechanism of this is that the hyperglycaemia plays a role in activation of oxidative stress and increased production of mitochondrial superoxide, thus initiating the metabolic pathways that cause vascular damage ([12], [15]).
- Dyslipidaemia - Recently shown to contribute to the progression of DN through abnormal lipoprotein metabolism. Furthermore, hyperlipidemia is also a risk factor for developing albuminuria [16].
- Physical inactivity / obesity - A sedentary lifestyle and a high body mass index (BMI), in combination with the other elements of the metabolic syndrome, contribute to the risk of kidney disease in DM. It is, however, difficult to assess each component's individual effects [16].
- Tobacco use - Smoking is considered an independent risk factor for the progression of DN and is associated with increasing albuminuria, ESRD and poorer survival outcomes once renal replacement therapy is instituted ([17],[18]).

1.6. Management

As there is no cure for DN, health care has to focus on possible prevention, early detection and optimum treatment to limit disease progression. This is only attainable if emphasis is placed on aggressive risk factor modification, refined management guidelines and possible identification of improved/novel biomarkers that could predict disease, hence allowing for primary prevention rather than limiting disease progression [19].

Albuminuria is defined as pathologic excretion of albumin into the urine secondary to changes that occur in the glomerulus. The gold standard to test for DN is the measurement of albuminuria over a 24 hour urine collection. However, for convenience, an estimation is attained via a spot albumin to creatinine ratio .

Currently, early detection of DN involves annual albumin to creatinine ratio (ACR) measurement, or more frequent checks if indicated by albuminuria or GFR. Yearly screening is instituted at five years post diagnosis in type 1 DM. However, due to the insidious nature of type 2 DM, screening for DN should occur at diagnosis. The South African guidelines for the management of type 2 DM, from the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA), are in line with these recommendations [3].

The 2017 SEMDSA guidelines suggest screening using a random urine ACR and a serum creatinine converted into estimated GFR (eGFR). SEMDSA also requires that an ACR ≥ 2.0mg/mmol or an eGFR < 60mL/min on 2 out of 3 samples within a 3 month period to diagnose CKD [20]. Timely, appropriate management of DM and its modifiable risk factors aim to prevent onset and delay the progression of DN. Current management recommendations include consideration of the following parameters.

1.6.1. HbA1c

Glycosylated Haemoglobin (HbA1c) measures the average mean levels of glycaemia over the previous 2 to 3 months, measured over the lifespan of the red blood cell. The HbA1c occurs as a “result of the non-enzymatic attachment of a hexose molecule to the N-terminal amino acid of the haemoglobin molecule” [21]. It increases in a predictable manner with an increase in blood glucose and is considered the gold standard to measure glycaemic control ([15], [22]). The American Diabetes Association (ADA) suggest HbA1c measurement quarterly for poorly controlled patients and biannually for well controlled patients [23]. Care should, however, be taken in interpretation of the result in circumstances that may effect the red blood cell and it’s ageing process, such as anaemia, abnormal haemoglobin subtypes and blood donors.

The landmark United Kingdom Prospective Diabetes Study (UKPDS) showed conclusively that complications of type 2 DM can be reduced by improving blood glucose and/or blood pressure control [24]. This is the basis of a target HbA1c < 7% for optimal glycaemic control and prevention of renal complications. Furthermore, trials such as ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release and Controlled Evaluation) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) demonstrated decreased albuminuria with tight glycaemic control (6,5% and 6%, accordingly). However, the risks versus benefit of tight control has to be considered in the elderly who are more prone to hypoglycaemia and its complications. Furthermore, the ACCORD trial was halted prematurely due to excess mortality in the intensive therapy arm [10].

1.6.2. Hypertension

Hypertension is a common comorbidity in patients with DM and increases the risk of development and progression of DN, as well as the cardiovascular morbidity and mortality associated with the condition [14]. The UKPDS trial suggests that for every 10mmHg decrease in systolic BP, there is a 12% reduction in DM-related complications and a 15% reduction in mortality. Meanwhile, RENAAL (Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan) trial showed a 6.7% risk increase of ESRD or death for a concomitant 10mmHg rise in systolic BP [25]. Blood pressure control is, therefore, essential.

A goal of <140/90mmHg is suggested as per the Eighth Joint National Committee Guidelines, which states that there is no significant improvement in either renal or cardiovascular outcomes with lower target BPs (<130/80mmHg) [26]. Although the ACCORD trial demonstrated a decrease in albuminuria with a target BP of <120mmHg, it had significantly more adverse events and electrolyte disturbances, with no significant difference in outcome as compared to the standard group [19].

First-line antihypertensive therapy should include angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin-receptor blockers (ARBs). Through their ability to reduce intra-glomerular pressure and dilate the efferent arteriole, proteinuria decreases, making ACE-I's and ARBs a better antihypertensive choice. The MARVAL (Micro-Albuminuria Reduction with Valsartan) study demonstrated further benefits of ARBs in a significant reduction of micro-albuminuria, for the same antihypertensive effect, as compared to a calcium channel blocker (CCB) i.e. amlodipine. Other studies have also shown the renoprotective benefits of RAAS blockade: namely the IDNT (Irbesartan Diabetic Nephropathy Trial) that indicated

decreased risk of serum doubling time and ESRD progression, and the RENAAL trial that also showed risk reduction of ESRD with losartan therapy [19].

It is important to note that there is little evidence to suggest that either ACE-I's or ARBs are superior, as the randomised controlled trial DETAIL (Diabetics Exposed to Telmisartan and Enalapril) demonstrated. Thus, ACE-I's and ARBs can be used interchangeably as first line therapy but should not be used in combination.

The ONTARGET (Ongoing Telmisartan Along and in Combination with Ramipril Global Endpoint Trial) suggested that ACE-I's and ARBs have similar renal benefit as mono-therapy. Dual therapy is not advisable as, although it decreases proteinuria to a larger extent, it is associated with poorer renal outcomes. The VA-NEPHRON-D (Veterans Affairs Nephropathy in Diabetes) trial further supports this, as it was stopped prematurely due to safety concerns. This study demonstrated that the benefit of combination ACE-I/ARB therapy diminishes over time and adverse events such as hyperkalaemia and acute renal failure are associated with dual therapy ([19],[25]).

1.6.3. Dyslipidaemia

Management of dyslipidaemia is essential in DM treatment. Individually, both DN and dyslipidaemia increase one's risk for cardiovascular disease and the two are frequently found in combination. Lipoprotein metabolism is impaired in type 2 DM causing an increase in very low density lipoprotein (VLDL-C) and low density lipoprotein (LDL-C) cholesterol and a decrease in high density lipoprotein (HDL-C). Insulin resistance results in the suppression of lipoprotein lipase (LPL) activity resulting in the increased serum triglyceride (TG) levels. Although studies such as the Framingham study, the United States National Health and Nutritional Examination Survey (NHANES), the UKPDS trial and the

Heart Protection Study (HPS) did not show significantly elevated LDL-C in the DM as compared to the general population, an elevated TG and lowered HDL-C levels were observed. There is also a change in the nature of the LDL-C molecule, making them small and dense (Oxidised-LDL and Glycated -LDL) and more atherogenic [27].

Dyslipidaemia promotes and exacerbates DN. In a review by Kawanamia et al, it is stated that this “lipid nephrotoxicity” occurs through the “enhancement of macrophage infiltration into the glomeruli” and “excessive extracellular matrix production in the glomeruli”. On the other hand, DN accelerates the abnormal lipoprotein metabolism described above, further advancing dyslipidaemia, the progression of DN and the cardiovascular risk. In order to halt this cycle, management of dyslipidaemia is imperative [27].

Statins are used as a lipid-lowering agent as well as for its renoprotective effect, as demonstrated by multiple clinical trials such as GREACE (Greek Atorvastatin and Coronary Heart Disease Evaluation, Pravastatin Pooling Project, TNT (Treating to New Target) study and CARDS (Collaborative Atorvastatin Diabetes Study). Data suggests a decrease in albuminuria and an improvement in GFR with statin therapy, however further studies are required to assess the benefit in ESRD ([16], [27]).

Other lipid lowering therapy such as fibrates, to tackle hypertriglyeridaemia, and ezetimibe, an inhibitor of the small intestine cholesterol transporter (NPC1L1), and long chain PUFAs (polyunsaturated fatty acids) can also be considered. The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study showed benefit of a fibrate in DN. One must consider the deterioration in renal function with combination therapy (statin and fibrate) seen in the ACCORD study. Thus, statin/fibrate combination therapy is contraindicated in moderate/severe kidney dysfunction. The simvastatin/ezetimibe combination therapy did

not aggravate renal dysfunction but did lower the “atherosclerosis-related events” in the SHARP (Study of Heart and Renal Protection) study, which was the largest study to date evaluating lipid therapy in advanced CKD. Despite, the DCCT trial suggesting that dietary intake of polyunsaturated fatty acids may be beneficial in DN, further conclusive evidence is necessary [27].

The KDIGO clinical practice guideline for Lipid Management in Chronic Kidney Disease (2013) recommends statin therapy (+/- ezetimibe) in all patients with CKD and DM who are less than 50 years of age and in all patients with CKD greater than 50 years of age (regardless of concomitant DM) [28].

1.6.4. Lifestyle

Levels of physical inactivity and obesity are rising rapidly and with it, their related complications. In DM an increased BMI is associated with higher risk of CKD and faster progression of DN. Obesity-associated related renal injury pathologically resembles DN and could possibly have a compounding effect. The relationship between obesity and CKD needs to be further investigated. The benefit of diet and physical exercise is apparent in the improvement of BP and glycaemic control, loss of weight and decrease in one’s cholesterol level; all contributing to the decrease in progression of DN. There has also been some research to suggest that low protein diet and an increased intake of lipids of vegetable origin are associated with reduced micro-albuminuria and an improvement in GFR ([12], [16], [17]).

1.6.5. Tobacco Use

Smoking is an independent risk factor for progression of DN, hence smoking cessation is paramount. Jose et al (2016) suggest that 12.9% of altered renal function can be attributed to smoking [18]. Multiple factors increase the risk of chronic renal failure: the greater number of cigarettes per day, the duration and the smoking pack years. If necessary, counselling, pharmacological and non-pharmacological assistance should be provided to attain the desired outcome [12].

1.7. Challenges in Management

The importance of targeted, evidence based therapy is essential for a good outcome. Naturally, there are a number of challenges that arise in the management of such a complex disease. Firstly, the achievement of targets, in particular BP and proteinuria reduction, remains elusive in many patients with type 2 DM and nephropathy as the ALICE-PROTECT study exhibits [1]. In a survey by Yokohama et al, close to half of patients failed to reach the recommended targets (blood glucose, blood pressure and lipids) [29]. Secondly, lifestyle modification is extremely difficult for patients, especially if done without support structures being available and accessible. This difficulty is particularly prominent in developing countries where resources are strained and services are sparse. Thirdly, the primary care healthcare setting is essential in diagnosis and identification of complications, if not to manage further but at least escalate management to secondary level. Research suggests that with routine screening and regular follow up at a primary care level, early detection and management of DN can be improved ([10], [30]). Fourthly, the understanding of the tools being used to target therapy has to be emphasised. The HbA1c, for example, is an important aspect of targeted therapy, as previously discussed. Variability in HbA1c is associated with the development of DN. As DN develops and progresses, the HbA1c decreases and patients require less insulin because insulin clearance is prolonged. Thus, an improvement in HbA1c may signify a decline in GFR [31].

Further headway can be achieved by improving patient insight into and education of their disease. A cross sectional study done in Iran by Mehravar et al (2016) indicated higher rates of nephropathy and neuropathy in type 2 diabetics with a “lower diabetes self management score”, which was measured using the Diabetes Self-Management Questionnaire [9].

Research has also suggested a benefit in accurate pathological diagnosis in DM if renal involvement is present, necessitating a renal biopsy (gold standard) in such patients. This is because there is a significant overlap in DM renal involvement. As described in a study conducted in China by Li et al, there is the entity of pure DN, non-diabetic renal disease (NDRD), and NDRD with underlying DN. There are numerous types of NDRD seen in DM, that can present with proteinuria and/or haematuria, some examples being “membranous nephropathy, minimal change disease, immunoglobulin A (IgA) nephropathy, focal segmental glomerulosclerosis, Henoch-Schonlein purpura, thin basement membrane disease, proliferative glomerulonephritis, collapsing glomerulopathy and pauci-immune crescentic glomerulonephritis” [17]. The significance of pathological diagnosis is prognostic in that DN is most often irreversible while NDRD can often be treated. In this study patients with DN had poorer renal function and outcomes than those with NDRD [32].

1.8. Therapies for the Future

Despite optimal targeted treatment, many patients still progress to ESRD. There is much need for improved preventative strategies, earlier predictors of DN and new, more effective therapy. There are a number of therapies to consider in future.

Research suggests that some oral hypoglycaemic agents have pleiotropic effects on DN risk factors beyond that of glucose and weight reduction.

- Metformin, a biguanide derivative, is used as first line therapy in type 2 DM, in South Africa and internationally. Metformin's hypoglycaemic effects include decreasing hepatic gluconeogenesis, improving peripheral insulin sensitivity and reducing glucose intestinal absorption, however it has a decreased risk of hypoglycaemia. Clinical trials have demonstrated multiple effects beyond this as it decreases LDL-C and TG levels, enhances weight loss, reduces microvascular complications and improves renal outcomes. Recently, the COSMIC (Comparative Outcome Study on Metformin Intervention versus Convention) trial showed no incidence of lactic acidosis, which was generally the most concerning complication of metformin use. Furthermore, evidence support metformin use even in patients with some renal dysfunction. In 2015 the US FDA (United States Food and Drug Administration) guidelines were revised, allowing metformin therapy based on GFR levels (50% dose in GFR between 30-45 and contraindicated in GFR <30). More research is advocated to assess the anti-diabetic and pleiotropic effects as they are affected via multiple signalling pathways, possibly protecting renal cells from cell damage by high glucose levels and other intracellular stress [11].

- Incretin based therapy provides another option in DN management.
    - Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. It blocks the incretin, GLP-1, which is an intestinal hormone released in response to food intake. Liraglutide has been shown to improve type 2 DM patients HbA1c and BMI as well as BP, albuminuria and GFR, thus attenuating the progression of DN [33].
    - Saxagliptin is a dipeptidyl peptidase 4 inhibitor (DPP4-I). It prevents the degradation of GLP-1 and therefore increases insulin secretion and decreases glucagon secretion, thus improving HbA1c. The SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction) trial showed an improvement in ACR but this did not affect GFR, suggesting that DDP4-I may have a reno-protective effect [34].
- The sodium-glucose cotransporter 2 (SGLT-2) inhibitors block the predominant mechanism responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. SGLT-2 inhibitors have been shown to be beneficial in patients with type 2 diabetes at high cardiovascular risk. In the EMPA-REG Outcome Trial, “Empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care” [35].

Adjusting the timing and dosing of current, recommended medication have also been reviewed in the hope of augmenting therapy. A systematic review by Person et al (2016) concluded that early RAAS inhibition using ACE-I’s /ARBs in type 2 diabetics with normo-albuminuria decreases the risk of developing micro-albuminuria [36]. In terms of optimal dosing of therapy, a study done in Canada by Callera et al, evaluating the renal effects of candasartan (ARB) at high doses, presented results that state “ultra-high dose

candesartan induces renal damage" while "intermediate-high dose candesartan is reno-protective", highlighting the importance of adequate dosing [37].

Preclinical diagnosis, having the ability to predict the complication, would be ideal as prevention would be the most effective method of managing DN. Greater emphasis in research is being placed on enhancing current biomarkers, and identifying newer, novel biomarkers and investigational therapeutic modalities. Evidence proposes a number of possible markers for detection of DN.

- Glycated albumin to glycated haemoglobin ratio (GA:HbA1c) has been identified as a good predictor of DN in type 2 DM and possibly a better glycaemic index in DN. This can probably be attributed to the variation in red blood cells (number and lifespan) that impacts HbA1c. GA reflects glucose levels over the preceding 2 to 3 weeks comparatively [38].
- Urinary tubular markers may also improve predictive capabilities. Examples of markers being assessed to detect DN are urinary glycosaminoglycans / proteoglycans (GAGs/ PGs), N-Acetyl-B-D-glucosaminidase (NAG) and neutrophil gelatinase-associated lipocalin (NGAL) (26). High levels of the following ratios were associated with a faster deterioration of renal function:
  - Urinary cystitis-C to creatinine ratio (UCCR)
  - Urinary angiotensinogen to creatine ratio (UANG)
  - Urinary NGAL to creatinine ratio (UNGAL)
  - Urinary KIM-1 to creatinine ratio (UKIM-1) [39]
- Investigation into the role of endothelial dysfunction in the development of DN, the associated molecular mechanisms and contributory factors are also underway [40].

1.9. Conclusion

Although, internationally, such novel and investigational options are in the pipeline, in the South African context, there is still much room for improvement. In our rapidly expanding diabetic population, achieving current screening and management recommendations is a significant endeavour. Many of our public hospitals establish specialised clinics, such as the HJAH Diabetic Clinic, to service the growing number of patients; aiming to optimise patient management within the framework of very limited resources. Evaluation of these types of clinics, to assess whether the targets for DN as set out by the SEMDSA guidelines are being achieved, is essential, and if not, where the pitfalls and weaknesses lay. This can subsequently be used in refining implementation of screening protocols and institution of therapy, hopefully impacting positively on patient care and the morbidity associated with DM and DN.

2. Chapter 2: Patients and Methods

2.1. Aims and Objectives

2.1.1. Primary Objectives –

To determine:

a. The prevalence of renal dysfunction, measured as CKD defined by the KDOQI guidelines, in patients attending the clinic.

b. To determine the stage of CKD as defined by the KDOQI guidelines:

   i. Stage 1 eGFR ≥90 ml/min/1.73m^2

   ii. Stage 2 eGFR 60-89 ml/min/1.73m^2

   iii. Stage 3 eGFR 30-59 ml/min/1.73m^2

   iv. Stage 4 eGFR 15-29 ml/min/1.73m^2

   v. Stage 5 eGFR ‹ 15 ml/min/1.73m^2

c. The time from diagnosis of Type 2 DM to the development of renal dysfunction (as determined by a decrease in eGFR).

2.1.2. Secondary Objectives

a. To describe the demographics (age, gender, smoking history, alcohol use and exercise participation) of the population being studied.

b. To determine the presence of any co-existing diseases that impacts on renal function (i.e. hypertension, dyslipidaemia and, in our setting, Human Immunodeficiency Virus (HIV)).

c. To compare the relationship between HbA1c in patients with normal renal function and those with renal dysfunction (as determined by a decrease in GFR)

d. To document the following parameters and determine whether there is an association between these parameters and renal dysfunction or degree of renal dysfunction:

    i. Body Mass Index

    ii. Urine Protein : Creatinine ratio (U-PCR) or Urine dipstick results

2.2. Methodology

2.2.1. Study Design

This study was a Retrospective Clinical Audit and Descriptive Study for the defined time period of 1 March 2015 to 31 April 2015.

This particular period was identified, in consultation with the Head of HJAH Diabetic Clinic, as the time of the year that experienced the least staff and pharmaceutical shortages and hence, the most appropriate time to measure the true capacity of the specialised clinic.

2.2.2. Study Setting

The study was conducted at the Diabetic Clinic in a tertiary institute, the Helen Joseph Academic Hospital, Gauteng Province, South Africa. This is a specialist clinic that caters for both type 1 and type 2 diabetics.

2.2.3. Study Population

a. Inclusion criteria

i. Patients attending the HJAH Specialist Diabetic Clinic - This specialist clinic caters for all type 1 patients and type 2 patients who fit certain criteria, namely:

- Insulin requiring Type 2 diabetics
- Documented target organ damage
- Poorly controlled Type 2 diabetics referred from the HJAH medical outpatients department.

ii. Insulin requiring type 2 DM.

iii. Patients aged greater than 14 years of age.

iv. Patients with DM for a minimum of 5 years (as documented from the date of diagnosis).

It has been documented that the first evidence of renal dysfunction occurs after approximately 5 years of disease duration. In type 2 DM the delay between onset and diagnosis may be variable, so in order to standardise the sample a cutoff of 5 years has been used.

b. Exclusion Criteria

i. Type 1 DM

ii. Non-insulin requiring type 2 diabetics - as per the clinic's eligibility criteria, non-insulin requiring diabetics would not be included in the patient population and, hence cannot be included as part of the sample.

2.2.4. Sample Size

The sample size was determined by the key research question to be answered. For the determination of the prevalence of CKD, a sample size estimation was based on a 40% prevalence, 5% precision and a 95% confidence interval. This requires a sample size of 369 patients. Changing the precision from 5% to 6%, leads to a sample size estimate of 257 patients. A sample size of 321 patients was achieved. The actual sample size of 321 patients in this study corresponds to a precision of 5.5% (rather than 5.0%), which is acceptable [41]. {See Appendix A for sample size formula}

2.2.5. Sampling Method

A convenience sampling method was used. Consecutive patients who attended the HJAH diabetic clinic during 1 March to 31 April of 2015 were assessed. No distinction in terms of age, gender, ethnicity or socio-economic status was made.

2.2.6. Data Collection

a. The files of the patients that attended the clinic on the chosen dates were retrieved and the inclusion/exclusion criteria were accommodated for. Data collection was done on an anonymous basis and confidentiality maintained by assigning each data sheet a study number. Record of patient names and numbers was made on a separate file, held by the principal researcher alone, for future reference if necessary. The data was collected from the files by the principal researcher and access to it was subsequently limited to principal researcher, the statistician and the two

supervisors of the study. All data was electronically captured on the RedCap system.

b. The data collected would have been routinely done at the clinic, as part of the clinic's standard clerking sheet, and measurements are usually done by specific diabetic clinic nurses. The following data was collected:

i. Demographics (gender, age, and ethnicity)

ii. Year of diagnosis and year of initiation of insulin

iii. Lifestyle details (exercise, smoking history, alcohol use)

iv. Medication (including dosage)

v. Biometrics:

- Weight – in kilograms, measured using the standard clinic scale.
- Height – in centimetres, using a wall height chart.
- Abdominal circumference – using the WHO standardised tape measure.

vi. Blood Pressure – Measured using the standard Dinamap Blood Pressure Monitor.

vii. Blood test results (U&E and HbA1c).

viii. Urine test results (Dipstick and U-PCR).

Results that were available from baseline, a second point in time and the most recent were documented, including the date that the test was performed.

2.2.7 Data Analysis

In the analysis, the time of diagnosis of diabetes was estimated as 1 July in the recorded year of diagnosis and two formulas were used for parameter measurement:

- The GFR was calculated from the above information using the MDRD (Modification of Diet in Renal Disease) Study equation:

  GFR (mL/min/1.73 m^2) = 175 x (Scr)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if Black) (conventional units)

- Quetelet's formula was used to calculate BMI from weight and height

  BMI = weight(kg)/height$(m)^2$

Descriptive analysis of the data was carried out such that categorical variables were summarised by frequency and percentage tabulation, and illustrated by means of bar charts. Meanwhile, continuous variables were summarised by the mean, standard deviation, median and interquartile range, and their distribution illustrated by means of histograms.

The prevalence of CKD (overall and per stage) in the study group was estimated, together with 95% confidence intervals.

The association between HbA1c levels or BMI and the presence/absence of CKD (as well as the association between HbA1C levels and insulin regimen), optionally controlling for the presence/absence of hypertension, dyslipidaemia and HIV was analysed by a General Linear Model (GLM). Post-hoc tests were conducted using the Tukey-Kramer correction for unequal group sizes.

The association between Urine dipstick or U-PCR outcomes and the presence/ absence of CKD, optionally controlling for the presence/absence of hypertension, dyslipidaemia and HIV was analysed by logistic regression.

Data analysis was carried out using SAS version 9.4 for Windows. The 5% significance level was used throughout (i.e. p-values <0.05 indicate significant results).

2.2.8 Ethics

Ethics approval was granted by the Human Research Ethics Committee of the University of the Witwatersrand (Clearance Certificate number: M151188) as well as by the HJAH Ethics Committee.

No informed consent was needed from the patients due to the retrospective nature of the analysis.

3. Chapter 3: Results

Data was collected from the files of 321 patients who attended the diabetic clinic over the stipulated two month period.

3.1. Demographics

3.1.1. Age: 59.4 years (sd 9.9 years; range 30-88 years) was found to be the mean age of the sample, with the youngest patient aged 30 years and the oldest aged 88 years. The age distribution is represented in Figure 1.

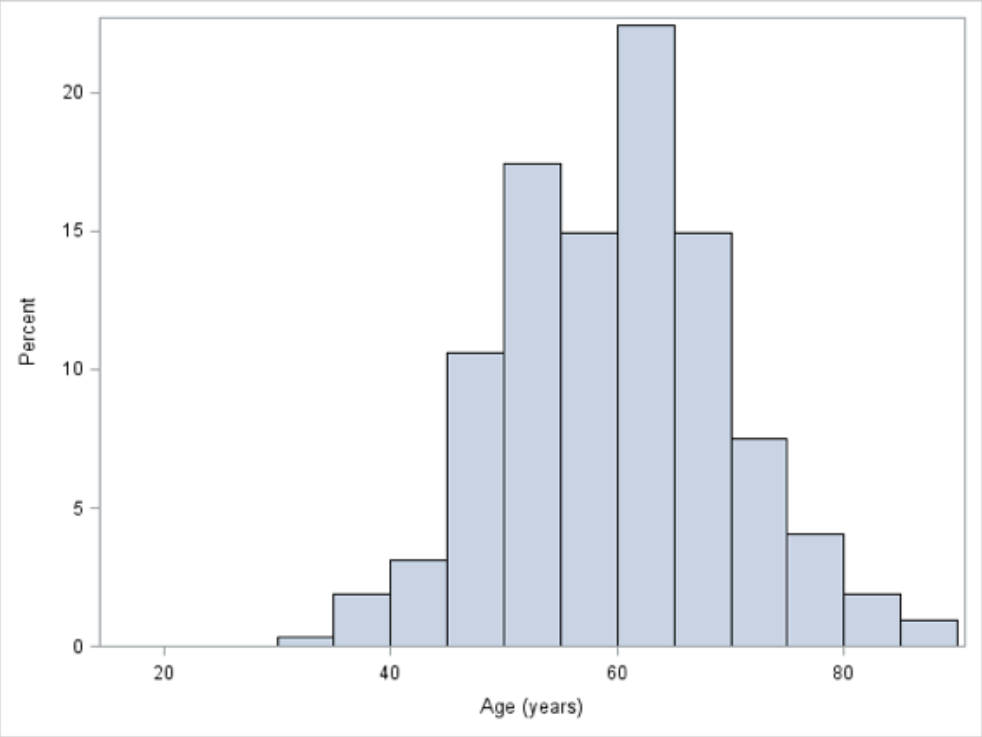


Figure 1: Age Demographics

3.1.2. Gender: 199 patients were female (62%) and 122 were male (38%).

3.1.3. Black and Coloured patients composed of the majority of the sample as seen in Table 3.1.

Ethnicity	Number of patients (n)	Percentage of patients (%)
Black	143	44.6
Coloured	109	34.0
Indian	44	13.7
White	25	7.8

Table 3.1: Patient Ethnicity

3.2. Year of Diagnosis

This is reflective of the length of time the patient has been living with DM. The documented year of diagnosis ranged from 1973 to 2010. The number of cases recorded per year is depicted in Graph 2, and shows that cases per year tended to be higher from 1995 onward. The data portrayed noticeable spikes in the years 1995, 2000, 2005 and 2008.

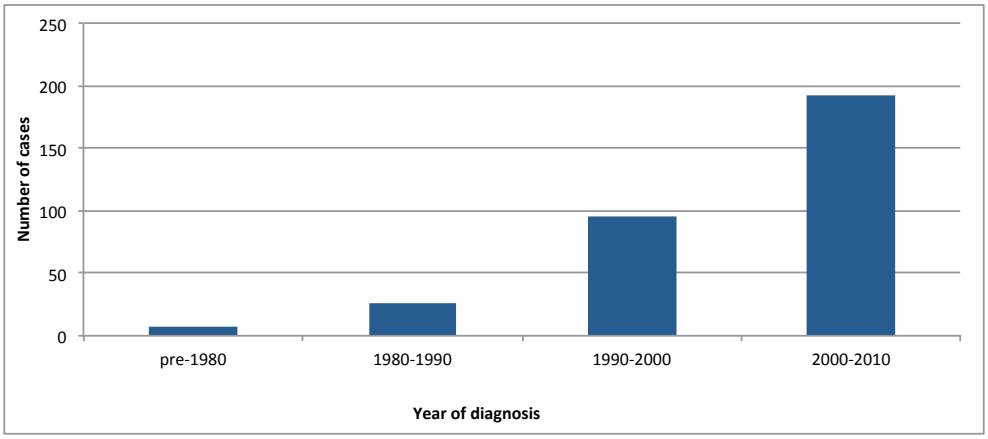


Figure 2: Year of Diagnosis

3.3. Co-morbidities

Hypertension and dyslipidaemia, as was documented in the patient's files, were identified as the most common co-morbidities, being present in 89.1% and 82.2% respectively. The combination of hypertension and dyslipidaemia was noted in 67.6% of the patients. Concurrent thyroid disease and HIV was, however, minimal. (Figure 3)

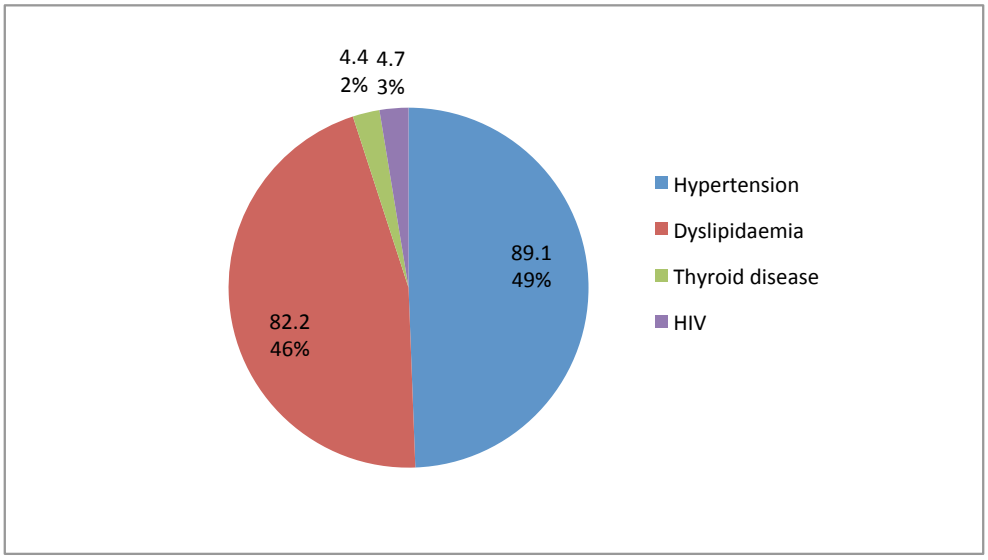


Figure 3: Prevalence of Co-morbidities
(HIV - Human Immunodeficiency Virus)

3.4. Lifestyle

3.4.1. Smoking: Of the 310 patients with adequate data, 12.5% were still smoking and 16.7% had smoked previously. 11 files (3.4%) were inadequately filled out.

3.4.2. Physical Activity: 43.7% of the 309 patients, who had documented information of exercise in their files, undertook exercise. There was no documentation in 12 files (3,7%).

3.4.3. Alcohol consumption: Amongst 311 patient files, 10.6% suggested regular alcohol use. 10 files (3.1%) had missing data.

3.5. BMI

Taking into consideration the most recent result set, in which 6.5% of the data was missing, the mean BMI was 32.1kg/m^2 and the median BMI was 31.3kg/m^2 (the interquartile range (IQR) being 26.6-36.0; with a range of 16.8-103.8 kg/m^2). The percentage of patients in each BMI category, as defined WHO BMI Classification, is shown Table 3.2 and the BMI distribution in Figure 4 [42].

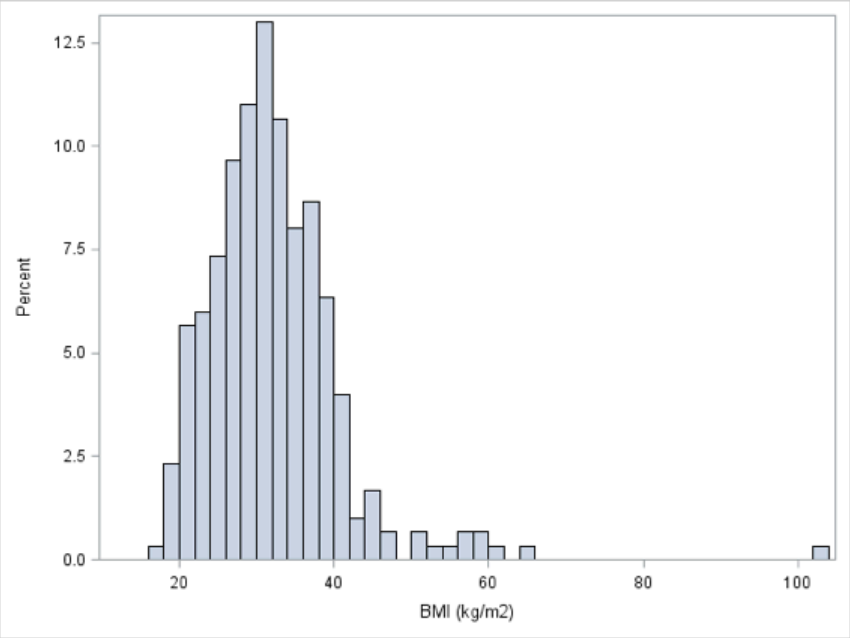


Figure 4: BMI of Study Patients
(BMI - Body Mass Index)

BMI Category	BMI value (kg/m2)	Female (n)	Male (n)	Total Number of Patients (n)	Percentage of Patients (%)	Percentage of patients without missing data (%)
Underweight	<18.5	3		3	0.9	1.0
Normal	18.5-24.9	19	31	50	15.6	16.7
Overweight	25-29.9	41	35	76	23.7	25.3
Obese I	30-34.9	49	33	82	25.5	27.3
Obese II	35-39.9	46	10	56	17.4	18.7
Obese III	>=40	28	5	33	10.3	11.0
Unknown		13	8	21	6.5	

Table 3.2: BMI of study patients
(BMI - Body Mass Index)

The data shows that 66% of females are classified as overweight/obese, in comparison to 42% of males.

3.6. Medication

3.6.1. Type of Insulin

The most common insulin regimen was twice daily Actraphane (73.2%). While 14.6% were on the basal bolus regimen of the Protophane/Actrapid combination, 11.2% used daily Protophane alone.

3.6.2. Other Medication

There were multiple other oral medications being taken by the patients, the most common being statins, aspirin, ACE-I's/ARBs, diuretics and CCBs. Close to 92% were being treated with a statin, while 71% were using metformin. (Table 3.3)

Medication	Number of Patients (n)	Percentage of Patients (%)
Statin	294	91.6
Aspirin	280	87.2
ACE-I/ARB	258	80.4
Metformin	228	71.0
Diuretic	216	67.3
CCB	191	59.5
Beta Blocker	82	25.5
Tryptanol	75	23.4
Proton Pump Inhibitor	75	23.4
Alpha blocker	50	15.6
Antiretroviral Therapy	28	8.7
Tegretol	21	6.5
Fibrate	7	2.2
Allupurinol	7	2.2
Colchicine	3	0.9
Thyroxine	3	0.9
Other	15	4.7

Table 3.3: Concurrent Medication

3.7. Time period

Each parameter (ie HbA1c, creatinine, PCR, urine dipstick etc) was measured at three different time intervals, namely: at diagnosis (Baseline), the most recent measurement available (Recent) and one point in between these intervals (Second). The measurements documented in the patient files were verified against the National Health Laboratory Service (NHLS) records to ensure that all available data was appropriately considered. Table 3.4 reflects the time periods between these data sets.

Time (years)	Number of participants (n)	Time between evaluations (years)					% missing data
		Mean	SD	Median	Interquartile Range		
Diagnosis to Baseline	288	11.1	8.0	9.2	4.9	15.5	10.3%
Baseline to Second	249	2.5	2.4	1.7	0.8	3.2	22.4%
Second to Recent	250	1.7	1.5	1.2	0.7	2.0	22.1%

Table 3.4: Time Period between Measurements

3.7.1. The median time between diagnosis and baseline measurement was 9.2 years (IQR 4.9-15.5 y, 00.0-38.1y) (10.3% missing data), as per Figure 5. The time of diagnosis were documented in the files, as reported by the patients during their initial assessment at the tertiary clinic. Thus, this time period reflects the fraction of time, as per records, from this reported date of diagnosis and the first available measurement (ie Baseline).

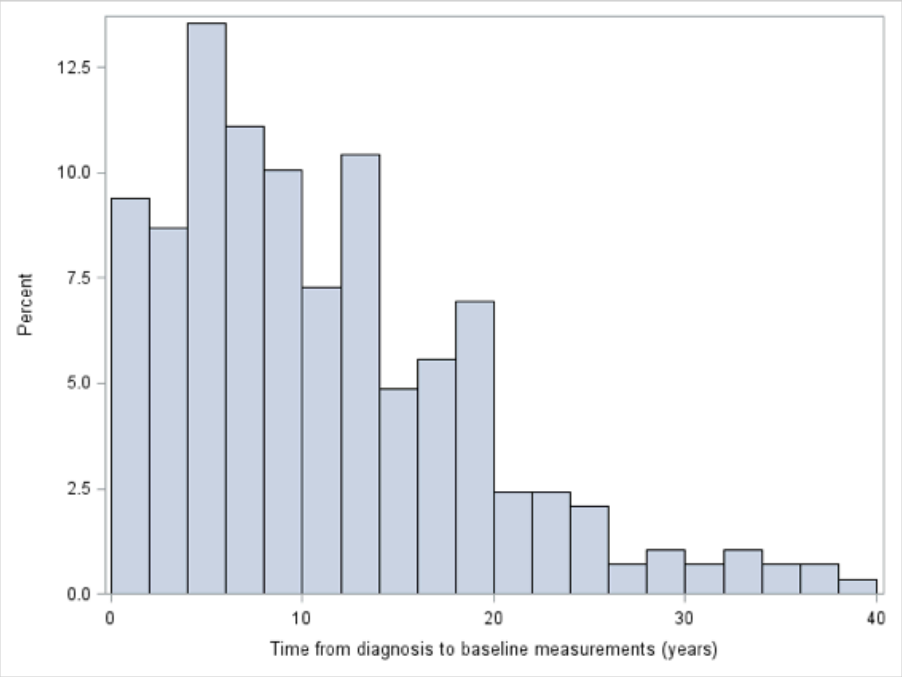


Figure 5: Distribution of time period between Diagnosis and Baseline Measurement (Time in years)

3.7.2. The median time between the baseline and second measurement was 1.7 years (IQR 0.8-3.2y; range 0.1-15.4y) (22.4% missing data), as per Figure 6.

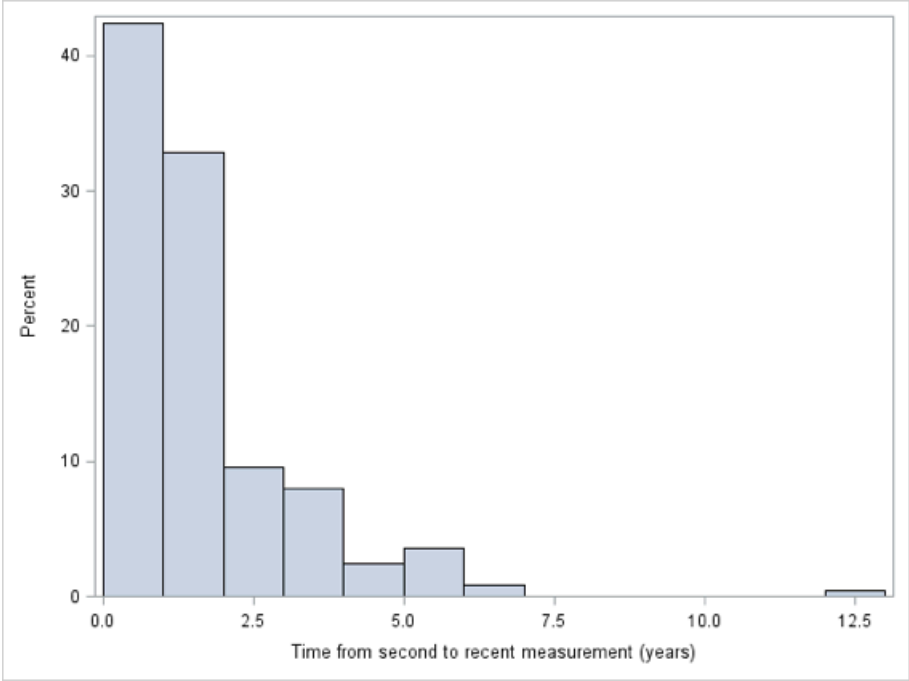


Figure 6: Distribution of time period between Baseline and Second result set.

3.7.3. The median time between the second and most recent measurement was 1.2 years (IQR 0.7-2.0y; range 0.1-12.6y) (22.1% missing data), as per Figure 7.

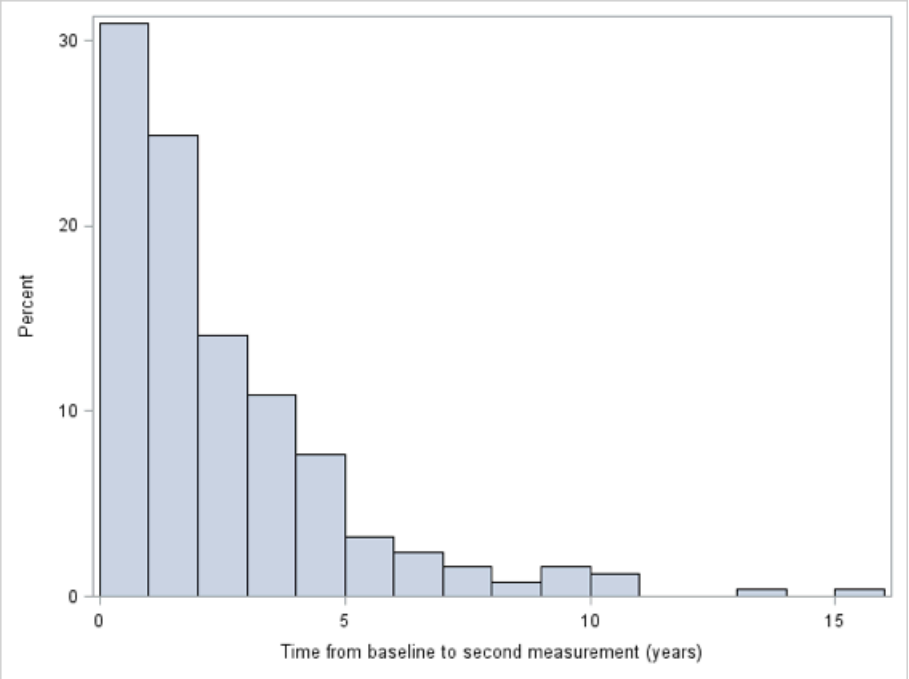


Figure 7: Distribution of time period between Second and Recent result set.

3.8. HbA1c

The most recent HbA1c results showed a mean of 9.5% (SD 2.4; range 3.9-16.2%. 22.1% of the data was missing, however. The target HbA1c of less than 7% was attained by only 49 patients (15.3%). Figure 8 shows the distribution of the HbA1c results.

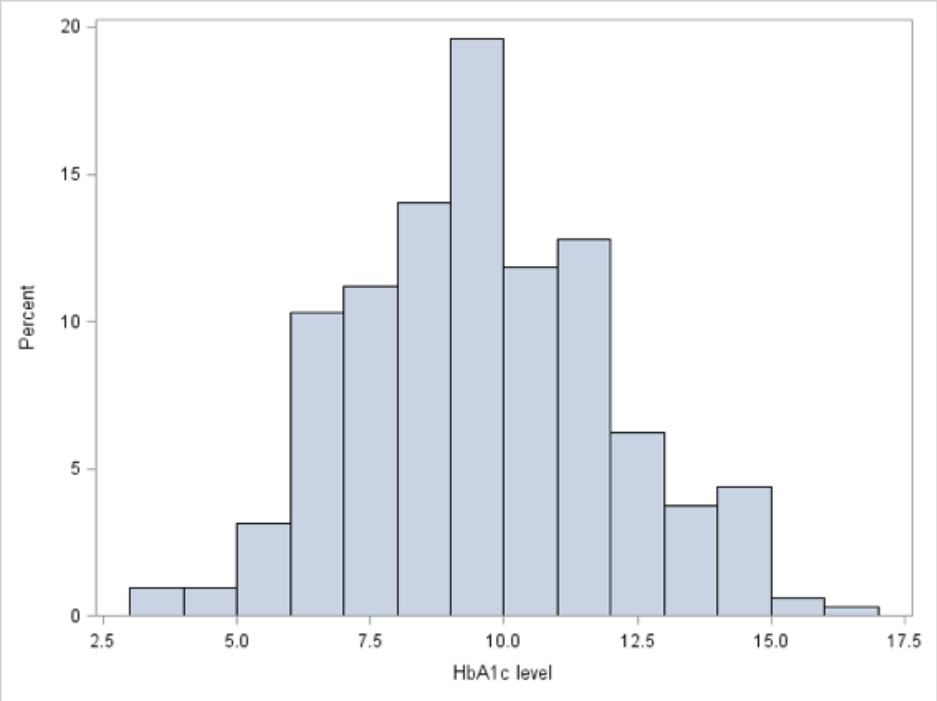


Figure 8: Measured HbA1c levels
(HbA1c- Glycated Haemoglobin)

3.9. GFR

The univariate statistics and distributions of the baseline, second and most recent GFR levels are given in Table 3.5 below. These levels are calculated values (using the MDRD Study Equation).

GFR category	CKD Stage	Number of patients (n)	Percentage (%)	Percentage without missing data (%)
Baseline	G5	0	0.0	0.0
	G4	5	1.6	1.8
	G3	54	16.8	19.4
	G2	132	41.1	47.5
	G1	87	27.1	31.3
	Missing	43	13.4	
Second	G5	1	0.3	0.4
	G4	13	4.1	5.6
	G3	47	14.6	20.2
	G2	108	33.6	46.4
	G1	64	19.9	27.5
	Missing	88	27.4	

GFR category	CKD Stage	Number of patients (n)	Percentage (%)	Percentage without missing data (%)
Recent	G5	3	0.9	0.9
	G4	14	4.4	4.4
	G3	68	21.2	21.3
	G2	128	39.9	40.1
	G1	106	33.0	33.2
	Missing	2	0.6	

Table 3.5: Distribution of Calculated GFR measurements
(GFR - Glomerular Filtration Rate, CKD - Chronic Kidney Disease)

The categorised GFR levels are shown in Figure 9. The levels of missing data are high for the baseline and second sets of measurements, so these results have been interpreted with caution.

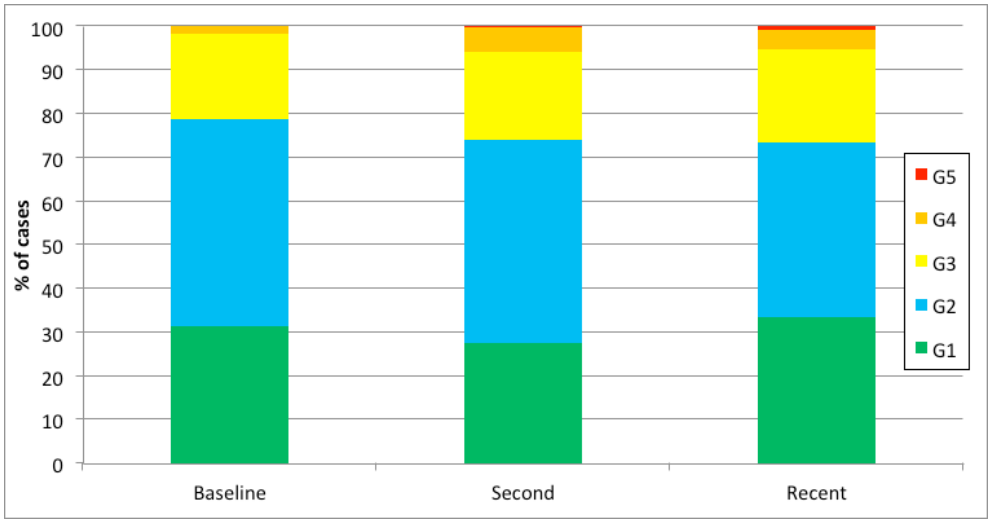


Figure 9: Categorised GFR Levels

3.10. Urine Dipstick

The most recent measurement set had 2.2% missing data. No abnormality was detected in 49.2% of patients. Evidence of proteinuria was present in 16.8% of patients and glycosuria in 37.7%. Figure 10 depicts the abnormalities detected.

Only the glucose, 1+proteinuria and 2+proteinuria data were considered for further analysis since the prevalence of the other findings was very low.

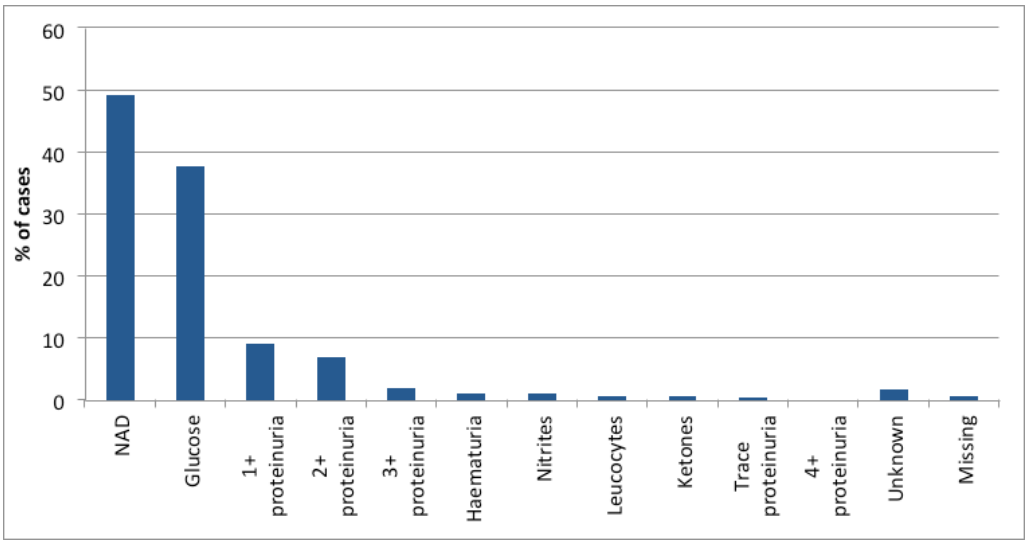


Figure 10: Abnormalities detected on urine dipstick
(NAD - No Abnormalities Detected)

3.11. Urine PCR

Any Urine-PCR measurement available from the patient files or the NHLS system, across all three time periods, was recorded in order to gain some insight into this parameter. However, due to the extent of missing data (ie 61.7%), this variable could not be analysed any further. Nevertheless, it is a significant parameter to consider when evaluating screening protocols and appropriate investigation in the health care facilities.

U-PCR Category	Number (n)	Percentage (%)
Nephrotic (>300mg/mmol Cr)	11	3.4
Sub-Nephrotic (<300mg/mmol Cr)	112	34.9
Unknown	198	61.7

Table 3.6: Urine PCR Outcome
(U-PCR - Urine Protein Creatinine Ratio; Cr - Creatinine)

3.12. Prevalence of CKD

The prevalence of CKD in the study group, overall and by stage, as determined by the most recent GFR level (n=319), with corresponding 95% CI's is tabulated in Table 3.7. 66.8% of the study group showed evidence of CKD, a large proportion of which were classified as Stage 2 CKD.

CKD Stage	Number (n)	Percentage (%)	95% CI
G1	106	33.2	28.3-38.6
G2	128	40.1	34.9-45.6
G3	68	21.3	17.2-26.1
G4	14	4.4	2.6-7.2
G5	3	0.9	0.3-2.7

Table 3.7: Prevalence of CKD in the study group (categorised by stage)
(CKD - Chronic Kidney Disease)

3.13. Time from Diagnosis to CKD Stage

Analysis was done using all three sets of GFR results, plotted against time (from diagnosis to Baseline, Second and most Recent). An example of the analysis for five patients is shown in Figure 11.

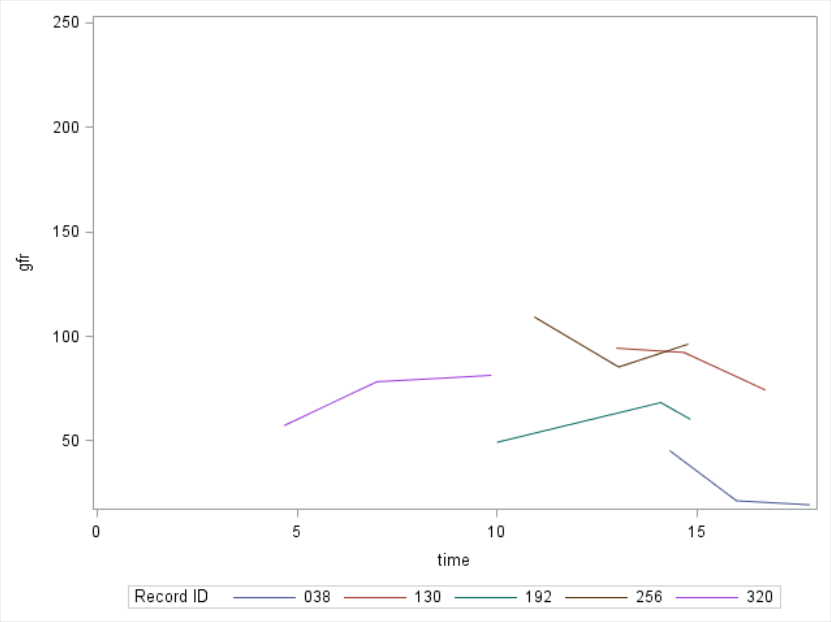


Figure 11: The GFR profile of five patients (time in months)
(GFR - Glomerular Filtration Rate)

The five patients' GFRs were then plotted against the CKD stage shown in Figure 12.

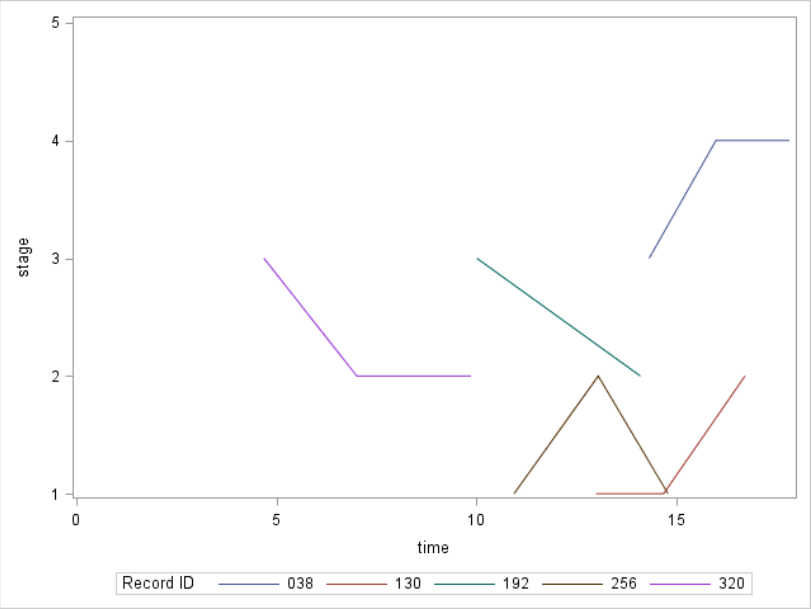


Figure 12: The CKD profile of five patients (time in months)
(CKD - Chronic Kidney Disease)

Extending this analysis beyond the five patients, to all patients in the study, did not reveal any discernible pattern as shown in Figure 13 (GFR) and Figure 14 (CKD stage)

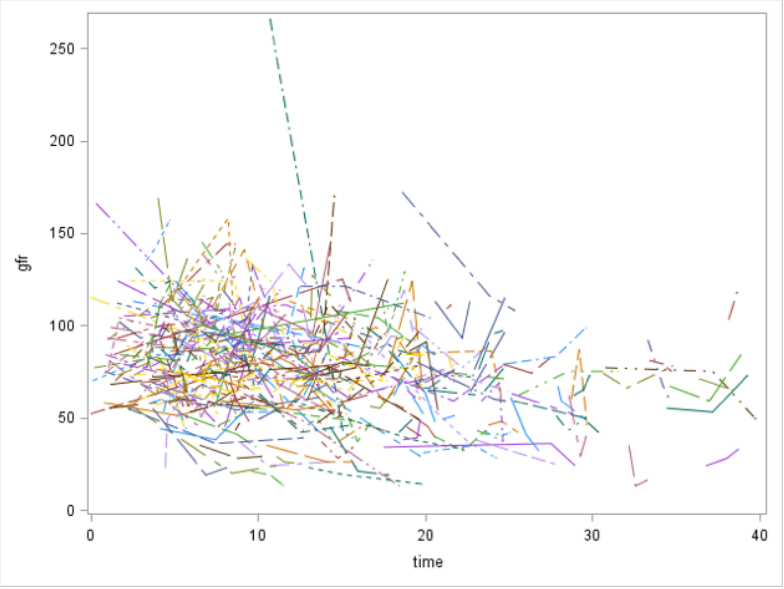


Figure 13: The GFR profile of each patient from time of diagnosis to each measurement point (Baseline, Second and Recent)
(GFR - Glomerular Filtration Rate)

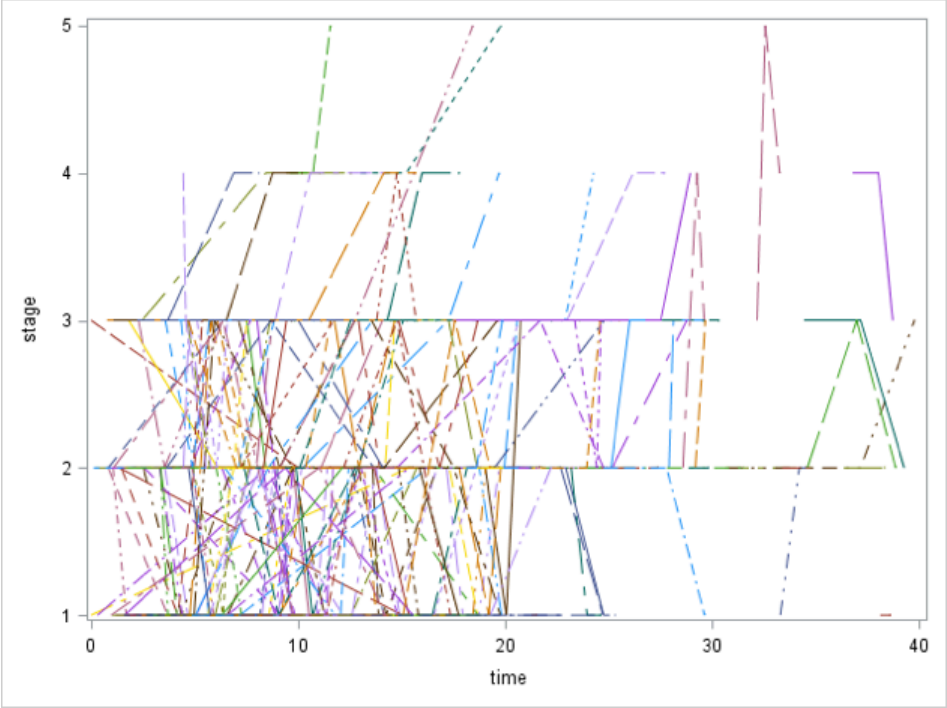


Figure 14: The CKD stage profile
(CKD - Chronic Kidney Disease)

We see that the GFRs do not worsen in general with time but rather tend to oscillate between stages.

From the 321 patients, 411 times from diagnosis to stages could be estimated, using Baseline, Second and Recent measurements. As it is presumed that all patients start at stage 1 and the stage 5 group was too small (n=4), time to stage 1 and stage 5 have not been considered. The remaining results are presented in Table 3.8.

CKD Stage	Number (n)	Time between evaluations (years)				
		Mean	SD	Median	Interquartile Range	
2	182	12.5	7.9	11.8	7.0	17.8
3	109	14.2	8.7	13.1	7.5	19.9
4	25	16.8	9.0	14.2	10.2	24.3

Table 3.8: Time from diagnosis to CKD Stage 2-4
(CKD - Chronic Kidney Disease)

Figure 15 shows the median time from diagnosis to each stage. The error bars denote the interquartile range. The median time to Stage 2 (11.8y; IQR 7.0-17.8y) was shorter than the median time to Stage 4 (14.2y; IQR 10.2-24.3y) (Wilcoxon rank sum test; p=0.028). There were no other significant differences.

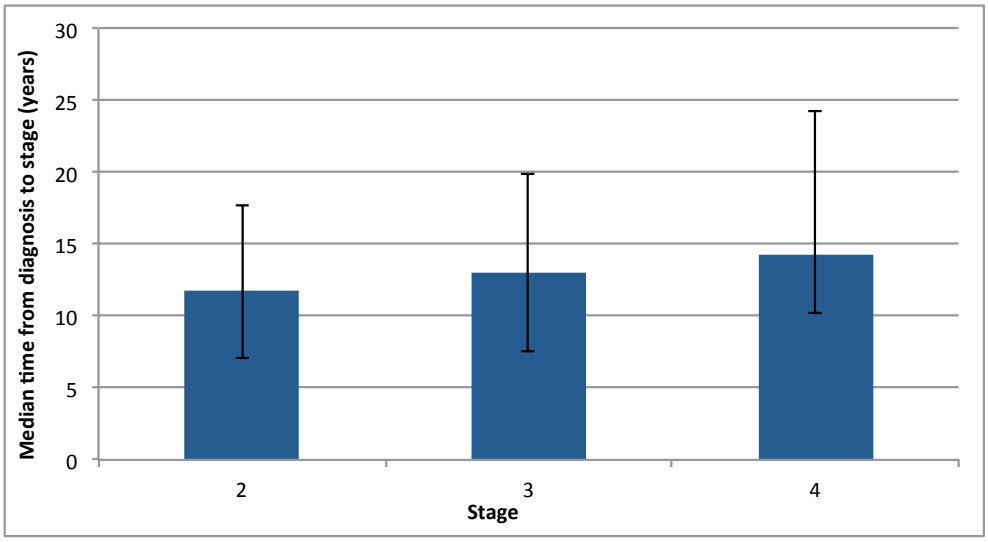


Figure 15: Median time from diagnosis to each CKD stage
(CKD - Chronic Kidney Disease)

3.14. Time between changes in CKD stage

Using all three sets of GFR results, the median time from each stage to the subsequent stage was estimated. From the 321 patients, 184 times changes in stage could be estimated, using baseline, second and recent measurements. We ignore the transitions with very small group sizes. The remaining results are presented in Table 3.9.

CKD Stage	Number (n)	Time between evaluations (years)				
		Mean	SD	Median	Interquartile Range	
1 to 2	39	3.0	3.4	1.7	0.9	3.5
2 to 1	48	2.1	2.2	1.5	1.0	2.1
2 to 3	38	2.5	2.0	2.1	0.7	3.6
3 to 2	27	2.3	2.0	1.6	1.1	3.0
3 to 4	11	2.5	1.4	2.2	1.4	3.2

Table 3.9: Time between changes in CKD stage
(CKD - Chronic Kidney Disease)

Figure 16 shows the median time from diagnosis to each stage. The error bars denote the interquartile range. There were no significant differences in the median times for these transitions between stages (Kruskal-Wallis test; p=0.59).

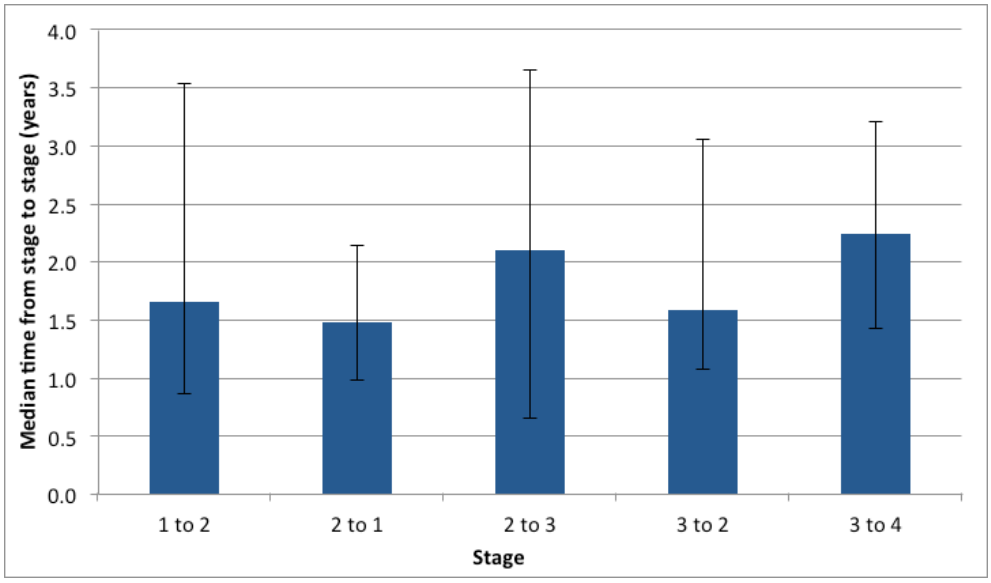


Figure 16: Median time for stage transition
(CKD - Chronic Kidney Disease)

3.15. HbA1c and Insulin

The association between the most recent HbA1c level and the insulin regimen being used by the patient is presented in Table 3.10 below.

Insulin Regimen	Number of Observations (n)	HbA1c Level			
		Mean	SD	Minimum	Maximum
Actraphane	235	9.4	2.4	3.9	14.8
Protophane	36	9.4	2.5	5.7	15.0
Protophane+Actrapid	47	10.4	2.4	4.7	16.2

Table 3.10: HbA1c Level according to Insulin regimen
(HbA1c- Glycated Haemoglobin)

- Not controlling for co-morbidities (n=318): Overall, there was a significant difference in the mean HbA1c levels between the three medication groups (p=0.021). Post-hoc tests showed that the (mean±95%CI) HbA1c level for the patients on Protophane+Actrapid (10.4±0.7) was significantly higher than that for patients on Actraphane (9.4±0.3). There were no other significant differences.
- Controlling for hypertension, dyslipidaemia, and HIV (n=318): Overall, there was a significant difference in the mean HbA1c levels between the three medication groups (p=0.022). Post-hoc tests showed that the (mean±95%CI) HbA1c level for the patients on Protophane+Actrapid (10.4±0.7) was significantly higher than that for patients on Actraphane (9.4±0.3). There were no other significant differences.

3.16. Renal Function

3.16.1. HbA1c

- Not controlling for co-morbidities (n=319): There was no significant difference in the mean HbA1c levels between the group with normal renal function (CKD 1) and the group with renal dysfunction (CKD 2-5) (p=0.80), as seen in Table 3.11.
- Controlling for hypertension, dyslipidaemia, and HIV (n=319): There was no significant difference in the mean HbA1c levels between the group with normal renal function and renal dysfunction group (p=0.87).

Recent eGFR	Number of eGFR Observations (n)	Number of HbA1c Observations (n)	Mean	SD	Minimum	Maximum
G2-G5	213	213	9.5	2.4	3.9	16.2
G1	106	106	9.5	2.4	5.3	14.8

Table 3.11: Association between the most recent HbA1c and renal function.
(eGFR - estimated glomerular filtration rate; HbA1c - Glycated haemoglobin)

3.16.2. BMI

The association between the most Recent BMI and normal renal function (CKD stage 1) compared with renal dysfunction (CKD stage 2-5) are categorised in Table 3.12.

Recent eGFR	Number of eGFR Observations (n)	Number of BMI Observations (n)	Median	IQR	Minimum	Maximum
G2-G5	213	198	31.5	26.7 - 16.8	16.8	103.8
G1	106	101	31.3	26.2 - 19.4	19.4	65.9

Table 3.12: Association of BMI and Kidney function
(eGFR - estimated glomerular filtration rate)

For the analysis, a log transformation of the BMI was used in order to meet the assumptions of the GLM technique.

- Not controlling for co-morbidities (n=298): There was no significant difference in the mean log(BMI) levels between the renal function and dysfunction groups (p=0.43).
- Controlling for hypertension, dyslipidaemia, and HIV (n=298): There was no significant difference in the mean log(BMI) levels between the renal function and dysfunction groups (p=0.68).

3.16.3. Urine Dipstick

The association between the most recent urine dipstick results and normal renal function (CKD stage 1) versus renal dysfunction (CKD stage 2-5) is presented in Table 3.13. Although stage 2 CKD due to DN is not usually associated with dipstick detectable proteinuria, it has been grouped together with CKD 3- 5 for analysis due to the small number of observations.

Urine Dipstick result		CKD Category			
		G1		G2 - G5	
		n	%	n	%
Glycosuria	No	67	63.2	132	62.0
	Yes	39	36.8	81	38.0
1+ Proteinuria	No	100	94.3	190	89.2
	Yes	6	5.7	23	10.8
2+ Proteinuria	No	103	97.2	194	91.1
	Yes	3	2.8	19	8.9

Table 3.13: Association of Urine dipstick and CKD Stage
(CKD - Chronic Kidney Disease)

a. Glycosuria:

- Not controlling for co-morbidities (n=319): There was no significant association between the presence/absence of this urine dipstick finding and the normal renal function and renal dysfunction groups (p=0.83).
- Controlling for hypertension, dyslipidaemia, and HIV (n=319): There was no significant association between the presence/absence of this urine dipstick finding and the normal renal function and renal dysfunction groups (p=0.72).

b. 1+ Proteinuria:

- Not controlling for co-morbidities (n=319): There was no significant association between the presence/absence of this urine dipstick finding and the normal renal function and renal dysfunction groups (p=0.14).
- Controlling for hypertension, dyslipidaemia, and HIV (n=319): There was no significant association between the presence/absence of this urine dipstick finding and the normal renal function and renal dysfunction groups (p=0.25).

c. 2+ Proteinuria:

- Not controlling for co-morbidities (n=319): There was no significant association between the presence/absence of this urine dipstick finding and the normal renal function and renal dysfunction groups (p=0.055).
- Controlling for hypertension, dyslipidaemia, and HIV (n=319): There was no significant association between the presence/absence of this urine dipstick finding and the normal renal function and renal dysfunction groups (p=0.064).

4. Chapter 4: Discussion

This study serves to demonstrate that the prevalence of CKD is significant in the study population. With generally poor glycaemic control, notable co-morbid diseases and poor lifestyle choices may contribute to the DN prevalence. Further, it is compounded by the inadequate implementation of screening protocols, resulting in delay in diagnosis and treatment, and ultimately, in poor long-term outcomes.

4.1. Analysis

The demographics of the study population is not truly reflective of South African society. Although the majority of the study subjects were black (44,6%) and coloured (34%), the 2011 South African Census suggests a much larger black population (79,2%) and a smaller coloured population (8,9%) in comparison [43]. The mean age of 59.4 years and the female predominance of 62% further reflects the nature of the DM epidemic in South Africa, portraying the higher prevalence with increasing age and in females as suggested in Esayas et al [44].

The number of cases per year, derived from the year of diagnosis documented, tended to be higher from 1995 onwards. This could possibly be attributed to when the clinic was established (early 1990s); the increased intake of patients with the escalation of DM in recent years; possible mortality associated with length of time living with DM; or even poor record keeping. There are spikes in the number of cases in the years of 1995, 2000 and 2005; this probably relates to patients' rounding off when asked to recall the year when first diagnosed.

With the current HIV/Aids epidemic in Southern Africa, it is surprising that the prevalence is so low in this population. There are many renal manifestations

associated with the HIV/Aids, including acute and chronic renal failure, and this may impact the prevalence of ESRD in future if HIV/Aids is present in the setting of type 2 DM.

With the rise of the entity of Metabolic Syndrome, it is not surprising that the majority of subjects have both hypertension an dyslipidaemia (67.7%). Hypertension was the most prevalent comorbidity (89.1%) while dyslipidaemia followed as a close second (82.2%). A study done in rural South Africa by Adeniyi et al in 2015 showed a prevalence of concomitant hypertension of 81% [45]. According to the SEMDSA guidelines “atherosclerosis accounts for up to 70% of all diabetic mortality in white, coloured and Asian patients” and although “still uncommon in black patients, it is on the increase” ([2], pg. 58). Multiple concomitant diseases increase the risk for complications and decreases quality of life in the long term.

As smoking is an independent risk factor for DN, it is notable that 12.5% of subjects still use tobacco. Although, the prevalence is less than the 17.6% of the adult South African population suggested in the survey by Reddy et al published in 2015 [46], it is still vital to address its prevalence in the overall management of DM. Although the modifiable lifestyle factors have been considered in this study, they have not been quantified (for instance smoking pack years, type and amount of exercise or units of alcohol consumed), hence limiting the conclusions one is able to draw from the data. Despite the 43.7% of patients having documented participation in ‘regular exercise’, the mean and median BMI level remains in the obese category (> 30kg/ m^2). One cannot ascertain what is considered as ‘regular’ or ‘exercise’ as is documented in the clinic file. Similarly, the extent of alcohol use/abuse cannot be assessed with only a prevalence of use of 10.6% and no further information.

Globally, obesity is on the rise. However, South Africa's obesity rate is the highest in Sub-Saharan Africa, with approximately 70% of women and 35% of men being either overweight or obese, according to the Heart and Stroke Foundation of South Africa [47]. This study demonstrates a similar proportion, as 66% of the females and 42% of the males were classified as either overweight or obese. An astonishing 40% of South African women are considered obese (BMI > 30kg/m^2). In this study 57.7% of the sample were obese, with a staggering 11% being morbidly obese, depicting the extent of the problem. Although there are many reasons as to why obesity is such a major issue in South Africa, including sedentary lifestyle choices, excessive alcohol intake, poor diet and even the negative connotations of loss of weight being associated with chronic illnesses such as HIV/Aids. Obesity is associated with multiple diseases for example type 2 DM, hypertension, cardiovascular disease and arthritis. In the setting of type 2 DM, loss of weight is an essential part of targeted therapy [47].

The majority of patients are on the bi-daily Actraphane regimen 73,2% (premixed fast and long acting insulin) although the basal bolus regimen, of separate Protaphane (long acting) and Actrapid (short acting), has been shown to more accurately mimic physiological insulin secretion. Despite the basal bolus regimen seeming more complex to patients, involving more injections and necessitating more patient education and insight, it allows for more flexibility in mealtimes and lifestyle and ultimately more stable and better glucose control. However, this call for a more patient centred approach to glucose control, with the aim to individualise therapy, often proves difficult in populations with poor insight and lower levels of education. In this sample, the mean HbA1c in patients on the basal bolus regimen

was significantly higher than in patients on the bi-daily premixed insulin regimen. This is possibly due to the premise that patients demonstrating poor control on bi-daily Actraphane are often subsequently switched to the basal bolus regimen [48]. This more intensive regimen is commonly implemented in the hope of achieving glycaemic targets but requires significant adherence and insight from the patient, which is often challenging.

Furthermore, one has to consider whether the insulin is being used as augmentation (with an oral hypoglycaemic agent) or replacement therapy. The importance of follow up to achieve appropriate titration and proper injection technique is essential to achieving glucose control. The bi-daily pre-mixed insulin (Actraphane) and daily long-acting (Protophane) regimens provide a more standardised approach, in which health care practitioners take more control in dosage adjustment and glucose control. Within an outpatient clinic setting, healthcare practitioners are often hesitant to make major alterations often leading to chronic poor glycemic control [48].

It is encouraging to note the high use of statins, ACE-I's/ARBs and metformin (91.6%, 80.4% and 71% respectively) in this clinic suggesting appropriate, targeted therapy. The extent to which therapy is monitored and evaluated once initiated, however, cannot be assessed. The prescription of aspirin as preventative therapy for cardiovascular disease is also high (87.2%). As we cannot ascertain the prevalence of atherosclerotic cardiovascular disease, we cannot assess the appropriateness of the therapy. The ADA Standards of Medical Care in Diabetes (2016) recommends anti-platelet agents in DM patients with increased cardiovascular risk (age > 50years and at least one other risk factor) [23]. Notably,

SEMDSA advocates the use of aspirin only as secondary preventative therapy (and not as primary prevention) [20].

As previously discussed, for optimal glycaemic control and prevention of renal complications, a target HbA1c < 7% is recommended, far lower than the mean HbA1c achieved in this study population of 9.5%. The majority of patients have levels greater than this target, increasing the likelihood of microvascular complications. It may also be prudent to mention that the patients identified with HbA1c measurements less than 5% were associated with poor GFR, suggesting renal impairment as the reason for low HbA1c and not improved glycaemic control. However, despite long-standing poor HbA1c levels, little progression was seen in CKD overall. It must be stated that, during data collection, confirmation of patients and their results were undertaken using the NHLS database to ensure accuracy (ie that the same patient was being used at each time period and that the results were truly theirs).

The extent that comorbidities (such as hypertension) impacted on the development and progression of CKD cannot be clearly defined as the corresponding level of control was not objectively measured in this study. The post trial monitoring of patients in the UKPDS suggested that benefits of previously improved BP control in patients with DM and hypertension, ie reduced risk of complications, are not sustained once BP control deteriorated [49]. This is in contrast to theories such as the “metabolic memory” described by the DCCT-EDIC trial or “legacy effect” described in the UKPDS. These terms refer to the phenomenon of ongoing beneficial effects on diabetic complications after a period of improved glycaemic control, even if subsequently followed by poorer glycaemic control [50]. It is possible

that such concepts played some part in the limited progression seen in CKD in this study, however, this contribution is immeasurable and hence, further evaluation and commentary is limited.

The time between the three different sets of results impact on the results. The median time between baseline and diagnosis was 9.2 years, compared to the time between baseline and second result set (3.2years), and second and recent result set (2 years). This suggests that the later estimation of the duration between diagnosis and CKD stages 2-5 may be over-estimated, since most of the durations between diagnosis and baseline measurements are very long (i.e. patients were not taken up in the clinic at the time of diagnosis) and there are no interim measurements. The times between measurements suggest that for some patients there were very long delays between measurements; hence the time for transitions between CKD stages may once again be over-estimated.

Furthermore, it appears that there is not much difference in the GFR category profile of the patients between the three sets of measurements, as seen in Figure 9, but this does not take into account the time difference (for each patient) between the sets of measurements. A large proportion, 40.1%, of subjects are categorised as Stage 2 CKD and then Stage 3 CKD comprises of 21.3%. There is a large decrease in Stage 4 and 5 with 4.4% and 0.9% respectively. If appropriate therapy, to control hypertension and regulate glucose levels, is instituted early in the process, remission to normo-albuminuria and therefore halting or slowing the decline of GFR is still a possibility [51].

The urine dipstick measurement was well documented, detecting abnormal levels in just over half of the subjects. The dipstick has been shown to be a useful, low cost point of care test to screen for poor glucose control (glycosuria, ketonuria) and infection (nitrites) and DN (micro-albuminuria/proteinuria) ([52], [53]). Some literature suggests that its diagnostic accuracy has not been sufficiently assessed in terms of evaluating proteinuria. Dongmin et al suggest that the urine dipstick can be used as a screening tool if PCR or ACR>300mg/g is used as the proteinuria reference standard, but not if ACR>30mg/g is used due to its low sensitivity [54]; and Nagagrebetsky et al found dipstick testing to be unreliable in detecting microalbuminuria [53].

Nevertheless, 42 patients in the CKD stage 2-5 category had detectable proteinuria, and although the unequivocal prevalence of DN would be difficult to ascertain, as PCR data is limited and further investigation (eg renal biopsy) was precluded by the retrospective design of the study, this number affords us some insight into this prevalence. Interestingly, the clinical paradigm that defines DN development as a progression from normo-, to micro-, and subsequently to macro-albuminuria has also been questioned recently, as some research has shown a group of DM patients with progressive renal dysfunction who are persistently normoalbuminuric [55].

The HJAH laboratory (National Health and Laboratory Service) does PCR testing, instead of the recommended ACR measurement. Despite its availability, it is significantly under-utilised. The majority of the data was missing (61.7%) precluding evaluation of an important screening tool. The extent of the missing data is disheartening as the measurement should have been recorded at least once (at the

patients first visit), as it is recommended at diagnosis of all type DM patients. The lack of data suggests that health practitioners overlook requesting this test while facilities in the hospital often makes it difficult for patients to provide urine samples. However, the relatively well documented urine dipstick results suggest that it is possible to attain urine samples despite this difficulty.

This screening deficiency is particularly concerning in light of the prevalence of CKD in the sample (66.8%), which is higher than evidence suggests, as ACR should be monitored to assess whether therapy is effectively reducing or slowing progression of the microvascular damage. A study by Gaede et al demonstrates a diminished GFR decline with improved albuminuria [51], and this clinic has not made adequate use of PCR as a screening and monitoring tool. The ALICE-PROTECT Study highlighted the difficulty in achieving BP and proteinuria targets , as only 39% and 21% reached the respective target level at 2 years and despite the early intervention mean eGFR dropped from 40ml/min/1.73m^2 to 33ml/min/1.73m^2 [9]. Data reflects that GFR levels and thus, CKD stage, do not worsen in general with time as is expected, but rather patients tend to oscillate between stages. This may be attributable to patient adherence to (or lack thereof) modifications made in lifestyle and treatment, which is often a dynamic component in DM therapy.

In terms of analysis of time periods from diagnosis and the different stages the only significant difference was the median time to Stage 2 (11.8 years) was shorter than that to Stage 4 (14.2 years). This is expected as one assumes progression from one stage to the next. There were also no significant differences in the median transition times between the stages of CKD.

A review by Onuigbo et al states that the CKD staging is useful as a guide however care needs to be individualised as “inter-patient and intra-patient CKD stages variability is immense” [56]. A large proportion of patient’s CKD stage remained static (non-progressors), some worsened (progressors) and others even improved compared to baseline in this study.

It is notable that the prevalence of renal dysfunction in this study is remarkably higher than what other South African studies demonstrate. A retrospective analysis by Motala et al (2001) undertaken in Durban reported that in patients with long-standing type 2 diabetes (exceeding 10 years duration) 25% exhibited persistent proteinuria, with 25,2% had an abnormal serum creatinine level [57]. More recently, a review of a diabetic population in the Tshwane district by Webb et al (2015) reported poor screening practices for diabetes complications (DN was only screened for in 21.4% of patients) and the prevalence of DN (eGFR stages 3-5) was found to be 7% [58].

Despite research suggesting otherwise, no significant difference (even when controlling for co-morbidities) was noted when taking into consideration the various parameters measured and the association between these parameters and renal function. From the literature review, one would expect a worsening renal function (declining GFR and progression of CKD staging) with a poorer HbA1c, higher BMI and presence of proteinuria (as assessed using urine dipstick instead of PCR, discussed above). Nonetheless, the prevalence of CKD is significantly higher than the average suggested in the literature (66.8% vs 20-40%) and within the CKD group 84% have HbA1c levels greater than the target of 7%.

Although the characteristics of this study population are comparable to those in other local studies [57, 58], an association with renal dysfunction and the traditional drivers of DN was notably lacking. Furthermore, the presence or absence of other microvascular complications (such as retinopathy or neuropathy) were not assessed as part of this study and there was significant lack of urine PCR data available. Without such an objective comparison, it is difficult to state with certainty that the renal dysfunction measured is, solely, due to DN.

4.2. Strengths and Limitations of the Study

The following strengths of the study have been identified:

- The large sample size allows for a good representation of the study population.
- This study contributes to the finite pool of scientific data on DM in South Africa.

The following limitations of the study have been identified:

- Selection Bias: The Specialist Diabetic Clinic is a referral clinic that accepts patients who are poorly controlled at primary care level. Thus patients attending the clinic generally have higher average HbA1c levels and may have a higher degree of target organ damage, probably making the audited sample not fully representative of the general population. The clinic's policy also determined that non-insulin requiring diabetic patients were not included in the study population.
- Measurement Bias: The reliability of observations/measurements taken by nursing sisters is sometimes questionable, and poor record keeping by doctors is a reality.
- Confounding Variables: As discussed, the assessment of lifestyle risk factors and modification such as diet, exercise and smoking cannot be quantified due to the nature of the clinic's record keeping. Hence, the extent of the impact of such factors cannot be fully evaluated.
- The category of CKD Stage 1 includes hyper-filtration, serum creatinine may decrease as GFR increases. This has not been accounted for in this study, categorising Stage 1 CKD together with normal renal function.
- Adequacy of control of the co-morbidities, as well as the nature of the dyslipidaemia present in this sample, were not measured making it difficult to assess the extent of its effect on the renal function.

- The retrospective design did not allow for the verification that the CKD documented truly signified DN, as concomitant microvascular complications and/or urine PCR could not be confirmed.
- Patient adherence was not reported on; it is an important factor in DM management.

4.3. Future considerations

There is a necessity for both patient and health practitioner alike to understand the disease process and its management to achieve optimum care. Patient adherence is enhanced by a good patient-doctor relationship, professional empathy, patient education and autonomy in decision-making [59]. Assessment of management is essential in training hospitals and this can be attained if some patient files are reviewed by more experienced practitioners and concerns subsequently highlighted in an appropriate setting. There is much that needs to be improved in terms of management of DN in the DM clinic setting and further research would be invaluable in identifying strategies for such improvement. An example of such a strategy would be the implementation of guidelines suggesting frequency and timing of particular screening tools. Appropriate screening and timeous therapy is essential in order to optimise the very limited resources the South African health sector has available.

4.4. Future Studies

Further studies for consideration include:

- A prospective study to evaluate improvement in renal outcomes if ACR/PCR measurement is mandatory in the clinic setting.
- Assessment of adequacy in control of co-morbidities, such as hypertension and dyslipidaemia, and its effect on DN.
- Impact of DN and necessary lifestyle modification strategies on patient quality of life.
- A comparative study of DM controls and DN prevalence in specialist DM clinic versus a general medical outpatient clinic.

4.5. Conclusion

Although many of South African public hospitals establish specialised clinics to service the growing number of DM patients, the evaluation of these facilities remain sparse. This study has demonstrated that the prevalence of CKD in specialised DM clinics is notably higher than literature suggests and glycaemic control is considerably poorer than targeted levels. Furthermore, there is significant under-utilisation of screening for micro-albuminuria which is an essential part of DM and DN management, possibly delaying institution of appropriate therapy and aggravating the progression of DN. Addressing these challenges with pertinent amendments in specialist clinics is crucial to improve patient overall management and care, which will in turn, hopefully, impact positively on the morbidity associated with DM and DN.

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Appendix A - Sample Size Calculation

Sample Size Calculation

Sample size for prevalence was determined using the formula:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where n = sample size,

Z = Z-statistic for the chosen level of confidence,

P = expected prevalence or proportion

d = precision

Appendix B - Data Collection Sheet

Page 1

Study No:

1. Demographics:

Race:	Black	White	Indian	Coloured	Other

Sex:	Male	Female

Age:

2. History:

Number of years with diabetes: _____

Year Insulin started: _____

Comorbidities:			***Lifestyle:***		
Hypertension	Yes	No	Exercise	Yes	No
Dyslipidaemia	Yes	No	Ex Smoker	Yes	No
HIV	Yes	No	Currently Smoking	Yes	No
Thyroid disease	Yes	No	Alchohol use	Yes	No

3.Treatment:

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

Page 2

Study No:			

4. Clinical Parameters	Baseline	Second	Recent	
Height				cm
Weight				kg
Systolic Blood Pressure				mm Hg
Diastolic Blood Pressure				mm Hg
Abdominal Circumference				cm

5. Laboratory findings:

Glycated Haemaglobin (HbA1C)				%
Sodium				mmol/l
Potasium				mmol/l
Chloride				mmol/l
CO2				mmol/l
Urea				mmol/l
Creatinine				mmol/l
Estimated GFR				
Urine PCR				
Urine Dipstix				

Appendix C - Ethics Approval Letters

1. Wits HREC

R14/49 Dr Zareena Angamia

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151188

NAME: (Principal Investigator)	Dr Zareena Angamia
DEPARTMENT:	Internal Medicine Helen Joseph Hospital
PROJECT TITLE:	The Prevalence of Renal Dysfunction in Insulin-Requiring Type 2 Diabetic Patients Followed up at a Specialist Diabetic Clinic at a Tertiary Academic Hospital
DATE CONSIDERED:	27/11/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Zaheer Bayat
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	11/03/2016

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature

Date 25/04/2016

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Gauteng Department of Health
Helen Joseph Hospital
Enquiries: Dr. M.R. Billa
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Tel :(011) 489-0306/1087
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E mail: Raymond.Billa@gauteng.gov.za

Dr.M.R.Billa
Chief Executive Officer
Helen Joseph Hospital

Dear Dr.Billa

STUDY: To determine the prevalence of Renal dysfunction I insulin-Requiring type 2 diabetic patients being followed up at a specialist diabetic clinic at a tertiary academic hospital.

RESEARCHER: Dr. Zareena Angamia

The above was discussed at the Research Committee Meeting. We recommend that permission be granted for Helen Joseph Hospital to be used as a site for the above research. However, since this is a research project involving voluntary participation. We cannot guarantee participation of individuals/patients.

Upon completion of the study, a copy thereof should be submitted to Helen Joseph Hospital.

Thank you

DR. Murimisi Mukansi
CHAIRPERSON
DATE: 22/February/2016

Approved

DR. M.R. BILLA
CHIEF EXECUTIVE OFFICER
DATE: 22.02.2016

2. HJAH Ethics Committee

Appendix D - Turnitin Letter from Supervisor

20/11/17

The Chair

Postgraduate Studies Committee

Faculty of health Sciences

University of Witwatersrand

Re: Turnit in report: Dr Zareena Angamia – Mmed

I have reviewed the Turn-it in report of Dr Zareena Angamia's dissertation. The report identifies a similarity index of 14%. Much of this similarity relates to definitions and explanations which are standardized. The other information which bears similarity are appropriately referenced.

Thank you

Yours sincerely

Dr Firdous Variava
MBBCH, FCP(SA), MMEd(wits)



Supervisor of the above study