The Burden of Chronic Kidney Disease in Ambulant Type 2 Diabetes Patients at Kenyatta National Hospital Diabetes Outpatient Clinics

A dissertation submitted in part fulfillment for the degree of Master of Medicine in Internal Medicine (M.Med Internal Medicine)

University of Nairobi

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2014

DECLARATION

I..... do hereby declare that this research is my original work and has not been presented before to any institution for the purpose of obtaining any award.

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APPROVAL

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ABBREVIATIONS

AKI	Acute Kidney Injury
BMI	Body Mass Index
BP	Blood pressure
CAD	Coronary artery disease
CKD	Chronic kidney disease
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
GFR	Glomerular filtration rate
HDL-C	High Density Lipoprotein Cholesterol
KDOQI	Kidney Diseases Outcomes Quality Initiative
KDIGO	Kidney Disease Improving Global Outcomes
KNH	Kenyatta National Teaching and Referral Hospital
LUTS	Lower urinary tract symptoms
MDRD	Modification of Diet in Renal Disease
NCDs	non-communicable diseases
NHANES	National Health and Nutrition Examination Survey
NSAIDs	Non-steroidal anti-inflammatory drugs
UACR	Urinary Albumin to Creatinine Ratio
UKPDS	United Kingdom Prospective Diabetes Study
UTI	Urinary Tract Infection
WHO	World Health Organisation

ACKNOWLEDGEMENT

There are many people who have by their action or inaction contributed immensely to the creation of this work.

I am especially grateful for the assistance given to me by Prof. C.F. Otieno and Prof. J.K. Kayima whose patience, wisdom and encouragement made this possible.

I thank all the patients who consented to participate in this study, the staff of the diabetes outpatient clinic, and the clinical chemistry department of the University of Nairobi.

I recognize all members of faculty of the department of clinical medicine and therapeutics I am indebted to all registrars, past and present, who have walked this journey.

My parents and sisters who have always believed in me.

My wife Mwende and son Jayden who have always been there when the doubts crept in. You are my pillars.

Thanks be to God. Through Him everything is possible.

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ABSTRACT

Background and Purpose-Chronic Kidney Disease (CKD) affects between 20 to 40% of patients with type 2 diabetes. The burden of chronic kidney disease in our ambulatory patients with type 2 diabetes here in Kenyatta National Hospital is unknown. This study aimed to look at the prevalence of CKD and risk factors associated with CKD in ambulatory type 2 diabetes.

Objective- To determine the prevalence of CKD and diabetes glomerulopathy in ambulant type 2 diabetes patients attending the KNH outpatient diabetes clinics.

Design – A cross-sectional descriptive study.

Setting - Kenyatta National Hospital Diabetes outpatient clinic.

Subjects – Two hundred ambulatory patients with type 2 diabetes, asymptomatic for kidney disease, on follow-up in the outpatient clinic were recruited into the study.

Sampling– Systematic random sampling.

Methods – Patients were recruited into the study by systematic random sampling. History was taken to obtain socio-demographic data, duration of diabetes, smoking habit, occurrence of cardiovascular disease, lower urinary tract symptoms. Physical examination included measurement of weight, height, BP, clinical cardiovascular examination. Their estimated GFR was calculated using the MDRD formula while albuminuria was quantified.

Data management and analyses- Statistical analysis was done using STATA version 12. Descriptive statistics was presented using percentages and frequencies for categorical or nominal data while mean, standard deviation, median, minimum and maximum for continuous/discrete variables. The prevalence of CKD was calculated as the percentage of ambulant type 2 diabetes patients detected to have decreased eGFR and/or albuminuria.

Results –The prevalence of CKD in ambulatory type 2 diabetes patients was found to be 54.5%. Less than half, 45% were found to have diabetic glomerulopathy. 78.5% of the patients were found to have low- to moderate risk of adverse cardiovascular outcome. 21.5% of the patients were found to have a high to very-high risk of adverse cardiovascular outcomes. Age and systolic BP were significantly related to CKD.

Conclusion– There is a high prevalence of CKD in ambulatory asymptomatic type 2 diabetes patients. Over 20% of type 2 diabetes patients with CKD are at a high or very high risk of adverse cardiovascular outcomes. Hypertension is the most important modifiable risk factor for patients with CKD. Risk stratification of patients is important and should be part of routine care to facilitate interventions to mitigate adverse outcomes.

1.0 INTRODUCTION

Of 57 million global deaths in 2008, 36 million were due to non-communicable diseases(NCDs).(1) These were caused primarily by cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes. Even in African nations, NCDs are rapidly rising and are expected to exceed communicable, maternal, perinatal and maternal diseases as the most common causes of death by 2030(1). Diabetes is the fourth commonest non-communicable disease.(1) It is a group of metabolic diseases characterized by hyperglycaemia due to defects in insulin secretion, insulin action or both.(2) Type 2 diabetes accounts for at least 90% of all the cases of diabetes seen worldwide.(3) Christensen et al in 2009 reported the prevalence of diabetes in Kenya to be 4.2%.(4) In a study done in South Africa, Motala A. et al, found a prevalence of 3.9%.(5)

Type 2 diabetes is a major global public health problem with developing countries bearing the largest burden. The diabetes epidemic has increased worldwide due to rise in obesity as a result of rapid urbanization, nutrition transition and increasing sedentary lifestyles.(6) In the past two decades there has been an explosive increase in the number of people diagnosed with diabetes worldwide. The greatest percentage increase will occur in Africa in the next 20 years.(7)According to a report by the International Diabetes Federation,366million people worldwide have diabetes and this number is expected to grow to 552million by the year 2030.(8) According to this report, 80% of people living with diabetes live in low- and middle-income countries with the largest proportion being between the ages of 40 – 59 years. Diabetes caused 4.6 m deaths in 2011 and cost $ 465 billion worldwide.11% of total healthcare expenditure in adults is related to management of diabetes.(9) The management of the complications of diabetes is putting a strain on the health budgets of resource-poor countries. For example a recent estimate in Tanzania showed that treatment of diabetes complications represented 31% of total outpatient costs in the main hospital in Dar es Salaam; with a yearly cost of $138 per person. This was 19 times more than the average outpatient costs per person.(10)

Type 2 diabetes mellitus is associated with a high rate of complications related to cardiovascular disease and diabetic nephropathy, retinopathy, and neuropathy. Chronic kidney disease (CKD) is a devastating complication of diabetes. It has been recognized for a long time that a significant proportion (20%–40%) of all diabetes patients will develop kidney involvement characterized by a progressive urinary loss of albumin and deteriorating creatinine clearance.(11) In type 2 diabetes, nephropathy may be present even at diagnosis. In the UKPDS 64, 6.5% of the patients had microalbuminuria at diagnosis of diabetes.(12) In the presence of kidney involvement,

diabetes—unless treated effectively—runs a relentless course usually ending either in premature cardiovascular events and death or end-stage renal failure requiring renal replacement therapy. An estimated glomerular filtration rate(GFR) of less than 60 ml/minute/1.73 m^2 is associated with a graded increase in the risk of each of the major adverse outcomes of chronic kidney disease, which are impaired kidney function, progression to kidney failure, and premature death caused by cardiovascular disease.(13) The rate of death among patients with type 2 diabetes is approximately twice as high as that among persons without the disorder.(14) In one study of patients enrolled in a health maintenance organization in the USA over a 5 year period, rates of renal replacement therapy were 1.3% and 19.9% for those in stage 3 & 4 chronic kidney disease(CKD) respectively. Corresponding mortality rates were 24.3% &45.7%.(15)

Diabetes nephropathy commonly occurs in tandem with other micro vascular complications. Up to 60% of type 2 diabetes patients with nephropathy have retinopathy.(16) In the Rochester Diabetic Neuropathy study, it was demonstrated that proteinuria as a marker of micro vascular disease is associated with severity of diabetic polyneuropathy.(17) The incidence and severity of coronary artery disease(CAD) increases as GFR decreases.(18) Among adults aged 40 years and above, with estimated GFR<60 ml/min per 1.73 m^2, National Health and Nutrition Examination Survey data from 1999 to 2000 reported a prevalence of peripheral arterial disease of 24%.(19) Stage 3–4 CKD is an independent risk factor for ischemic and hemorrhagic stroke, with a relative risk of approximately 1.4.(20)

In Kenya, diabetic nephropathy is one of the leading causes of end-stage renal disease. It is important to note that apart from diabetic nephropathy, there are other causes of CKD in patients with diabetes. These include age, obesity, hypertension, hyperuricaemia, obstructive uropathy, use of non-steroidal anti-inflammatory drugs, chronic pyelonephritis, ischaemic nephropathy, glomerulopathies, contrast nephropathy, toxic nephropathy e.g. due to herbal medication.

Early-stage CKD is essentially asymptomatic. For patients with diabetes, effective strategy should aim at earlier identification and (where possible) prevention of progression to established renal failure. The challenge is to: identify people with or at risk of developing CKD; determine who will develop progressive kidney disease and or complications of kidney disease and how they may be identified and managed to prevent these outcomes.

Thus in our type 2 diabetes patients conscientious screening is important as it provides opportunity for therapeutic interventions to prevent or delay onset of complications and improve outcomes.

2.0 LITERATURE REVIEW

2.1 Type 2 Diabetes And Chronic Kidney Disease

Between 20-40% of patients with type 2 diabetes will develop kidney disease.(11) This will manifest as either microalbuminuria, albuminuria or reduced glomerular filtration rate. Type 2 diabetes patients with increased urinary albumin excretion suffer increased morbidity and mortality as compared to normoalbumiuric patients. It has been demonstrated that increased urinary albumin excretion, endothelial dysfunction and chronic inflammation are interrelated processes that develop in parallel, progress over time and are strongly and independently associated with increased risk of death in type 2 diabetes patients.(21) Among European patients with type 2 diabetes, those with proteinuria have a fourfold excess of premature death compared with patients without proteinuria.(22) In one study conducted in Canada, the risk of death, myocardial infarction and progression to kidney failure at a given level of estimated glomerular filtration rate(eGFR) were independently increased in individuals with higher levels of proteinuria.(23) In a meta-analysis of 13 cohort studies involving 21,688 patients, every 15ml/min/1.73m^2 decrease in GFR was associated with a 47% increase in the risk of death and a six fold increase in the risk of ESRD. This was noted in subjects with an eGFR<45ml/min/1.73m^2.(24) Prospective studies have shown that diabetes mellitus is a strong independent risk factor for end-stage renal disease (ESRD), even for end-stage renal disease ascribed to causes other than diabetes.(25) Among patients who require dialysis, those with diabetes have a 22% higher mortality at one year and a 15% higher mortality at five years than patients without diabetes.(26)

The presence of CKD in patients with diabetes increases their morbidity due to the presence of other complications. The presence of anemia is strongly predictive of complications and death from cardiovascular causes. An analysis of 4 major studies showed that patients with anemia and CKD were at an increased risk of stroke, myocardial infarction and death.(27) Patients with CKD have altered mineral metabolism and bone structure. This places these patients at increased risk of fractures, hypocalcaemia, cardiovascular calcification and mortality. It is known that patients with diabetes are predisposed to developing adynamic bone disease.(28) The kidneys are involved in the metabolism, degradation, & excretion of thyroid hormones. Among a nationally representative sample of adults, reduced glomerular filtration rate was associated with a higher

prevalence of hypothyroidism, with many subclinical cases.(29) CKD is associated with abnormalities in growth hormone regulation, including changes in its plasma concentration, in the regulation of its release, and in end-organ responsiveness.(30) The kidney normally contributes to the excretion of cortisol and its water soluble metabolites. CKD is associated with prolonged serum half-life of cortisol which possibly contributes to negative nitrogen balance & insulin resistance.

2.2 Chronic Kidney Disease in Diabetes

In clinical practice, the presence of chronic kidney disease (CKD) is defined as a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 and/or kidney damage determined by abnormal findings in urine, such as proteinuria, albuminuria, hematuria, abnormal imaging, and/or histology, lasting for 3 months or more.(31)

Diabetic nephropathy is the commonest cause of CKD in patients with diabetes. The markers of nephropathy include albuminuria and GFR. The Kidney Disease Outcome Quality Initiative (KDOQI) divides chronic kidney disease into five stages.(31) An early clinical marker of renal involvement in patients with type 2 diabetes is microalbuminuria (urinary albumin excretion, 20 to 200 μg per minute or <300mg/24hours). The United Kingdom Prospective Diabetes Study(UKPDS) provides a large amount of data as to the development and progression of nephropathy in type 2 diabetes.(12) At ten years following diagnosis, the prevalence of microalbuminuria, macroalbuminuria, and either an elevated plasma creatinine concentration (defined as ≥ 175 μmol/L) or requirement for renal replacement therapy was 25, 5, and 0.8 %, respectively. Based upon a statistical model, an estimation of the median time spent in each stage without progression to another nephropathy stage was 19, 11, and 10 years for those with no nephropathy, microalbuminuria, and macroalbuminuria, respectively. It is important to note that this was an observation made under strict study conditions. Type 2 diabetes patients with microalbuminuria have a median risk ratio of developing diabetic nephropathy of 8.5.(32)

Locally, P.Ngugi in 1989 found that diabetic nephropathy had a prevalence of 15.8%.(33) Of note he found that the prevalence increased with the duration of illness in type 1 diabetes patients but this was not true for type 2 diabetes patients. In a study done locally in 1994 the prevalence of microalbuminuria in type 2 diabetes was found to be 40.5%.(34) In a review of prevalence and characteristics of complications seen in diabetes patients across Africa, Mbanya JC found the prevalence of nephropathy to be between 32-57%.(35)

The confounding effect of variations in urine volume on the urine albumin concentration can be avoided by calculation of the urine albumin-to-creatinine ratio in an untimed urine specimen. A value 30 to 300 mg/g of creatinine (or, using standard [SI] units, 3.4 to 34 mg/mmol of creatinine) suggests that albumin excretion is between 30 and 300 mg/day and, therefore, that microalbuminuria is probably present.(36) Values above 300 mg/g (or 34 mg/mmol) are indicative of macroalbuminuria.

In one report, 24-hour urine collections and random, single-void urine specimens for albumin and creatinine were obtained in 14 normal subjects, 13 with type 1 diabetes, and 12 with type 2 diabetes.(37) A close correlation was noted between the two measurements and the within-patient variability was very small. A random albumin-to-creatinine ratio above 30 mg/g had a sensitivity of 100 percent for the detection of microalbuminuria.

Another marker of chronic kidney disease is the estimated glomerular filtration rate(eGFR). Accurate measurements of GFR by clearance of exogenous filtrated markers, often is considered too complex and, therefore, surrogate markers such as creatinine are used in clinical practice. Guidelines from the National Kidney Foundation recommend measurement of serum creatinine for practical estimation of the glomerular filtration rate.(38) The Executive summary states that the modification of diet in renal disease study(MDRD) equation provides a useful way of estimation of GFR.eGFR=175 x (serum creatinine in mg/dl)$^{-1.154}$ x (years)$^{-0.203}$ x (0.742 if female) x (1.210 if African-American).(39) On comparing the results of eGFR by MDRD and Cockcroft-Gault(CG) equation,to GFR measured by an isotope reference method, the MDRD was better correlated to GFR than was the CG.(40) There are some limitations to the use of GFR estimation methods. Variability in serum creatinine measurement means these methods are less accurate in the normal and slightly increased range of serum creatinine. These estimation methods have not been validated in patients older than 75 years, patients with serious co-morbidities, extremes of body weight, body size, muscle mass or nutritional status.(40)

2.3 Other Risk Factors For Chronic Kidney Disease In Patients With Type 2 Diabetes

There are other factors which increase the risk of developing CKD in a patient with diabetes. These include older age, gender, race, family history of CKD, obesity, hypertension, obesity, high protein diet, cardiovascular disease, anaemia, dyslipidemia, hyperuricaemia, smoking.

Other factors directly cause or initiate kidney damage in a susceptible individual e.g. nephrotoxic drugs, primary glomerulopathies, urinary tract obstruction.

a) Age

In the 3rd National Health and Nutrition Examination Survey (NHANES III) 68% of individuals aged 70 years and older had CKD in the absence of diabetes and hypertension.(41) A 2005 hospital-based study by Mbogo looking at type 2 diabetes patients with CKD found the mean age of patients studied to be 56.2 years.(42) This suggests that patients with diabetes in our setting are older and therefore this predisposes them to developing CKD.

b) Gender

In diabetes, even though the male sex still appears to be a risk factor, this relationship is not as strong as it is in non-diabetic renal disease. Many studies, however, report that the male sex is still a risk factor for the development of renal disease in diabetes(43) but that the female sex appears to accelerate progression of the disease.(44) The Irbesartan Diabetic Nephropathy trial and RENAAL showed that proteinuria develops more rapidly in women compared with age-matched males.(45,46) Local studies have been hospital based. With limitations of access to care due to socioeconomic status, geographic proximity and referral policy, these studies may not give the true gender proportions of the Kenyan population with CKD.

c) Genetics

The observed incidence patterns in different ethnic and familial clustering have suggested that genetic factors play an important role in the development and progression of diabetic nephropathy. The incidence and severity of diabetic nephropathy has been found to be increased up to 6 fold in African populations compared to Caucasians.(47) The likelihood of developing diabetic nephropathy is markedly increased in patients with a diabetic sibling or parent who has diabetic nephropathy; these observations have been made in both type 1 and type 2 diabetes.(48) In patients with type 2 diabetes, the DD polymorphism of the Angiotensin Converting enzyme gene has been associated with an increased risk for the development of diabetic nephropathy, more severe proteinuria, greater likelihood of progressive renal failure, and mortality on dialysis.(49) Multiple other gene traits have been demonstrated but no local genetic studies have been done.

d) Socioeconomic factors

Krop et al observed that blacks with diabetes were three times more likely to develop CKD in unadjusted analysis.(50) On subsequent adjustment for additional covariates, 6% of the excess risk for development of CKD was explained by income and education levels. Suboptimal health behaviours and poor control of glucose and blood pressure accounted for the majority of the remaining risk. There is a strong relationship between socioeconomic status, health behaviours, and glycemic and hypertensive control, therefore the 6% figure given is an underestimation of the effect of socioeconomic factors.

e) Glycaemic control

In the UKPDS trial a 1% reduction in the HbA1c levels was associated with a 37% decrease in the prevalence of micro vascular complications.(51) In the ADVANCE trial, patients receiving intensive therapy had a reduction in the incidence of nephropathy compared to those receiving standard , with a relative risk reduction of 21%.(52) A local study by Mbogo L. in 2005, found that 57.6% of patients with nephropathy had poor glycaemic control.(42) Otieno C.F. et al, in a study of 305 diabetes patients found only 39.5% achieved a mean HbA1c of less than or equal to 8%.(53) These studies show that glycaemic control in diabetes patients locally is only optimal in a relatively small proportion of patients.

f) Hypertension

In a local study of 100 patients with recently diagnosed type 2 diabetes, Mwendwa F.M., found that 50% of patients were hypertensive.(54) In a series of over 3500 newly diagnosed type 2 diabetes patients, 39 percent were already hypertensive.(55) Analysis of UKPDS showed that every 10 mmHg reduction in systolic BP is associated with a 13% reduction in the risk of micro vascular complications, with the smallest risk among those patients with systolic BP <120 mm Hg.(56)

g) Acute Kidney Injury

Several studies have revealed that recovery from acute kidney injury (AKI) is associated with a substantially increased risk of CKD and death. Thakar CV et al, followed up 4082 patients with diabetes for a period of 10 years. AKI was a significant predictor of stage 4 CKD independent of other major risk factors of kidney disease progression.(57)

h) Obesity

A high body mass index (BMI) has been associated with an increased risk of chronic kidney disease among patients with diabetes.(58) In addition, diet and weight loss may reduce proteinuria and improve kidney function among patients with diabetes.(59) Twahir A. in a study of 112 type 2 diabetes with microalbuminuria, found that 43.7% were obese.(34) In humans, severe obesity is associated with increased renal plasma flow, glomerular hyperfiltration, and albuminuria, abnormalities that are reversed by weight loss.(60)

i) Dyslipidemia

High triglycerides and low High Density lipoprotein Cholesterol (HDL-C) appear to be associated with deterioration in kidney function.(61) Insulin resistance and the ensuing hyperinsulinemia are associated with hypertriglyceridemia and low serum HDL-C concentrations. The Study of Heart and Renal Protection (SHARP) trial demonstrated that lowering of low density lipoprotein cholesterol (LDL-C) slows the progression of nephropathy and reduces cardiovascular events.(62) The ARIC study demonstrated that elevated triglycerides and low HDL-cholesterol predict an increased risk of renal dysfunction.(63)

j) Hyperuricemia

Intype2 diabetic individuals with preserved kidney function, hyperuricemia seems to be an independent risk factor for the development ofincident CKD. A prospective study of type 2 diabetes patients followed up for 5 years demonstrated that hyperuricemia was associated with an increased risk of chronic kidney disease with an adjusted odds ratio of 2.1.(64) There is an association between hyperuricemia and progression of chronic kidney disease.(65) In several population-based studies, hyperuricemia was identified as an independent risk factor for subsequent increase in serum creatinine concentration and development of CKD.(66)

k) Anaemia

Anaemia is common among patients with type 2 diabetes and CKD and greatly contributes to patient outcomes. Anaemia is an independent risk factor for progression of nephropathy to ESRD in type 2 diabetes. In a study of 1513 individuals enrolled in the RENAAL study and followed-up for 3.4 years, for every 1g/dl decrease in hemoglobin levels there was an 11% increase in the relative risk for ESRD.(67)

l) Cardiovascular disease

Cardiovascular disease may exert effect on the kidneys that promote initiation and progression of CKD. In a study of hospitalized medicare beneficiaries, the prevalence of stage 3 or more severe CKD was 60.4% among those with heart failure and 51.7% among those with myocardial infarction. The presence of CKD in addition to heart disease was associated with significant increases in risk of progression to ESRD and risk of death.(68) Insulin resistance, hyperinsulinemia, and elevated blood glucose are associated with atherosclerotic cardiovascular disease. The mean age of patients diagnosed with type 2 diabetes in KNH is 53 years.(54) These patients are at increased risk of developing ischemic renal disease due to atherosclerosis.It has been estimated that ischemic renovascular disease may be responsible for 5 to 22% of patients with advanced renal failure who are over the age of 50.(69)

m) Nephrotoxins

Patients with type 2 diabetes in our setting constitute the elderly population. This predisposes them to degenerative conditions which may warrant the use of analgesic medication. It is known that altered prostaglandin metabolism plays a role in the initiation and progression of CKD. The use of non-steroidal anti-inflammatory drugs(NSAIDS) results in vasoconstriction and decrease in intraglomerular pressure.(70) Among 1697 women in the Nurses Health Study, consumption of more than 3000g of acetaminophen was associated with an increased risk of GFR decline of more than 30 ml/min over 11 years, but use of higher amounts of aspirin or nonsteroidal anti-inflammatory drugs was not associated with increased risk.(71) In another study, acetaminophen use apparently increased the odds of ESRD in patients with a variety of underlying renal diseases, including diabetic nephropathy.(72)

Smoking appears to promote onset and progression of diabetic kidney disease. In diabetic patients, smoking causes a substantial increase in risk for both micro vascular and macro vascular disease.(73) This includes evidence of increases in albuminuria and the risk of end-stage renal disease and of decreased survival once dialysis is begun (74). In a study done in KNH on patients with diabetes and chronic kidney disease, only 11.8% of patients had a history of smoking with just 1.8% reported as current smokers.(42)

The role of alcohol consumption as a potential risk factor for CKD remains unclear. Some population-based studies have revealed that alcohol consumption is not related to CKD risk(75)whereas another similar study demonstrated an association.(76)

Exposure to heavy metals – This includes lead, cadmium, mercury, arsenic and uranium. Exposure may occur occupationally or through industrial environmental contamination of groundwater which is also recognized as an important source of exposure that may result in kidney disease in populations without direct occupational exposure.(77)

n) Obstructive uropathy

Obstruction of urine outflow from the kidneys can be one of the initiating factors of chronic kidney disease. This may be due to anatomic abnormalities of the outflow tract, neoplasm, stones, strictures, prostatic enlargement. In men lower urinary tract symptoms and benign prostatic enlargement, increase rapidly with age starting at around 50 years.(78) This is the mean age at which patients are diagnosed with type 2 diabetes. It is important to note that over 50% of men and women with diabetes have bladder dysfunction.(79) This may result in obstruction of urine outflow. Lower urinary tract symptoms (LUTS) include storage and/or voiding disturbances which are common in aging men. LUTS may be due to structural or functional abnormalities in one or more parts of the lower urinary tract which comprises the bladder, bladder neck, prostate, distal sphincter mechanism and urethra. It must also be remembered that LUTS may result from abnormalities of the peripheral nervous systems which provide neural control to the lower urinary tract. Storage symptoms include frequency, nocturia, urgency and the voiding symptoms include feeling of incomplete emptying, intermittency, and straining, weak stream.

o) Primary Renal Disorders

Primary renal disorders include primary glomerulonephritis, adult polycystic kidney disease, medullary cystic disease, tuberous sclerosis, Von Hippel Lindau. These conditions are associated with progressive deterioration in renal function. In the MDRD study, a diagnosis of autosomal dominant polycystic kidney disease was an independent predictor of a greater rate of GFR decline.(80)

p) Dietary protein intake

Concern exists that high protein diet may induce clinically important alterations in renal function. High protein consumption has been found, under various conditions, to lead to glomerular hyperfiltration and hyperemia; acceleration of chronic kidney disease (CKD); increased proteinuria; diuresis, natriuresis, and kaliuresis with associated blood pressure changes;

increased risk for nephrolithiasis; and various metabolic alterations. The mechanism by which dietary protein affects renal hemodynamics is not completely understood. It is important to note that there is no consensus as regards the definition for high protein diet. Using the Atkins diet, high protein diet is defined as: (1) deriving approximately 25% or more of daily caloric intake from protein, or (2) daily protein consumption greater than 1.5 g/kg.(81)

2.4 Screening for CKD

End-stage renal disease and its precursor chronic kidney disease are emerging public-health challenges due to their associated adverse clinical outcomes, poor quality of life, and high healthcare costs. Systematic screening for CKD is important as it improves clinical outcomes. Most persons with early stages of CKD are not clinically recognized. Observational studies suggest that CKD monitoring could identify patients who are unrecognized and who are at increased risk for adverse clinical outcomes. Coresh et al noted in the NHANES III that only 10% of adults with albuminuria and eGFR greater than 60, and 18.6% of adults with moderately decreased kidney function(eGFR=30-60mls/min), had previous knowledge of the presence of kidney disease.(82)

The measurement of albuminuria provides a sensitive marker of CKD. The gold standard of measurement of albuminuria is the 24-hour urine collection however there is the inconvenience and errors involved with a timed urine sample. A spot urine sample for albumin-to-creatinine ratio is an accepted screening method. Houlihan et al examined the accuracy of the albumin-creatinine ratio as a screening test and found sensitivities of greater than 90%.(83) Jafar et al found a specificity of above 95%.(84) The Kidney Disease Outcome Quality Initiative in 2002 recommended the use of spot urinary albumin to creatinine ratio and measurement of serum creatinine and estimation of GFR for screening for kidney disease in all diabetes patients.(36)

2.5 Staging Of CKD

Chronic Kidney Disease (CKD) is defined as abnormalities of kidney structure and or function present for greater than 3 months with implications for health.(85) The Kidney Disease Initiative Improving Global Outcomes(KDIGO) 2012 guidelines provide state of the art guidance on the evaluation, management and treatment of all patients with CKD.

CKD is present if either one of the following is present.

1. Markers of kidney damage include:

- Albuminuria i.e. Albumin excretion rate(AER) > 30mg/24 hrs or Urine albumin creatinine ratio(UACR) ≥ 30 mg/g
- Urine sediment abnormalities
- Electrolyte and other abnormalities that are due to tubular dysfunction
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation

2. Decreased eGFR< 60 ml/min/1.73m^2

Therefore to stage CKD you require albuminuria category and GFR category as shown in the table 1& 2 below:

Table 1: GFR categories in CKD

GFR category	(ml/min/1.73m^2)	Term
G1	≥ 90	Normal or High
G2	60 – 89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	< 15	Kidney failure

Table 2: Albuminuria categories in CKD

Category	AER(mg/24hrs)	ACR(mg/mmol)	ACR(mg/g)	Terms
A1	<30	< 3	< 30	Normal or mildly increased
A2	30 – 300	3 – 30	30 – 300	Moderately increased
A3	> 300	>30	> 300	Severely increased

A collaborative meta-analysis was conducted to examine the relationship between eGFR and albuminuria to mortality and kidney disease outcomes.(86) This helped stratify patients by prognosis as low risk/no CKD, moderate risk, high risk and very high risk. They are represented by colour codes green, yellow, orange and red respectively in table 3 below.

Table 3: KDIGO 2012 staging of CKD

GFR category (mls/min)	A1 (< 30 mg/g)	A2 (30 - 300 mg/g)	A3 (> 300 mg/g)
G1 (>90)			
G2 (60 – 89)			
G3a (45 -59)			
G3b (30 – 44)			
G4 (15 – 29)			
G5 (< 15)			

3.0 JUSTIFICATION

CKD is an important cause of non-communicable diseases. Diabetes is one of the leading causes of CKD in our setting. There is a global trend of an increase in the prevalence of type 2 diabetes with the majority being seen in low- and middle-income countries. Ambulant patients with type 2 diabetes are asymptomatic for chronic kidney disease. Yet it is known that the kidneys are affected in about one-third of patients with diabetes.

Data concerning the prevalence and severity of CKD in type 2 diabetes patients is of importance in planning a well-coordinated approach to the management of these patients. Early detection of CKD will help in the design and implementation of appropriate interventions to arrest the progression of CKD and reduce morbidity and mortality from cardiovascular disease.

It is important also to identify associated risk factors especially those that can easily be identified in our local health delivery system, and more so those that are modifiable. Public health interventions can be put in place to try to ameliorate the effect of these modifiable risk factors.

Internal audit of an aspect of a disease at repeated intervals will help in detecting emerging trends.

RESEARCH QUESTION

What is the burden of CKD in ambulant type 2 diabetes patients at Kenyatta National Hospital Diabetes Outpatient Clinics?

4.0 OBJECTIVES

4.1 BROAD OBJECTIVE:

To determine the burden of CKD in ambulant type 2 diabetes patients attending the KNH outpatient diabetes clinics.

4.2 SPECIFIC OBJECTIVES

1. To determine the prevalence of CKD in ambulant type 2 diabetes patients at KNH diabetes outpatient clinics
2. To determine the KDIGO stage of CKD in ambulant type 2 diabetes patients at KNH diabetes outpatient clinics
3. To determine the prevalence of diabetic glomerulopathy in ambulant type 2 diabetes patients at KNH diabetes outpatient clinics

4.3 SECONDARY OBJECTIVES

1. To document the presence of other risk factors associated with CKD in ambulant type 2 diabetes patients in KNH outpatient clinics including:-

- age
- Gender
- Duration of diabetes
- Family history of CKD
- History of cardiovascular disease
- socio-demographic factors
- history of smoking
- hypertension
- Body Mass Index(BMI)
- clinical evidence of cardiovascular disease
- exposures to nephrotoxins (like herbs, NSAIDS, radiocontrast media)
- urinary tract outflow disorders(presence of LUTS)

5.0 METHODOLOGY

5.1 Study Site

The study was conducted at the Kenyatta National Hospital Diabetes Outpatient clinics.

Kenyatta National Hospital is located in Nairobi, the capital city of Kenya. It is the largest referral and teaching hospital in Kenya. Between Monday and Thursday, a total of between 20 to 40 patients are seen at the diabetes mini-clinic which is located in clinic number 17. This clinic is conducted by trained clinical officers, nurses, podiatrists and nutritionists. On Friday mornings there is a main diabetes clinic which is conducted by the Endocrinologists with the assistance of the residents in the department of clinical medicine and therapeutics. This clinic sees between 80 to 120 patients on every clinic day.

5.2 Study Design

Hospital-based cross-sectional descriptive study.

5.3 Study Population

Ambulant type 2 diabetes patients.

5.4 Case definition

1. Type 2 diabetes – file diagnosis of type 2 diabetes
2. CKD will be defined by the presence of an eGFR of less than 60 mls/min/1.73m^2 and/or UACR $\geq$ 30 mg/g.(85)
3. Diabetic glomerulopathy will be defined by the presence of urinary albumin-creatinine ratio (UACR) $\geq$ 30 mg/g (significant albuminuria).(85)

5.5 PATIENT SELECTION

5.5.1 Inclusion Criteria

Diagnosed type 2 diabetes patients who are ambulant.

Informed written consent from the patient.

5.5.2 Exclusion criteria

Refusal of consent.

Patients known to have CKD or on follow-up in the renal clinic.

5.6 Sampling technique

Systematic random sampling was used to recruit patients who satisfied the inclusion criteria during the study period. After perusal of all the files at the beginning of the clinic, the principal investigator and his assistants would select those that satisfied the inclusion criteria. These files were allocated numbers such that every third patient was selected for inclusion in the study.

5.7 Sample Size

The sample size was determined by the following formula(87):

$$n = \frac{z^2\, p\,(1-p)}{d^2}$$

Where *n* = desired minimum sample size;

z = standard normal distribution value (1.96)

p = known prevalence rate for the factor of interest under study

d = the level of desired precision (0.05).

Prevalence of 15% for diabetic nephropathy as found by the 1989 study by Ngugi P.(33)

When this formula was applied at d = 0.05, z = 1.96, p = 0.85 1-p= 0.85

n = 196.

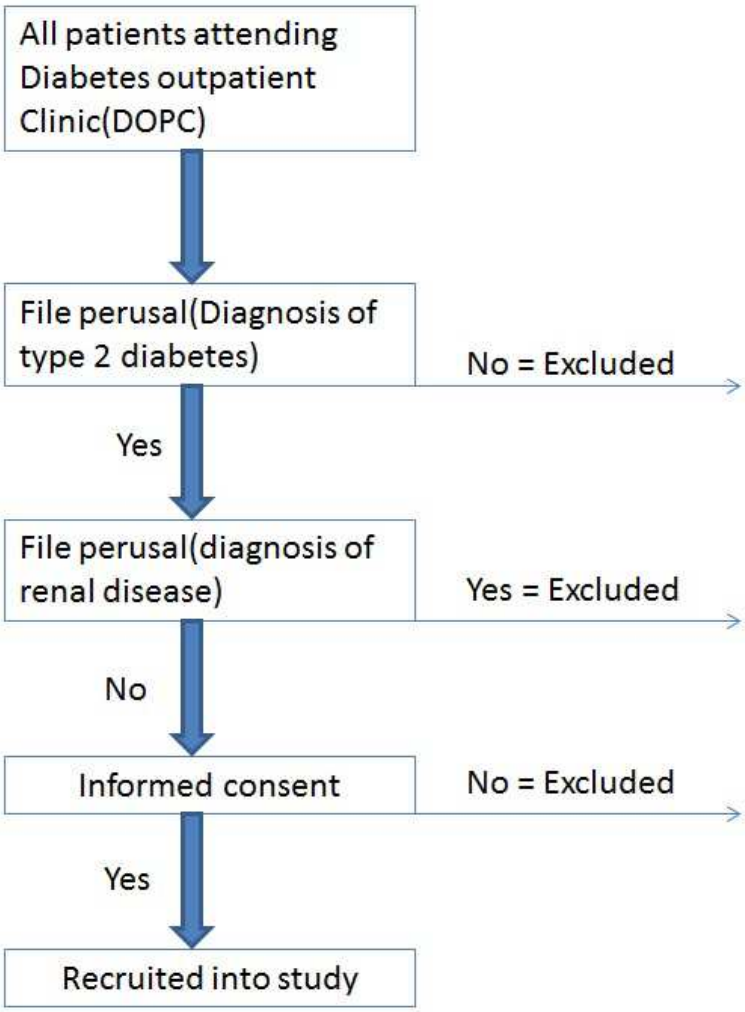
5.8 Study period

Patients were recruited over a six-month period between September 2013 and February 2014.

5.9 Screening and recruitment

The study was conducted at the diabetes mini- and outpatient clinic. The principal investigator and his assistants perused all the files at the beginning of the clinic and selected those diagnosed with type 2 diabetes and not on follow-up in the renal clinic. Systematic random sampling was used in selecting the cases for inclusion in the study. Patients identified were then called individually to the consultation room for explanation of the study procedure. Signed informed consent was then sought from the patient.

Figure 1: Flow chart of Screening and Recruitment



6.0 DATA COLLECTION

6.1 Clinical Methods

A study proforma was used to obtain demographic data and a complete medical history.

Presence of lower urinary tract symptoms including frequency, nocturia, urgency, feeling of incomplete emptying, intermittency, straining, weak stream was recorded.

6.1.1 Blood pressure

The blood pressure was then measured with the patient having rested for 5 minutes.

It was measured in the supine position using a mercury sphygmomanometer with the standard adult cuff. Systolic blood pressure was recorded on appearance of the first sounds (Korotkoffs phase 1) while diastolic pressure corresponded to the disappearance of the sounds. Two readings

were taken from the top of the meniscus and to the nearest 5mmHg. The blood pressure was then recorded as the mean of the 2 readings.

6.1.2 Weight

Measured with the patient in light clothing and wearing no shoes using a standard weighing machine in the clinic. It was then recorded to the nearest half a kilogram(kg).

6.1.3 Height

Measured using a vertical scale and recorded to the nearest half centimeter (cm).

6.1.4 Body Mass Index

The Body Mass Index(BMI) was calculated using the World Health Organization(WHO) criteria.(88)

6.1.5 Waist circumference

Measured mid-way between the lower costal margin and the iliac crest to the nearest centimeter.

6.1.6 Examination of the pulses

The peripheral pulses were then examined. This included the carotid arteries, femoral, popliteal, posterior tibial and dorsalis pedis. It was then recorded whether the pulses were felt or not. The carotid, renal and femoral arteries were then auscultated for the presence of bruits. Any anomaly detected was taken as evidence for the presence clinically of peripheral arterial disease.

6.2 Laboratory Methods

The patient provided 10mls of a midstream specimen of urine in a sterile bottle. Dipstick urinalysis was then carried out on the specimen. If urinalysis detected leucocytes and nitrites then these were considered as indices for infection and subsequently the albuminuria test would be invalidated. The patient suspected to have urinary tract infection(UTI) would be offered empiric treatment in addition to referral to the laboratory for culture of the urine specimen.

If the sample was acceptable, calculation of urinary albumin to creatinine ratio was done by Clinitek® Microalbumin Analyzer in the University of Nairobi Clinical Chemistry department.

2 mls of venous blood was drawn into an plain specimen bottle and taken to the clinical chemistry department for determination of creatinine levels using the Mindray® Clinical Chemistry Analyzer

6.2.1 Quality Control Measures

The recommended procedures for specimen collection were adhered to at all times, including proper phlebotomy site cleaning and the use of appropriate vacutainers. Proper labelling of the specimens and storage ensured minimal pre-analytical sources of errors. The Mindray® Clinical Chemistry Analyzer and Clinitek Microalbumin Analyzer were calibrated according to manufacturer's recommendations. The University of Nairobi Department of Clinical Chemistry laboratory runs daily internal quality control on all tests before sample analysis to validate the results obtained.

6.0 DEFINITION OF STUDY VARIABLES:

6.1 Dependent Study Variables

CKD will be defined by the presence of an eGFR of less than 60 mls/min/1.73m^2 and/or UACR > 30 mg/g.(85)

Creatinine clearance(eGFR) was estimated using the MDRD equation as follows(39):

Estimated Glomerular filtration Rate(eGFR) in mls/min = 175 x (serum creatinine in mg/dl)$^{-1.154}$ x (years)$^{-0.203}$ x (0.742 if female) x (1.210 if African-American)

The patient was staged according to the KDIGO 2012 stages of chronic kidney disease(See Table 3).

Normoalbuminuria-UACR < 30mg/g

Microalbuminuria-UACR 30-299 mg/g

Macroalbuminuria-UACR 300 mg/g or more.

6.2 Independent Study Variables

Age

Gender

Level of education

Duration of diabetes

Blood pressure

BMI

Exposures to nephrotoxins including NSAIDS, herbal medication, radiocontrast media

Lower urinary tract symptoms(LUTS)

Clinical evidence of cardiovascular disease

Cigarette smoking :

Current smokers were defined as those who have smoked at least 100 cigarettes in their lifetime and are still smoking.

Former smokers were those who have smoked at least 100 cigarettes but would have quit smoking at the time.

Non-smokers were those who have smoked less than 100 cigarettes or have never engaged in smoking.(89)

History of cardiovascular disease:-

History of non-traumatic amputation, history of cerebrovascular accident, myocardial infarction, percutaneous coronary interventions(PCI)

7.0 DATA MANAGEMENT AND STATISTICAL ANALYSIS

All data was collected in the study questionnaire and was then entered into MS access computer data base. The data was cleaned and verified. Statistical analysis was done using STATA version 12. Descriptive statistics were presented using percentages and frequencies for categorical or nominal data while mean, standard deviation, median, minimum and maximum for continuous/discrete variables. The chi-square test was used to compare categorical data while the Student's t-test was used for the continuous variables to determine statistical significance for normally distributed data and Mann Whitney U test was used in the analysis where such continuous data was skewed. The prevalence of CKD was calculated as the percentage of ambulant type 2 diabetes patients detected to have decreased eGFR and/or albuminuria.

8.0 ETHICAL CONSIDERATIONS

Permission to carry out the study was sought from the Kenyatta National Hospital-University of Nairobi Scientific and Ethical Review Committee.

Patients were enrolled after prior explanation as to the nature of the study and tests to be carried out.

The patients were informed that the study is entirely voluntary in nature and no treatment was to be denied those who declined to enroll in the study.

Consent was duly witnessed and signed.

Patient usual care was not interrupted and where necessary it was facilitated.

Patient confidentiality was maintained at all times.

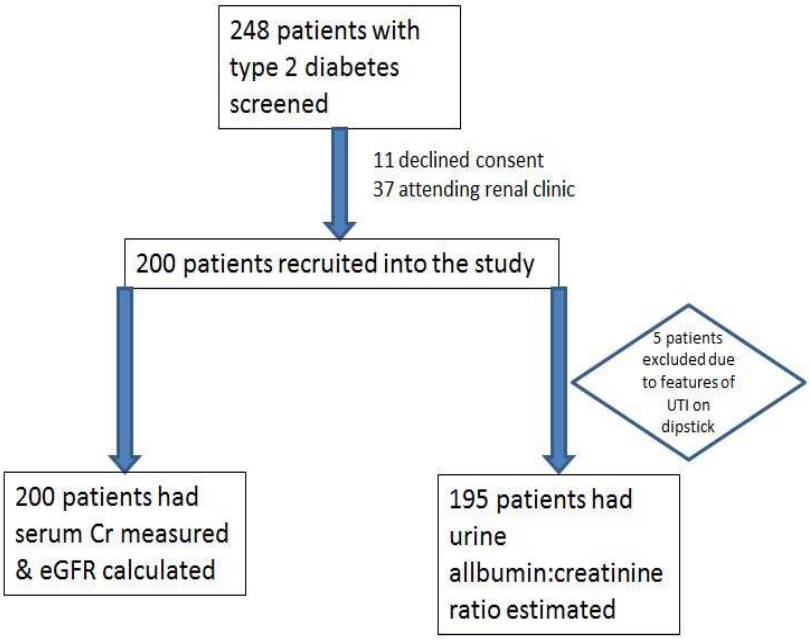
Data was entered into a password protected data base under the custody of the principal investigator.

Results obtained were made available in the patient records and appropriate interventions recommended where need arose.

9.0 RESULTS

Between September 2013 and February 2014, 248 ambulant type 2 diabetes patients who were asymptomatic for any kidney complications, attending KNH outpatient clinics were screened for possible enrollment into the study. Thirty seven patients were excluded as they were already known to have CKD and 11 declined consent. Thereafter 200 participants were enrolled in a prevalence study and screened for CKD using eGFR and urinary albumin-to-creatinine ratio. Five patients did not have their calculation of the UACR due to dipstick evidence of UTI.

Figure 2: Flow chart of patient enrolment



Of the 200 patients recruited into the study, 122 (61%) were female. The mean age of the study subjects was 59.4 years (±10.6) with a range between 34 and 88 years. Majority of the study subjects(33.5%) were in the 50-59 years age group and 31% were aged between 60 and 69 years

Mean duration of diabetes in the study subjects was 9.3 years (± 7.3) with a range of between 1 to 36 years. Table 4 below illustrates the socio-demographic characteristics of the study subjects.

Table 4: Socio-demographic characteristics of the study patients

	Frequency(N)	Proportion(%)
Age category	n = 200	
30-39 years	6	3.0
40-49 years	30	14.5
50-59 years	67	33.5
60-69years	62	31.0
70 years and above	35	17.5
Gender		
Male	78	39.0
Female	122	61.0
Level of formal Education		
None	21	10.5
Primary	78	39.0
Secondary	53	26.5
Tertiary	44	22.0
Adult education	4	2.0
Marital status		
Single	15	7.5
Married	150	75.0
Divorced	3	1.5
Widowed	25	13.0
Separated	6	3.0

1. CKD prevalence and KDIGO staging

One hundred and nine(109) patients were found to have CKD giving a prevalence of 54.5%.

Majority of the patients with CKD were between 50 to 70 years of age(67.9%).

Ambulant asymptomatic type 2 diabetes patients were staged as illustrated in table 5:

Table 5: Staging of CKD in the study participants

				Albuminuria categories Description and range			
				A1	A2	A3	
	Staging of CKD by eGFR and albuminuria categories: KDIGO 2012			Normal to mildly Increased	Moderately Increased	Severely increased	
				<30 mg/g	30 – 300 mg/g	>300 mg/g	
GFR categories mls/min/1.73m^2 (Description and range)	G1	Normal or High	≥ 90	42(21%)	26(13%)	1(0.5%)	n=69
	G2	Mildly decreased	60-89	49(24.5%)	33(16.5%)	1(0.5%)	n=83
	G3a	Mildly to moderately decreased	45-59	7(3.5%)	13(6.5%)	1(0.5%)	n=21
	G3b	Moderately to severely decreased	30-44	10(5%)	8(4%)	1(0.5%)	n=19
	G4	Severely Decreased	15-29	2(1%)	5(2.5%)	-	n=7
	G5	Kidney Failure	<15	-	-	1(0.5%)	n=1
				n=110	n=85	n=5	Total = 200

Table 6: Cardiovascular Disease Risk Stratification of study participants

KDIGO stage	Risk Strata	Frequency(N)	Proportion(%)
1	No CKD/low risk	91	45.5
2	Moderately increased risk	66	33.0
3	High risk	25	12.5
4	Very high risk	18	9.0

2. Prevalence of diabetic glomerulopathy

Ninety patients were found to have diabetic glomerulopathy(evidenced by albuminuria) which represented 45% of the total population studied and 82.6% of the patients with CKD(eGFR<60ml/min/1.73m^2 and/or albuminuria).

Table 7 below compares the prevalence of individual risk factors in the population identified to have CKD to the non-CKD population.

Table 7: Comparison of Risk factor prevalence between CKD and non-CKD population

	CKD n=109	**No CKD n=91**	**P value**
Age category in years, n (%)			
Below 50 yrs	14 (12.8)	22 (24.2)	**0.038**
50 yrs and above	95 (87.2)	69(75.8)	
Duration of DM in years	9.4 ± 7.3	9.1 ± 7.3	0.808
Sex, n (%)			
Males	36(33.0)	42(46.2)	0.058
Females	73(67.0)	49(53.8)	
Education, n (%)			
None/ adult/ primary	79(72.5)	73(80.2)	0.202
Secondary/ tertiary	30(27.5)	18(19.8)	
Positive smoking history, n (%)			
Never smoked	88(80.7)	62(68.1)	**0.040**
Former/ current smoker	21(19.3)	29(31.9)	
Hypertension, n (%)	82(75.2)	61(67.0)	0.201
SBP (mmHg)	143 ± 22.9	132.5 ± 13.4	< **0.001**
DBP (mmHg)	83 ± 14.4	81 ± 10.1	0.255
Family history of CKD	8(7.3)	5(5.5)	0.598
History of cardiovascular disease	8(7.3)	5(5.5)	0.598
Lower urinary tract symptoms	22(20.2)	24(26.4)	0.300
Evidence of peripheral arterial disease	2(1.8)	4(4.4)	0.290
Exposure to NSAIDs	8(7.3)	10(11.0)	0.369
Exposure to herbal medicine	4(3.7)	7(7.7)	0.214
Exposure to radio-contrast medium	11(10.1)	9(9.9)	0.962
BMI, mean ± SD	28.3 ± 5.1	28.3 ± 5.0	0.984

On univariate analysis, age greater than 50 years($p=0.038$), positive history of smoking($p=0.04$), and systolic blood pressure($p<0.001$) were significantly associated with CKD. Female gender showed a strong association with CKD but this did not achieve statistical significance. The other risk factors which were studied did not show statistically significant association with CKD.

10.0 DISCUSSION

The population of patients with type 2 diabetes in sub-saharan Africa is rising.(6) This implies that the health sector in Kenya will face an increasing burden of CKD attributable to diabetes in the coming years. This has major implications on the Kenyan health sector in terms of efforts to prevent kidney failure and need for dialysis for those who may develop ESRD. This study set out to determine the prevalence of CKD in ambulant type 2 diabetes patients who were asymptomatic for CKD, and describe some specified associated risk factors.

This study evaluated 200 patients overall. The population studied was predominantly female who comprised 61% of the participants with a male to female ratio of 1:1.6. Global estimates suggest that in sub-Saharan Africa there is an excess of males with diabetes. (90) Recent studies done in the same population of patients reveal similar gender disparity.(54) Similar gender disparity has been observed in sub-saharan studies such as one conducted in Jos University Teaching hospital, Nigeria, which found 58% of patients recruited to be female.(91) This disparity may represent the health-seeking behavior of the patients attending this clinic, though the reasons for the skewed gender proportions of CKD are yet to be established.

The mean age of the study participants was 59.4 years(± 10.6). Majority of the patients(87.2%) with CKD were older than 50 years. This represents the peak age of social and economic responsibility. Uloko et al in their Nigerian Diabcare study, found the mean age of their study population was 57.7 years.(92) Watanabe Y. et al in a cross-sectional survey conducted in type 2 diabetes outpatients in Tokyo, found the mean age of participants to be 61 years(±12).(93) Aging is a known risk factor for decline in renal function. This difference in age between sub-saharan countries and western countries can be attributed to either population characteristics, socioeconomic status, healthcare organization, and differences in health-seeking patterns.

The prevalence of CKD in these ambulant patients with type 2 diabetes was found to be 54.5%. In a recent cross-sectional study of 369 patients with diabetes conducted at Bugando Medical Centre in Tanzania, the prevalence of CKD was found to be 83.7%.(94) The Tanzanian study reported a very high prevalence of CKD in their study patients who included patients with type 1 diabetes although they were a minority and albuminuria was assessed using a non-quantitative test. Also the study did not determine non-diabetic causes of renal disease which may have led to a higher prevalence of CKD. The use of Cochroft-Gault equation for estimation of GFR could also have led to an underestimation of GFR and thus a higher prevalence of CKD. This large

disparity in the prevalence of CKD could also represent differences in the quality of care or genetic make-up of the population. A cross-sectional study done in 3071 Japanese patients with type 2 diabetes found a 46% prevalence of CKD.(95) The methodology of this study was similar to ours except for the use of the first morning specimen of urine for estimation of ACR. They also used a different formula recommended by the Japanese nephrology society to estimate GFR. In a cross-sectional analysis of data from NHANES IV, the prevalence of CKD in patients with type 2 diabetes was found to be 39.7%.(96) The lower prevalence of CKD in these non-African populations is not unusual as there have been studies which have shown an increased risk of diabetic renal disease in African than in caucasian populations.(97) All the patients included in this study were asymptomatic for CKD. This means that our clinicians in the diabetes outpatient clinics need to be aware of the high prevalence of CKD and referral made to nephrologists as early as possible.

According to their relative risks of an adverse cardiovascular outcome, patients are classified as either low, moderate, high, or very high risk.(85) There is a graded association between lower levels of the estimated GFR and the risks of death, cardiovascular events, and hospitalization. This becomes evident at an eGFR of < 60 ml/min/1.73 m^2 and even more substantially increased with an eGFR of less than 45mls/min/1.73m^2.(13) The KDIGO 2012 guideline for evaluation and management of CKD elaborates on the identification & prognosis of CKD. (85) In this study, 78.5% of the study population was in the low and moderate risk group of CKD which means their risk of all-cause or cardiovascular mortality is two times higher than those without CKD. Over twenty percent(21.5%) of ambulant type 2 diabetes patients are in the high or very high risk category. Their risk of adverse cardiovascular and all-cause mortality is upto14 times higher than patients without CKD. These are patients who require to be followed up closely by a team of heart and kidney specialists with the aim of reducing cardiovascular morbidity and mortality.

The prevalence of diabetic glomerulopathy in this study was found to be 45%. The diagnosis of diabetic nephropathy in the ideal situation requires a renal biopsy to be done. In this study patients with significant albuminuria(UACR ≥30 mg/g) were classified as having diabetic glomerulopathy. It has been demonstrated that increased urinary albumin excretion, endothelial dysfunction and chronic inflammation are interrelated processes that develop in parallel, progress over time and are strongly and independently associated with increased risk of death in type 2 diabetes patients(21). Among European patients with type 2 diabetes, those with proteinuria have

a fourfold excess of premature death compared with patients without proteinuria.(22) Twahir A. in a 1994 study of type 2 diabetes patients found a 40.6% prevalence of microalbuminuria.(34) A study conducted in Northern Tanzania by Ghosh S et al found a 29% prevalence of microalbuminuria.(98) These two studies did not include patients who had dipstick positive albuminuria i.e. urine ACR > 300mg/g. This would account for the lower prevalence of albuminuria in these populations. The UKPDS study found that at 10 years the prevalence of microalbuminuria in type 2 diabetes patients was 25%.(12) The lower prevalence of microalbuminuria in the UKPDS study was probably due to the strict study conditions which the patients were in. The high level of albuminuria noted in our study may probably be attributable to the generally poor glycaemic control which has been demonstrated in previous studies done locally.(42, 53) However this study deliberately excluded analysis of glycaemia from the risk factors. Studies have shown that a spot urine sample is an accepted screening method for CKD. (83,84) There is a strong correlation between albuminuria, progression of kidney disease and adverse cardiovascular events and mortality.(99) This therefore means that our patients are at a high risk of adverse events. It is important to note that patients with albuminuria represented 82.6% of the population with CKD, therefore UACR is a simple and reliable test which can be used to screen for CKD even in our diabetic population.

In this study, age was found to be significantly associated with an increased risk of CKD. Over eighty percent(87.2%) of patients with CKD were older than 50 years. In a study done in Ghana looking at the prevalence of proteinuria in type 2 diabetes, they found the mean age of patients to be 54.9 years.(100) It is known that increasing age is a susceptibility factor for CKD. Aging is also associated with an increase in the prevalence of other risk factors such as cardiovascular disease, hypertension and obesity.(101)

Over seventy percent(71.5%) of the study patients were found to be hypertensive with a mean systolic BP of 138.3±19.8 and a mean diastolic BP of 82.1 ±13.2.The eGFR showed a weak negative correlation with systolic blood pressure but not with diastolic blood pressure. Motala A.A. in a 2001 study of 172 South African patients with type 2 diabetes patients found that 68% were hypertensive. (102) Brenyah RC et al in a prevalence study conducted at a teaching and referral hospital in Ghana, found that both systolic and diastolic blood pressures significantly correlated with nephropathy.(100) Hypertension is a consequence of reduced renal function but in itself is important in the progression of CKD. It is known that lower BP targets in type 2 diabetes is associated with lower cardiovascular and all-cause mortality. Reduction of BP by

5.6/2.2 mmHg results in reduced cardiovascular mortality of 3.8% compared to 4.6% and a reduction in all-cause mortality of 7.3% compared to 8.5%.(103) In the patients with type 2 diabetes we should aim for strict BP control as it is a significant risk factor for CKD. Joint National Committee(JNC 8) advocates for systolic BP of less than 140 mmHg and diastolic BP of less than 90 mmHg.(104)

There was a trend towards association between female gender and increased risk of CKD, but this did not achieve statistical significance. Many studies report male sex as a risk factor for development of renal disease in type 2 diabetes.(43,105)

In this study, the level of education was used as a surrogate marker of socioeconomic status. This was because it is difficult to reliably assess income levels of patients by self-reporting. We recognize that our population of patients in KNH may be relatively homogenous in terms of their socioeconomic status. In fact the level of education may act as a surrogate of health literacy rather than economic status. In this study, no significant association was found between the level of education and CKD. Krop et al had observed that blacks with diabetes were three times more likely to develop CKD in unadjusted analyses.(50) On adjustment for additional covariates, 6% of the excess risk for development of CKD was explained by income and education levels.

In this study the prevalence of cigarette smoking was found to be 25%. Only 5% of the patients studies were current smokers. A study conducted in the same clinic by Otieno CF et al looking at cardiovascular risk factors in type 2 diabetes, found that 15% of study participants were active smokers.(106) In a study conducted by Ghosh S et al in Northern Tanzania 39% of the patients were found to be smokers.(98) There was significant association between smoking and CKD. Smoking promotes the onset and progression of diabetic kidney disease. This is because of an increased risk of both microvascular and macrovascular disease.(73)

In this study the presence of arterial disease was determined clinically by palpation of peripheral pulses and auscultation of bruits. This method is not sensitive and is highly operator dependent. We found a 3% prevalence of peripheral arterial disease. A similar study conducted in Ethiopia found a prevalence of 6%.(107) We know that in our public health care system there is lack of availability of screening tests such as the ankle-brachial index (ABI). This study shows that health-care providers should routinely carry out thorough physical examination of type 2 diabetes patients as this will enable patients to be referred for earlier cardiovascular evaluation before limb loss occurs.

In the population of patients with CKD, the prevalence of cardiovascular morbidity, presence of LUTS, use of herbal medicines, exposure to radiocontrast media did not achieve statistically significant levels. It is important to note that these risk factors are present in our population of type 2 diabetes and clinicians should be alert to this. It is difficult to make any intepretations as documentation of exposure to a risk factor depended on proper record keeping, also patient recall and even duration/dose of the risk factor. Thus it is likely there was a high level of under-reporting and non-estimation where reported.

11.0 CONCLUSION

1. Ambulant patients with type 2 diabetes had a high prevalence of CKD (54.5%). The condition was asymptomatic in these patients.

2. Our population of patients with CKD were older than 50 years with a high prevalence of CKD (54.5%). This has potentially grave consequences in terms of adverse cardiovascular morbidity and mortality.

3. Albuminuria is highly prevalent in asymptomatic patients with CKD (85%). This means that the detection of albuminuria is highly predictive of CKD.

4. Significant association was demonstrated between advanced CKD stage and rising systolic BP and increasing age.

12.0 RECOMMENDATIONS

- Ambulatory patients with diabetes should be routinely screened and risk-stratified for cardiovascular disease at whatever stage they are found.
- Albuminuria is a significant marker of CKD and can be used to detect CKD in our setup.
- Systolic hypertension is a modifiable risk factor with significant association with CKD. It is important to manage hypertension appropriately and optimally.
- Longitudinal studies are needed to look at outcomes in our type 2 diabetes population especially in terms of outcomes with respect to cardiovascular risk strata.

13.0 LIMITATIONS

- This is a cross-sectional survey and doesn't allow for review of long-term outcomes
- Patients on follow-up in the renal clinic were excluded and they usually have more advanced CKD
- The use of serum creatinine to estimate the GFR is sub-optimal for a number of reasons. These include the tubular and extra-renal secretion of creatinine, the wide between-individual variation in creatinine production
- The use of the MDRD equation to estimate GFR
- To confirm CKD ideally we should have measured eGFR and UACR more than once in a period of at least 3 months. Therefore this is likely to cause an over-estimation of albuminuria.

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APPENDIX I

LABORATORY METHODS

1. SERUM CREATININE ESTIMATION (MINDRAY® CLINICAL CHEMISTRY ANALYZER)

Principle of the method:

Creatinine reacts directly with picrate ion under alkaline conditions to form a red-orange compound, called a Janovski complex, with an absorbance peak at 520 nm whose color intensity is directly proportional to the creatinine concentration in the sample. The analytical procedure will be fully automated.

Procedure:

1. 10µl of sample will be mixed with 1500µl of working reagent and mixed well
2. The mixture will be incubated for 5 min at 37o C
3. Absorbance will be read at 520 nm
4. Serum creatinine concentration will be expressed in µmol/L

2. Urine albumin-creatinine ratio (Clinitek® Microalbumin Analyzer)

Principle of the method:

Albumin: This test is based on dye binding using a high affinity sulfonephthalein dye. At a constant pH, the development of any blue colour is due to the presence of albumin.

Creatinine: This test is based on the peroxidase-like activity of a copper creatinine complex that catalyzes the reaction of diisopropyl-benzene dihydroperoxide and 3,3',5,5'-tetramethylbenzidine.

Albumin is then recorded as concentration in mg/L, and creatinine in mmol/L. Albumin-creatinine ratio is then finally given in mg/mmol

APPENDIX II

STATEMENT OF INFORMATION FORM

The Burden of Chronic Kidney Disease in Ambulant Type 2 Diabetes patients at Kenyatta National Hospital Diabetes Outpatient Clinics

Purpose of the study.

I Dr. Stephen Nyamai 'am undertaking this study on the burden of Chronic Kidney Disease in Ambulant Type 2 Diabetes patients at Kenyatta National Hospital Diabetes Outpatient Clinics

Procedures

You are being asked to participate in this survey that will take about 30 minutes. If you agree to participate I will ask you to sign a consent form. There will be a series of questions that I will ask you in confidence and all your responses will be noted down. Most questions have a 'No or Yes' for an answer and will require you to remember some things in the past. I will also take your blood pressure, height, weight and waist circumference. Following this I will conduct a physical examination to look for signs of cardiovascular disease.

There after my assistant/or I will collect from you a blood sample of about 2mls that will be taken to the laboratory for evaluation for serum creatinine levels. A sample of urine measuring about 10mls will also be collected to determine protein excretion levels in your urine.

The tests results will be revealed to you (recorded in your file) at the soonest possible for your continued care. Tests results shall remain confidential.

Risks to you as a participant.

There will be some discomfort from the needle prick at the site of blood sample removal (usually from the cubital area or any other appropriate site).

Rarely swelling or bleeding may occur from the puncture site but I will make sure bleeding has stopped before I leave. In the event that bleeding appears kindly contact me or any nearest heath worker for assistance.

Benefits

You will not be charged for any of the lab tests.

The findings of the physical examination and laboratory tests will form part of your usual care. Copies of the test results shall be available to you and will be recorded in your personal file.

This study will provide an opportunity to estimate the burden of kidney disease in patients with diabetes in our clinic. This will inform health policy in our country with an aim to prevent or delay onset of kidney disease in diabetics and also improve outcomes for those already with kidney disease.

Right to refuse.

Your participation in this research is voluntary. You are free to withdraw from the interview at any time and you shall not be discriminated upon. You are free to ask any questions and have a right to satisfactory answers before you sign the consent form.

If you agree to participate in this survey you may kindly sign on the consent form.

Thank you

TAARIFA YA HUDUMA

The Burden of Chronic Kidney Disease in Ambulant Type 2 Diabetes patients at Kenyatta National Hospital Diabetes Outpatient Clinics.

Madhumuni ya utafiti

Mimi Dkt Stephen Nyamai nafanya utafiti kuhusu kiwango cha maambukizi ya ugonjwa wa figo katika wagonjwa wanaotembea wenye kisukari kwenye hospitali kuu ya Kenyatta kliniki ya kisukari.

Taratibu

Unaulizwa ushiriki kwenye utafiti ambao utachukua muda wa dakika thelathini. Ukikubali kushiriki kwenye utafiti nitakuuliza utie sahihi kwenye fomu ya ridhaa. Kutakuwa na mfululizo wa maswali nitakayo kuuliza kwa siri na majibu utakayonipa nitayarekodi. Maswali mengi yanajibu “ndio” au “la” naitakubidi uyakumbuke baadhi ya mambo katika siku ya nyuma. Nitakupima kipimo cha shinikizo la damu, urefu, uzito, naupana wa kiuno. Kisha nitakupima mwili ilikutafuta ishara ya ugonjwa wa moyo.

Baadaye msaidizi wangu au mimi nitachukua sampuli ya damu ya kiasi ya mililita tano ambayo itapelekwa kwenye mahabara kwa ajili ya kutathmini kiwango cha “serum creatinine”. Kiwango cha mililita kumi ya mkojo kitachukuliwa ilikubaini kiwango cha protini. Katika mkojo wako.

Utajulishwa matokeo ya vipimo zote na pia yatahifadhiwa kwenye faili yako kwa haraka iwezekanavyo. Matokeo yako yote yatawekwa siri.

Madhara kwako kama mshiriki

Utahisi uchungu kwenye sehemu ya kutolewa kipimo cha damu. Kuna uwezekano wakuvimba au kuvuja damu baada ya kudungwa sindano lakini nitahakikisha damu imewacha kuvuja kabla ya kuondoka. Iwapo damu itaendelea kuvuja, unaweza kuwasiliana name ama mshauri wowote wakiafya aliyekaribu nawe kwa usaidizi.

Manufaa kwako kama mshiriki

Hakuna malipo yoyote utakayoulizwa. Matokeo ya vipimo vyako yatakuwa kama matunzo yako ya kawaida. Nakala ya matokeo yako itajulishwa kwako napia itahifadhiwa kwenye faili yako yakibinafsi. Utafiti huu utatoa fursa ya makisio ya mzigo wa ugonjwa wa figo kwa wagonjwa wenye ugonjwa wa kisukari katika kliniki yetu. Hii itawezesha sera zakiafya kuwekwa ambazo zitakuwa na lengo yakuzuia na kucheleweshe ugonjwa wa figo katika kisukari na pia kuboresha matokeo kwa wale ambao tayari wamegonjeka figo.

Haki ya kukataa

Ushiriki wako katika utafiti huu ni kwa hiari yako. Una uhuru wakujiondosha kutoka mahojiano wakati wowote wala hutabaguliwa ukifanya hivyo. Unauhuru wakuuliza maswali na haki ya kupata majibu yanayokuridhisha wewe kabla ya kutia kidole fomu ya ridhaa.

Ahsante.

APPENDIX III

CONSENT FORM

I……..consent to participate in the study on The Burden of Chronic Kidney Disease in Ambulant Type 2 Diabetes patients at Kenyatta National Hospital Diabetes Outpatient Clinics. I do this with the knowledge of the purposes of the study and the procedures thereof. The purposes of the study and procedures have been explained to me clearly by DR.STEPHEN NYAMAI or his assistant. I am also aware that I can withdraw from this study without losing any benefits and quality of care of my medical condition.

Signature of patient……Date……...

Signature of witness.…….……Date……..

If you have any questions during the course of the study, you may contact the following.

Dr. Stephen Nyamai

Mobile number. 0733375035

OR

The Chairman of the Ethical and Review committee

Kenyatta National Hospital

Tel 020-2726300/0722-829500/0733-606400 Ext,44102

FOMU YA RIDHAA

Mimi ……...nakubali kushiriki katika utafiti “The Burden of Chronic Kidney Disease in ambulant Type 2 Diabetes patients at KNH diabetes outpatient clinics”. Na fanya hivi nikiwa na maarifa ya madhumuni na taratibu za utafiti huu. Zimeelezwa wazi na Dkt. Stephen Nyamai au msaidizi wake. Mimi pia nafahamu kwamba naweza kujitoa katika utafiti huu bila kupoteza faida yoyote na ubora wa huduma za kiafya.

Sahihi ya mgonjwa……Tarehe……...

Sahihi ya shahidi…..…….……Tarehe……..

Ukiwa na maswali wakati wowote wa utafiti huu unaweza wasiliana na anwani uliopewa.

Dkt. Stephen Nyamai

Simu ya rununu 0733375035

AMA

The Chairman of the Ethical and Review committee

Kenyatta National Hospital

Tel 020-2726300/0722-829500/0733-606400 Ext, 44102

APPENDIX IV

STUDY PROFORMA

Name (initials) ……

Study ID number ……

Clinic …….

Date of Birth (dd/mm/year) ……..

Date of diagnosis of diabetes …….

SOCIO-DEMOGRAPHICS

1. Gender a) Male b) female
2. Race a) African b) Caucasian c) Asian
3. Usual residence
4. Usual occupation
5. Level of formal education
   a) none b) primary c) secondary d) tertiary
   e) Adult education
6. Marital status

a) single b)married c) divorced d) widowed

e) Separated

PAST MEDICAL HISTORY

7. Have you ever been told by a health-worker that you have hypertension?

a) Yes b) No

If yes, in which year?.....

8. Have you suffered from any stroke, myocardial infarction, amputation due to non-traumatic reasons?(This will also be checked from patient files)

a) stroke b) myocardial infarction c) amputation d) none

9. Have you had any radiological examination involving injection of contrast material(This will be confirmed from the patient files)

a) yes b) No

FAMILY HISTORY

10. Did/do any of your relatives suffer from kidney disease?

a) Yes b) No

If yes:

1=1 parent

2=both parents

3=sibling

4=others (specify)

SMOKING HABITS

11. What is your current smoking status?

a) never been a smoker

b) former smoker

c) current smoker

12. If the patient has a history of smoking:

a) When did you start smoking(year)?

b) When did you stop smoking(year)?

c) Approximately how many cigarettes did or do you smoke per day?.....

CURRENT MEDICATIONS

13. Oral hypoglycaemic agents?
    a. Sulphonyl urea
    b. Metformin
    c. NSAIDs
    d. Paracetamol
    e. Alternative medicine e.g. herbal medicine
    f. Others(specify)

14. Insulin treatment(formulation & dose)
15. Anti-hypertensive medication(drug and dose)
    a. ACEI(angiotensin converting enzyme inhibitor)
    b. ARB (angiotensin receptor blocker)
    c. B-blocker(Beta blocker)
    d. dCCB(dihyropyridine Calcium channel blocker)
    e. Others.
    f. Diuretics

16. Lipid lowering agent(specify drug and dose)

LOWER URINARY TRACT SYMPTOMS (LUTS)

17. Do you suffer from any of the following symptoms? frequency, nocturia, urgency, feeling of incomplete emptying, intermittency, straining, weak stream

    a) Yes b) No

PHYSICAL EXAMINATION

Height (m) ……..

Weight (kg) …….....

BMI (kg/m^2) ……

Waist circumference (cm) ……

Supine Blood pressure(mmHg)	Systolic	Diastolic
1st reading		
2nd reading		
AVERAGE BP(mmHg)		

BRUIT	Present	Absent
Carotid		
Renal		
Femoral		

PALPABLE PULSE	Present	Absent
Carotid		
Femoral		
Popliteal		
Dorsalispedis		

Serum Creatinine (µmol/l) ……

MDRD eGFR(mls/min/1.73m^2) ……

Urine albumin/creatinine (mg/g) ……

KDOQI stage …….