Determinants of diabetic nephropathy among adult type II diabetic patients attending Kenyatta National Hospital; A Case-Control study

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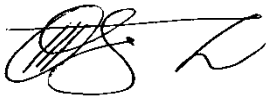
Signature:  **Date:** 11th November 2022

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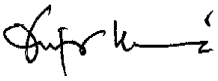
Signature:  **Date**: 11th November 2022

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LIST OF ABBREVIATIONS AND ACRONYMS

ACE- Angiotensin Converting Enzymes

AKI- Acute Kidney Injury

aOR-Adjusted Odds Ratio

ARB- Angiotensin Receptor Blockers

BMI-Body Mass Index

CDs- communicable disease

CI-Confidence interval

CKD- chronic kidney disease

DCCT- Diabetes Control and Complications Trial

DKD-Diabetic Kidney Disease

DM-Diabetes Mellitus

DN-Diabetic Nephropathy

EDIC-Epidemiology of Diabetes Interventions and Complications

eGFR-estimated Glomerular Filtration Rate

ESRD-End Stage Renal Disease

EURODIAB- European Diabetes Study

GFR-Glomerular Filtration Rate

HBA1c- Glycated hemoglobin

IDF-International Diabetes Federation

IFMSA- International Federation of Medical Students Association

KNH-Kenyatta National Hospital

LPD- low protein diet

MOH-Ministry of Health

NCDs-non-communicable diseases

NHIF-National Hospital Insurance Fund

NKF-National Kidney Foundation

NSAIDs-Non-Steroidal anti-inflammatory drugs

OR- odds ratio

RENAAL- Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan

T1DM- Type I Diabetes Mellitus

T2DM-Type II Diabetes Mellitus

UHC-Universal Healthcare Coverage

UKPDS-United Kingdom Prospective Study

WHO-World Health Organization

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

DEFINITION OF OPERATIONAL TERMS

Adherence to diabetic diet- defined as a diabetic patient having followed the recommended diabetic diet as well as strict adherence to diet restrictions.

Alcohol use - reported consumption of alcohol either currently or formerly.

Diabetic nephropathy- Was defined as GFR <60ml/min/1.73m^2 among study participants based on the latest clinical report.

Duration of diabetes morbidity- the period since diagnosis of DM2 among the participants.

Nephrotoxin exposure- use of herbal medicine or NSAIDs by diabetic patients within the last 12 months.

Poorly managed glycemia- HBA1C levels of more than 7% or non-adherence to antidiabetic agents, or absence of home-based self-monitoring plan for blood sugar.

Poorly managed hypertension- SBP more than 140 mmHg and/or DBP more than 90 mmHg or non-adherence to antihypertensive agents or absence of individual BP monitoring plan at home as reported by a patient and missing home records.

Tobacco use -smoking, chewing, sucking, or snuffing any tobacco product either currently or formerly.

ABSTRACT

Background: Diabetic nephropathy (DN) is the most serious sequelae resulting from uncontrolled T2DM and a great predictor of end-stage renal disease (ESRD) globally. Despite several studies having explored determinants associated with its occurrence, there is a paucity of data in the African region, especially in Kenya evidenced by scarce published data. With the steady rise of T2DM, its complications, such as DN are expected to rise.

Objective: To elucidate factors associated with the occurrence and progression of DN among adult T2DM patients at Kenyatta National Hospital (KNH), Nairobi, Kenya.

Methods: Hospital-based case-control study was conducted. Diabetes patients seeking care at KNH Diabetic clinic were the source population. Adult T2DM patients, ≥18 years with established diabetic nephropathy (outcome), evidenced by increased urinary albumin (>30mg/d) for at least six months and/or estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73m^2 were the cases. Diabetic patients free from established diabetic nephropathy and, ≥18 years were the controls of the study. All cases meeting the case definition and eligibility criteria were recruited and the control group was recruited by systematic random sampling within the study period to achieve a sample of 395, (the case-to-control ratio being 1:3) 99 cases and 296 controls. Data collection on socio-demographics, behavioral, medical history/biomedical, and healthcare system factors were collected through patient records review and interviewer-administered questionnaire, in form of ODK (Open Data Kit) software.

Analysis and results: Data was cleaned in excel and then exported to SPSS vs 27 for analysis. descriptive statistics were used to summarize continuous data while for categorical variables, percentages and proportions were used. In assessing the association between predictor variables on the response variable, univariable and multivariable logistic regression analyses were conducted. Significance levels were then determined at p-value ($p<0.2$) in the univariable analysis and ($p<0.05$) in the multivariable analysis.

In the univariable analysis, age, well-managed blood pressure, diabetic diet adherence, exposure to nephrotoxins, duration of living with diabetes, ACE/ARB inhibitors use, diabetic retinopathy complication, positive family history of diabetic nephropathy, the perception that diabetes nutritional guidelines are ineffective, and inefficient healthcare system showed significant association with DN.

In the multivariable analysis, well-managed BP (aOR 0.43; 95% CI: 0.20-0.91), nephrotoxin exposure (aOR 10.04; 95% CI: 3.15-31.96), duration since diagnosis of DM (aOR 0.06; 95%

CI: 0.02-0.19), family history of DN (aOR 52.67: 95% CI: 13.11-211.64), the perception that nutritional guidelines are ineffective in delaying the development and progression of DN (aOR 17.52; 95% CI 7.09-43.31), and the perception that healthcare system at KNH is inefficient (aOR57.14; 95%; CI 8.70-398.18) significantly showed association with diabetic nephropathy.

Conclusion

In this study, well-managed Bp, nephrotoxin exposure, duration since diagnosis of DM, family history of DN, the ineffectiveness of diabetes nutritional guidelines, and healthcare system inefficiency were found to be major predictors of DN. With these findings, efforts towards reversing trends of type 2 diabetes should be made with a focus on curtailing complications such as DN. This can be achieved by blood pressure management, sensitization on the proper use of NSAIDs and herbal medicine, improved lifestyle for those with a family history of DM and DN, strict diabetic diet adherence as well as more studies using more rigorous scientific methods be carried out to identify determinants of diabetic nephropathy.

CHAPTER ONE

INTRODUCTION

1.1 Background information

According to WHO, non-communicable diseases (NCDs) are currently the major cause of mortality, associated with roughly 41 million deaths annually equivalent to 71% of global deaths. The major NCDs are of four categories namely cardiovascular diseases accounting for approximately 17.5 million, cancers at 8.5 million, congestive respiratory diseases ranking at 4 million, and lastly, diabetes at 1.5 million deaths. These four NCDs are directly responsible for over 80 percent of NCD-related premature deaths globally (WHO, 2018). Apart from their mortality burden, NCDs have been shown to negatively affect economies globally hence burdening the healthcare system. Early unexpected deaths due to NCDs are readily avoidable since they majorly result due to four major risk factors, which are; harmful use of alcohol, cigarette smoking, poor and unhealthy dietary habits as well as low or lack of physical activity (IFMSA, 2018).

Globally, among these major NCDs, diabetes mellitus comes in as the fourth leading cause of death as well as the top ten overall in both NCDs and communicable diseases (CDs) (Zheng et al., 2017). Complications due to diabetes pose a major global health burden threat as 1 in 11 adults globally is diabetic (International Diabetes Federation, 2015).

Diabetes mellitus variances are of two types namely Type 1 (T1DM) and Type 2 (T2DM) diabetes mellitus and has grown from 4.7% in 1980 to 8.5% in 2014 globally (WHO, 2016). T2DM is a major concern of public health affecting 95% of the diabetic population (WHO, 2019)with symptoms resembling those of T1DM or, are often rare or absent hence the disease may go unnoticed or undiagnosed for several years resulting in serious diabetes complications. In 2015-2040 International Diabetes Federation (IDF) projections, diabetes was shown to be associated with 5 million deaths, and prevalence was estimated at 8.8% and projected to be at 10.4% in 2040 (Outsoar et al., 2017).

These complications are in two forms; macro-vascular complications such as cardiovascular disease and microvascular complications namely, diabetic neuropathy, retinopathy, and nephropathy, a form of CKD (IDF, 2013; Musabayane, 2012) making it the most important cause of ESRD (Ioannidis, 2014; Remuzzi et al., 2006) and the focus of this study.

Type 2 diabetes cases are rising in every country (Wang et al., 2019) including Kenya with a national prevalence rate of 3.1 % to 4.6%. This is between 1.4 million and 2.1million people, meaning, 1 in every 17 Kenyans has diabetes, and consequently, diabetes complications such as diabetic nephropathy.

Globally, T2DM is associated with CKD presenting in form of diabetic nephropathy, a known leading cause of ESRD globally (Prischl & Wanner, 2018; Remuzzi et al., 2006; Shafi et al., 2012; Webster et al., 2017) with approximately 20 to 30 percent of T2DM patients have kidney damage (Betônico et al., 2016). T2DM is associated with renal damage occurring through kidney growth and glomeruli enlargement (Remuzzi et al., 2006).

Diabetic nephropathy is signified by increased albumin in urine or decreased rate of glomerular filtration (GFR) or at times both (Gheith & Al-otaibi, 2016). It impairs blood vessels rendering the kidney less efficient and may even result in renal failure. It is therefore evident that with the ever-increasing incidence and prevalence of diabetes, more diabetic nephropathy conditions and other diabetes complications are to be anticipated (Chiang et al., 2014; IDF, 2013; Rue et al., 2015).

In 2017, International Diabetes Federation predicted that, based on statistics from the UK and the US, 40% of diabetics would acquire chronic kidney disease, with roughly 20% exhibiting symptoms consistent with stages three to five of the condition (Cho et al., 2018). According to 2002 US data, diabetes was found to be responsible for between 44% and 45% of kidney disease among incident ESRD cases, hence placing the US among the highest countries globally (Boer et al., 2014).

A systematic review in Africa indicates that upon T2DM diagnosis, some patients are most likely to progress to DN and later develop ESRD after more than 5 years of living with diabetes (Noubiap JJN et al, 2015).

In Kenya, national diabetes prevalence in the adult population is estimated at 4.6% and is associated with 20,000 deaths annually. The urban settings are more highly affected than the rural settings with prevalence roughly at 11% and 3% respectively whereas CKD prevalence stands at 10%, i.e., about 4 million Kenyans are affected, and anticipated to affect 4.8million persons before 2030. Among these CKD cases, DN is a major contributor with a prevalence of 15% according to a recently available study (Ngugi, 1989).

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

Both diabetes and hypertension are known to be the major leading causes of both CKD and ESRD globally. Diabetic nephropathy is greatly exacerbated by factors such as socio-demographic, cultural, nutritional, behavioral, biology and genetics, clinical, and even environmental factors.

High blood pressure (hypertension), obesity, uncontrolled or poor blood sugar control, and longer periods of diabetes morbidity have been found to highly aggravate the risk of CKD among diabetics of African origin (Noubiap JJN et al, 2015). Despite diabetic nephropathy being known to be a majorly DM complication as well as the cause of mortality and morbidity among diabetics globally, its determinants have not been fully elucidated here in Kenya.

Early diabetes diagnosis, treatment, management, and controlled blood pressure are known to slow DN outcome. Due to the existence of both modifiable and non-modifiable risk factors, DN disproportionately affects this population as some may not progress to ESRD. Modifiable ones include hypertension, glycemic control, dyslipidemia, alcohol use, and smoking which have been majorly associated with DN and can be prevented. The main non-modifiable factors are genetics, and cannot be prevented (Press, 2014).

In assessing the extent of kidney damage, proteinuria and eGFR tests are effective. Among type 2 diabetic patients, approximately 20% to 30% advance to microalbuminuria after 15 years of living with diabetes while less than half advance to actual nephropathy. This trend was demonstrated in both the Danish 18-year study and the EURODIAB prospective complications study in both types of diabetes. This was no different from the UKPDS study on T2DM patients which showed an annual microalbuminuria incidence of 2% and a 25% prevalence post-diagnosis (Retnakaran et al., 2006). Proteinuria prevalence in T2DM ranges between 5% and 20% (Gheith & Al-otaibi, 2016; Thomas, 2018).

Despite available studies having explored and associated most common risk factors such as socio-demographic, behavioral, biomedical, and health system factors to DN development, these risk factors vary across populations (Hintsa et al., 2017a; Noubiap et al., 2015) and therefore need to undertake this study, especially in Kenya. This is because, there is no research

specifically on diabetic nephropathy determinants/risk factors, to the best of our knowledge exists, and therefore, need to fill this knowledge gap. The study findings are expected to inform policy for redesigning prevention programs for T2DM, its complications such as DN, and holistic support for this group. This would result in saving an already burdened Kenyan healthcare system in terms of healthcare financing, essential medical supplies, healthcare workforce, health information, leadership, and governance.

2.2. Risk factors

According to a systematic review in the United States, economic status, educational status, and community support are associated with the outcomes of diabetic patients (Clark & Utz, 2014).

2.2.1. Socio-demographic factors

Age

According to a cross-sectional study in Tehran, renal failure was high in older diabetic patients with the mean age among micro-albuminuric and macroalbuminuric patients being 42 +/- 11.1 and 55.5+/- 10.5 respectively (Heydari et al., 2010) and since DN is a risk factor for renal failure, it might have contributed to the finding.

Among people with diabetes, advancing in age is an independent risk factor of DN (Noubiap et al., 2015). In another study comparing nephropathic and non-nephropathic patients, the latter was advanced in age, i.e., 63 and 59 years respectively, and had been diabetic for a long (18.81 vs. 12.85 years) (Al-rubeaan et al., 2014).

From the findings of an Ethiopian Hospital cross-sectional study, both age and sex were associated with diabetes complications among which diabetic nephropathy is one of them. (Abejew et al., 2015). From a retrospective study in Shakiso Health Center in southern Ethiopia, the occurrence of nephropathy is independently accelerated by increasing age (Tefera, 2014).

A study in Menoufia, Egypt that looked at the prevalence of proteinuria, showed that albuminuria, an indicator of diabetic nephropathy significantly increased proportionally with the patients' age in the micro-albuminuria and macro-albuminuria groups (Mohamed et al., 2013).

According to a study on predicting the initiation and progression of CKD, most population-based studies concluded that increased age raised proteinuria, CKD, and ESRD incidences (Taal & Brenner, 2006).

Sex

Sex is positively associated with diabetes-related complications (Abejew et al., 2015) higher incidence of diabetic nephropathy and ESRD has been shown to rampantly occur in the male sex unlike in the female sex in the general population (Taal & Brenner, 2006).

2.2.2. Behavioral factors

Management of hypertension

Blood pressure is the force exerted by the heart pumping on the blood vessels. High blood pressure, therefore, is an increased amount of force placed by blood on the vessels during blood circulation also known as hypertension.

High blood pressure (BP) is nearly two times more prevalent among diabetics unlike in the general population. In nephropathic patients, mean BP increases by 5%-8% annually (Muhammad & Nazar, 2014a) Hypertension is a strong correlate of DN progression in people of African origin with T2DM patients being 1.33-1.45 times more likely to have nephropathy (Noubiap et al., 2015).

A study on DN with vascular comorbidities in T2DM patients in developing countries found arterial hypertension to be an independent risk factor of DN ($p=0.04$) with 50%-90% of T2DM patients having arterial hypertension regardless of albumin excretion rate where an increase in it is an early marker of DN (Bentata et al., 2015).

According to a systematic review in Sub-Saharan Africa among DN and hypertensive diabetics, pooled point estimates showed that among diabetics with hypertension, diabetic nephropathy risk was elevated compared to those without hypertension with OR=1.67, 95% CI 1.31-2.14. This finding reinforces the fact that indeed, diabetic nephropathy is almost inevitable among diabetics hence an emphasis on the management and control of blood pressure in this population (Wagnew et al., 2018a).

An American-based study found out that recently diagnosed T2DM patients if treated to a <150/85mmHBP, significantly lowered microvascular risks by about 37%. Generally, systolic BP of more than 140mmHg in type 2 diabetic patients has been linked with an increased risk of ESRD and mortality (Alicic et al., 2017). Antihypertensive drugs inhibiting the renin-angiotensin system have proved to slow down DN progression better than other inhibitors, even though there is no change in the reduction of blood pressure (Tziomalos & Athyros, 2015).

Progression of diabetic nephropathy is accelerated by both systolic and diastolic blood pressure calling for more strict ways of management hence preventing falls in GFR. Proper antihypertensive measures can highly improve life expectancy in type 2 diabetic patients (Breyer & Harris, 2008) and it is without a doubt that proper control of hypertension is an effective intervention for delaying and preventing DN (Musabayane, 2012).

Uncontrolled glycemia

A study in Ethiopia has associated poor glycemic control with DN events (Abejew et al., 2015). Non-adherence in glycemic control and high HBA1C levels are crucial predictors in the occurrence of DN across diabetes mellitus populations (Tziomalos & Athyros, 2015). In the DCCT/EDIC observational study, improved control of glycemia among T2DM patients showed a reduction in DN incidence with moderate albuminuria patients with HBA1C levels decreased had reduced risk of progression to severe albuminuria and ESRD.

Nutrition and diet adherence

Diet is of great importance in managing and treatment of most NCDs, diabetes, and its complications such as DN, notwithstanding in conjunction with the use of conventional medication. A well-balanced diet enhances outcomes in this group of patients.

Protein-rich foods are important in keeping the body healthy, repairing body muscles and tissues as well as aiding in wound healing. However, a diet high in protein may cause kidney damage hence the toxicity resulting from protein by-product accumulation, unlike a well-moderated protein diet which has been shown to have clinical benefits among renal patients (Jee et al., 2017). Kidneys have an important role as far as protein and amino acid metabolism, breakdown, and excretion of the end product are concerned in which case if the proteins are excess, the kidneys are overworked rendering them less effective or even causing damage due to proteinuria.

A high protein diet, that is, more than 1.2 grams of protein per Kg of body weight per day (g/kg/day) induces noticeable changes in kidney health and function (Kalantar-zadeh et al., 2016) therefore limiting dietary protein has been associated with a decrease of proteinuria by 20-50% among chronic kidney disease patients.

Diet with sodium less than 5g (<2000mg), approximately 1 teaspoon, is recommended per day in CKD. Salt intake has been associated with kidney dysfunction outcomes (Sugiura et al., 2018). This is because elevated salt intake alters sodium balance thus reducing renal function

by reducing the removal of water thus raising blood pressure. This in turn strains the kidneys, therefore, damages the kidneys. It also raises urinary protein which is a major risk of developing kidney disease.

Fruits and vegetables; To ensure a balanced diet among DM-CKD patients, fruits and vegetables remain an important nutritional aspect as they contain essential minerals such as potassium required in the proper functioning of nerves, muscles, and heart as well as help counteract harmful effects of sodium on BP and act as a source of dietary fiber (Opiyo et al., 2019). This is because, as CKD progresses, potassium levels in the blood tend to rise since the kidneys can't properly regulate it, therefore cannot adequately remove excess potassium and this can be detrimental (Martinez Hassett, 2018).
World Health Organization (WHO) recommends at least 400g, translating to about five servings of vegetables and fruits per day (WHO, 2015).

Physical activity

Body movements requiring energy expenditure refer to physical activity. This, therefore, means that physical inactivity doesn't cause energy expenditure and has been ranked the fourth leading risk factor for worldwide mortality with approximately 6% of global deaths and responsible for about 30% of ischemic heart disease and 27% of DM burden (ADA, 2019a). Physical activity is important among diabetic patients as it aids in weight loss, muscle strengthening, cardiorespiratory fitness, reduced hypertension, and improved mood (Huffel et al., 2014).

According to WHO, physical activity is a crucial determinant in NCD prevention and every individual is encouraged to engage in it as often as possible with global recommendations indicating that adults aged between 18 to 64 years ought to take part in not less than two and a half hours of moderate-intensity aerobic physical activity spread throughout the week or at least one hour and 15 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of both notwithstanding ethnicity, race, gender even in adults with chronic conditions such as among diabetics and hypertensive patients (WHO, 2011b).

Both T1DM and T2DM patients are required to undertake at least 150 minutes of moderate to vigorous intense exercises weekly or consider at least 75 minutes of vigorous exercises weekly in the younger and physically fit individuals. Each adult, more so, type 2 diabetics ought to

lessen the duration spent in daily sedentary behavior as well as interrupt prolonged sitting after half an hour with an aim of proper glucose regulation, particularly with type 2 diabetic patients (ADA, 2019b).

Metabolic Equivalent for Task (MET) refers to the oxygen amount required in physical activity performance. MET determination on activities uses the following spectrum to classify whether an activity is vigorous or moderate-intensity, i.e., 1 MET indicates at rest; 2 METs indicate Light activity; 3-6 METs indicate Moderate activity; 7 or more METs indicate Vigorous activity.

Activities to Achieve 2008 Exercise Guideline Recommendations

Moderate-Intensity Aerobic Activities >150 min/week	Vigorous-Intensity Aerobic Activities >75 min/week
Brisk walking (>3 miles/h)	Uphill walking or race walking
Bicycling (<10 miles/h)	Bicycling (>10 miles/h)
Water aerobics	Running or jogging
Tennis (doubles)	Tennis (singles)
Ballroom dancing	Aerobic dancing
General gardening	Heavy gardening (digging/hoeing)

From the Centers for Disease Control and Prevention guidelines (12).

Figure 1: Metabolic Equivalent for Task (MET)

A study in Cairo, Egypt, found that creatinine and urea were lowered by roughly 1.5% and 41% respectively following aerobic exercise while resistance exercise in this same population reduced creatinine and urea by 3.5% and 35.7% respectively after three months. This shows that apart from a reduction in urea and creatinine, both types of exercise can reduce glucose and blood pressure, therefore, exercise can be adopted in the management of diabetic nephropathy (Youssef & Phillips, 2016).

Tobacco use

According to National Kidney Foundation, cigarette smoking can affect kidneys by affecting medicines used to treat high blood pressure in addition to slowing down the blood flow to the kidney among other important organs hence accelerating kidney disease.

Smoking and the harmful use of alcohol are lifestyle risk factors for both chronic kidney disease and diabetic nephropathy in which case, smoking accelerates kidney damage in those individuals with metabolic syndrome (Genet et al., 2008).

In 2002 WHO declared smoking to be among the four major risk factors for NCDs (Ort, 2002). Smoking on its own, for a long time, has been an issue of public health importance. In both CKD and DM, it brings along an even greater burden as it raises rates of both morbidity and mortality. Cigarette smoking was found solely to be an independent factor in CKD incidence, especially among the general adult population (Xia et al., 2017) as it increases both CKD and ESRD. However, upon cessation, a significant reduction in CKD incidence would be realized. This systematic review further linked cigarette smoking to insulin resistance among diabetics.

Other systematic review studies showed a significant increase in diabetes mellitus risk among smokers which in most cases progresses to diabetic nephropathy. The statistical significance and a pooled HR=1.07; (95% CI: 1.01-1,13; p=0.01 and on sub-group analysis, whether current or total, smoking would increase DN development risk. Previous smoking was found to significantly increase diabetic nephropathy risk with HR=1.04; 95% CI=1.03-1.05; $p<0.001$. Among diabetics, those who smoked were found to have an increased risk of DN unlike non-smokers (Liao et al., 2019).

In both types of DM, whether T1DM or T2DM, Smoking is known to accelerate stages of diabetic nephropathy by increasing microalbuminuria risk and progression to macroalbuminuria hence progression from early diabetic nephropathy to ESRD.

According to a Korean study looking at the association between cigarette smoking behavior post-DM diagnosis and DN, smoking behavior after DM diagnosis significantly had a role in DN development with both unadjusted and adjusted ORs being 1.83 and 2.12 respectively (Yeom et al., 2016).

Harmful use of alcohol

Just like cigarette smoking, the harmful use of alcohol is among the major risk factors of public health importance associated with premature deaths and disability(WHO, 2009). It is attributable to about 4% of all deaths and 4.5% of disease or injury, as well as premature deaths worldwide measured in DALYs (disability-adjusted life years) lost (WHO, 2011).

Harmful use of alcohol entails alcohol drinking aspects ranging from volume ingested over time or pattern of drinking whether occasionally, regularly, or even to alcohol intoxication. Each body organ is prone to damage from alcohol such as the kidney and the liver among others. Its use is responsible for over sixty diseases and conditions. It is estimated to be responsible for about 2.3 million global premature mortalities in 2002 ranking it fifth among the leading causes of global disease burden (WHO, 2009).

Alcohol ingestion of more than 20 grams per day was found to elevate the hazard ratio of urinary albumin but upon ingestion of fewer than 20 grams per day, the effect declined (Yamagata et al., 2007).

Apart from exacerbating diabetes complications such as DN, harmful use of alcohol may cause drug interactions or alter the functioning of anti-diabetic agents and other drugs, such as metformin (Emanuele et al., 1998) in addition to elevating blood pressure (Koning et al., 2015; Mukamal et al., 2001).

In the Australian-based study, AusDiab, albuminuria development was associated with moderate to high consumption of alcohol (Ausdiab et al., 2004) indicating a possibility of alcohol being a determinant of diabetic nephropathy among the diabetic population.

Exposure to nephrotoxins e.g., herbal medicine and NSAIDs

Traditional herbal medicine is utilized by about 70-95% of populations in developing nations as remedies for treating a majority of diseases (Chawla et al., 2013) including NCDs (Stanifer et al., 2015) such as diabetes. Based on a study conducted in Northern Tanzania, 77% of diabetic patients claimed they used herbal medicine for managing the condition (Stanifer et al., 2015).

This high trend may be so since herbal medicines are easily available making them affordable, highly marketed, prescribed in large quantities, and encouraged by family members and friends. Besides, perceptions that herbal medicines are easy to take or use (Rutebemberwa et al., 2013), effective (Baldé et al., 2006), and have reduced side effects compared to biomedical medicine may explain the high usage.

In the management of diabetes, some traditional medicines have exhibited health-related benefits hence improved outcomes. However, some may have potential adverse effects such as gastrointestinal disorders, hypoglycemia, or skin problems based on a Guinean study (Baldé et al., 2006).

Taking into consideration herbal medicine's wide use, the fact remains that there is limited knowledge of its physiological efficacy as well as deleterious effects resulting from its use (Kasole et al., 2019), therefore is a need for more scientific evidence. Increased vulnerability of the kidneys to toxins is exacerbated by factors such as its high concentration in the medullary interstitium and active uptake by tubular cells making them a cause of kidney injury (Bagnis et al., 2004) among other side effects mentioned afore.

In a review that aimed at looking into the beneficial and harmful effects of herbal medicine on kidney health, it reported evidence of nephrotoxicity due to various herbal medicine and their products as both heavy metals and inorganics were found to negatively alter the activity of the nephron as well as causing other health problems (Asif, 2012).

In a qualitative study to determine herbal medication use among T2DM in Kenya, four Key informants in the study reported that herbal medicine had fewer adverse effects unlike allopathic medicine, and claimed that their formulations reduced DM complications as well (Chege et al., 2015).

NSAIDs are a category of medication globally used mainly because of their anti-inflammatory, antipyretic as well as analgesic effects on prostaglandin synthesis resulting from cyclooxygenase (COX) enzyme inhibition (Hörl, 2010). Whereas NSAIDs have been known to prevent and treat inflammatory disorders such as arthritis, in diabetes, the efficacy of this group of drugs in reducing disease progression and preventing complications is still unclear, and worse, the side effects resulting from use include renal impairment (Bellucci et al., 2017; Robbinson, 2016).

Renal impairment occurs by NSAIDs inhibiting the functioning of COX hence reducing the production of prostaglandin in addition to causing a change in kidney hemodynamics hence kidney failure. Other adverse effects such as sodium retainment, hypertension, and modification of glomerular filtration rate are attributable to NSAIDs use (Plantinga, L., Grubbs, V., Sarkar, U., Hsu, C.Y., Hedgeman, E., Robinson, B., Saran, R., Geiss, L., Eberhardt, M., Powe, 2011).

A nationwide longitudinal study in Taiwan found that NSAIDs significantly enhanced the risk of developing chronic kidney disease among type 2 DM patients (Tsai et al., 2015).

2.2.3. Medical history and biomedical

Duration of living with diabetes

According to a study in Ethiopia, age was found to be a determinant of DN development as it indicated that with a one-year increase in age, a diabetic patient had a risk of DN by 3.7% (Hintsa et al., 2017a). An increase in age and diabetes condition interact hence increasing the risk of diabetic nephropathy in the diabetic population unlike the general population (Abejew et al., 2015).

Age was depicted as a correlate of CKD-DN with odds of microalbuminuria, an indication of DN. In both type 1 and 2 diabetic patients diagnosed over 10 years ago, analyses showed that they were roughly 4.2 times more likely to develop microalbuminuria unlike those with less than 10 years post-diagnosis (Noubiap et al., 2015).

In a Saudi study that compared nephropathic and non-nephropathic patients, nephropathic patients were significantly older, that is 63 vs. 59 years, and had been diabetic for long, approximately 19 and 13 years respectively ($p=<0.0001$) (Al-rubeaan et al., 2014) and this trend is supported by (Tziomalos & Athyros, 2015).

Body Mass Index (BMI) (overweight and obesity)

Increased or decreased body weight plays a pivotal role in individual health issues such as those related to blood pressure which in turn have an impact on kidney blood vessels. Body Mass Index (BMI) is determined by body weight making it a screening tool for overweight and obesity status among adults and measures how weight-height relationship and places individuals in categories of normal body weight (BMI 18.5-24.9); overweight (BMI 25-29.9); obesity (BMI 30-39.9) and extreme obesity (BMI >40). BMI lower than 25 and higher than 18.5 is ideal to keep blood pressure in check and avoid kidney blood vessel impairment.

Glycated hemoglobin concentration (HBA1C) level

HBA1C is defined as glucose-bound hemoglobin and is used to test for long-term monitoring of diabetes control. Poorly controlled DM increases HBA1c levels in the red blood cells. Since the glucose attaches to hemoglobin for the rest of its lifetime, usually about 3 months, the higher the blood glucose, the higher the HBA1C level. Everyday fluctuations of blood glucose

don’t affect HBA1C level, therefore HBA1c level reflects levels of blood glucose for the previous three months.

Increased HBA1C proportionally increases the risk of diabetic nephropathy. In a Taiwan-based study, an HBA1C estimate of more than 13.44% was attributed a to more than 1.5-fold higher risk of diabetic nephropathy unlike the HBA1C level less or equal to 6.68% (Lin et al., 2013).

HBA1C level of between 4%-5.6% is the normal range for a healthy population without diabetes. Levels between 5.7% to 6.4% imply a greater risk of diabetes whereas a level above 6.5% would imply the presence of diabetes condition. The target HBA1c among diabetics is usually less than 7%, in which case if higher, there is an increased risk of having diabetes complications in which case DN is one of them (Foundation, 2012a; M. Lee et al., 2018).

Use of ACE/ARB inhibitors antihypertensive agents

Anti-hypertensive drugs have been proven to be effective in the control and management of high blood pressure. The available major classes of antihypertensive agents include ACE inhibitors (Angiotensin Converting Enzymes), ARB inhibitors (Angiotensin Receptor Blockers), Beta (β-) blockers, Calcium Channel Antagonists, Central Sympatholytic drugs, and thiazide diuretics. Some of these antihypertensive agents, for example, ACE and ARB inhibitors whether used individually or combined, are most effective in DN because of their target to the renin-angiotensin even though others have been shown to negatively influence in control of glycemia (Musabayane, 2012).

ACE inhibitors function by preventing Angiotensin I conversion to angiotensin II while Angiotensin II receptor blockers block the action of angiotensin II by preventing it from binding to angiotensin II receptors on the muscles surrounding blood vessels. Angiotensin II is a potent chemical substance that narrows blood vessels by causing vasoconstriction which in turn causes hypertension thus overworking the heart (Chan et al., 2000; Maione et al., 2011).

The available standards for care in DN emphasize stern control of hypertension using the renin-angiotensin-aldosterone system and glycemic control. Hypertension, a modifiable risk factor for DM complication, is known to independently amplify the occurrence of both micro and macro-vascular outcomes among diabetics.

Among patients with urinary albumin and established kidney damage, there’s a two-fold benefit, that is apart from delaying the progression of renal disease, it also lowers

cardiovascular morbidities and mortalities associated with CKD and diabetes which act as the leading cause (Devonald & Karet, 2002).

Among type 2 DM patients with underlying high blood pressure and on ACE inhibitors, a reduction of both kidney function and elevated levels of urinary albumin has been shown to exist (Chan et al., 2000) (Ptinopoulou et al., 2013).

According to RENAAL, post hoc analyses evaluating more than a thousand T2DM patients, ESRD or deaths rose by 6.7% with every increase of 10mmHg SBP at baseline Brenner et al., (2001) and for every 10mmHg reduction in SBP, a likelihood of 12%-15% reduction of DM complications and death respectively exist (Tang et al., 2016).

Use of anti-diabetic agents

The development and progression of DN are greatly influenced by increased hyperglycemia which can be managed by the use of anti-diabetic agents (Prischl & Wanner, 2018). These agents are aimed at lowering blood glucose hence reducing complications that would result due to poor control of glycemia or lack thereof (Babiker & Dubayee, 2017).

As much as some anti-diabetic agents are effective and of great benefit in diabetes management and treatment, some are potentially harmful (Schernthaner & Prischl, 2017) and could as well aggravate the occurrence of complications such as diabetic nephropathy.

Insulin; traditionally, insulin has been found effective in managing diabetics with renal disease (Betônico et al., 2016). It enhances cell use of glucose hence lowering its levels in the blood. Availability of various insulin types such as human regular insulin, aspart, glulisine, lispro, glargine, and Insulin NPH is mainly based on the duration of action they exhibit.

Sulfonylureas: Sulfonylureas stimulate beta cells to release insulin and are indicated for those patients with relatively mild disease and are therefore contraindicated in kidney failure due to some known side effects which include hypoglycemia and gaining weight. The most prescribed sulfonylureas include tolazamide, tolbutamide, glipizide, chlorpropamide, and glyburide even though the use of oral agents has declined as better control is emphasized as a means of delaying the development of late complications.

Glinides/prandial insulin releasers; are insulin-secreting drugs aimed at boosting insulin upon digestion and are taken before meals. This, in turn, reduces after-meals hyperglycemia hence lower inter-prandial hypoglycemia risk and since their half-life is shorter, they are to be

taken before meals (Bailey & Krentz, 2010). **Repaglinide** can be used in any CKD stage and even in hemodialysis due to its potency and its ability to be primarily eliminated in bile. **Nateglinide** however is unadvisable in CKD even though its readily metabolized in the liver as its degradation result in active metabolites which are then excreted by the kidneys. Due to their shorter half-lives, both drugs can produce hypoglycemia, although in lesser magnitudes unlike it is with sulfonylureas.

Metformin: this is a biguanide impairing gluconeogenesis hence lowering glucose production levels in the liver even though it raises glucose uptake by the muscles. Its use is however contraindicated in CKD patients in stages 3, 4, and 5.

Glitazones: Act by increasing the uptake of muscular glucose and fat tissue hence increasing body sensitivity to insulin thus lowering the degree of both fatty acid synthesis and glucose formation. Since it is excreted in stool after its metabolization in the liver, it can be used at all CKD stages. This drug is however contraindicated in heart failure patients as it causes water retention and an increase in body weight as well as fractures such as distal fracture among the female gender. it has been shown to increase cardiovascular and bladder cancer risks in some cases and therefore has been removed from the market.

α-Glycosidase inhibitors act by producing a competitive and reversible inhibition of α-glycosidase in the intestinal microvilli hence slowing complex carbohydrate absorption, therefore, lowering post-prandial hyperglycemia (Bailey & Krentz, 2010). Acarbose inhibits the metabolism of sucrose to glucose and fructose and mono-therapy. These drugs are however contraindicated in patients with eGFR <25 ml/min/173m^2, i.e., Stages 4 and 5 and severe CKD stages even though they don't aid in body weight gain or hypoglycemia. They decrease HBA1C by 0.5- 0.8% (Martínez-Castelao et al., 2012).Can cause side effects, majorly bloating, flatulence, and abdominal cramps.

Dipeptidyl-peptidase 4 inhibitors: (i.e., Gliptins) this is a new group of anti-diabetic agents in T2DM. They work by inhibiting the enzyme dipeptidyl-peptidase IV by lowering the breakdown of the incretin hormones, such as glucagon-like peptide 1 (GLP-1resulting due to ingestion of food thus leading to the production of insulin in a glucose-dependent way. This then lowers the release of glucagon. This group of drugs is prescribed for CKD as it doesn't cause hypoglycemia hence an advantage in this group as they are prone to the hypoglycemic condition. Since some of the drugs in this class are eliminated via the kidneys, dose adjustments are advised in CKD patients whereas others, e.g., linagliptin can be removed through the bile

and live as its half-life is longer and can last within 14 to 18 hours in both CKD and diabetic patients on hemodialysis (Martínez-Castelao et al., 2012).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors

This class of anti-diabetic agents employs glycosuric actions by inhibiting the SGLT2 protein which aids in the reabsorption of glucose in the blood hence forcing the excretion of excess glucose in urine via SGLT1, unlike other anti-diabetic agents which either increase insulin production or elevate insulin sensitivity. Clinical trials have associated SGLT2 inhibitors' use with both preserved kidney function and reduction of albuminuria (Alicic et al., 2019) as well as safety in the control of hyperglycemia. As much as it lowers the reabsorption of filtered glucose and increases glucose loss in urine, it requires a reasonably functioning kidney.

SGLT2-Inhibitors have minimal side effects on hypoglycemia but are prone to side effects such as weight loss, glucosuria, urinary tract infections due to glucose in the urine, reduced blood pressure due to osmotic diuresis, a slight increase in cholesterol, and, in rare cases, diabetic ketoacidosis. Contraindicated in patients with low GFR levels of <45 due to reduced efficacy and increased adverse effects.

Family history/Genetics

The overall risk of DN development may be a result of the interplay of both environmental and genetic/family history factors (Currie et al., 2014).

Due to polygenetic susceptibility, DN disproportionately affects vulnerable diabetics. Genetic polymorphisms may explain familial clustering in diabetic nephropathy (Barbosa J.; Goetz FC; Rich S; Seaquist ER, 2010).

2.2.4. Health system factors

Screening services

CKD screening is an exercise meant to capture kidney-related conditions early enough before progression to irreversible stages. This exercise is increasingly becoming popular in its detection and management making it a major critical exercise to delaying the progression to ESRD and therefore averting mortality related to kidney disease outcomes. Kidney disease is known to occur silently making it hard to be detected at earlier stages. This, therefore, requires that early screening of obesity, hypertension, serum creatinine, and urinary albumin be treated

with utmost seriousness (Sumaili & Cohen, 2010) as it will greatly work towards saving the situation to a larger extent (Whaley-Connell et al., 2011).

Early screening services are important in the prevention of progression to DN among Diabetics. Some studies such as from South Africa, Bosnia, Sri- Lanka, and Malaysia concluded there were poor assessment records of risk factors for DN among diabetic patients. Compared to developed countries, more than 70 percent of diabetic patients had been screened for DN risk factors mainly in the line of management of their condition. In most developing countries such as Kenya, screening for renal disease in at-risk groups is poor (Wagnew et al., 2018b). This situation can be attributed to patient-related factors such as low social class status and ignorance; medical personnel factors such as laxity and ignorance or health system-related such as limited lab facilities, lack of protocol, and guidelines for prevention, detection, and treatment of DN among other T2DM complications.

In a Saudi study, the finding was that DN prevalence was underrated owing to limited screening programs, even though risk factors of DN are similar throughout societies hence a recommendation of screening programs aimed at the prevention of DN among the Saudi population (Al-rubeaan et al., 2014). This is the case in Africa where delayed detection, as well as the scarcity of both screening and diagnostic resources, independently attributed to the highest magnitudes of DN (Wagnew et al., 2018b).

In a CKD screening program in Kinshasa, DRC, 38 percent recorded good control of blood glucose at baseline but during screening, the proportion rose to 63% therefore enough emphasis on the importance of well-trained healthcare personnel in CKD prevention both in rural and urban areas (Sumaili & Cohen, 2010). This clearly emphasizes the importance of trained personnel in the prevention of CKD in cities and in rural areas especially in developing economies such as Kenya.

Diabetic kidney disease screening recommendation is that urinary albumin tests be carried out at least annually and eGFR assessment carried out in all diabetics with comorbid hypertension, T1DM living with DM over 5 years, and all T2DM patients (American Diabetes Association, 2018; Wald et al., 2007).

Cost of diabetes and CKD care

NCDs prevalence is rising in LMICs such as Kenya disproportionately to the entire globe hence a burden to healthcare as a result of the ever-rising double burden of disease (Subramanian et al., 2018).

Diabetes among other non-communicable diseases has burdened the already straining health system in terms of healthcare infrastructure such as diagnostics, medications, and vaccines.

Anti-diabetic and anti-hypertensive agents are expensive especially due to their urgent and constant need with ever-increasing cases of T2DM which in most cases is coupled with various complications such as CKD. In a study to quantify patient payments in receiving NCD services in Kenya's private and public health, yearly costs of drugs were up to 234 dollars in public and up to 418 dollars in private health institutions with dialysis for CKD being among the most expensive (Subramanian et al., 2018).

In a study aimed at determining direct medical costs of T2DM patients with hypertension based on proteinuria levels and progression of DN, normoalbuminuric patients had significantly lowered outpatient and total healthcare costs, that is, inpatient, outpatient, and pharmacy services compared with those in microalbuminuria and macroalbuminuria stages (Nichols et al., 2011). Those progressing to nephropathy incurred higher costs than those who did not progress to DN. Normoalbuminuric patients that got to the microalbuminuric stage experienced high costs of between 37%-41% in cases they progressed from micro- to macroalbuminuria stages of renal disease.

A study in Alberta, Canada, that aimed at determining costs incurred in CKD patient's care, not on dialysis or baseline transplant, concluded that those of low-socioeconomic status, those with increased comorbidities, lower estimated GFR and albuminuria incurred higher costs in hospitalization, medication, ambulatory care and physician costs (Manns et al., 2019).In Kenya, the health system largely depends on tax revenue funding either by National or County governments as well as funding from donors and National Hospital Insurance Fund (NHIF) funded by individual or household contributions, private insurance in addition to out-of-pocket payments before or post service.

NHIF is Kenya's single largest public insurance mandated and operated by the government and available to members of the public individually, families, SMEs, and corporates. Despite the continuous upscale of services by NHIF with aim of universal healthcare coverage (UHC)

(National Hospital Insurance Fund, 2018), there are still loopholes that derail the sector such as in financing, a building block of the healthcare system for example, in purchasing (Munge et al., 2018) of effective, efficient and quality medical equipment such as diagnostics and medications.

Studies have shown that costs incurred by diabetic patients triple compared to those incurred by non-diabetics (Chatterjee et al., 2011; Oyando et al., 2020; Subramanian et al., 2018) coupled with complications, delayed diagnosis, poor or lack of quality care, presence and severity of complications and other comorbid conditions interact hence heightening the costs.

In some situations, many ESRD does not cover non-dialysis dependent patients, that is those with CKD but not ESRD (Webster et al., 2017) to DN among diabetes-comorbid patients. This would force such CKD patients to consider other means of offsetting their health bills such as out-of-pocket payments or private medical insurance plans which may not be affordable.

In Kenya, a minority of the population is privileged to benefit from healthcare. Formal sector staff who have access to health insurance coverage make less than one-fifth of overall employment in Kenya, and this group benefits from the National Hospital Insurance Fund (NHIF) which caters for specific health services whether inpatient or outpatient (Subramanian et al., 2018) such as dialysis, lab works, and medications in public healthcare facilities which is not the case with private healthcare facilities making individual patients resort to other forms of payments such as out-of-pocket or private insurance which in most cases are expensive and unaffordable to the low socio-economic status group.

Adequacy of the healthcare workforce

The healthcare workforce globally suffers an acute shortage with both Asia and Sub-Saharan Africa regions being the most affected as they are low-income economies. This has significantly stalled the realization of some development goals in the global healthcare sector. Kenya, being among the LMIC, is not left out of the health workforce shortage especially in specialized health sectors just as it is in most LIC (Miseda et al., 2017) such as diabetes care.

One of the SDGs' aspirations is the achievement of universal healthcare coverage in which case the number of the healthcare workforce is of great importance. With Kenya's population's vast growth rate of 2.7% and over 46 million people, and a life expectancy of 61.71 years, there is a dire need to raise the healthcare workforce's density in response to population growth (UNICEF, 2015).

Diabetes screening services, on the other hand, have proved to be effective in slowing or rather avoiding both micro-vascular and macro-vascular complications of diabetes (Lund et al., 2009) such as diabetic nephropathy controlled glycemic and blood pressure levels are more important in diabetes care (Shani et al., 2014).

In a study that examined how measures targeted at healthcare staff to improve DM management at various levels were effective, regular nurse interaction, structured recalling and routine care resulted in T2DM care improvement among patients (Renders et al., 2001; Shani et al., 2014).

This intervention of structured patient follow-up and adequate healthcare workforce specializing in diabetes and renal health services, if well utilized in Kenya's healthcare system, would improve quality of life and delay complications resulting from T2DM such as diabetic nephropathy.

Dietary guidelines

The nutritional aspect is effective in the management and treatment of diabetes as well as its complications such as diabetic nephropathy. However, due to controversies and gaps regarding some interventions surrounding nutritional issues, such as protein restrictions among diabetic populations, available clinical practice guidelines have failed to address the issue of dietary management.

Dietary protein restriction among DN patients targeting consumption of 0.8 grams per kilogram of body weight per day for CKD stages 1-5 based on moderate to strong available evidence (Ko et al., 2017a). However, later in 2012, KDIGO guidelines suggested that evidence showing dietary protein intake of less than 0.8 g/kg BW/day to be of benefit in DN was limited (Foundation, 2012b) rather it suggests that reduced protein intake of 0.6-0.8 grams per Kg of body weight per day, as well as the introduction of high biologic value protein of between 25% -50%, would be an effective intervention as suggested by other experts.

As much as these guidelines on dietary requirements for diabetic and CKD patients are available, it faces challenges of intervention and provision for example access to nutritional counseling, access to and affordability of the recommended dietary food items, preparation in some cases, quantity and quality, and therefore need to assess on this important factor.

2.3. Problem Statement

Type 2 Diabetes Mellitus is the leading cause of CKD globally affecting 90%-95% of the diabetic population (Alicic et al., 2017; WHO, 2019). It is highly associated with diabetic

nephropathy (DN) occurrence (Umanath & Lewis, 2018), a complication of diabetes clinically characterized by increased urinary albumin (>30mg/d) and/or lowered glomerular filtration rate (eGFR<60ml/min/1.73^2 (Gheith et al., 2016) or both. These increased levels of albumin and decreased GFR impair blood vessels rendering the kidneys less efficient hence result in renal failure hence the need for renal replacement therapies (RRTs) such as dialysis or kidney transplant that are known to be generally expensive. DN is the leading cause of ESRD affecting 10%-20% of T2DM patients worldwide (Hoogeveen, 2022; Sharaf et al., 2017).

DN disproportionately affects people of low socioeconomic status, probably because this group tends not to afford early diabetes complications screening services (Kumar & Hospital, 2018). The high cost and adherence to the use of anti-hyperglycemic and anti-hypertensive agents (Mwangi, 2017), long duration of diabetes, and poor health behavior practices such as smoking, harmful use of alcohol, physical inactivity, unhealthy diets required for diabetes and CKD management play a role in DN development and progression hence a comparatively high risk of disease among this population globally and in Kenya.

The costs of treating DN complication is way higher for governments as well as individuals and families globally more so in Africa (Tesfaye & Gill, 2011), and therefore necessary that in Kenya, the focus be shifted to the prevention of known risk factors of development and progression of DN among T2DM patients. This could help slow development and progression reducing the need for renal therapy and hence minimizing the burden on the already strained healthcare system (Haileamlak, 2018).

Despite available studies having explored and associated the most common risk factors such as socio-demographic, behavioral, and medical history/biomedical factors to DN, these risk factors vary across populations (Hintsa et al., 2017a; Noubiap et al., 2015), and therefore need to undertake this study, especially in Kenya as no research specifically on diabetic nephropathy risk factors, to the best of our knowledge exists and therefore need to fill this knowledge gap. Furthermore, this study findings will inform policy for redesigning prevention programs for T2DM related DN complication. This would result in averting the DN-related mortality standing at half a million annually (WHO, 2019). The outcome would lead to a reduction in DN prevalence currently between 39%-54.5% (Otieno et al., 2020; S. Nyamai, 2014) hence reduced healthcare burden in terms of costs incurred in renal replacement therapies associated with diabetic nephropathy and thus improved quality of life among T2DM population.

2.4. Theoretical and Conceptual frameworks

2.4.1. Theoretical framework

To achieve this study's objective, the ecological perspective model was employed to measure and achieve the study objectives. The objectives sought to determine the demographic, behavioral, medical history/biomedical, and health system factors that lead to the development and progression of diabetic nephropathy among T2DM patients. This model was necessary because it emphasizes how an individual's health is affected by interplay and interdependence of factors within and across all levels of a health problem (Glanz & Rimer, 2005) such as **individual/intrapersonal** factors such as sex, age, income, education, residential area, individual health behaviors such as physical activity, control of hypertension and blood glucose and clinical status such as hypertension, duration of diabetes morbidity, body weight, HBA1C level; **interpersonal factors** e.g. social support, family dietary and feeding patterns, peer influence to Smoking and harmful use of alcohol, family influence on use of herbal medicine; **institutional/organizational factors** such as screening of diabetes complications, consultation costs, patient follow-up services, availability and adequacy of healthcare providers; **community level factors** e.g. access to the Diabetic clinic, community assessment, linkage and referral of T2DM patients and **public policy factors** e.g., insurance coverage, access to drugs and other diabetes commodities, standardization of blood glucose and definition of herbal medicines and alternative medicines and regulation of food labelling (Ministry of Health, 2015).

Theoretical framework

Source: Centers for disease prevention and control (CDC)

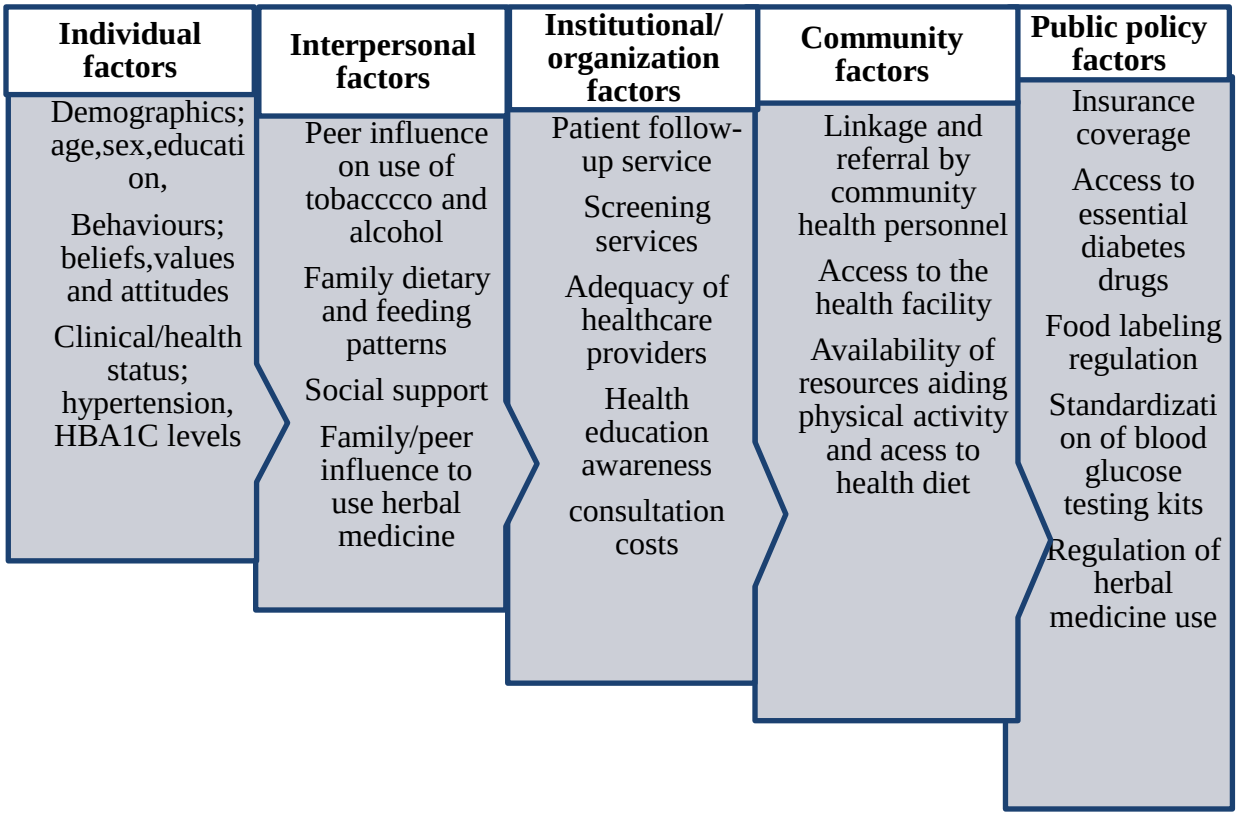

Figure 2: Ecological model perspective

2.4.2. Conceptual framework

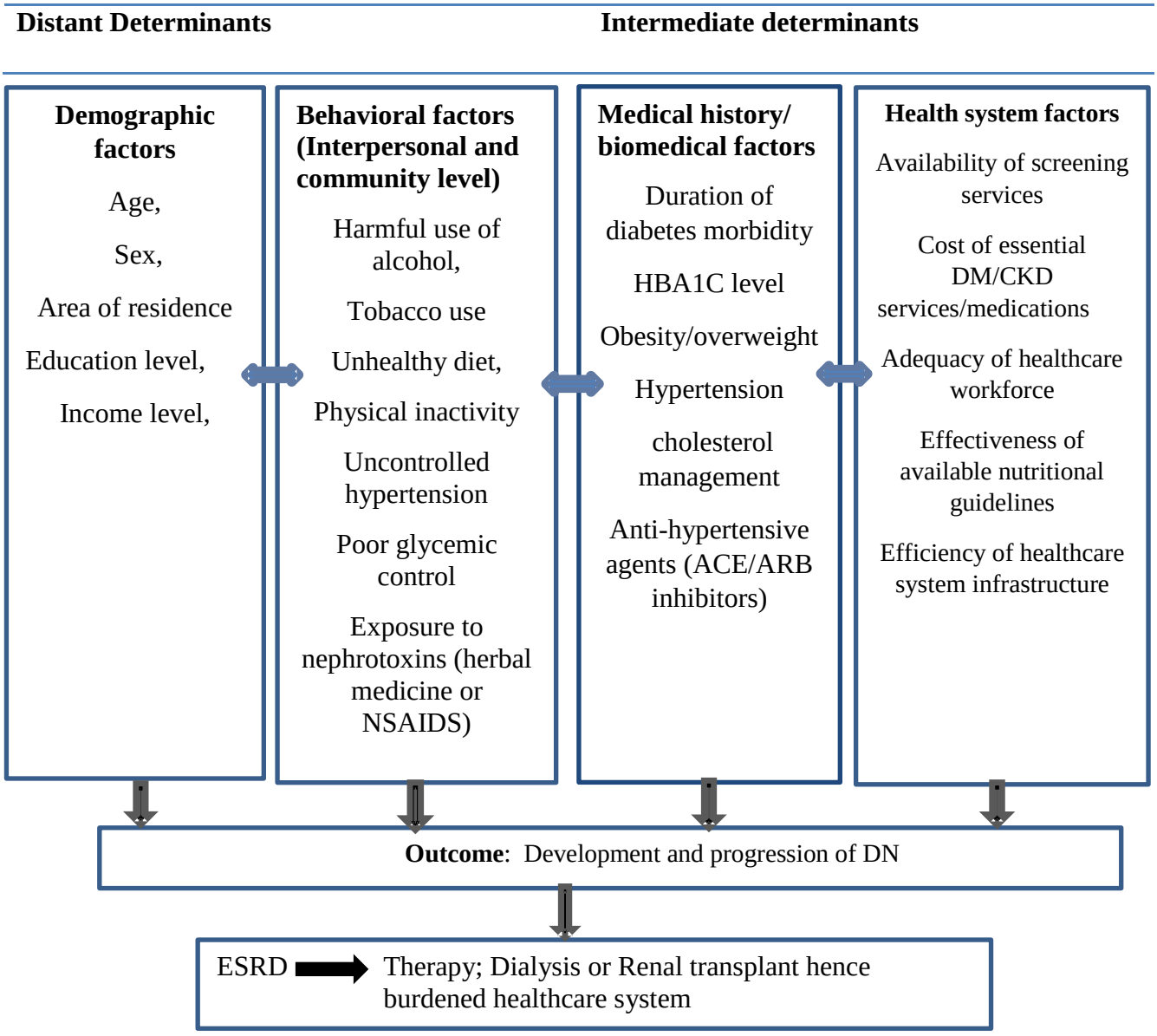

Figure 3: Conceptual framework

Source: Adopted from CDC ecological perspective model

2.5. Research Questions

1. Is there an association between individual socio-demographic factors and the development of diabetic nephropathy?
2. Is there an association between behavioral factors and the development of diabetic nephropathy?
3. Is there an association between medical history and biomedical factors and the development of diabetic nephropathy?
4. Is there an association between health system factors and the development and progression of diabetic nephropathy?

2.6. Study objectives

2.6.1. Broad objectives

To identify determinants of diabetic nephropathy among adult type 2 diabetic patients attending Kenyatta National Hospital Diabetic clinic.

2.6.2. Specific objectives

1. To identify socio-demographic determinants of diabetic nephropathy
2. To identify behavioral factors associated with the development of diabetic nephropathy
3. To identify medical history/biomedical factors associated with the development of diabetic nephropathy
4. To assess health system factors associated with the development and progression of diabetic nephropathy.

CHAPTER THREE

METHODOLOGY

3.1. Study design

This was an unmatched hospital-based case-control study with both cases and controls being obtained from the hospital.

3.2. Study area

The Kenyatta National Hospital, one of Kenya's referral and training institutions was the study site. KNH acts as the largest referral hospital in East and Central Africa offering a varied array of services ranging from in-patient to out-patient services including specialized services such as renal, diabetic, and cancer among others. The study took place in the diabetic clinic at The Kenyatta National Hospital. The majority of the patients attending this clinic come from Nairobi County and others from various parts of Kenya as referral cases for management by specialists. The patients are usually clinically and physically assessed during the visits by the clinicians and consultants among other healthcare providers within the clinic. The clinic visits are on Monday, Tuesday, Wednesday, Thursday, and Friday with an average of 50 patients on each of these days. This facility was chosen because of its outstanding provision of specialized healthcare services hence the participants of the study were conveniently identified.

3.3. Study Population

The potential study Population was diabetics attending the KNH diabetes clinic. Both case and control groups were selected from this population based on eligibility criteria for both case and control groups as defined below;

3.3.1. Case definition

The case patient was an adult type 2 diabetic patient > 18 years with established DN and primary cause being T2DM with urinary albumin of >300mg/g based on positive dipstick urinalysis test and persistent proteinuria (+1) for at least 6 months or eGFR of <60ml/min/1.73m2 ascertained by clinical records (Wang et al., 2019b).

3.3.2. Control definition

Adult type 2 diabetic patients $\geq$ 18 years of age without established T2DM-related DN as in the case of case-patients defined above.

3.4. Eligibility criteria

Inclusion-DM Patients with established DN for cases, free from DN for controls, willing to give consent, and should have been following care at KNH Diabetic clinic and clinical records available.

Exclusion- DM patients who couldn't consent for both controls and cases. Those patients whose clinical records were unavailable and expectant women, evidenced by an ante-natal clinic report/booklet for evidence of a positive pregnancy test.

3.5. Sampling

3.5.1. Determination of sample size

CDC Open Epi statistical software was used to determine the study sample size with 95% CI, power at 80%, a case-to-control ratio of 3, P_2 of 0.46, and OR=2.

According to Kelsey et.al, the formula is;

$$\mathbf{n_1} = [(Z_\alpha + Z_\beta)^2 \bar{p}\bar{q}(r+1)] / r(p_1-p_2)^2$$

$$\mathbf{p_1} = p_2 OR / 1 + p_2(OR-1)$$

$$\bar{\mathbf{p}} = [p_1 + rp_2]/r+1$$

$$\bar{\mathbf{q}} = 1 - \bar{p}$$

$$\mathbf{n_2} = rn_1$$

whereby; $\mathbf{n_1}$= number of diabetic nephropathy cases; $\mathbf{n_2}$= number of controls, diabetic patients without DN; $\mathbf{p_1}$= the proportion of DN cases; $\mathbf{p_2}$= proportion of controls exposed which is at 54.5% prevalence of DN in Kenya according to a recent study (S. Nyamai, 2014); $\mathbf{z_\alpha}$ =confidence level set at 95 % (1.96); $\mathbf{z_\beta}$= value of desired power at 80% (-0.84); r= 3 as the specified ratio of cases to controls and **OR**= 2.0 (universally accepted).

Hence, a **sample size** of 395 participants; 99 cases, and 296 controls as computed by Open-Epi open-source calculator, version 3.

3.5.2. Sampling procedure

A review of patient records was made to identify cases and controls. Considering that the KNH Diabetic clinic attends to at least 50 diabetic patients on average per day, to attain the required sample size, all cases meeting the aforementioned case definition seeking care at the clinic

were recruited into this study within the study period. Controls were patients within the Diabetic clinic without DN ascertained from patient records. They were recruited based on systematic random sampling to attain the desired number of controls of 296. This was computed by calculating an interval, i.e., the k^{th} individual was selected. KNH Diabetic clinic on average serves approximately 500 patients monthly and since our study period is anticipated to run for 3 months, the total population would be 1500 patients. Therefore, the K^{th} was obtained by dividing the total population within 3 months of study (N=1500) by the number of controls (n=296) making the K interval every 5^{th} patient in the control group.

K= N/n; k=1500/296=5.0675675…. $k^{th} = 5^{th}$

A random number was picked between the start and the interval (1^{st} -5^{th} control patient) for a start and sampling interval (5) was repeatedly added to the subsequent control patient, i.e., in this case, the start was the 2^{nd} patient reporting to the triage, after which 5 was added making it the 7^{th} patient, therefore, the 2^{nd}, 7^{th}, 12^{th},17^{th}, 22^{nd},27^{th}, …. 296 controls.

3.6. Study Variables and their measurement

The **response** variable in this study was diabetic nephropathy (DN), which is a binary variable indicating DN present or DN absent.

The predictor variables of this study were demographic, behavioral, biomedical, and health system factors. **Demographic factors** included age, sex, marital status, income level, education level, and occupation status. **Behavioral factors** included diet adherence, alcohol use, tobacco use, uncontrolled hypertension, uncontrolled glycemia, and the use of herbal medicine. **Medical history and biomedical factors** included BMI, HBA1C level, glomerular filtration rate (GFR), duration of diabetes morbidity, use of anti-diabetic agents, and use of antihypertensive agents (ACE/ARBs**)**. **Health system factors** included insurance cover (NHIF), Cost of healthcare services, availability of screening services, Adequacy of healthcare staff, and Patient follow-up services.

Table 1: Study variables

Variable	Method of measurement
Demographic factors	
Diabetic nephropathy (nominal) (outcome variable	Measured based on patient files and was a binary variable, i.e., presence or absence of DN
Age (continuous)	Captured in complete years
Sex (nominal)	Binary variable, either male or female
Area of residence (nominal)	the assessment was in two levels, i.e., urban or rural
Education level (ordinal)	Based on the highest education attainment level, i.e., None, primary, secondary or tertiary levels
Marital status (nominal)	The assessment was on three levels, single, married, and Others (divorced, widowed, separated)
Employment status	Assessed in two levels, i.e., *Employed* (at least Ksh.30,000income per month or *Unemployed* (Less than Ksh.30,000 income per month)
Behavioral factors	
History of alcohol (ordinal)	Was assessed on two levels; *YES*- positive history of alcohol use *NO*- has never consumed alcohol in their lifetime
History of tobacco use (ordinal)	Was assessed on two levels; *YES*- current or former smoker *NO*- has never used any form of tobacco in their lifetime
Glycemic control (ordinal)	Target- HBA1C less than 7% to curtail or slow the progression of microvascular complications of diabetes such as diabetic nephropathy prevent *(<7%) Proper control of glycemia*- monitoring of blood glucose at home, HBA1C test at least once in 6months, use of and adherence to antidiabetic agents. *(>7%) Poor control of glycemia*- lack of monitoring of blood glucose at home, lack of HBA1C test at least once in 6 months, and non-use of and non-adherence to anti-diabetic agents

Control of hypertension (ordinal)	Target BP less than or equal to 130/80mmHg; hypertension defined as BP >140/90mmHg *Well-controlled hypertension*- regular monitoring of BP at home and use of anti-hypertensive agents as prescribed by the physician. *Poor-controlled hypertension* - lack of regular Bp monitoring at home and non-use of or non-adherence to antihypertensive agents or Bp $\geq$ DBP of 140; SBP of 90
Adherence to a healthy diabetic diet (ordinal)	Was assessed on two levels; *(YES) Adherence*-having the recommended number of meals a day, a balanced diet, taking the right amount of recommended food products such as proteins (eggs, white meat, red meat, processed meat (sausages, smokies, bacon) legumes, starch (rice, ugali, wheat products, sweet and Irish potatoes, fruits and vegetables, sodium (table salt) *(NO) Non-adherence*- having less than recommended meals a day, a non-balanced diet, not taking the recommended amount of food products such as proteins (eggs, white meat, red meat, processed meat (sausages, smokies, bacon) legumes, starch (rice, ugali, wheat products, sweet and Irish potatoes, fruits and vegetables or excess intake of sodium (table salt), i.e., more than 1.5gm in a day
Exposure to nephrotoxins i.e., Herbal medicine/NSAIDs use (nominal)	WHO definition; "herbs, herbal materials, herbal preparations, and finished herbal products that contain whole plants, parts of plants, or other plant materials, including leaves, bark, berries, flowers, and roots, and/or their extracts as active ingredients intended for human therapeutic use". NSAIDs include any drug used as an anti-inflammatory, analgesic, and antipyretic. This was assessed on two levels; *Exposed*-this means the use of any form of herbal medicine/NSAID *Not exposed*- lack of use of any form of herbal medicine/NSAID
Medical history and biomedical factors	

Duration of diabetes morbidity (ordinal)	Defined as the period a patient has been diabetic since diagnosis of T2DM and assessed in years based on patient self-reporting and confirmed from patient records. More than 10 years; less than 10 years.
BMI (Body Mass Index)	This will be assessed in three standard levels; Underweight (<18. 5%), Normal weight (18.5-24.9), Overweight (≥25)
Use of ARB/ACE anti-hypertensive agents (nominal)	Was assessed in two levels, i.e., use or non-use as well as adherence and non-adherence. *Adherence*-strict compliance with drug prescriptions for at least three-quarters of the recommended daily or weekly dose. *Non-adherence*- lack of strict compliance with drug dosage, i.e., less than three-quarters use either daily or weekly.
Cholesterol management (to assess dyslipidemia	Assessed based on triglycerides and HDL levels; *Well-managed* -lowered Triglycerides (<1.7mmol/l) and high HDL (>0.9mmol/l) *Poorly managed* - High triglycerides (>1.7mmol/l) and low HDL (<0.9mmol/l)
Presence of diabetic retinopathy as a complication of T2DM	Was assessed in two levels *Yes* or *no* based on either medical reports and self-reporting
Family history of DN	Assessed in two levels, Yes or No based on patient reporting where a close family member had DN
Health system factors	
Screening services for DM and CKD, general medical costs of DM and CKD, adequacy of healthcare staff, availability and effectiveness of nutritional guidelines in diabetes management	A 2-point Likert scale was used to measure this variable, assessing the participant perception of different healthcare system building blocks (i.e. Financing, healthcare workforce, medical equipment and supplies, HIS, governance, and leadership Agree | Disagree

3.7. Data collection procedure/methods

Prior to data collection, the principal investigator trained two registered nurses at the Diabetic clinic with a diploma qualification in nursing and have at least 2 years of experience working in the Diabetic clinic setting. The training entailed ethical consideration on how to obtain informed consent from the willing participants, reviewing patient records to identify eligibility, the general approach of the questionnaire for thorough completion as well as the abstraction of data tools to capture medical history, the biomedical aspect of the study. Patient records were reviewed to identify those who fitted the case and control definitions. A structured questionnaire, in form of ODK (Open Data Kit) partly adopted from the WHO STEPS survey in Kenya, (MoH-Kenya, 2015) was administered in a language understood by the participant.

3.8. Recruitment and consenting of study participants

Study participants were recruited with the assistance of two hospital-based research assistants as mentioned above.

Data on study participants, that is adult DM patients was collected 4 days a week since clinic days are on Mondays, Tuesdays, Thursdays, and Fridays for three months. This was done within the Diabetic clinic in a spacious enclosed room to ensure privacy and confidentiality. DM type was first identified by the researcher by checking through the patient's file/ prescription for evidence of oral hypoglycemic drugs after which, if present, evidence of DN evidenced by UA > 300mg/g based on recent positive dipstick urinalysis test and persistent proteinuria for at least 6 months was checked and eGFR of below 60. The researcher then gave eligibility information, study purpose, and study procedure as well as addressed any concerns of the potential study participant before obtaining consent. The diabetic patients that consented were interviewed (Appendix 2) after understanding, agreeing, and signing the consent form.

3.9. Training of research assistants

Given that case-control studies are prone to several biases such as interviewer and instrument biases that may affect study findings, attempts to minimize them were deliberately made by training research assistants on sound interview techniques.

3.10. Quality assurance

This being a quantitative study, a questionnaire was developed and before the actual study, pilot testing was carried out to validate and clarify the tool as well as training of research assistants.

3.11. Ethical considerations

Permission from the KNH-UON Ethics Research Committee was sought before undertaking this study. Permission from KNH management was also sought. Informed and signed consent was sought from study subjects before recruitment into the study and confidentiality was maintained throughout the study.

With the current COVID-19 pandemic, safety was ensured by the researchers and other study participants by strictly adhering to the ministry of health guidelines and directives on the prevention of COVID-19. This was done by researchers putting on the standard protective gear i.e., gown, facemask, face shield, disposable latex gloves, disposable aprons, handwashing, or hand sanitizing before and after interviewing study participants, keeping a safe distance of at least 1.5 meters where possible, sanitizing before touching patient files.

3.12. Data processing, analysis, and presentation

Prior to data collection, the questionnaire and abstraction tool were assessed for completeness and accuracy. After collection and abstraction, data cleaning, coding, and entering into a Microsoft Excel spreadsheet were done and then exported to SPSS vs 27 for data analysis.

Descriptive statistics were used in summarizing data for continuous variables, which include mean, median, standard deviations, and interquartile ranges. For categorical variables, the generation of descriptive data was done using percentages and proportions in data analysis.

logistic regression analyses were then carried out in two stages, that is, Univariable analysis for determining the association between specific predictor variables (sociodemographic, behavioral, medical history/biomedical factors, and health system factors) on odds of the outcome, that is, diabetic nephropathy at P-value (P=<0.2) (Dohoo et al., 2012). Variables that showed statistical significance in the univariable analysis stage were then fitted into a multivariable logistic regression model then backward elimination was adopted to remove variables with a p-value of greater than 5 % (p=>0.05). Non-significant variables with more than 30% effect in regression coefficients of the remaining variables upon exclusion (Dohoo et al.,2012) were eliminated from the model. In the final model, 2-way interaction fitting was done on the variables that remained to assess their significance. Data was then presented in tables and figures bearing cORs, aOR, and P-Values.

3.13. Study results and dissemination plan

The results are to be orally presented to a panel before publishing in a scientific journal. After publication, the results will be shared with stakeholders to inform policy on matters of diabetic management and care which would, in turn, reduce diabetes complications such as diabetic nephropathy hence cushioning the Kenyan healthcare system as well as the patients and families affected.

3.14. Study limitations and mitigation

In this study, the participants were strictly T2DM patients seeking care at the KNH Diabetic clinic which might limit the generalizability of the study results as well as exclude participants who might not be following care at this institution is a hospital-based study unlike if it had been a population-based study.

Case-control studies are subject to biases such as recall, selection, interviewer, and information biases. These biases were minimized by training research assistants hence minimizing interviewer bias, ascertainment of medical records hence minimization of information, and recall and selection biases were minimized by clear and specific case and control definitions.

CHAPTER FOUR

RESULTS

4.1. Descriptive statistics of the study

From adult type 2 diabetic patients attending KNH, a sample of 395 participants were enrolled in this study that aimed at looking into determinants of diabetic nephropathy among adult type 2 diabetic patients after having been randomly selected and consented. This comprised 99 cases and 296 controls. Below is a flowchart diagram illustrating the recruitment and enrollment process of study participants.

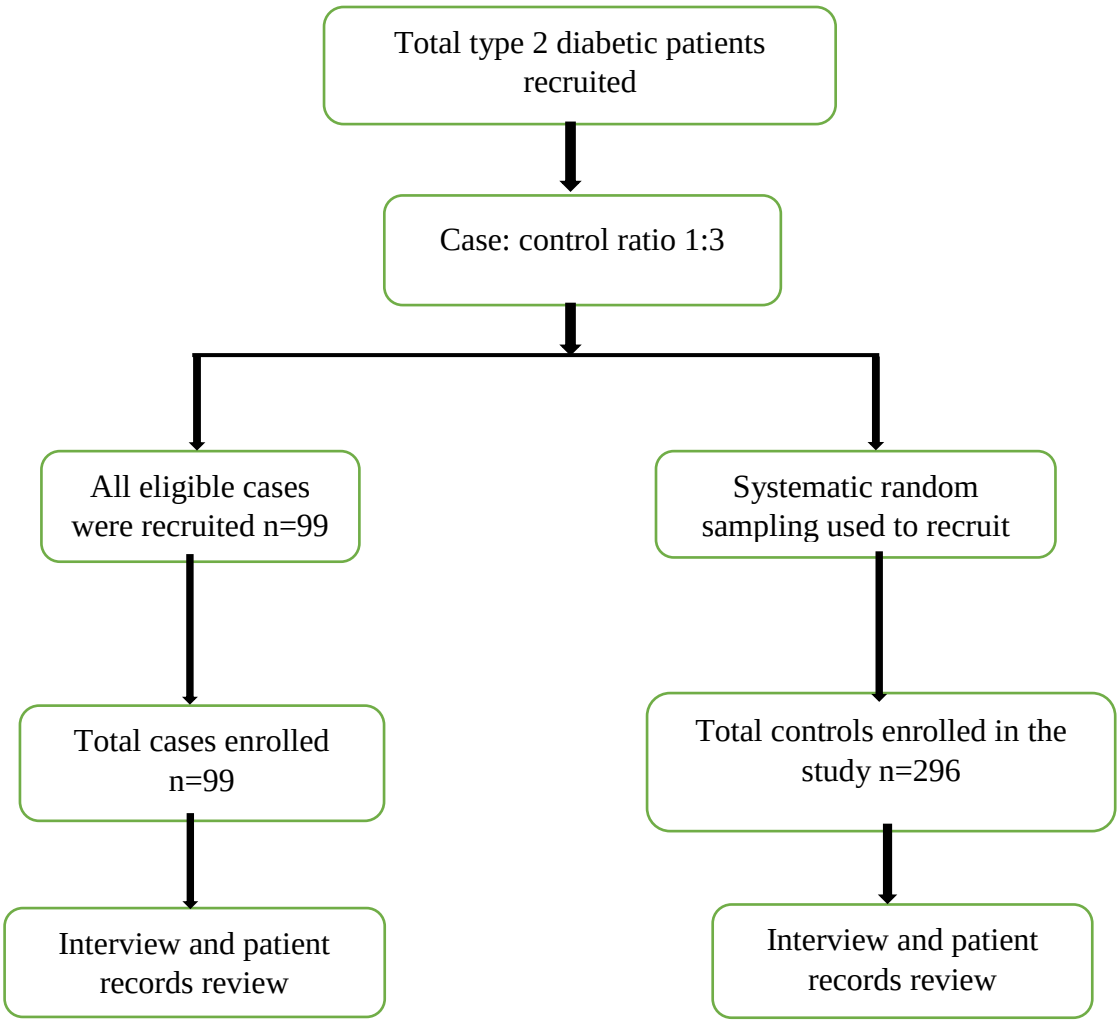

Figure 4:Study Flow Chart

Socio-demographic characteristics

The results of socio-demographic factors indicate that the overall mean age was 62.0 (±SD 10.94). The majority were female 52.9 % (n=209) of which 50.5% (n=50) were cases and 53.7% (n=159) were controls. The majority of the participants resided in urban/peri-urban settings 95.7% (n=378) of which 97.0% (n=96) were cases and 95.3% (n=282) were controls. The majority of the study participants, 58.4% (n=231), had up to a tertiary level of education of which 53.5 % (n=53) were cases and 60.1% (n=178) were controls. The majority of the participants, 96.2% (n=380), were married of which, 100% (n=99) were cases and 94.9 (n=281) were controls. The majority of participants, 71.4% (n=282), were unemployed with less than Ksh.30,000 monthly income. 66.7% (n=66) were cases and 73.0% (n=216) were controls.

Behavioral factors

Among the study participants, 22.5% (n=89) had a **history of alcohol use** of which 26.3% (n=26) were cases and 21.3% (n=63) were controls. **Regarding tobacco use, 12.7% (n=50)** had a history of tobacco use of which 14.1% (n=14) were cases and 12.2% (n= 36) were controls. Regarding **glycemic control,** 27.3% (n=108) had well-controlled glycemia in which case 23.2% (n=23) were cases and 28.7% (n=85) were controls. **Concerning Bp management,** 31.3% (n=31) of cases, and 57.1% (n=169) of controls had well-managed BP. Regarding **healthy diet and diabetic diet adherence**, 87.9% (n=87) of cases and 75.3% (n=223) of controls adhered. Regarding **exposure to nephrotoxins**, that is herbal medicines and NSAIDs, 23.2% (n=23) of cases and 3.0% (n=9) of controls were exposed.

Medical history and biomedical factors

Slightly more than half of the study participants, 56.2 % (n=222) had lived with type 2 diabetes for more than 10 years since its diagnosis of which 89.9 % (n=89) were cases and 44.9 % (n=133) were controls. Concerning the **BMI** (**body mass index**), 35.4% (n=35) of cases and 33.8% (n=100) of controls were overweight/obese. Regarding **ACE/ARB use**, the majority of the participants, 99.0% (n=98) of cases and 87.5% (n=259) of controls reported use. Concerning **cholesterol management**, the majority of the study participants, 82.8% (n=82) of cases and 84.8% (n=251) of controls had well-managed cholesterol. Although a majority of the study participants having no complications of DM, **diabetic retinopathy** was common among those that had complications with 15.2% (n=15) of cases and 15.1% (n=15) of controls having it. **Regarding the family history** of DN, 37.4% (n=37) of cases and 3.0% (n=9) of controls reported positive history.

Healthcare system factors

Regarding Staff adequacy, the majority of the study participants, 98.0% (n=97) of cases and 94.3% (n=279) of controls perceived that healthcare staff in the clinic were adequate, that is, they were able to serve them as expected. On **Nutritional guidelines,** only a few of the study participants, almost a quarter, 48.5% (n=48) of cases and 10.8% (n=32) of controls perceived that available nutritional guidelines for diabetics were ineffective in delaying complications of type 2 diabetes such as diabetic nephropathy. **Regarding healthcare system efficiency,** the majority of cases, 97.0% (n=96) and 85.8% (n=254) of controls disagreed that it was efficient and effective.

Table 2: Descriptive characteristics of Type 2 diabetic patients attending KNH

	(n)	Cases	Controls
Age, *mean (SD)*	395	62.0 (10.9)	53.9 (13.4)
Sex, *n (%)*			
Male	186	49 (49.5)	137 (46.3)
Female	209	50 (50.5)	159 (53.7)
Residence, n (%)			
Urban	378	96 (97.0)	282 (95.3)
Rural	17	3 (3.0)	14 (4.7)
Education, *n (%)*			
None	39	12 (12.1)	27 (9.1)
Primary	48	17 (17.2)	31 (10.5)
Secondary	77	17 (17.2)	60 (20.3)
Tertiary	231	53 (53.5)	178 (60.1)
Marital status, *n (%)*			
Married	380	99 (100.0)	281 (94.9)
Single	4	0 (0.0)	4 (1.4)
Other	11	0 (0.0)	11 (3.7)
Employment status *n (%)*			
Unemployed (≤30K)	282	66 (66.7)	216 (73.0)
Employed (>30K)	113	33 (33.3)	80 (27.0)
Behavioral factors			
History of alcohol, *n (%)*			

Yes	89	26 (26.3)	63 (21.3)
No	306	73 (73.7)	233 (78.7)
History of tobacco, *n (%)*			
Yes	50	14 (14.1)	36 (12.2)
No	345	85 (85.9)	260 (87.8)
Glycemic control, *n (%)*			
≤7% (well controlled)	108	23 (23.2)	85 (28.7)
>7% (poorly controlled)	287	76 (76.8)	211 (71.3)
BP management, *n (%)*			
Well managed	200	31 (31.3)	169 (57.1)
Poorly managed	195	68 (68.7)	127 (42.9)
Diet Adherence, *n (%)*			
Adherence	310	87 (87.9)	223 (75.3)
Non-adherence	85	12 (12.1)	73 (24.7)
Nephrotoxin exposure, *n (%)*			
Exposed	32	23 (23.2)	9 (3.0)
Not Exposed	363	76 (76.8)	287 (97.0)
Biomedical and medical history factors			
Duration (years) since diagnosis, *n (%)*			
≤10	173	10(10.1)	163 (55.1)
≥10	222	89 (89.9)	133 (44.9)
BMI, *n (%)*			
Underweight	10	5 (5.1)	5 (1.7)

Normal	250	59 (59.6)	191 (64.5)
Overweight/Obese	135	35 (35.4)	100 (33.8)
ACE/ARB Antihypertensive use, *n (%)*			
User	357	98 (99.0)	259 (87.5)
None user	38	1 (1.0)	37 (12.5)
Cholesterol management, *n (%)*			
Well managed	333	82 (82.8)	251 (84.8)
Poorly managed	62	17 (17.2)	45 (15.2)
Diabetic Retinopathy, *n (%)*			
Yes	30	15 (15.2)	15 (5.1)
No	365	84 (84.8)	281 (94.9)
Family history of DN, *n (%)*			
Yes	46	37 (37.4)	9 (3.0)
No	349	62 (62.6)	287 (97.0)
Health system factors			
Staff adequacy *n (%)*			
Agree	376	97 (98.0)	279 (94.3)
Disagree	19	2 (2.0)	17 (5.7)
Nutritional guidelines eff, *n (%)*			
Agree	80	48 (48.5)	32 (10.8)
Disagree	315	51 (51.5)	264 (89.2)

Healthcare system efficiency, *n (%)*			
Agree	45	3 (3.0)	42 (14.2)
Disagree	350	96 (97.0)	254 (85.8)

4. 2. Univariable analysis

Of the **socio-demographic** factors assessed, those that had a significant association with diabetic nephropathy were age (p=<0.001). Concerning **behavioral factors** well-managed BP (p=0.001, diabetic diet adherence (p=0.010), and exposure to nephrotoxins (p=<0.001) were significantly associated with diabetic nephropathy. Of the **biomedical and medical history factors** assessed, duration of more than ten years of living with diabetes since its diagnosis (p=<0.001), ACE/ARB inhibitors use (p=0.010), diabetic retinopathy as DM complication (p=<0.001), and positive family history of diabetic nephropathy (p=<0.001) were significantly associated with diabetic nephropathy. Of the **healthcare system** factors assessed, the perception that diabetic nutritional guidelines are ineffective (p=<0.001), and the perception that the healthcare system is inefficient (p=0.006) in slowing the development and progression of DN were significant. (Table 3)

Table 3: Univariable analysis

DM patients (n)	**COR**	**95% CI**		**p-value**
		Lower	**Upper**	
Age, *mean (SD)**	1.05	1.03 – 1.07		<0.001
History of alcohol, *n (%)*				
Yes	1.32	0.78 – 2.23		0.306
No	Reference			
Glycemic control HBA1c				
Well managed glycemia	0.75	0.44 – 1.28		0.290
Poorly managed glycemia	Reference			
BP management*				

Well managed	0.34	0.21 – 0.56	<0.001
Not well managed	Reference		
Diet Adherence, *n (%)* *			
Adherence	2.37	1.23 – 4.59	0.010
Non-adherence	Reference		
Nephrotoxin exposure, *n (%)* *			
Exposed	9.65	4.29 – 21.72	<0.001
Not Exposed	Reference		
Duration since diagnosis*			
≤10	0.09	0.05 – 0.18	<0.001
>10	Reference		
ACE/ARB use*			
User	14.0	1.90 – 103.43	0.010
None user	Reference	-	
Diabetic retinopathy*			
Present	3.35	2.44 – 18.37	<0.001
Absent	Reference	-	
Family history of DN, *n (%)* *			
Yes	19.03	8.74 – 41.45	<0.001
No	Reference	-	
Nutritional guidelines eff, *n (%)* *			
Agree	Reference	-	
Disagree	7.77	4.53–13.30	<0.001

Healthcare Syst. Efficiency*			
Agree	Reference	-	
Disagree	5.29	1.60 – 17.47	0.006

***Variables to be included in the multivariable model (p=≤0.2)**

4.3. Multivariable analysis

From the multivariable analysis, well-managed BP nephrotoxin exposure, duration since diagnosis of DM, family history of DN, the perception that nutritional guidelines are ineffective in delaying the development and progression of DN, and the perception that the healthcare system at KNH is inefficient were found to be statistically significant at 5 % significance level (Table 4).

The exclusion of non-significant variables from the model did not cause a change of more than 30% in the regression coefficients of the variables that remained.

In comparison, DM patient participants with well-managed BP had 0.43 times (OR=0.43;95% CI 0.20-0.91) less likelihood of developing DN unlike those with poorly managed BP, after controlling for nephrotoxin exposure, duration since diagnosis of DM, family history of DN, the ineffectiveness of nutritional guidelines and the inefficiency of healthcare system.

Compared to participants who were not exposed to nephrotoxins, those exposed to nephrotoxins had 10.04 odds (OR=10.4; 95% CI 3.15-31.96) of DN after controlling for BP management, duration since diagnosis of DM, family history of DN, availability of nutritional guidelines, and the efficiency of medical infrastructure.

The participants with less than 10 years after diagnosis of DM had 0.06 odds of DN (OR=0.06; 95% CI 0.02-0.19) in comparison to those with a duration of more than 10 years since diagnosis of DM controlling for BP management, nephrotoxin exposure, family history of DN, availability of nutritional guidelines and the efficiency of medical infrastructure.

Those with a positive family history of DN had 52.67 odds (OR=52.67; 95% CI: 13.11-211.64) of DN compared to those with absent DN family history controlling for BP management,

exposure to nephrotoxin, duration since diagnosis of DM, availability of nutritional guidelines and the efficiency of medical infrastructure.

Those that disagreed that nutritional guidelines are effective in delaying the development and progression of DN had 17.52 odds (OR=17.52; 95% CI:7.09-43.31) of DN compared to those who agreed, controlling for BP management, nephrotoxin exposure, duration since diagnosis of DM, family history of DN, and the efficiency of medical infrastructure.

Participants who disagreed that the KNH healthcare system is efficient and effective in delaying the development and progression of DN had 57.14 odds (OR=57.14; 95% CI:8.20-398.18) of DN compared to those who agreed, controlling for BP management, exposure to nephrotoxin, duration since diagnosis of DM, family history of DN, and availability of nutritional guidelines.

Table 4: Multivariable analysis

	cOR	**95% CI**		**p-value**	**aOR**	**95% CI**		**p-value**
		lower	**Upper**			**Lower**	**Upper**	
BP management, *n (%)*								
Well managed	0.34	0.21 – 0.56		**<0.001**	0.43	0.20 – 0.91		**0.027**
Poorly managed	Ref							
Nephrotoxin exposure, *n (%)*								
Exposed	9.65	4.29 – 21.72		**<0.001**	10.04	3.15 – 31.96		**<0.001**
Not Exposed	Ref							
Duration (years) since diagnosis, *n (%)*								
≤10	0.09	0.05 – 0.18		**<0.001**	0.06	0.02 – 0.19		**<0.001**
>10	Ref							
Family history of DN, *n (%)*								
Yes	19.03	8.74 – 41.45		**<0.001**	52.67	13.11 – 211.64		**<0.001**

No	Ref	-				
Nutritional guidelines effectiveness, *n (%)*						
Agree	Ref	-				
Disagree	7.77	4.53–13.30	**<0.001**	17.52	7.09 – 43.31	**<0.001**
Healthcare system efficiency, *n (%)*						
Agree	Ref	-				
Disagree	5.29	1.60 – 17.47	**0.006**	57.14	8.20 – 398.18	**<0.001**

*aOR- adjusted Odds ratio

CHAPTER FIVE

DISCUSSION

Well-managed Bp was shown to be protective against DN among adult type 2 diabetic Mellitus patients in this study. Participants with well-managed Bp had 0.43 times lower odds of DN compared to those with poorly-managed Bp (Table 3). This corroborates with other studies (Bentata et al., 2015; Buren et al., 2011; Hintsa et al., 2017; Noubiap JJN et al, 2015; Wagnew et al., 2018). This may be so, since a dense network of blood vessels supplies the nephrons, over time, poorly managed hypertension causes narrowing, weakening, and hardening of arteries around the kidney hence compromised functionality. This in turn makes arteries not able to deliver enough blood to the kidney tissue. High BP on the other hand can be a complication of CKD (Giunti et al., 2006; Muhammad & Nazar, 2014b; van Buren & Toto, 2011).

Nephrotoxin exposure (NSAIDs and/or herbal medicine use history) was found to be highly associated with diabetic nephropathy in the current study with those exposed having 10.04 times the odds of diabetic nephropathy. This finding is in agreement with other findings by (Asif, 2012; Bellucci et al., 2017; Plantinga, L., Grubbs, V., Sarkar, U., Hsu, C.Y., Hedgeman, E., Robinson, B., Saran, R., Geiss, L., Eberhardt, M., Powe, 2011). NSAIDs have been shown to affect COX function and thus suppress the production of prostaglandin which is important in renal failure. This finding is supported by a retrospective cohort study in Taiwan that compared NSAID users and non-users for at least three months and found that users had a higher risk of CKD development (Tsai et al., 2015).

Shorter duration since diagnosis of DM was a protective factor of DN with those having been diabetic for less than 10 years having 0.06 lower odds of developing DN than those with more than 10 years of living with DM. This agrees with an observational study in Ethiopia that found out that a year increase in diabetes morbidity was responsible for DN development by 9 %, this implies that for a 10-year increase in the duration of living with DM, the probability DN development rises as well (Hintsa et al., 2017). This was also observed in a systematic study in Africa that showed that for every year increase in the age of a diabetic, the outcome of DN rose by 3.7%, meaning, after every ten years post DM diagnosis, DN probability rises by 1.43 times, that is, 43% (Noubiap JJN et al, 2015). This could be so because as one ages, the kidneys are weakened and at risk of diabetic complications which are exacerbated by the increase in age.

Family history of DN was found to be strongly associated with DN development with those reporting positive history having 52.67 times higher odds of DN. Diabetic nephropathy, being a long-term DM complication was found to be exacerbated, not only by environmental and behavioral interactions but also by an individual's genetic makeup (Wei et al., 2018). This finding is supported by recent studies that have linked DN development to more than one hundred and fifty genes (Rich, 2018).

DN being one of the chronic complications of DM, nutritional guidelines are important in lowering the odds of DN. The current study found that available nutritional guidelines are ineffective in slowing the development and progression of DN with those disagreeing having 17.52 higher odds of developing diabetic nephropathy. The nephrotoxic diet should be avoided(Kim, 2014) as well as aggressive diet management to delay the progression to diabetic nephropathy is important. Dietary protein and sodium are the most important aspect of nutrition in the management of diabetes in addition to pharmacologic management interventions. This will in turn slow the progression of kidney function decline (Ko et al., 2017). Several studies have shown a few beneficial effects of low-protein diets with improved renal function in diabetic nephropathy patients (Jee et al., 2017; G. S. L. Lee et al., 2005; Mohamed et al., 2013; Aziz et al., 2021).

Healthcare system efficiency was found to be associated with the development of diabetic nephropathy with those perceiving that it is inefficient having 57.14 higher odds of developing DN compared with those that perceived it was efficient. This entails aspects of healthcare infrastructure ranging from financing and healthcare workforce to medical equipment. All these play an integral part in the prevention and management of diabetic complications generally. Early screening, detection, and treatment of the complications such as DN are only possible if the health infrastructure is streamlined, making it effective and efficient (Jones, 2013; Shani et al., 2014; Shannon et al., 2019). Costs due to medicine have been shown to reduce adherence to medication and demand for health services by patients with NCD. A study that was done to determine the costs incurred in healthcare found it was catastrophic and suggested that DM care, especially for those in the lower social whose capacity to pay is limited compared with those in the higher social class be enhanced. This is a concern given that poverty rates in Kenya are high (36.1%) and that only 19 % of Kenya's population has a form of health insurance (Oyando et al., 2020).

After accounting for other variables in the multivariable analysis, age, diabetic diet adherence, ACE/ARB inhibitors use, and diabetic retinopathy were found not to be statistically significant.

Age was found not to be a determinant of diabetic nephropathy in this study. This finding agrees with results from a cross-sectional study in Tehran, Iran that found age not to be statistically significant in the development of diabetic nephropathy (Heydari et al., 2010) and disagrees with several studies that found age to be a significant factor (Abejew et al., 2015; Hintsa et al., 2017; Noubiap JJN et al, 2015; Tefera, 2014).

Diet Adherence was also found not to be a determinant of DN in this study. This finding disagrees with other studies that found diabetic diet adherence to be an important determinant of diabetic nephropathy (Molina et al., 2021) in the way it slows its development and progression

ACE/ARB Antihypertensive has been reported by other studies to be reno-protective with benefits among diabetic patients (Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G & SM, Zhang Z, 2001; Devonald & Karet, 2002) contrary to the findings in this study. This could be explained by the difference in study settings and study participants. The previous studies involved both type I and type II diabetic patients while the current interviewed type ii diabetic patients only.

5.1. Study Limitations

Since the current study was a Case-control design, it is subject to biases such as recall and selection biases. Recall bias might have made the cases overreport on the exposure than the controls hence bias in effect estimates which was minimized by standard training of researchers to ask questions in a similar way for both case and control groups. Selection bias might have occurred as well because the study participants might not have been representative of the general population. Having relied on medical reports in this study, some information might have been erroneously entered.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

6.1. Conclusion

The findings of this study show that none of the socio-demographic factors is associated with diabetic nephropathy among adult type 2 diabetic patients. However, Management of BP and exposure to nephrotoxins were behavioral factors associated with diabetic nephropathy. Among medical history/biomedical factors, those that were associated with diabetic nephropathy were duration since T2DM diagnosis and family history of both DM and DN. Among the healthcare system factors, the ineffectiveness of nutritional guidelines and healthcare system inefficiency were significantly associated with diabetic nephropathy.

6.2. Study Recommendations

From the current study findings, the following recommendations are made with the hope of halting if not reversing trends of diabetic nephropathy as a complication of diabetes among adult type 2 diabetic patients;

Health education and sensitization among type two diabetic patients at KNH on the importance of strict adherence to healthy lifestyle behaviours such as physical activity aimed at improving blood pressure outcomes as well as the adoption of a blood-pressure self-monitoring plan at home in addition to antihypertensive use.

Diabetic patients be sensitized on the importance and benefits of adherence to diabetic and CKD diets with an emphasis on the reduction of dietary sodium and excess protein and encourage diets rich in fruits and vegetables and low in saturated fats. This finding as well is a wake-up call to responsible health institutions to harmonize nutritional guidelines specific to type two diabetic and CKD patients.

Sensitization of diabetic patients on the effects of nephrotoxic products such as NSAIDs and herbal medicine on the kidneys as evidenced by the findings of this study.

Healthcare systems at KNH be made more efficient, effective, and accessible, especially in terms of medical products and equipment as well as increase healthcare workforce capacity to be able to handle specialized cases such as diabetic complications.

Finally, more studies, using more rigorous scientific methods be carried out as case-control studies, as this current study, only provide early clues to inform further research.

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APPENDICES

Appendix 1: Consent Form

Research Title: **Determinants of diabetic nephropathy among adult type 2 diabetic patients attending Diabetic clinic at Kenyatta National Hospital, Kenya**

Introduction

Principal Investigator; Fanis Chemtai Barboi- I am a student from the University of Nairobi pursuing Master of Public Health.

Telephone number- 0718717999

Email- fanschem@gmail.com

You are invited to participate in this investigation. It is crucial that you comprehend why the research is being conducted and what it entails before deciding whether or not to participate.

Study introduction and purpose

The study seeks to identify determinants of diabetic nephropathy among adult type 2 diabetic patients attending the Diabetic clinic at KNH. The results will be used to develop better and more effective diabetes policies by the Ministry of Health and other stakeholders and to help foster management and care among diabetics by delaying the development and progression of Diabetic nephropathy hence reducing the economic burden and improving the quality of living.

Study procedure

The information will be collected using a structured pre-tested questionnaire that will be administered by an investigator who is a health provider and where necessary, your patient records will be reviewed.

Role of participant

As the participant of this study, kindly accord the necessary cooperation by answering the questions as asked according to your own opinion. You are free to ask for clarification and ask for guidance where necessary.

Expected interview duration- upon agreement to be interviewed, it shall take you approximately 15 minutes to respond to the questionnaire.

Benefit - participating in this study attracts no compensation and you will receive the same standard of care as any other client seeking similar services.

Confidentiality

Any personal identifying information will be removed before data storage. Information collected in this survey was secured and kept confidential. The data will then be analyzed to help build an understanding of the determinants of diabetic nephropathy.

Voluntary participation

Taking part in the study is voluntary and therefore you can withdraw at any point in the study. In the event you are unable to read and write, this form was read to you by the investigator and upon consent, your thumbprint was requested.

In a scenario where you have questions and need clarification on any matter relating to this study, feel free to reach the principal investigator via Tel. 0718717999 or E-Mail-fanschem@gmail.com

Please impend your signature below if you agree to undertake this survey;

Participant's signature: ……

Date: …….

Researchers' information

Researcher/Research assistant Signature: ……

Telephone number ……...

Email …….....

Date: …….

KNH-UoN ERC Secretary contacts

Telephone- 2726300 ext. 44102

Email- uonknh_erc@uonbi.ac.ke

Appendix 2: Questionnaire

Research Title: **Determinants of diabetic nephropathy among adult type 2 diabetic patients attending Kenyatta National Hospital, Kenya**

I) Socio-demographic characteristics

S.N.	Questions	Response
1)	Card number	……
2)	Age in years	……. years
3)	Sex	□ Male □ Female
4)	Where do you reside?	□ urban area □ rural area
5)	The highest education level attained	□ None □ Primary education □ secondary education □ Tertiary education
6)	Marital status	□ Single □ Married □ Others (Divorced / Separated/Widowed)
7)	What is your monthly income range? (Ksh.)	□ Less than 30,000 (employed) □ More than 30,000 (unemployed)

II) Behavioral factors

8)	Have you ever consumed alcohol in your lifetime?	□ Yes □ No
9)	Have you ever used any form of tobacco in your lifetime?	□ Yes □ No
10)	Do you have a glucometer for glucose self-monitoring plan at home?	□ Yes □ No

11)	Are you on any high-blood pressure drugs?	□ Yes □ No
12)	If yes, do you have a blood pressure machine for BP self-monitoring at home?	□ Yes □ No
13)	Do you adhere to recommended diabetic diet? *Adherence*-strictly stick to diet always; non-adherence- stick to restriction but not always	□ Yes □ No
14)	Have you ever or do you currently use any form of herbal medicine or NSAIDs (*User*- used herbs/NSAIDs at least thrice in the last 12 months; *non-user*- less than thrice)	□ Yes □ No

III) Biomedical and medical history and factors

15)	For how long have you been diabetic?	□ Less than 10 years □ More than 10 years
16)	Upon diagnosis of T2DM, were you informed of diabetes complications?	□ Yes □ No
17)	Do you have diabetic retinopathy as a complication of DM? (Confirm from records)	□ Yes □ No
18) I	Do you have a family history of diabetic nephropathy?	□ Yes □ No

IV) Health system factors

The Likert scale on Health system factors

Kindly tick **(√)** the box that conforms to your level of agreement concerning the statements below.

19)	Screening for DM complications is important in delaying the development and progression of complications such as DN	□ Agree □ Disagree

20)	Costs incurred during clinic visits and services are high	□ Agree □ Disagree
21)	Generally, diabetes care and management of complications are very expensive	□ Agree □ Disagree
22)	Healthcare workers in this clinic are inadequate/ not enough hence the low quality of service	□ Agree □ Disagree
23)	Available nutritional/dietary guidelines for diabetics are effective in delaying the development and progression of DN	□ Agree □ Disagree
24)	The Healthcare system (test and treatment machinery and equipment) in this hospital is efficient and effective	□ Agree □ Disagree
25)	Anti-diabetic and anti-hypertensive drugs are readily available and affordable in this hospital	□ Agree □ Disagree

Appendix 3: Data Abstraction Tool

To be filled by the research assistant after ascertaining from the study participants' files.

Note: write **NA** (NOT AVAILABLE) if no result/details are available in the patient records/file.

Patient ID			
Biomedical factors			
1.	DN present	□ Yes □ No	
2.	Duration of living with DM		
3.	BMI	Height(cm) ……. Weight (Kgs)……	
4.	HBA1C level		
5.	eGFR level-serum/creatine		
6.	Average FBS		
7.	Blood Pressure	SBP- DBP-	
8.	Medications	Anti-hypertensive agents □ Yes □ No	If yes, list them down 1. ……. 2. ……. 3. …….
		Anti-diabetic agents	List down 1. …….. 2. …….. 3. ……..

9.	Lipid profile	Total Cholesterol HDL-C……. LDL-C…… Triglycerides……...	
10.	Family history of diabetes	Yes No	
11.	Current CKD therapy	RRT Hemodialysis Drugs	Duration ……
12.	Weekly hemodialysis sessions		