TITLE:

PREVALENCE OF RISK FACTORS ASSOCIATED WITH PROGRESSION OF NEPHROPATHY IN DIABETIC PATIENTS WITH CHRONIC RENAL INSUFFICIENCY AS SEEN AT KENYATTA NATIONAL HOSPITAL

A DISSERTATION PRESENTED IN PART FULFILLMENT FOR THE DEGREE OF MASTER OF MEDICINE (INTERNAL MEDICINE), UNIVERSITY OF NAIROBI

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DECLARATION

I declare that this is my own original work and has not been presented or published elsewhere for a degree in any university.

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DEDICATION

This work is dedicated to my mother Mary, and my late father Justus who made me believe in myself and taught me that something worth having never comes easy, and my family Francis, Sandra, Mule and Casey for going through with me this period.

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LIST OF ABBREVIATIONS AND SYNONYMS

ACE	-	Angiotensin Converting Enzyme
ADA	-	American Diabetes Association
AGE	-	Advanced Glycation End Product
ANP	-	Atrial Natruretic Peptide
ATPIII NCEP	-	National Cholesterol Education Programme
BMI	-	Body Mass Index
CCB	-	Calcium Channel Blocker
CKD	-	Chronic Kidney Disease
CRI	-	Chronic Renal Insufficiency
DCCT	-	Diabetes Control and Complication Trial
DN	-	Diabetic Nephropathy
ESRD	-	End Stage Renal Disease
FBS	-	Fasting Blood Sugar
GRF	-	Glomerular Filtration Rate
HbAIc -	-	Glycated Hemoglobin
HDL	-	High Density Lipoprotein
IDDM	-	Insulin Dependent Diabetes Mellitus
KNH	-	Kenyatta National Hospital
LDL-C	-	Low Density Lipoprotein Cholesterol
NDDG	-	National Diabetes Data GP
NIDDM	-	Non – Insulin Dependent Diabetes Mellitus
NKF	-	National Kidney Foundation

PKC	-	Protein Kinace C
RRT	-	Renal Replacement Therapy
TGF/β	-	Transforming Growth Factor Beta
UKPDS	-	United Kingdom Prospective Study
WHO	-	World Health Organization
WHR	-	Waist Hip Ratio

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ABSTRACT

Background: Forty-five percent of new cases of end stage renal disease in the USA result from diabetic nephropathy. The absolute number and proportion of kidney failure cases caused by diabetes is expected to rise dramatically as the prevalence of diabetes mellitus increases over the next decade because of an epidemic of obesity.

Diabetic patients with chronic kidney disease pose unique problems different from the rest of the chronic renal insufficiency population. Several studies have shown that diabetics enter into renal replacement programs earlier since they are not able to tolerate uraemia as well as non-diabetic renal patients. They have more difficult vascular access due to accelerated artherosclerosis and they have poorer outcome due to higher cardiovascular complications, which are also the major cause of death pre and post-dialysis They require special attention at renal transplantation: meticulous glucose control, more difficult surgery because of artherosclerosis, and higher incidence of complication due to immunosuppressive therapy and artherosclerosis. The annual cost for dialysis in a diabetic patient is more than for non-diabetic patient and diabetic dialysis and transplant recipients have higher mortality and morbidity. More importantly, renal replacement therapy (RRT) is very expensive. Many type 2 diabetics are elderly, have much co-morbidity and are not transplantable by the time they reach end stage renal failure. Therefore, it is extremely important to delay or stop progression to ESRD.

Several studies have shown that modification of specific risk factors can retard or halt progression of CKD, depending on when these measures are introduced in the management.

No data existed *on the prevalence of risk factors associated with progression of nephropathy in* diabetic patients at KNH.

Objectives: The aim of the study was to determine the prevalence of modifiable risk factors associated with progression of CRI in diabetic patients especially poor glycaemic control, hypertension, anaemia, hyperphosphataemia, elevated calcium phosphate product, macroproteinuria, cigarette smoking and dyslipidaemia.

Design: Cross sectional prevalence descriptive study.

Study Area: The Renal and Diabetic outpatient clinics and Medical wards KNH.

Patient selection: Consecutive sampling of Diabetics with CRI. CRI was defined as estimated GFR from calculated creatinine clearance of less than 90-mls/min. Creatinine clearance was derived using the Cockroft -Gault formula.

Methods: Eligible patients had a blood sample drawn for estimation of urea and creatinine levels (from which calculated glomerular filtration rate was estimated using Cockcroft Gault formula). The prospective candidates for the study were given a detailed explanation on the study, after which the patient signed a standard consent form. They were then asked to come fasted on a suitable day where data was prospectively obtained via a standard questionnaire administered by the Investigator. Details of age gender, duration of diabetes, personal and family history and smoking history were taken. Physical examination including blood pressure, BMI and WHR were taken and recorded. Blood sampling was done including fasting blood sugar; glycated haemoglobin, urea, creatinine, albumin, calcium, phosphate, fasting lipid profile and haemoglobin levels. Urinalysis was performed according to study protocol.

For patients in medical ward screening was done and all eligible were recruited.

Results: Between May and December 2004, 111 diabetic patients with chronic renal insufficiency were studied, 65% females and 35% males. The mean GFR was 26mls/min with a Standard Deviation (SD) of 15.51. 33.3%of the patients were in ESRD, 26.1% had severe renal

failure, 38.8% had moderate kidney disease, and 1.8-% mild disease. The mean age was 56.2years (SD 15.188). 11.8% had a history of smoking, all being males and only 1.8% were current smokers. The mean BMI was 26.57 (SD 4.87), 55.9% were either over weight or obese. 63.1% had central obesity. 81.1% were hypertensive with 76.6% on anti hypertensive therapy. 60.4% had poor glyceamic control despite 61.1% being on Insulin therapy.18% had elevated total cholesterol, 33.3% had high LDLc, 25.2% had low HDLc and 19.8% had high triglyceride levels. The mean haemoglobin concentration was 10.31g/dl (SD 2.066). 75.7% had anaemia with only 9% of the patients on haematinics and none on erythropoeitin. 61.3% had hyperphosphataemia with only 9% on phosphate binders. 19.8% had high calcium phosphate product. 85.6% had macroproteinuria. 61.1% were on ACE inhibitors or ARB.

Conclusion: There is a high prevalence of modifiable risk factors, frequently multiple, associated with progression of renal disease in diabetics seen at KNH.

INTRODUCTION AND LITERATURE REVIEW

Diabetes mellitus is a term applied to a group of metabolic disorders characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. (1)

The resulting chronic hyperglycaemia is associated with long term damage, dysfunction and failure of various organs especially the eyes, kidneys, nerves, heart and blood vessels.

In 1980, the World Health Organization (WHO) and National Diabetes Data Group (NDDG), classified diabetes purely on clinical criteria (2) but in 1997, The American Diabetes Association (ADA) proposed a new classification based on etiology (1).

ADA divides diabetes into four categories namely:

(i) Type 1 Diabetes mellitus characterized by beta cell destruction mainly by immunologically medicated mechanisms eventually leading to absolute insulin deficiency

(ii) Type 2 representing individuals with predominant insulin resistance mainly as part of the "metabolic syndrome ".

(iii) Gestational diabetes and

(iv) Other specific forms

Type 1 and 2 are the most frequently encountered; Type 2 being more prevalent.

Life expectancy is reduced due to chronic complications with poor quality of life from angina, stroke, blindness, renal failure and neuropathy.

In the United Kingdom Prospective Diabetes Study (UKPDS), (3) 11% of the type 2 patients had microalbuminuria at time of diagnosis of diabetes .In the Diabetes control and complication Trial Research Group (DCCT) – (4), intensive treatment reduced the mean adjusted microalbuminuria by 34 % in the primary prevention control and by 43% in the secondary prevention cohort while the risk

of albuminuria was reduced by 56% in the secondary intervention cohort (albuminuria 54% and microalbuminuria 39% in the combined cohort)

Several risk factors have been implicated in the progression of renal failure in patients with diabetic nephropathy.

Locally, several studies have been done to try and determine prevalence of diabetic nephropathy. Abdullah in 1976 (5) demonstrated a prevalence of 46% of diabetic population in attendance at Kenyatta National Hospital (KNH). Ngugi in 1989 (6) found 15.8% of 359 diabetic patients screened to have overt nephropathy.

In 1994, Twahir (7) found a prevalence of microalbuminuria in 40.6% of the 79 type 2 patients assessed.

Mwendwa in 2001, (8) demonstrated that within two yrs of diagnoses of type 2 diabetes, 26.3% of 100 patients assessed had albuminuria, with 96% microalbuminuria and 4% macroalbuminuria. She was able to demonstrate that hypertensive patients had significantly lower mean creatinine clearance compared to non- hypertensive patients.

1.0 DIABETIC NEPHROPATHY

Diabetic nephropathy (DN) is the most common, single cause of End Stage Renal Disease (ESRD) in the world.

1.1 PATHOGENESIS

The pathogenesis of diabetes nephropathy is multifactorial and remains poorly understood to date. There are various hypotheses and several factors have been implicated in its pathogenesis.

1.1.1 Hyperglycaemia

Hyperglycaemia has been implicated to play a permissive role in the initiation and progression of diabetic micro vascular disease. The UKPDS (3) demonstrated that improved glycaemic control might reverse microalbuminuria.

In the UKPDS and DCCT, better glycaemic control was demonstrated to lead to a lower incidence of DN and delay or stop progression to ESRD (3,4)

Various mechanisms have been suggested in which hyperglycemia may lead to the functional and structural abnormalities characteristic of DN

(A) Advanced Glycation End Products (AGE)

Formation of Advanced Glycation end – products (AGE's) is a potential pathway for glycaemic-induced injury. Glucose reacts with amino acids on proteins to form covalent bonded glycated products, an example of which is the glycated haemoglobin used to monitor the long-term control of glucose in patients with diabetes.

Glycation of glucose and amino group matrix (Maillard reaction) occurs and subsequently, Schiff base is converted to Amadori products. Initially, there is an Amadori product, which is stable, but reversible with better glucose control (9, 10). However with sustained hyperglycaemia further

chemical rearrangements occur with dehydration, fragmentation and cross linking reactions to form Advanced Glycation End Products (AGE) which are nearly irreversibly formed and thus once created, respond very little to improvement in glycaemic control. (11)

This alteration change functions of affected proteins. When AGE reacts with receptors on cells such as macrophages, they liberate cytokines and vascular adhesion molecules.

In addition, AGE may stimulate growth factor release from activated macrophages resulting in smooth muscle cell proliferation and vascular occlusion. Protein glycation itself may give rise to oxygen free radicals. Glycation of glomerular basement membranes interferes with its thickening, as well as mesangial matrix accumulation, which, may result in changes in permeability through vascular walls.

(B) Polyol Pathway

With sustained hyperglycaemia, there is increased activation of the polyol pathway in which excess glucose is shunted into sorbitol and fructose via the high aldose reductase (12).

Accumulation of sorbitol leads to alteration of cellular osmotic effects with subsequent cellular oedema and compensatory depletion of other important osmolytes such as myo-inositol and taurine. Depletion of myo–inositol is in part responsible for concomitant reduction in Na+ /K+ ATPase activity which has been identified within the glomerulus (12).

Aldose reductase, the enzyme required in this pathway, requires NADPH as a cofactor. Activation of aldose reductase thus depletes oxidized glutathione, which in turn affects synthesis of nitric oxide, an anti–oxidant. In this way, the polyol pathway is linked to oxidative stress.

This increase in the NADH / NAD+ ratio is also associated with de novo synthesis of diacyl glycerol (DAG) and subsequent stimulation of protein kinase (PKC) activity.

The activation of PKC stimulates extra cellular matrix production, presumably due to increased *de novo* synthesis of DAG. In murine mesangial cells, high ambient glucose promotes collagen IV gene transcription (13).

Hyperglycaemia *per se* (or high glucose concentration) causes a relevant influence on renal cell growth and extra cellular matrix metabolism. In tissue culture, high glucose concentrations stimulate proximal tubular cell hypertrophy as well as mesangial cell production of types I and IV collagen and laminin of which acute repeated and sustained hyperglycemic show similar effects (14).

1.2 Trophic factors

Transforming growth factor-beta –(TGF-β) is a central cytokine in cell growth and extracellular matrix production. There is evidence implicating it in the pathogenesis of diabetic renal disease (15). The development of renal hypertrophy is probably linked to the increased expression of TGF *B* 1 and the type II TGF B receptor in kidney as evidenced by attenuation of both hypertrophy and the increase in mRNAs encoding α1 – collagen and fibronectin after treatment of streptozocin induced diabetic mice with anti- TGF B antibodies. (16).

In humans, glomeruli from kidneys of patients with diabetic nephropathy over- express TGF β protein and increase in TGFβ and m RNA might be correlated with degree of hyperglycaemia. (17)

Although biomolecular and structural bases for diabetic proteinuria remain unresolved, changes in charge and in permeability selectivity of the glomelular basement membrane are believed to contribute consistently to this phenomenon. There is a close correlation between selective proteinuria and the heparan–sulphated proteoglycan synthesis and alters the sulphation patterns of epithelial cells. (18)

1.3 Haemodynamic effects

Glomerular hydrostatic pressure and glomerular filtration rate (GFR) increase within months of development of hyperglycaemia by a mechanism still being defined, but appears to involve atrial natriuretic peptide (ANP). Glycosuria triggers increased reabsorption of glucose coupled to sodium in the renal proximal tubule thereby increasing total body sodium and extracellular fluid volume. This leads to compensatory release of ANP from cardiac myocytes and induces natriuresis in part by triggering afferent arteriolar dilatation and thereby increasing intraglomerular pressure and GFR. Short term, this is not deleterious to the kidney. Long term, this sustained glomerular hypertension provokes thickening of glomerular basement membrane, increased mesangial matrix production and glomerulosclerosis, and disruption of barrier function.

Studies in experimental animals have demonstrated that this hyperfiltration is associated with elevations in glomerular capillary pressures, which may also occur in non-renal capillaries. This elevation in glomerular capillary pressure may in their own rights or through interacting with the effects of glycation or the structural glomerular enlargement induce pathologic glomerular capillary changes, mesangial proliferation, matrix expansion and basement membrane thickening. (19) In keeping with this, angiotensin converting enzyme inhibitors, which lower intraglomerular pressure, slow progression of DN even in normotensive patients.

It is likely that haemodynamic and metabolic factors act in concert to generate the final glomerulosclerotic phenotype in genetically predisposed patients.

2.0 NATURAL HISTORY OF DIABETIC NEPHROPATHY

Once initiated, the natural course of DN is one of progressive decline in renal function. It is therefore important to prevent or delay the process by identifying and controlling modifiable risk factors. (3,4).

2.1 Type 1 diabetes

Much is known about the natural history of diabetic nephropathy in type 1 diabetes. The progression of renal disease in type 1 diabetes is very different from patient to patient. Moreover, only a percentage of type 1 diabetic patients develop overt nephropathy.

Morgensen in 1989 described several stages, though arbitrary, in the development of diabetic nephropathy (20). These have been confirmed in other studies.

These are: -

Stage 1: Renal hyperfunction and hypertrophy:

In this stage, there is increase in the glomerular filtration rate (GFR) with concomitant increase in renal size. This is the stage of normoalbuminuria occurring within 5 years of Type 1 diabetes and depends on degree of glycaemic control.

Stage 2: Clinical Latency:

This is characterized by micro albuminuria with urinary albumin excretion rate between 30 and 300 mg in 24 hrs corresponding to 20- 200 ug/min in a timed specimen collection or to 30 -300mg /g of creatinine in a randomly collected sample.

Stage 3: Incipient nephropathy:

This is characterized by persistent micro albuminuria with elevated urinary albumin excretion rate, at a rate of about 10–20 % per year to the stage of overt nephropathy.

The GFR begins to fall and there is gradual increase in glomerular hypertension with a slight to moderate increase in systemic blood pressure.

Stage 4: Overt nephropathy:

In this stage there is clinical albuminuria or macroalbuminuria (urinary albumin excretion rate (UAER) of more than 300mg per 24hr) over a period of 10 – 15 years. Without specific intervention(s), the GFR gradually falls at a rate that is highly variable from individual to individual (2–20 mls /min/year). Systemic hypertension also develops along the way.

Stage 5: Renal failure:

This is end stage Renal Disease (ESRD) with uraemia developing in 50% of Type 1 diabetic individuals with overt nephropathy within 10 years and in over 75% by 20 years. (21). However the cumulative incidence of diabetic nephropathy seems to have decreased over the years. (21) (22).

2.2 Type 2 diabetes

Though the majority of research in diabetes has been directed toward type 1 diabetes, majority of diabetic patients have type 2 diabetes. The natural history and exact percentage of type 2 diabetic patients that develop nephropathy are still unknown.

A high proportion of individuals with type 2 diabetes are found to have microalbuminuria and overt nephropathy shortly after diagnosis of their diabetes. This is because diabetes has actually been present for many years before the diagnosis is made and also the presence of albuminuria may be less specific for the presence of diabetic nephropathy. (23). Moreover, type 2 diabetes is a complex syndrome in which obesity, hypertension, dyslipidaemia and microalbuminuria often precede onset of

frank hyperglycaemia or development of diabetes may be part of the metabolic syndrome or 'Syndrome X".

Microalbuminuria precedes overt proteinuria but only 20% of microalbuminuric type 2 patients develop overt nephropathy in a ten year period (24), and by 20 years after onset of overt nephropathy, only 20% will have progressed to ESRD. Once the GFR begins to decline, the rate of decline varies between individuals but may not be substantially different between type 1 and 2 patients. Nephropathy has a different impact in different ethnic groups. In Type 2 diabetes, Asian Pacific Islanders have the highest risk followed by Hispanics and African – Americans with Caucasians having the least risk.

Among Pima Indians, a group of Native Americans living in Arizona where 50% develop type 2 diabetes, the rate of nephropathy is 50 % after 20 yrs of type 2 diabetes. The GFR is often increased at onset of diabetes and remains elevated as long as normal urinary albumin excretion or microalbuminuria persists. After the onset of macroalbuminuria in Pima Indians, the GFR declines at least as rapidly as reported in type 1 diabetic patients. (25, 26)

3.0 RISK FACTORS

Several risk factors have been implicated in enhancing progression of diabetic nephropathy. Most of these risk factors interplay such that modification of modifiable risks factors would therefore delay or stop progression of the disease.

(i) Genetics

There appears to be familial predisposition to nephropathy in certain diabetics supported by the fact that only 50% of patients ever develop DN regardless of metabolic status or duration of disease. (27,28). This genetic predisposition for nephropathy has been linked to polymorphism of the Angiotensin converting enzyme (ACE), angiotensinogen and angiotensin receptor genes. (29)

Studies have shown a better response to ACE inhibitors in those with the double insertion genetic variation of the ACE gene and a more accelerated progression of disease in those with the double deletion genotype.

A study done in Austria by Barnas et al (30) in type 1 diabetic patients with and without diabetic nephropathy, the double deletion genotype was more prevalent in patients with renal disease, and more so in the subgroup of patients with diabetes for more than 20 years. Earlier, in 1996, Quinn et al (31) examined concordance for diabetic nephropathy in families with multiple 1DDM siblings. For pro-bands and siblings combined, the cumulative incidence of advanced diabetic nephropathy after 30 years of 1DDM was 35%, but the risk in siblings varied according to the probands renal status. The cumulative risk in siblings after 25 years of 1DDM (Post–puberty) was 71.5% if the proband did not have nephropathy. This difference of nearly 50% in the risk to 1DDM siblings, depending upon

the 1DDM probands renal status, was consistent with a major gene effect that predisposes an individual with IDDM to develop advanced diabetic nephropathy.

This familial clustering has also been observed in Pima Indians the majority of who have type 2 diabetes. Pettitt et al (28) found that proteinuria was present in 14 % diabetic offspring in whom neither parent had proteinuria, 23 % in whom one parent had proteinuria and in 46% in whom both parents had proteinuria.

(ii) Gender

Male sex has been significantly associated with diabetic nephropathy (32,33) in type 2 diabetes. However its role in diabetic nephropathy may be minor, as most studies do not report gender disparities (34).

(iii) Hyperglycaemia

Hyperglycaemia, transient or persistent, is the most important factor in both type 1 & 2 diabetes before the stage of overt nephropathy. Rasmuseen et al did a two-year study of Type 1 diabetics with incipient nephropathy, which demonstrated that intensive blood glucose control does prevent persistent proteinuria and rise in blood pressure. Notably, the glomerular filtration rate also fell during insulin infusion but remained unchanged in the conventional insulin treatment group.(35). The DCCT showed intensive therapy reduced the risk of microalbuminuria by 34% and that of albuminuria by 54%.(4). It also predicted that intensive treatment gained 5.8 additional years free from ESRD and 5.1 additional years of life expectancy.

Rossing et al (34) showed HbAic to be a significant predictor of progression from normoalbuminuria to microalbuminuria or macroalbuminuria. In other studies (35,36) the incidence and progression of microalbuminuria was significantly associated with poor glycaemic control.

In type 2 diabetes, the UKPDS (3) conclusively demonstrated that intensive blood glucose control was highly beneficial in reducing the incidence of diabetic microvascular complications. Each per cent reduction in HbAic was associated with 35% reduction in microvascular complications, 25% reduction in diabetes related deaths and 7% reduction in all cause mortality. .

(iv) Hypertension

Controlling systemic hypertension may be the most important intervention to slow progression of established nephropathy.

In both type 1 and type 2 diabetes, hypertension is a significant risk factor for nephropathy, accelerating its progression and perhaps even causing the onset of glomerulopathy (37). In the Microalbuminuria Collaborative Study Group, the patients who progressed to microalbuminuria had raised blood pressure and albumin excretion rate before microalbuminuria became persistent (38) . Mogensen (39) was able to demonstrate that treatment of hypertension can slow progression of established nephropathy. It appears that strict metabolic control also reduces blood pressure (35). In type 2 diabetes, hypertension is a common finding either preceding or diagnosed at time diabetes is found, probably as part of the 'metabolic syndrome.' Nielsen et al showed that systolic blood pressure was related to the rate of decline of glomerular filtration rate (40). Like in type 1 diabetes, several studies have shown hypertension to be related both to the development and progression of diabetic nephropathy (33,41,42,43). Similarly, strict blood pressure control has been shown to reduce the incidence and progression of renal disease in type 2 diabetes (44). Antihypertensive agents of

almost any therapeutic class may be appropriate but Angiotensin-converting enzyme (ACE) inhibitors have been particularly effective in slowing progression of renal insufficiency in patients with and without diabetes mellitus by reducing angiotensin II effects on renal hemodynamics, local growth factors, and perhaps glomerular permselectivity (45,46,47). Non-dihydropyridine calcium channel blockers were also shown to retard progression of renal insufficiency in patients with type 2 diabetes mellitus. Recently, angiotensin receptor blockers have been shown to have renoprotective effect in diabetic nephropathy and the effect is independent of the reduction in blood pressure (48-52) Early detection and effective treatment of hypertension to desired levels is essential to retard the progression of chronic kidney disease. The benefit of aggressive blood pressure control is most pronounced in patients with urinary protein concentration of more than 3 g/24-h and benefits patients with both diabetic and nondiabetic renal disease (53). Target Blood Pressure is less than 130/80mmHg in diabetics and all patients with renal disease and less than 125/75mmHg in proteinuric renal disease. (54).

(v) Smoking

Smoking causes vasoconstriction impaired platelet function, abnormal regulations of coagulation and a transient rise in blood pressure, which may aggravate vascular damage. Cigarette smoking has been associated with progression of nephropathy in both type 1 and 2 diabetes. In the Microalbuminuria Collaborative Study Group (38) smoking was found to be an aggravating factor in the process and in another study (34) it was found to be a putative risk factor for progression of nephropathy in type 1 diabetes. Yokota et al (35) studied 54 patients with type 2 diabetes who had established nephropathy to evaluate the risk factors for the progression of the nephropathy. Smoking was associated with decline in renal function whereas non-smokers did not show that tendency. In addition, the relation

between decline in renal function and mean arterial pressure was relatively stronger in smokers without hypercholesterolaemia than with non-smokers with hypercholesterolaemia. This association was also reported by Ravid et al (33).

(vi) Duration of diabetes and age of patient

In type 1 diabetes, longer duration of diabetes has been associated with increased incidence and progression of diabetic nephropathy (36) but not in some studies (34).

In type 2 diabetes, the incidences of all micro vascular complications have been shown to increase with duration of diabetes (55). At one study patients diagnosed after age of 50 years had a higher prevalence and degree of microalbuminuria than those diagnosed before age 40 years. However, the later age of diagnosis may suggest a longer duration of preclinical metabolic abnormalities exerting their damage on the kidney. However, in the UKPDS, age was not found to be one of the factors that influenced progression of microalbuminuria (3), while in another it influenced progression (33). In the latter, study duration of diabetes was not a risk factor for progression of nephropathy.

(vii) Dyslipidaemia

Lipid abnormalities may be evident with only mild renal impairment and contributes to the progression of CKD (56,57) and the increased cardiovascular morbidity and mortality of these patients.

Lipoprotein lipase activity falls in patients with GFR of 50 ml/min or less, and triglyceride levels start to rise when GFR is in the range of 15-30 ml/min (58,59). Abnormalities include hypercholesterolaemia, elevated ratio of low- to high-density lipoproteins, elevation of lipoprotein a, and elevated chylomicron remnant levels.

Hypercholesteroalaemia plays a pathogenic role in the development of progressive renal injury. It is known that LDL binds to the LDL receptors on the surface of the mesangial and epithelial cells and can stimulate cell proliferation, generation of monocyte chemo attractant proteins, and production of matrix proteins. (56)

In experimental animals, lipid-lowering agents have been shown to protect against progressive renal injury. In human renal disease, the evidence is limited but preliminary studies (60) suggest that these agents may reduce proteinuria and stabilize renal function.

(viii) Proteinuria

Recent studies suggested that proteinuria, previously considered just a marker of the severity of kidney disease, may itself be pathogenic (61). In chronic non-diabetic nephropathies, baseline urinary protein excretion rate is the best single predictor of renal disease progression. The higher the urinary protein excretion, the faster the subsequent decline in GFR and, even more important, the quicker the progression to ESRD (62).

Pharmacologic interventions that reduce urinary protein excretion also limit progressive decline in renal function in both diabetic and non-diabetic proteinuric glomerulopathies.

Angiotensin blockade with ACE-inhibitors or angiotensin receptor blockers have clearly shown that at comparable levels of blood pressure control, these agents are more effective than conventional antihypertensive agents in reducing proteinuria, GFR decline and progression to ESRD. (48-52).

(ix) Dietary protein

Dietary protein restriction may be beneficial by preventing glomerular hyperperfusion and hypertension and compensatory hypertrophy and by reducing the intrarenal formation of angiotensin

II and thromboxane. It is also known that low-protein diets reduce the generation of nitrogenous wastes and inorganic ions that cause many of the clinical and metabolic disturbances characteristic of uraemia. Moreover, low-protein diets can diminish the ill effects of hyperphosphataemia, metabolic acidosis, hyperkalaemia and other electrolyte disorders. Whether dietary protein restriction slows the progression of CKD remains controversial (63,64). Various smaller studies suggested that dietary protein restriction might slow the rate of decline in kidney function but were criticised for their small size and methodology. The largest and better-controlled study – the Modification of Diet in Renal Disease (MDRD) Study failed to find an effect of protein restriction on decline of kidney function (65). Recently, the results of MDRD study have been re-examined using correlation analyses based on achieved protein intake rather than on the intention to treat analysis. Secondary analysis suggested that a lower protein diet retards the progression in both moderate (66) and advanced (64) renal disease.

(x) Phosphate

Hyperparathyroidism appears to be one of the earliest manifestations of renal disease as a response to impaired renal function. Increased parathyroid hormone (PTH) levels have been demonstrated when the GFR falls below 60 to 80 ml/min (67). This causes increased calcium and phosphate reabsorption from the gut with the net result of increase in the same.

Progression of CKD occurs from chronic tubulo-interstitial inflammation caused by increases in single-nephron filtered load of phosphate, absolute tubular reabsorption of phosphate, and calcium-phosphate product in the tubular lumen and by precipitation of calcium phosphate in the tubules and interstitium, facilitated by reduced concentration of citrate in the tubular fluid (68). This hypothesis is supported in experimental animals showing that a high-phosphate diet aggravates CKD, whereas a

low-phosphate diet, administration of phosphate binders, and 3-phosphocitrate (an inhibitor of calcium phosphate precipitation) slows progression of CKD.

In a study of 246 human renal biopsies, elevated tissue calcium levels were found to exist early in renal disease. Renal calcium content correlated significantly with serum creatinine and serum phosphorus, but not with serum calcium. The severity of renal calcification was closely related to hyperphosphataemia and Ca x P product. This finding supports the hypothesis that phosphate-mediated renal calcification is an important factor that may influence the rate of kidney disease progression (69). Hence, it is recommended to reduce the exposure of kidney to calcium phosphate precipitation by adequate fluid intake, modest dietary phosphate restriction, and administration of phosphate binders, preferably using calcium-free phosphate binders to avoid calcium load (70).

A recent study identifies a strong relationship between elevated serum phosphate, Ca x P product, and parathyroid hormone (PTH) and cardiac causes of death, especially deaths from coronary artery disease and sudden death, in haemodialysis patients (71)

Treatment goals (72) recommended are: serum phosphorus range of 0.8-1.87 mmol/L (2.5 – 5.5 mg/dL); serum calcium range of 2.3-2.4 mmol/L (9.2 – 9.6 mg/dL); Ca x P product of less than 4.4 $mmol^2/L^2$ (less than 55 mg^2/dL^2) and serum PTH of 100-200 pg/mL.

(xi) Anaemia

Anaemia of CKD is normochromic and normocytic and is invariably present and begins early, when GFR falls below 30-35% of normal. This is primarily due to decreased erythropoietin (EPO) production by the failing kidney (73) though other concomitant factors should be considered in the evaluation of anaemia in patients with CKD.

Whether anaemia accelerates the progression of kidney disease is controversial.

Anaemia decreases both oxygen delivery and protection against oxidative stress and may favor tubular obstruction secondary to interstitial fibrosis. Hypoxia and oxidative stress probably stimulate the production of extra cellular matrix by fibroblasts, increasing fibroblasts and creating a vicious cycle.

Anaemia is independently associated with the development of left ventricular hypertrophy (LVH) and other cardiovascular complications in CRI patients (74,75). CRI, anaemia and cardiovascular disease are associated with each other in a complex vicious cycle and contribute to progression of chronic kidney disease, commonly referred to as cardio-renal anaemia syndrome.

Whether treatment of anaemia with recombinant human erythropoietin (rHuEPO) slows the progression of CKD remains elusive. In two small prospective studies (76,77) correcting anaemia with rHuEPO significantly slowed the progression of CRI.

There is a suggestion that treatment of anaemia with rHuEPO may slow progression of CKD.

The NKF-DOQI guidelines (78) recommend that patients with CRI and anaemia should be investigated and treated for iron deficiency and other causes of anaemia. The maintenance haematocrit and haemoglobin target for CRI patients remains uncertain. A target level of 33% to 36% of haematocrit (haemoglobin of 11-12g/dl) for dialysis and predialysis patients is recommended. Numerous studies in CRI population suggested that this range could be safely achieved with no increase in the rate of progression of CKD (79-82). However, treatment of anaemia with rHuEPO can elevate blood pressure or require an increase in antihypertensive medications (79,81,83) to control hypertension effectively or to prevent its development.

TABLE 1: RISK FACTORS

NON – MODIFIABLE	MODIFIABLE
Age of patient	Hyperglycaemia
Genetics	Hypertension
Gender	Tobacco Use
Duration of Diabetes	Hyperlipidaemia
	Proteinuria
	Anaemia
	Hyperphosphataemia

TABLE 2: MODIFIABLE RISK FACTORS

RISK FACTORS	RATIONALE / TARGET	INTERVENTION
Hyperglycaemia	Normal or nearly normal blood glucose levels	Diet Oral hypoglycaemia agents Insulin
Hypertension	BP<125/75 mmHg in patients with proteinuria	ACE inhibitors ARB
Tobacco use	Discontinue	Counselling Nicotine replacement therapy (e.g. patches)
Hyperlipidaemia	LDL <1.7 mmol/L TG <1.7 mmol/L HDL >1.03mmol/L	Diet HMG CoA reductase Inhibitors (statins) Diet Niacin exercise
Proteinuria	Reduce or Stop	Diet ACE I ARB
Hyperphosphataemia	Normal	Diet Phosphate binders
Anaemia	Normal or near normal Hb 11 – 13 g/dl (PCV 33 – 36%)	Diet Iron EPO

4.0 JUSTIFICATION

Diabetes has become the most common single cause of end stage renal disease (ESRD) in the wo
This is mainly because diabetes mellitus (DM) is increasing in prevalence (especially type 2 whicl
soon reaching epidemic proportions), these patients live longer and diabetic patients are now be
accepted for treatment in ESRD programmes where formerly they had been excluded.

Several studies have shown that diabetics enter into renal replacement programs earlier since they
not able to tolerate uraemia as well as non-diabetic renal patients. Moreover, diabetic renal patie
pose special problems at ESRD programmes since they have more difficult vascular access due
accelerated artherosclerosis and they have poorer outcome due to higher cardiovascu
complications, which are also the major cause of death pre and post-dialysis. They require spec
attention at renal transplantation: meticulous glucose control, more difficult surgery because
artherosclorosis complications, and higher incidence of complication due to immunosuppress
therapy and artherosclerosis. More importantly, renal replacement therapy (RRT) is very expensi
Diabetics form about one-third of patients on dialysis at the Renal Unit of KNH. On avera
patients on dialysis at KNH spend a minimum of 55 US dollars per session (440 US dollars
month). This is basically out of reach for many Kenyans. For those who enter RRT, this po
enormous social, cultural and economic demands and implications to the individuals, relativ
community and eventually the nation at large. This high socio –economic burden may threaten
overwhelm existing infrastructure.

It is therefore very important to look at the prevalence of factors associated with progression of CKD
so that we can plan better on how to timely put in place modalities that delay or, if possible, stop the
progression to ESRD.

Fortunately, there is evidence to show that modification of specific risk factors can retard and / or lengthen time to ESRD. It is therefore useful to determine modifiable risk factors for intervention. It would also improve morbidity and reduce mortality of those who eventually enter ESRD programmes.

This study aimed at providing data on prevalence of these risk factors in the hope of influencing clinicians on adopting complete management of these patients. It also formed basis for future studies.

5.0 AIM AND OBJECTIVES

AIM

To study modifiable risk factors associated with progression of renal failure among diabetic patients with chronic renal insufficiency.

SPECIFIC OBJECTIVES

1. To determine prevalence of modifiable risk factors associated with progression of nephropathy in diabetic patients with chronic kidney disease that is:

   Poor Glycaemic control

   Hypertension

   Macroproteinuria

   Anaemia

   Dyslipidaemia

   Hyperphosphataemia

   Elevated Calcium-Phosphate Product

   Cigarette Smoking

2. To describe possible clustering of these risk factors among diabetic patients with CRI.

6.0 DESIGN AND METHODS

STUDY DESIGN

Descriptive cross sectional study

STUDY POPULATION:

All diabetic patients attending diabetic and/or renal medical clinics and all diabetic patients admitted in medical wards with Glomerular Filtration Rate (GFR) less than 90mls/min expected using Cockroft-Gaults formula.

STUDY DURATION:

Seven months, from May 2004 to December 2004.

SAMPLING:

All consecutive patients meeting inclusion criteria were recruited.

7.0 PATIENT SELECTION

7.1 INCLUSION CRITERIA

1) All diabetic patients diagnosed to have Chronic Renal Insufficiency (CRI)

CRI was defined as estimated GFR, using calculated creatinine clearance (Cockroft-Gault formula), of less than 90ml/min, with no identifiable reversible cause (85) such as acute renal failure, diabetic ketoacidosis, and acute infection.

2) A duly signed informed consent from the patient.

7.2 EXCLUSION CRITERIA

1) History of current steroid use
2) Patients with gestational diabetes or diabetes in pregnancy.
3) Patients unwilling to give consent
4) Patients already on dialysis because the GFR was artificial.
5) Patients with or suspected to suffer from condition known to interfere with HbA1c assay for example haemoglobinopathies, haemolytic anaemia and lead poisoning.

8.0 MATERIALS AND METHODS

For all recruited patients, history was taken to include demographic data, pertaining to current age, gender, age at diagnosis of diabetes, usual residence, level of formal education, and occupation. Age was confirmed with national ID where possible.

Medical history with attention to prior diagnosis of hypertension and or treatment with anti hypertensive agents were obtained.

8.1 DRUG, PAST MEDICAL AND FAMILY HISTORY

Family history of Diabetes Mellitus or Hypertension -first degree relative or not; or any co-morbidity; record of all current regular medications and dosages were made (Appendix III).

8.2 HISTORY OF SMOKING

Current smokers were patients who would have smoked at least 100 cigarettes in their lifetime and were still smoking or would have quit smoking within the preceding year.

Former smokers were those who would have smoked at least 100 cigarettes in their lifetime but would have quit smoking more than one year earlier.

Individuals who would have smoked less than 100 cigarettes or who had never smoked were considered as non-smokers. (85).

8.3 PHYSICAL EXAMINATION

Weight was measured to nearest half kilogram (kg) with patient in light clothing and no shoes using a standard weighing chair or machine in the clinic or ward. Height was measured against a vertical scale while patient had no shoes and recorded to nearest half centimeter (cm)

Waist circumference was measured as minimum circumference between the coastal margins and the iliac crest, to nearest half centimeter (0.5cm). Hip circumference was taken as circumference at the level of the great trochanteric prominences; where these were not palpable then the greatest gluteal circumference was measured, to nearest half centimeter (0.5cm)

Calculated BMI = weight (kg)/height ^{2} (m^2.) (86)

Waist: Hip circumference ratio was determined and android obesity defined as waist /hip ratio >0.85 females and >1.0 for males.

Blood pressure was measured with patient in supine position, after a rest of 15 minutes, by normal manual technique using mercury sphygmomanometer and an 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 (phase 5) (JNC VII). Two such readings were taken; with the reading being taken from the top of the meniscus and expressed to the nearest 5 mmHg and the blood pressure was then expressed as a mean of the two readings.

Hypertension was defined as a systolic BP ≥130mmHg and/or a diastolic of ≥80 mmHg or if normotensive (BP 130/80mmHg] but previously diagnosed as having hypertension and on antihypertensive medication.

Hypertension was grouped into categories as per the JNC VII criteria (54):

If the diastolic and systolic BP fell into different grades then the higher of the two determined the grade of hypertension.

8.4 LABORATORY METHODS

Following at least 8 hrs of fasting, 8 mls of blood was drawn by venepuncture under aseptic technique for the following investigations:

1. Serum urea, creatinine electrolyte and albumin assays were performed at the renal unit Kenyatta National Hospital with the Random Access clinical chemistry analyzer RA 1000 (Technicon Instruments, USA). Creatinine was assayed using the alkaline picrate reaction. Urea was assayed using enzymatic kinetic method. The ion selective electrode (ISA) method was used to assay sodium, potassium, calcium, albumin and phosphate using bromocresol green.

Predicted GFR was calculated from the serum creatinine measured using Cockroft-Gaults formula: (87) as shown below:

Males =(140-age in years) x (weight in kg)/ (plasma creatinine (mg/dl) x72)

Females: above value x 0.85

CKD was classified using the NKF NDQI guidelines as follows (91)

TABLE 3; CKD CLASSIFICATION

CKD STAGE	GFR MLS/MIN	CLINICAL CORRELATE
STAGE 1	>90	NORMAL
STAGE 2	>60-90	MILD
STAGE 3	>30-60	MODERATE
STAGE 4	>15-30	SEVERE
STAGE 5	O-15	ESRD

Glycated haemoglobin (HbA1c) assay was done using Turbimetric inhibition immunoassay (TINA). (Roche) method on an automated immunoassay analyzer (AEROSET) at Nairobi Hospital Laboratories.

The method uses Tetradecyltrimethylammoniumbrode (TTAB) as detergent in haemolysing reagent to eliminate interference from leucocytes. The HbA1c determination is based on the turbimetric inhibition immunoassay (TINIA) for haemolysed whole blood in 2 steps.

- Sample and addition of R1 (buffer/antibody) glycohaemoglobin (HbA1c) in the sample reacts with anti-HbA1c antibody to form soluble antigen-antibody complexes
- Addition of R2 (buffer/polyhapten) and start of reaction: The polyhaptens react with excess anti HbA1c antibodies to form an insoluble antibody polyhapten complex, which can be determined turbidimetrically. Haemoglobin concentration is determined in a second channel. Liberated haemoglobin in the haemolysed sample is converted to a derivative having a characteristic absorption spectrum, which is measured bichromatically. HbA1c is calculated as a percentage of the haemoglobin.

Lipid profile assays were performed at the Nairobi Hospital, Department of Clinical Chemistry aboratory using AEROSET® automated machine.

'lasma total cholesterol was assayed after enzymatic hydrolysis of cholesterol esterase to cholesterol nd free fatty acids. Cholesterol oxidase then oxidized free cholesterol including that originally resent. HDL cholesterol was assayed by solubising the HDL lipoprotein particles using a detergent ontaining polyanion 4 aminoantipyrine and a buffer solution that released HDLc which was then etermined after enzymatic hydrolysis and oxidation as for total cholesterol.

LDL-cholesterol was assayed by solubising the non HDL lipoprotein particles by enzymatic hydrolysis and oxidation as for total cholesterol. The remaining LDL particles were solubised using N, N-bis (4 sulfobuty)-M-toludine disodium and a buffer solution, and a chromogenic coupler leading to colour change

Triglycerides were determined by enzymatic hydrolysis by lipoprotein lipase to free fatty acids and glycerol. Glycerol was then phosphorylated by adenosine triphosphate (ATP) in the presence of glycerol kinase to glycerol-3-phosphate, which was then oxidized by molecule oxygen hydrogen peroxide (H202) and dihydroxyacettone phosphate (DAP). The H202 was used to oxidatively couple p-chlorophenol and 4 aminoantipyrine (4-AAP) catalysed by peroxidase (POD) to a red dye, whose absorbance would be proportional to the concentration of triglyceride in the plasma sample

Dipstick analysis of urine was undertaken on an early morning mid stream specimen (MSSU) urine using the Combur 10 test strips (Bayer). This assessed the presence of ketones, leucocytes, protein nitrite, glucose, red blood cells and pH of urine.

9.0 DEFINITION OF STUDY VARIABLES

CIGARETTE SMOKING

Current smokers were patients who would have smoked at least 100 cigarettes in their lifetime and were still smoking or would have quit smoking within the preceding year.

Former smokers were those who would have smoked at least 100 cigarettes in their lifetime but would have quit smoking more than one year earlier.

Individuals who would have smoked less than 100 cigarettes or who had never smoked were considered as non-smokers. (85).

OBESITY

Calculated BM1 = weight (kg)/height ^{2} (m^2.) (86)

BM1 kg/m^2	Degree of Obesity
<18.5	Underweight
18.5-24.9	Ideal
25.0-30.0	Overweight
30.0-34.9	Grade 1
35.0-39.9	Grade 2
>40	Grade 3

Obesity was defined as BMI >30.0

Android obesity defined as waist /hip ratio (WHR) >0.85 for females and >1.0 for males.

HYPERTENSION

Hypertension was defined as a systolic BP ≥130mmHg and/or a diastolic of ≥80 mmHg or if normotensive (BP 130/80mmHg] but previously diagnosed as having hypertension and on antihypertensive medication.

Hypertension was grouped into categories as per the JNC VII criteria (54):

BP Classification	Systolic BP mmHg		Diastolic BP mmHg
Normal	<120	and	<80
Pre-hypertension	120-139	or	80-89
Stage 1 Hypertension	140-159	or	90-99
Stage 2 Hypertension	≥160	or	≥100

If the diastolic and systolic BP fell into different grades then the higher of the two determined the grade of hypertension.

GLYCAEMIC CONTROL

GLYCATED HAEMOGLOBIN

Degree of glycaemic control classified as follows; (88)

HbA1c	Control
4.5-6.0	Ideal
6.0-6.9	Good
7.0-8.0	Fair (Marginal)
>8.0	Poor

Poor glycaemic control was defined as HbA1c >7%

FASTING BLOOD GLUCOSE

FBS	Control
<4mmol/l	Low
4-7mmol/l	Good
>7mmol/l	High

Poor glycaemic control was defined as fasting blood sugar >7mmol/l

DYSLIPIDAEMIA

Lipid abnormalities were classified using the ATPIII (NCEP) (89) as follows;

Hypercholesterolaemia	>6.2mmol/L	High
	4.9-6.18mmol/L	Borderline high
	<4.9mmol/L	Desirable

Hypercholesterolaemia was defined as total cholesterol >4.9mmol/l

LDL cholesterol	<2.58mmol/L	Optimal
	2.58-3.33mmolL	Near optimal
	3.34-4.11mmolL	Borderline high
	4.12-4.88mmolL	High
	>4.91mmol/L	Very high

High LDLc was defined as LDLc >2.58mmol/l

HDL cholesterol	<0.9mmol/L	males	Low
	<1.15mmo/l	females	Low

High HDLc was defined as >1.15mmol/l in females and >0.9mmol/l in males

Hypertriglyceridaemia was defined as TG>1.7mmol/l

ANAEMIA

Anaemia was defined as <11g/l in pre menopausal females and

<12g/l in males and postmenopausal females (78)

HYPERPHOPHATAEMIA

Hyperphosphataemia was defined as serum phosphate >1.45mmol/(72)

CALCIUM AND PHOSPHATE PRODUCT

Elevated Calcium phosphate product was defined as Ca *PO4>4.4mmol^2/l (72)

PROTEINURIA

Macroproteinuria was defined as from trace protein on dipstick.

10.0 SAMPLE SIZE

The sample size for this study was estimated using a statistics table for descriptive studied for dichotomous variables. The study sample size was based on a 90% confidence level and with 8% precision maximum using the following formula:

$$N = \frac{Z_{1-1\alpha/2} \times P(1-P)}{d^2}$$

Where N is the calculated sample size

P is the expected proportion

d is the precision

Z is a constant

The least prevalent risk factor was used to calculate the sample size. The prevalence used in this study is indicated in the following table, having been established from previous studies (6,8,90).

RISK FACTOR	PREVALENCE
Poor glycaemic control	37.5%
Hypertension	61%
Cigarette smoking	19%
Anaemia	59%
Dyslipidaemia	56%
Proteinuria	15.6%
Hyperphosphataemia	70%

From the above data the minimum sample size derived was 108 patients.

11.0 DATA ANALYSIS

Data was collected using a standard questionnaire (Appendix I) and coded before being entered into a computer using SPSS version 10.0 package software.

Data were summarized into means, range, standard deviation and modes. The data was presented in the form of tables, histograms, bar charts and pie charts. Categorical data were examined for association using Chi squared Pearson test and a p value of 0.05 was taken as significant. Significant difference between different groups was determined using the Mann Whitney test. A p value of 0.05 was used to assess the level of significance.

12.0 ETHICAL CONSIDERATIONS

1. Permission to carry out the study was sought from, and granted by, the KNH Ethics and research committee.
2. The patient or the guardian for those under 18 years was to sign an informed written voluntary consent.
3. The usual care and evaluation procedures were facilitated.
4. Results of the investigation were communicated to the primary health care providers to facilitate improved care of the patient.
5. Any medication contraindicated in CRI was discontinued and medications with compelling indication were suggested.
6. All patients were referred to a kidney specialist in the renal clinic or unit.
7. The process of renal replacement therapy was facilitated for patients with immediate indication for dialysis.
8. Those who declined to give consent were not discriminated upon.
9. Confidentiality was maintained.

13.0 RESULTS

Three hundred patients were screened between May 2004 and December 2004. One hundred thirty-three patients satisfied the inclusion criteria. Of these, eleven died before recruitment, three failed to turn up and three withdrew their consent, one had concomitant bone marrow failure and four had haematuria. Of one hundred eleven recruited, seventy-six were from the medical wards, ten from diabetic clinic and twenty-five from renal clinic.

a) DEMOGRAPHICS

Of the one hundred eleven patients recruited, 65% were females and 35% were males. The mean age of the study population was 56.2 years (SD 15.2) ranging between 18 and 88 years. Most patients (68%) were between 51 and 70 years.

The age and gender distribution is shown in Figure 1 below.

Figure 1: Age and Gender Distribution among Study Population

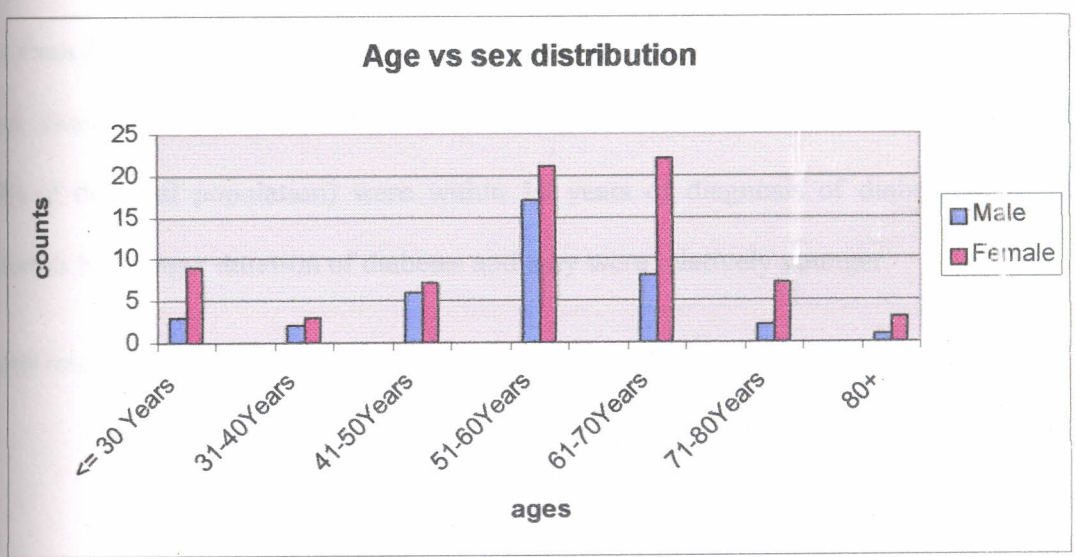
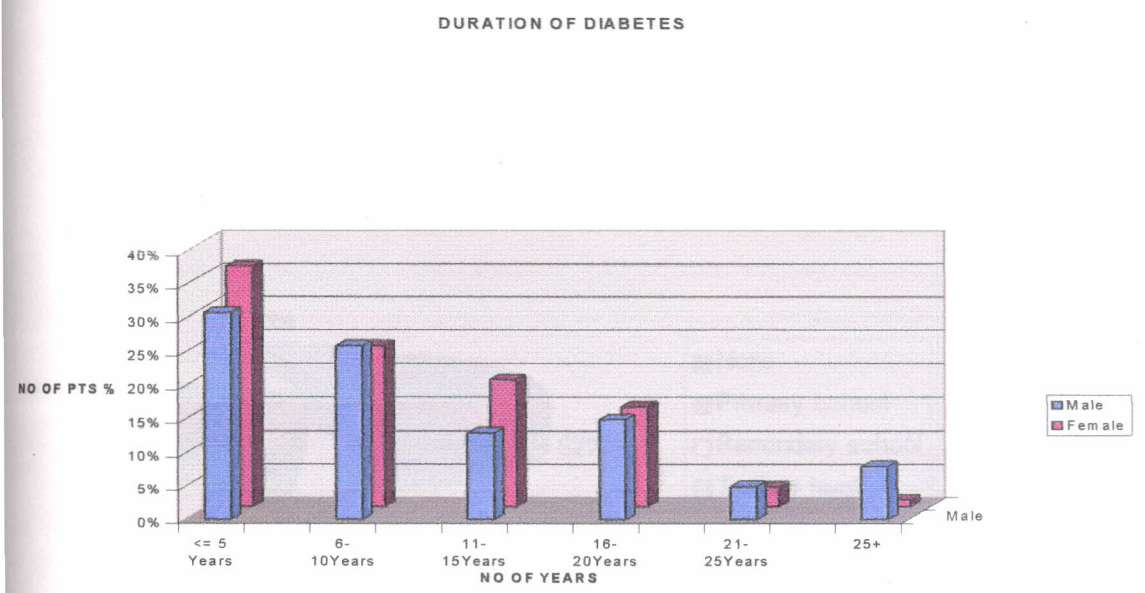


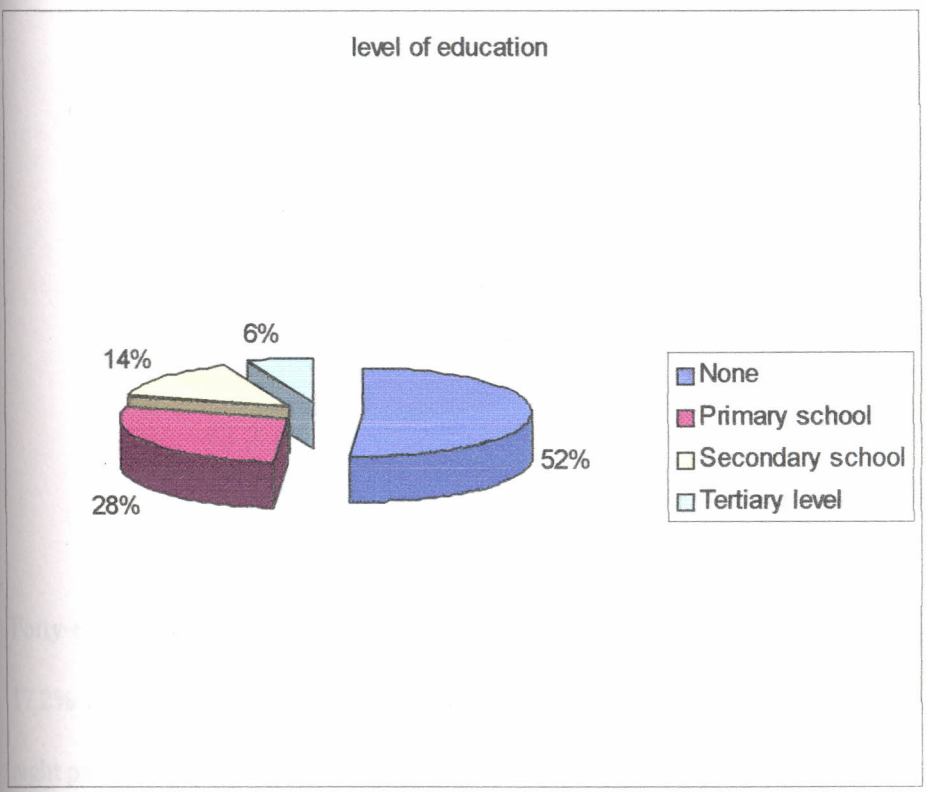
Figure 2: Duration of Diabetes Among Study Population



The mean duration of diabetes was 10 +/- 7.336 years ranging from less than one year to eighty- eight years. Thirty-eight patients (34%) had been diagnosed with diabetes for 5 years. Sixty-four patients (58% of the total population) were within 10 years of diagnosis of diabetes (Figure 2). Type 1 Diabetics had longer duration of diabetes and they were relatively younger.

Eighty one patients (73.4%) came from Nairobi and its environs.

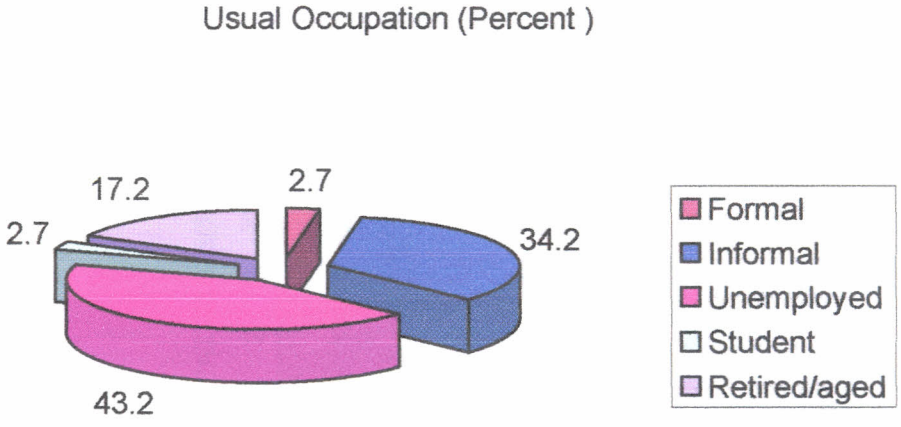
Figure 3: Level of Formal Education



Fifty-eight patients (52%) had no formal education. Thirty-one patients (28%) had primary education, Fifteen patients (14%) had secondary education and only seven patients (6%) had tertiary education (Figure 3). The level of education significantly correlated inversely with GFR with a significant p=0.00511. In this population, patients with lower level of education tended to have more advanced renal dysfunction.

Usual Occupation of the Entire Study Population

Figure 4: Usual Occupation of the Entire Study Population



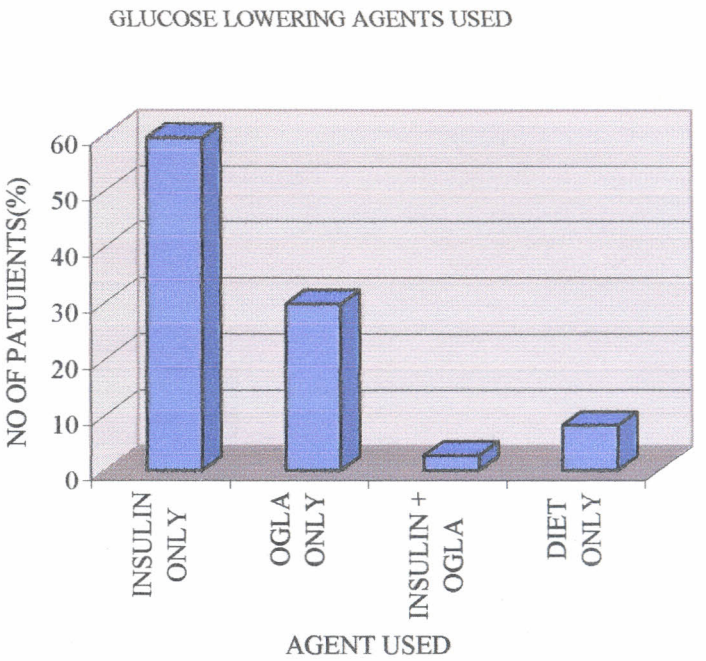
Forty-eight (43.2%) of the patients were unemployed, thirty-eight (34.2%) had informal employment. 17.2% were retired or aged and 2.7% were students and only 2.7% had formal employment. Sixty-eight patients (61.3 %) had to rely on other family members for their livelihood.

Sixty-three patients (56.8%) were known hypertensives, of which 71.3% were within 5 years of diagnosis. Forty-six patients had concurrent co-ormobidities. Seventeen patients (15.3%) had peripheral neuropathy, twelve patients (10.8%) had retinopathy of whom two were blind, three patients (2.7%) had had amputation and 12% had either recurrent hypoglycemia (11.3%), or heart failure (2.7%) and one had recovered from a previous stroke.

Forty-one patients (36.9%) had relatives with diabetes of which 78% were first-degree relatives. One patient had both parents and all 6 siblings with DM. A family history of hypertension was present in 17.1% of the patients and all were first-degree relatives. Only six patients (5.4%) had relatives with nephropathy, all were first degree

b) MEDICATIONS USED BY STUDY POPULATION

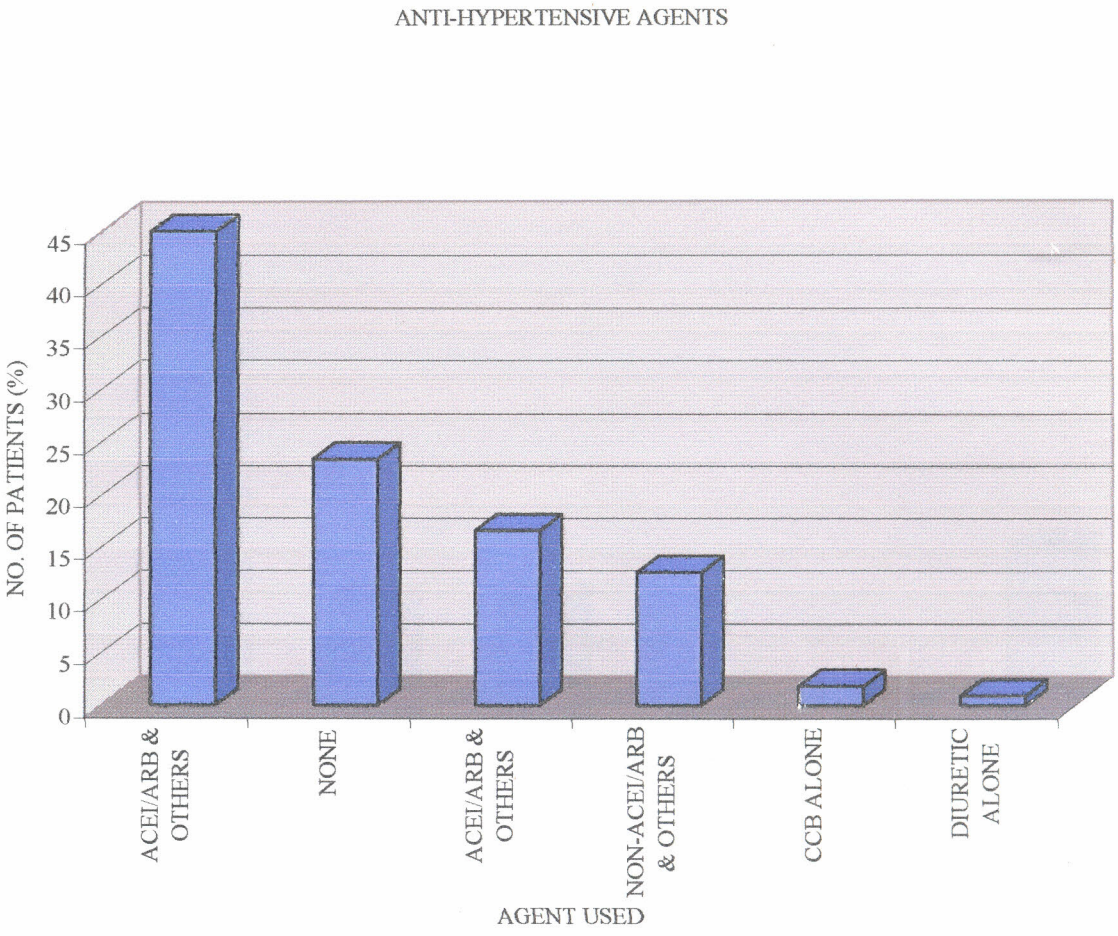
Figure 5: Glucose Lowering Agents Used by the Study Population



Nb:OGLA is Oral Glucose Lowering Agents

Sixty-six patients (59.5%) were on Insulin monotherapy, thirty=three patients (29.7%) were on oral glucose lowering agents monotherapy, three patients (2.7%) were on the combination therapy of insulin and oral glucose lowering agents and nine patients (8.1%) were controlled on diet alone.

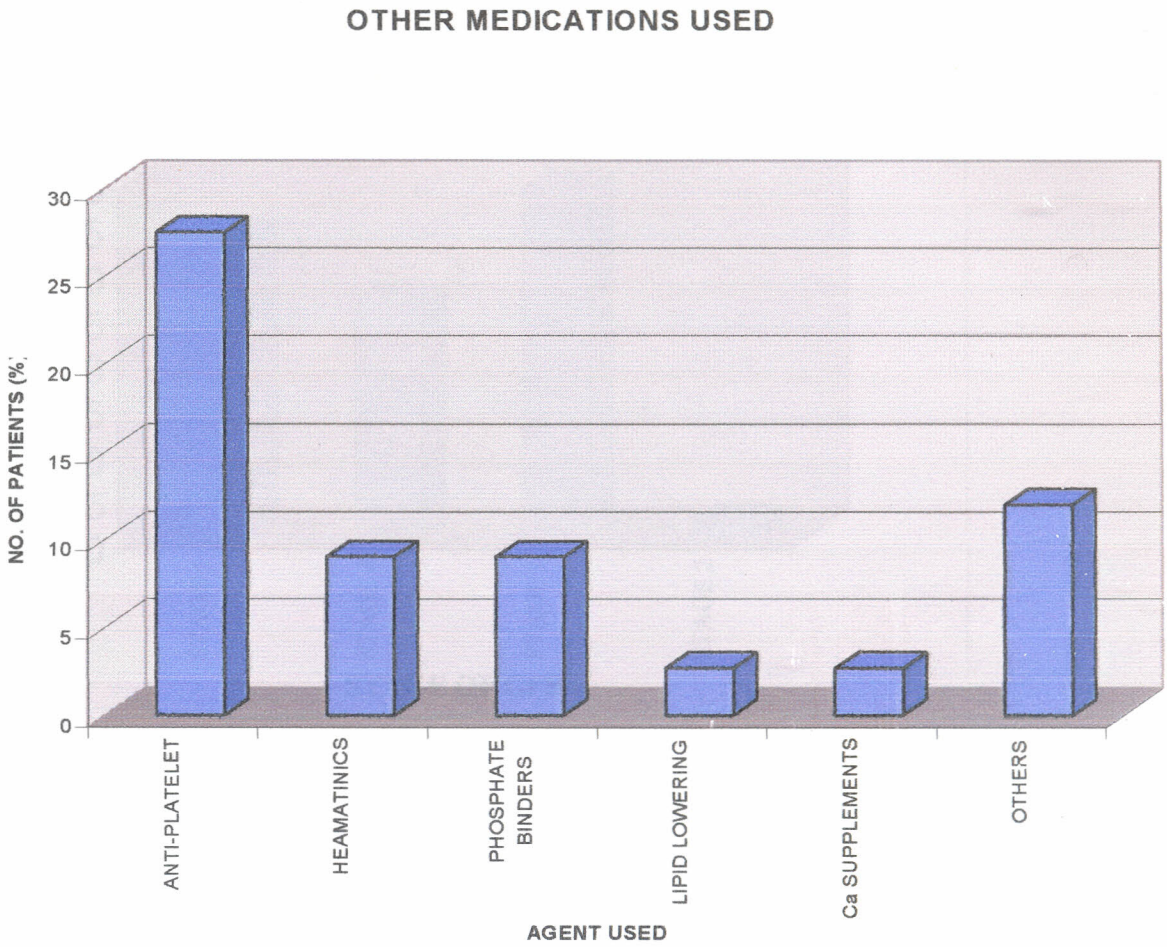
Figure 6: BP Lowering Drug Use Among Study Population



Nb:ACEI= Angiotensin Converting Enzyme Inhibitors, ARB= Angiotensin Receptor Blockers,CCB=Calcium Channel Blockers

Fifty patients (45%) were on ACEI/ARB containing combination therapy. Eighteen patients (16.6%) were on ACEI/ARB monotherapy, fourteen (12.6%) were on non-ACEI/ARB containing combination therapy while twenty-six patients (23.4%) were not on any BP lowering agent. There were only two patients (1.8%) on CCB monotherapy and one patient (0.9%) on diuretic monotherapy.

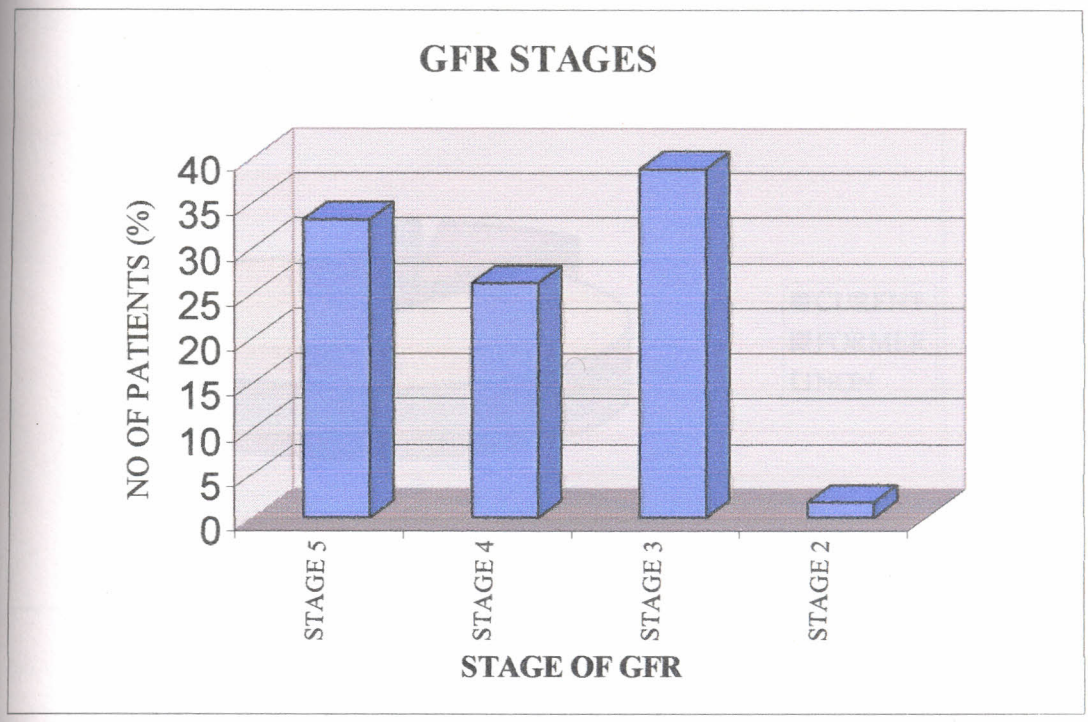
Fig 7 **Other Medications Used By Study Population**



Ten patients (9%) were taking heamatinics and ten (9%) were on phosphate binders. Three patients (2.7%) were on lipid lowering agents and three patients (2.7%) on calcium supplements. Thirty patients (27.5%) were on an antiplatalet, Junior Aspirin (ASA). Thirteen patients (12%) were on other drugs including vitamin supplements and analgesics. There was no patient on erythropoeitin.

c) STAGES OF CHRONIC KIDNEY DISEASE

Figure 8: Stages of Chronic Kidney Disease in Study Population

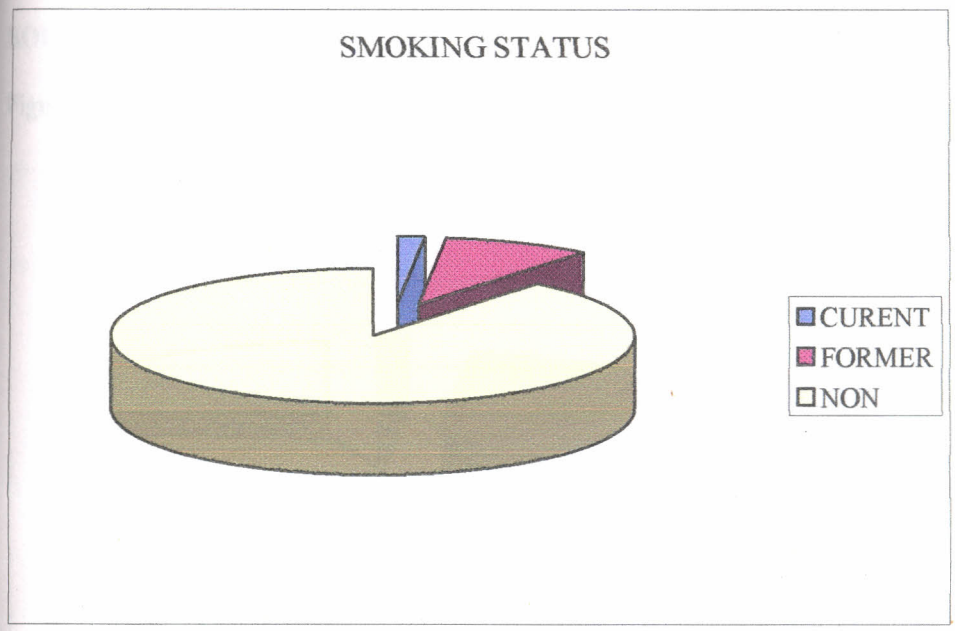


Nb; Stage5= GFR <15mls/min , Stage 4e= GFR of 15 to <30mls/min, Stage 3= GFR of 30 to <60 mls/min Stage 2= GFR of 60 to <90.mls/min

Thirty-seven patients (33.3%) were in end stage renal disease (Stage 5), twenty-nine patients (26.1%) had severe renal dysfunction (Stage 4), forty-three patients (38.8%) had moderate renal dysfunction (Sage 3) and two (1.8%) had mild renal failure (Stage 2) (Figure 9) .The mean GFR was 26mls/min+/-15.6 with a range of 1.13 to 61.9 mls/min.

d) CIGARETTE SMOKING

Figure 9: Distribution Of Study Population According To Smoking Status

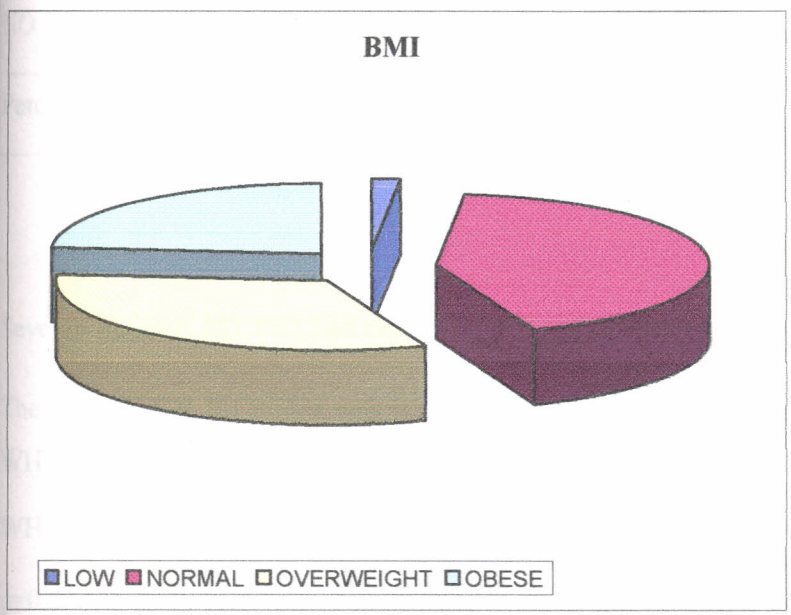


Ninety-eight patients (88.2%) were lifetime non-smokers. Thirteen (11.8%) of the patients had smoked cigarettes in their lifetime and all were males. Only three patients (1.8%) were current smokers with an average 10.2 pack years. However there might have been under reporting of smoking.

e) MEASURES OF OBESITY

BODY MASS INDEX

Figure 10: BMI Categories Among Study Population



Sixty-one patients (55.9%) were either overweight or obese. Twenty-five patients (23.5%) were obese while thirty-seven patients (32.4%) were overweight. Forty-seven patients (42.3%) had normal BMI with only two (1.8%) undernourished patients (Figure 10). The mean BMI was 26.57kg/m2+/- 4.845 with a range of 17.6 to 42.7 kg/m2. The mean BMI for females was 26.89kg/m2 +/- 5.519 while the mean BMI for males was 25.987kg/m2+/- 3.24. Females had higher BMI but there was no statistical difference between males and females with p=0.688.

WAIST HIP RATIO

Table 4: WHR Among Study Population

WAIST HIP RATIO			
NO OF PATIENTS	NORMAL	ABNORMAL	TOTAL
NO	41	70	111
Percentage	36.9	63.1	100

Seventy patients (63.1%) had central obesity while forty-one patients (36.9%) had normal WHR.

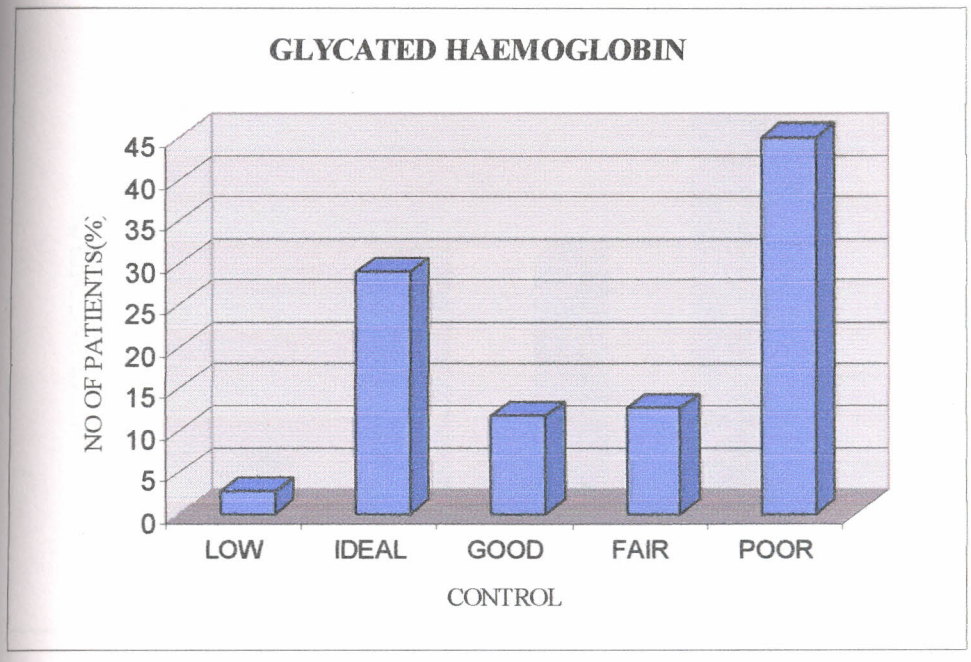
The mean WHR for males was 0.992 +/- 0.067 and for females 0.931 +/- 0.101. Females had higher WHR with a significant p value <0.05. (NB: WHR for M>1, F> 0.85)

WHR inversely correlated with GFR using Pearson correlation which attained statistical significance p=0.03231 implying obese patients had worse renal function. Since WHR is a better marker of obesity, thus obesity is positively correlated with worse renal function.

f) MEASURES OF GLYCAEMIC CONTROL

GLYCOSYLATED HAEMOGLOBIN (HbA1c)

Figure 11: Glycaemic Control As Measured by HbA1c in Study Population



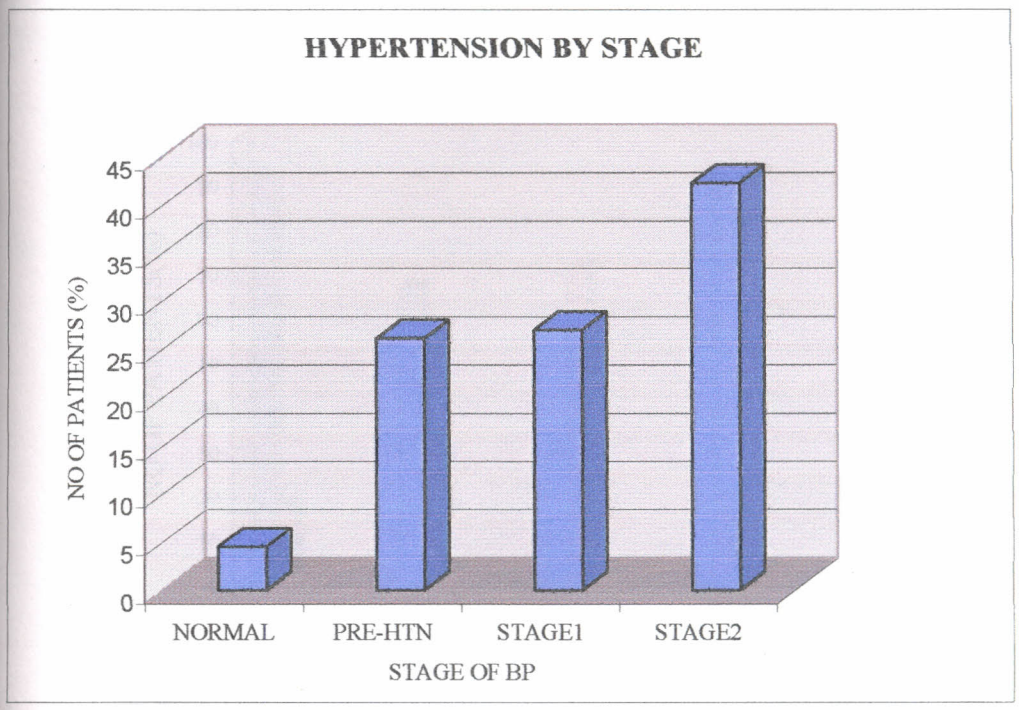
Sixty-four patients (57.6%) had poor glycaemic control (HbA1c>7%), thirteen patients (11.7%) had good control, thirty-one patients (28.1%) had ideal control and three patients (2.7%) had low level of control. The mean HbAic was 9.3% with a range of 3.4-22.7 %. Patients with mild to moderate renal failure had worse HbA1c as compared to patients with ESRD with a significant p=0.011.

FASTING BLOOD GLUCOSE (FBS)

Using FBS as a measure of glycaemic control, forty-seven patients (42.3%) had poor control forty-four patients (39.6%) had good control whereas twenty patients (18%) were hypoglycemic. The mean FBS was 7.436 +/- 4.193mmol/l.

g) BLOOD PRESSURE

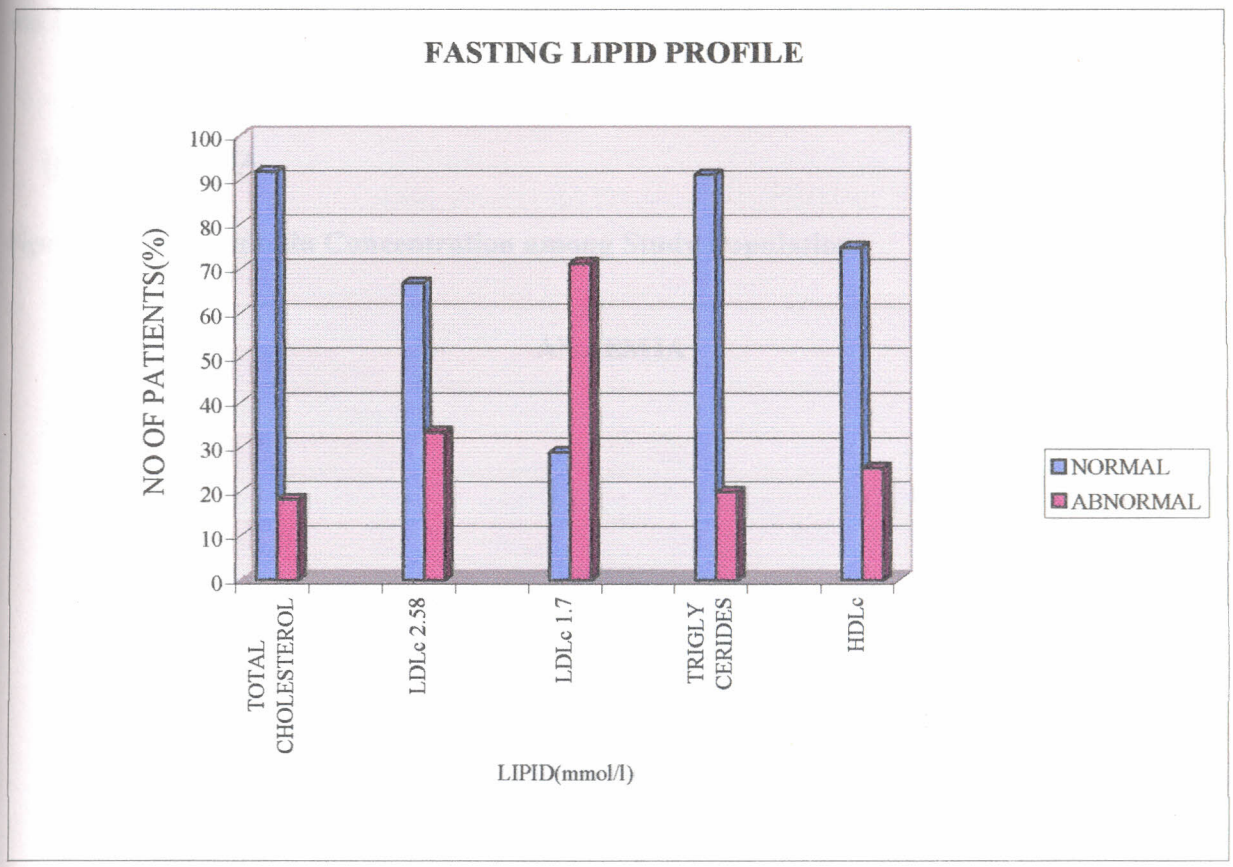
Figure 12: Blood Pressure Stages Among Study Population



Ninety patients (81.1%) fulfilled the definition of hypertension in the study. Five patients (4.5%) had normal blood pressure, twenty-nine (26.1%) were pre-hypertensive, thirty (27%) had stage 1 hypertension and forty-seven (42.3%) had stage 2 hypertension. The mean systolic BP was 151.3mmHg +/- 26.64 with a range of 95-245mmHg and mean diastolic BP 89.9 mmHg +/- 13.87 with a range of 55-125mmHg. Higher BP as a whole was not associated with worse GFR, p = 0.102. Patients with higher systolic BP had worse GFR. Diastolic BP had no relation with GFR (P=0.063). The mean pulse pressure was 61.15 +/- 19.36. Forty-eight patients (43.2%) had high pulse pressure~ the higher the pulse pressure, the worse the GFR with a significant p value of 0.00. Blood pressure control was uniformly poor despite sixty-two patients (56.3%) being on blood pressure lowering agents.

h) DYSLIPIDAEMEA

Figure 13: Fasting Lipid Profile in Study Population



Mean LDLc was 2.339 mmol/l.+/- 0.868 with a range of 1.01 to 5.27mmol/l. Using the ATPIII NCEP criteria the prevalence of high LDLc was 33.3%. However, using newer guidelines for LDLc for coronary artery disease risk equivalence, (LDLc>1.7 mmol/l), the prevalence rose to 71.2%.

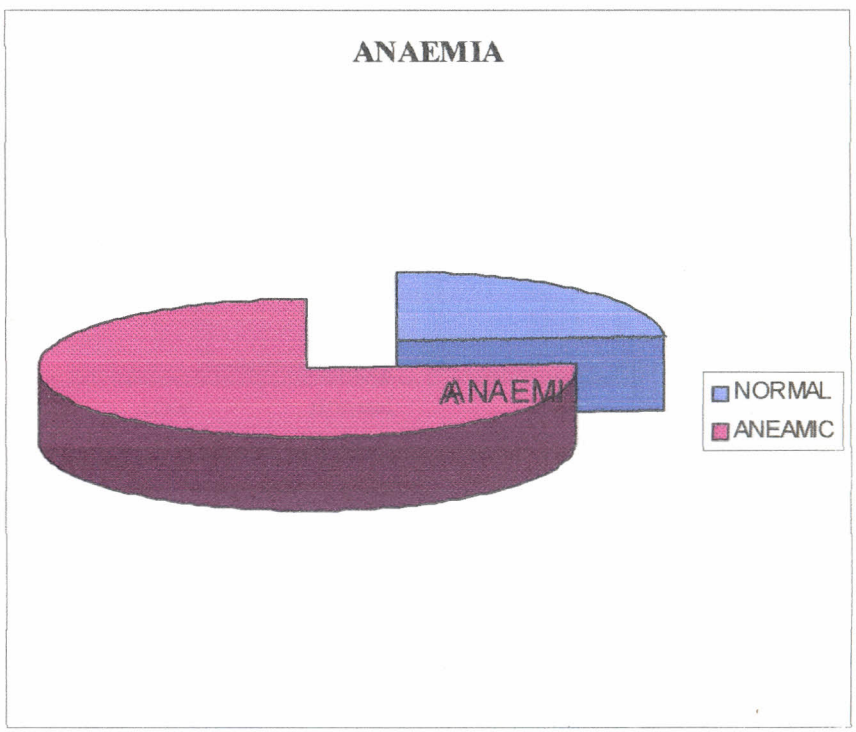
Twenty-two patients (19.8%) of the study population had high triglceride levels and eighty-nine patients (90.2%) had normal values. The mean TG was 1.338mmol/l +/- 0.789, with a range of 0.34-5.4mmo,l. There was no relation between GFR and triglyceride level p=0.141.

The mean total cholesterol (TC) was 3.996mmol/l +/- 1.201 with a range of 2.17 to7.69mmol/l. Twenty patients (18%) had high levels while ninety-one patients (82%) had normal values.

The mean HDLc was1.226mmol/l +/- 0.349 ranging from 0.62 to 2.5mmol/l. Twenty-eight patients (25.2%of the patient population) had lower than the recommended level while eighty-three patients (74,9%) had normal HDLc. The mean HDLc for males was 1.189 +/- 0.286mmol/l and for females was 1.307 +/- 0.044mmol/l. Females had higher HDLc with a significant p value of 0.0456.

i) ANAEMIA

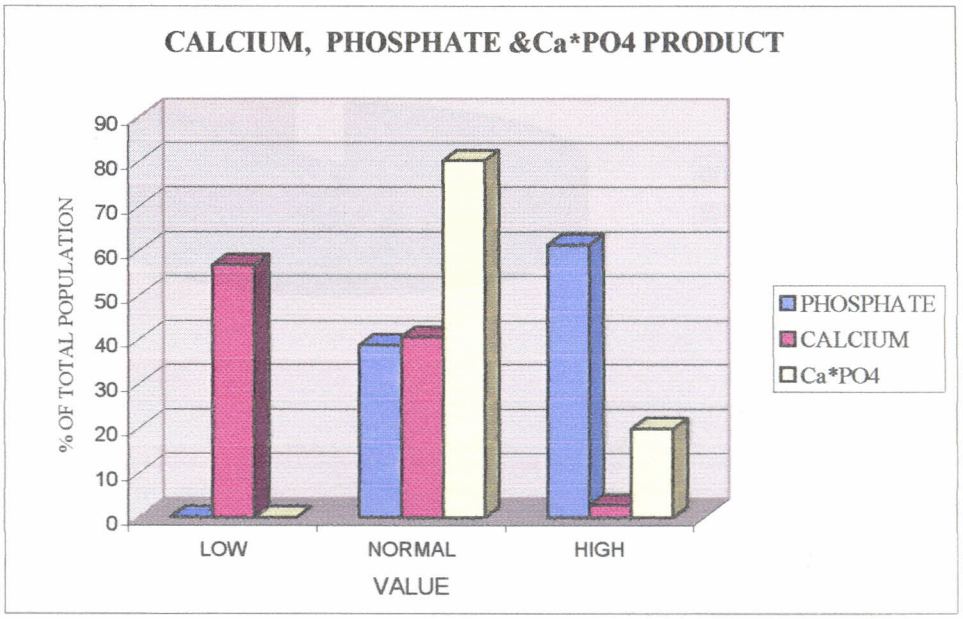
Figure 14: Haemoglobin Concentration among Study Population



The mean haemoglobin concentration was 10.317g/dl +/- 2.066. The prevalence of anaemia, corrected for menopausal status of women, was 75.7% and only 24.3% of the study population was not anaemic. Degree of anaemia was worse with worse renal function.

j) HYPERPHOSPHATAEMIA AND ELEVATED CALCIUM PHOSPHATE PRODUCT

Figure 15: Distribution of Calcium, Phosphate and Calcium* Phosphate Product among Study Population

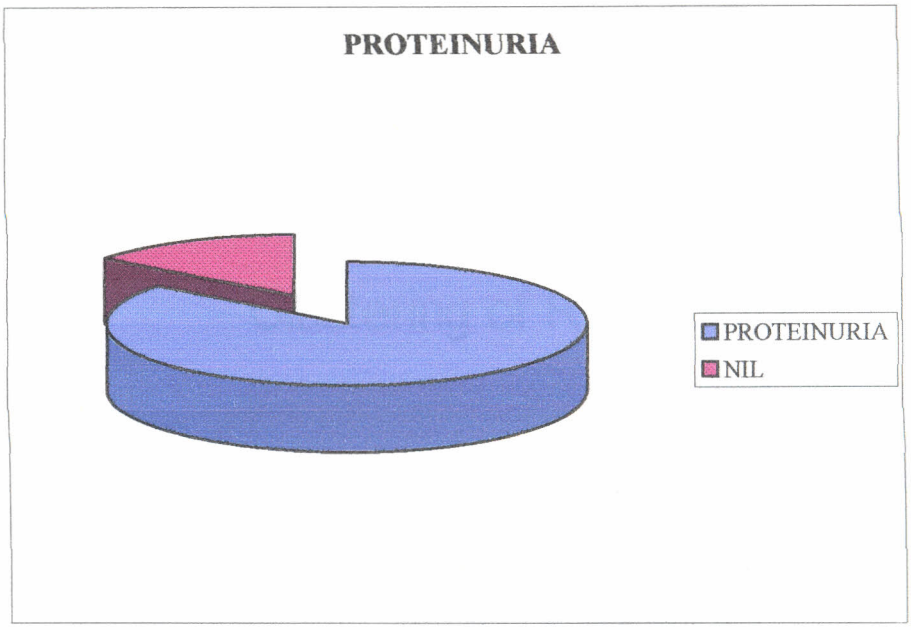


Sixty-eight patients (61.3%) had hyperphosphataemia and forty-three patients (38.7%) had normal phosphate levels. The mean phosphate level was 1.753 +/- 0.665mmol/l with a range of 0.73 to 3.65mmol/l. Sixty-two patients (56.8% of the study population) had low calcium, forty-six patients (40.5%) had normal calcium and only 2.7% had high calcium levels. Though calcium is not a known risk factor of progression of CKD, it relates to phosphate in the formation of $CaXPO_4$ product, a risk factor of progression of CKD. The higher the phosphate, the lower the calcium with significant $p < 0.05$. The mean serum calcium, corrected for serum albumin concentration, was 2.1 +/-0.332, a range of 0.8 to 4.08mmol/l.

Twenty-two patients (19.8%) had high $CaXPO_4$ product. The mean calcium phosphate product was 3.54 $mmol^2/l^2$ with a range of 1.42-7.25 $mmol^2/l^2$.

k) PROTEINURIA

Figure 16: Distribution Of Macroproteinuria In Study Population

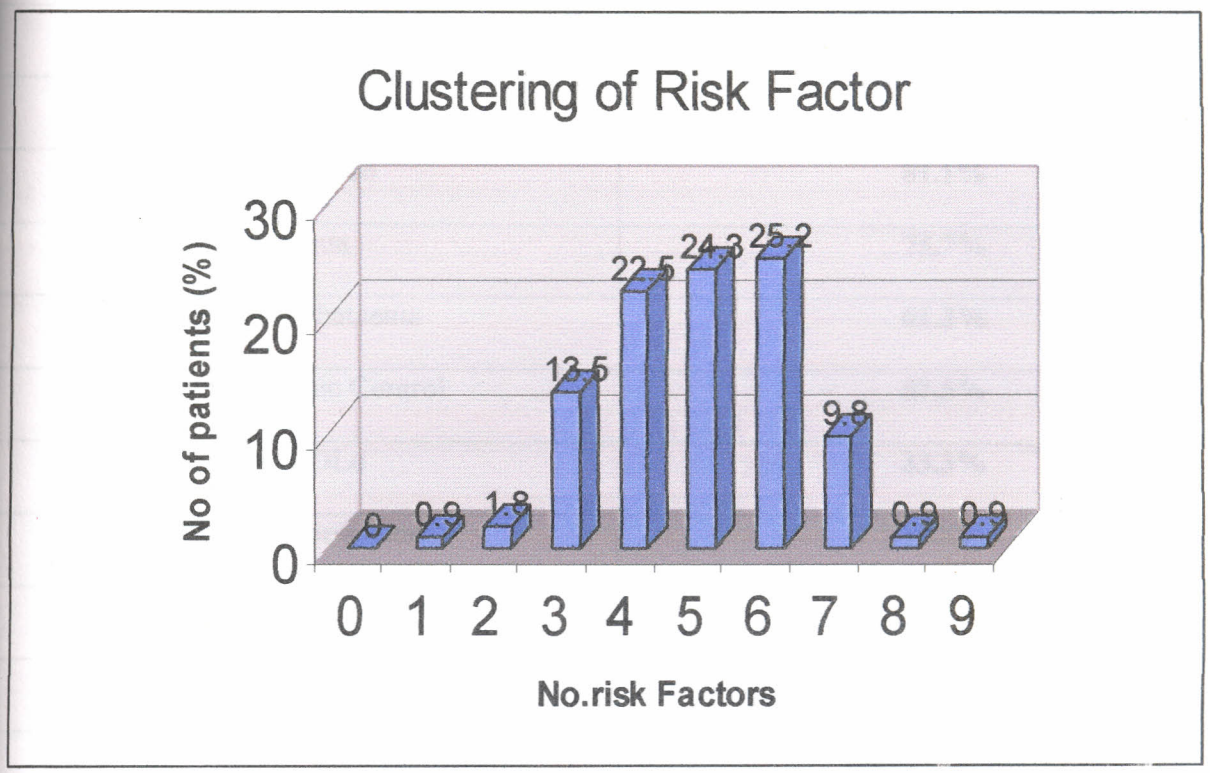


Ninety-four patients (85.6%) had macroproteinuria and seventeen patients (14.4%) had no protein by dipstick analysis. The mean serum albumin was 35.5 +/- 5.437 mmol/L with a range of 22 to 59mmol/l., which was directly related to GFR. Patients with worse proteinuria had lower albumin level.

Patients with macroproteinuria had higher mean systolic blood pressure (153.5) and pulse pressure both of which achieved statistical significance (p=0.0494 & 0.013 respectively). These patients also had higher mean diastolic blood pressure, and longer duration of diabetes mellitus. However, their HbA1c was higher, 9.6% compared to 9.306% for non-proteinuric patients.

l) CLUSTERING OF RISK FACTORS

Figure 17: Clustering Of Risk Factor Among Study Population



One hundred and eight patients (97.2%) had at least 3 risk factors. Each patient had at least one risk factor. Eighty patients (72%) had between 4 and 6 risk factors. The mean number of risk factors per patient was 3.8.

m) PROGRESSION RISK FACTORS PREVALENCE IN DIABETIC NEPHROPATHY

Table 5: Prevalence Of CKD Progression Risk Factors In Diabetic CRI Patients in KNH

RISK FACTOR	PREVALENCE
Macroproteinuria	**85.6%**
Hypertension	**81.1%**
Anaemia	**75.7%**
Hyperphosphataenia	**61.3%**
Poor Glycaemic Control	**57.5%**
High LDLc	**33.3%**
Hypertriglyceridaemea	**19.8%**
Elevated Calcium Phosphate Product	**19.8%**
Cigarette Smoking	**11.8%**
CLUSTERING OF RISK FACTORS	
Mean number per patient	**3.8**
3 or more risk factors	**92.7%**
4 to 6 risk factors	**72.6%**

4.0 DISCUSSION

iabetic nephropathy is becoming an increasingly important complication because patients are living nger and diabetes account for one third of the population of patients undergoing chronic dialysis for SRD in KNH renal unit.

his study evaluated diabetic patients with chronic kidney disease for risk factors associated with ogression of CKD. Twenty-seven percent were Type1 diabetic. The male to female ratio was 1:1.8. his was different from a number of studies, which found male gender to be an independent risk factor r renal failure (32,33). Sheikh in his study of cardiovascular risk factors in CKD in general, had a ale to female ratio of 2.5:1 (90). Our population was diabetic with majority being type 2 where males predominate. Other studies (32.33) reported male gender as risk factors for nephropathy but ot another (34). Males were under represented which may be a reflection of health-seeking behaviour etween males and females in our population. Additionally, most of the patients were older: Females ave a longer life expectancy, how that would influence this observed gender disparity is difficult to etermine.

lost of the patients were from Nairobi and its environs, most likely due to proximity to Kenyatta ational Hospital, which is also the main referral hospital.

he mean age of the study patients was 56.2 +/- 15.2 years with majority (68%) between 51-70 years. his was similar to other studies (36,55) where older age especially for Type 2 diabetes is associated ith diabetic nephropathy but in another study (8,33), age was not found to be a factor that influenced rogression of microalbuminuria within that period. One study showed that patients diagnosed after 0years had higher prevalence of, and degree of microalbuminuria than those diagnosed before age 0years. (33). However, older patients tended to have worse GFR. Older patients are more likely to be ss transplantable and thus need to predominantly depend on conservative management.

he duration of diabetes was skewed to the left with a sharp decline after 20 years. This finding is imilar to a study, (30) which showed that, if a patient was to develop diabetic nephropathy, he was to o so within 20 years of diagnosis of type 1 diabetes, after which the incidence falls sharply. The eason for this observation was not evaluated in this study. This is similar to one study (36) which ssociated longer duration of diabetes to increased incidence of and progression of nephropathy. In his study, Type 1 diabetics had longer duration of diabetes. CKD in our population tend to occur arlier rather than later probably due to type 2 diabetics who have nephropathy by the time of iagnosis. (8,55). This means that our diabetes mellitus patients need to be screened for CKD as early s possible after diagnosis.

y-one patients (36.9% of the study patients) had relatives with diabetes, of which 78% were first ee relatives. This is similar to a study done in Kenyatta National Hospital studying 100 cases in two years of clinical diagnosis (8). In this study, 17.1 % had relatives with hypertension and % had relatives with diabetic nephropathy; all were first degree relatives. Several studies have gested genetic predisposition to diabetic nephropathy, which include polymorphism of angiotensin verting enzyme, angiotensinogen and angiotensin receptor gene (29). Defects in Apo E and Na-Li ransporter genes are also implicated. In this study, the association was low but we cannot rule out fact that some patients may not have known about other relatives with these conditions and there ght have been recall bias.

ycaemic control was poor in 57.6% using HbA1c; 42.3% had poor control using fasting blood ucose (FBS) though neither was associated with low mean GFR. In this study, patients with higher FRs had higher HbA1c and FBS, while on the other hand patients with ESRD had lower FBS and bA1c.The higher HbA1c with higher GFR may be the initial and on going injury to the renal omerula by high glucose concentration which contributed to the final lesion of diabetic nephropathy. may also reflect the poor glycaemic control experienced by the patients. Poor glycaemic control is sitively associated with the development and progression of renal failure (35). The lower HbA1c ith low GFR may imply nutritional factors where uraemia plays a major role. These patients are also n dietary control comprising of low protein, low fat and especially low carbohydrates. It is also robable that insulin, whose degradation and excretion is reduced in renal failure, accumulates in the ody, having a longer half-life. Therefore, both endogenous insulin in type 2 diabetics and exogenous n type 2 diabetics, would keep lower glycaemia especially on sub-optimal nutrition seen in uraemia.

With advanced renal failure (that is in patients with overt nephropathy), glycaemic effects become less mportant as risk factors of progression of CKD. (35).

DCCT (4) showed that intensive therapy reduced the risk of albuminuria by 54%. A model derived rom DCCT predicted that intensive glucose treatment gained 5.8 additional years free from ESRD nd 5.1 years of life expectancy. HbA1c is a significant predictor of progression from Stage 1 through o Stage 5 (34). UKPDS (3) showed intensive treatment reduced all micro vascular complications. This gives us an opportunity to maximise control and delay progression of renal disease and reduce cardiovascular complications. About 32.4% of patients were on oral glucose lowering agents. The most commonly prescribed oral hypoglycaemic were glucophage and chlopropamide. Since these are patients already in CRI, they should have been on insulin since most of these agents are contraindicated in renal failure. However patients on insulin therapy did not necessarily have better GFR. The type of glucose lowering agents did not significantly affect GFR. Glucophage had to be discontinued in several patients

g JNC VII criteria, 81.1% of the patients had high blood pressure beyond treatment target. olic blood pressure was significantly associated with poor GFR (p=0.005) but not diastolic blood sure (P=0.06). This has been reported in other studies (40) especially in type 2 diabetes. Systolic rtension is associated with older age. Sheikh (90) looked at cardiovascular risk factors in CKD nts, 33% of whom were diabetics, found a prevalence of 61.5% among his study population.

pite use of multiple blood pressure lowering agents, none of the study patients already on tment were achieving target blood pressure levels recommended. Sixty-two patients (56.8%) e known hypertensives therefore 24.3% were newly diagnosed. Patients on ACE1/ARB had lower n systolic and diastolic blood pressure. No patient was on combination of ARB and ACEI. Only e patients were on the ARB lorsatan .

teinuria was the most prevalent risk factor at 85.6%. Proteinuria, previously considered just a rker of the severity of kidney disease may itself be pathogenic (61), the higher the urinary protein retion, the faster decline in GFR and the quicker the progression to ESRD (62). Measures to luce it should be employed such as use of ACE1, and or ARB, which have been shown to reduce omerular hypertension thus reducing proteinuria as shown in the IRMA (49) and MARVAL (52) dies. CALM study (51) showed combination of ACE I and ARB to be beneficial in retarding phropathy in type 2 diabetes. However, there was no patient on ACE I and ARB combination erapy. Sixteen patients (14.4%) of the study patients did not have proteinuria, probably because they ad tubulo-interstitial disease.

Dietary protein intake was not assessed in this study. The modification of diet in renal disease MDRD) study failed to find an effect of protein restriction on decline of renal function. (65). However, a secondary analysis suggested that a lower protein diet retards progression in both moderate (66) and advanced renal disease (64). However these are patients who were already on low carbohydrate, low fat and low protein diet with high fibre. In a more recent analysis of the MDRD, low protein diet was shown to reduce hypertension.(92).

Prevalence of hyperphosphataemia was very high (61.3%). Patients with high phosphate had worse stage of CKD with a significance p=0.00258. No local study has looked at phosphate levels in CKD. Phosphate causes chronic tubulo-interstitial inflammation when filtered and re-absorbed. Calcium phosphate is filtered and precipitates in tubules and interstitium (68) causing damage. Calcium phosphate causes vascular calcification which worsens both CKD and contributes to cardiovascular complications, the major cause of death in these patients. Intervention studies with low phosphate diet, administration of phosphate binders and 3 phosphocitrate, an inhibitor of CaXPO4 precipitation, have been shown to slow progression of chronic kidney disease. (68,69).

ly 10 patients (9%) were on phosphate binders, mainly calcium carbonate, and phosphate was still ›ve target. This again presents an opportunity to modify an important risk for progression, and diovascular risk.

venty-four patients (75.5% of study population) was anaemic. Sheikh (90) found a prevalence of %. Notably, only 9% of the study patients were on haematinics. Anaemia develops primarily due to creased erythropoietin (EPO) production by the failing kidney (73) though other concomitant factors ould be considered in the evaluation of anaemia in patients with CKD. Whether anaemia accelerates e progression of kidney disease is controversial. Anaemia decreases both oxygen delivery and rotection against oxidative stress and may favor tubular obstruction secondary to interstitial fibrosis. ypoxia and oxidative stress probably stimulate the production of extracellular matrix by fibroblasts, ıcreasing fibroblasts and creating a vicious cycle. In two small prospective studies (76,77) correcting naemia with recombinant human erythropoieitin (rHuEPO) significantly slowed the progression of RI. Correcting anaemia is another opportunity for retarding renal failure and modifying ardiovascular risk.

Thirty-nine males (35.9% of males) in this study were or had been heavy smokers. Only 1.8% were urrent smokers which might be under-reporting since it is now being viewed as a 'negative' vice. The prevalence may have been higher. That all smokers were males could suggest cultural acceptability of moking associated with males and not females. However, there are more female smokers with urbanisation' who do not volunteer to the fact that they are or have been smokers. Mwendwa had a prevalence of 75% among study population, which was a different population from this study. Sheikh, whose study population was similar to this study, had a prevalence of 19.69%. Sheikhs definition of moking was also similar to the one used in this study.

Smoking is a risk factor for progression of diabetic nephropathy. In fact one study reported a higher rate of decline in GFR in smokers without hypercholesterolaemia compared to non-smokers with hyper cholesterolaemia. (33). Although the prevalence was low, all diabetic renal patients should be advised to stop smoking.

Females were more centrally obese as evidenced by a higher mean WHR compared to males, which was statistically significant. Central obesity was significantly associated with low mean GFR (P=0.032). This may have been contributed to by the fact that most patients were females, were older actually post –menopausal and most had type 2 diabetes which may be part of the metabolic syndrome. WHR is a better measure of obesity. BMI was not associated with lower mean GFR.

Surprisingly, all the lipids were not that high. Interestingly, patients with higher GFR had higher total cholesterol and LDLc. With lower mean GFR, these lipid levels were actually lower probably

flecting nutritional adjustments when uraemia worsens. It appears then, that it might be more portant to anticipate and therefore address lipid abnormalities in patients with mild renal sfunction. However, lipids were assessed using quantitative analysis yet the quality of the olesterol is equally important..

wenty-two patients (19.8%) had high triglycerides levels. Sheikh (90) found a prevalence of 15.3 % his study population though he reported higher levels in his diabetic sub group, which was not atistically significant. Mwendwa (8) reported a prevalence of 50 % in her study population, These fferences may be explained by the fact that this study and Sheiks study had patients with significant nal dysfunction, unlike Mwendwa whose study population had mild or no CKD. Twenty patients (18 % of this population) had high total cholesterol while Mwendwa had 82% though she used a cut off oint of 4.2 mmo/l while Sheikh had 15.7 % of his study population with high total cholesterol (cut off 5.17mmol/l).

Thirty-three percent of the population had high LDLc, Mwendwa had 35% of her population with high LDLc and Shiekh had 24 % of his study population with high LDLc. HDL cholesterol was low in 25.2% of the study population. Females had higher HDLc levels. Shiekh had 88% of his patients with low HDLc while Mwendwa had only 9%. In this study, only 2.7% were on lipid lowering agents-statins, yet every diabetic and every CKD patient should be on these agents. Statins lower LDLc, and are now known to have anti-inflammatory properties. Diabetes is a coronary artery disease equivalent and therefore these patients should have been on lipid lowering agents.

Majority of our patients had no formal education. Low formal education is often associated with unemployment, poor socio-economic status and poor, and or inadequate social support structure. In a study that targeted patients who require active management, then the association was not surprising. This may reflect on poor understanding of diabetes and nephropathy per se translating to decreased adherence to dietary measures and proper use of medications prescribed and possibly health seeking behaviour. Low level of education means that these patients are difficult to teach and are often second party taught. Therefore modification of teaching methods should be addressed.

15.0 CONCLUSIONS

There was a high prevalence of risk factors of progression of renal disease in diabetics with established renal insufficiency.

A high proportion of patients had aggregation of multiple risk factors. Majority of the patients (97.2%) had at least three risk factors. There was no patient without a risk factor.

The most prevalent risk factors were proteinuria (85.6%) hypertension (81.1%) and anaemia (75.7%)

Proteinuria was the most prevalent risk factor.

Hypertension was present in 81.1%. Patients known to have hypertension had lower GFR, which was not a surprise since it is a risk factor, which worsens GFR. Hypertension is probably the most important risk factor in established chronic renal failure.

Anaemia was found in 75.5% of study population and related to stage of renal failure.

Hyperphosphataemia was prevalent in 61.3% .

Calcium phosphate product elevated was elevated in19.8% of the patients. The prevalence was low probably due to generally low calcium (corrected for albumin) levels.

Glycaemic control was poor in 57.6% of the patients.

LDLc cholesterol was elevated in 33.3% of the patients.

Hypertriglyceridaemea was prevalent in 19.8% of the patients. The low lipid assays were probably related to poor nutrition.

Smokers were few and they were all males.

16.0 RECOMMENDATIONS

1. All diabetics found to have chronic renal insufficiency should be screened and managed for modifiable risk factors associated with progression of the CKD
2. Greater efforts should be made in controlling hypertension hyperglycaemia, dyslipidaemia, proteinuria, anaemia and hyperphosphataemia. All diabetic CRI patients should be encouraged to stop smoking.
3. There is need for prospective studies to identify the actual roles of these risk factors in the progression of nephropathy

7.0 STUDY LIMITATIONS

The study population was a highly select group being patients who are near Kenyatta National Hospital, a tertiary level of health care of the population of Kenya.

Some of the information used in the study required patient recall which could have been inaccurate thus introduce bias especially relating to family history of diabetes, hypertension and kidney disease.

A set of two blood pressure readings could not be used as a substitute for long term control monitoring.

A single HbA1c measurement and fasting blood sugar was used to assess Glycaemic control. HbA1c may not reflect long term control over many years of diabetes as it measures control over three months using red cell survival. The half-life of red cells is reduced in renal disease.

Quantitative aspects were used in lipid profile assessment. Qualitative measurements may be more accurate.

Only qualitative measure of proteinuria was assessed. Quantitative measurements such as urine albumin excretion rate are more accurate in measurement of proteinuria.

Diet was not assessed which might have influenced proteinuria. However, these were patients already on highly select diet consisting of low fat, low protein, and low carbohydrates.

No attempt was made to confirm differential diagnosis of diabetic nephropathy because it was not part of the study and other nephrotoxic agents were not studied.

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APPENDIX I

CONSENT EXPLANATION

INVESTIGATOR: DR. L. W. MBOGO

POST GRADUATE STUDENT

DEPARTMENT OF MEDICINE

UNIVERSITY OF NAIROBI.

This is a research activity aimed at findings out the presence of risk factors associated with progression of renal disease in diabetic patients with chronic renal insufficiency. Kidney failure is a known complication of diabetes. Once it starts, it runs a course which can be interrupted by looking or and treating modifiable risk factors.

Results of this study will form a basis for recommendation of screening for these factors. It may also form part of recommendation of use of recombinant human eythropoieitin, ACE I, insulin and phosphate binders. This may delay entry into renal replacement therapies, which are so expensive.

After an overnight fast where the patient does not take anything after midnight of morning of exam, 10mls of blood will be taken from a peripheral vein using a sterile needle and sterile syringe. There will be a little pain and minimal bleeding from the puncture site. 2mls of blood will be taken for glycosylated haemoglobin ($HbAI_C$) and fating blood sugar (FBS); 3mls for haemoglobin assay and 5mls for fasting lipid profile, serum creatinine, calcium, phosphate, albumin, sodium and potassium. Subsequently the patient will be given a plain bottle to void urine after cleaning perineum for analysis..

The investigator will ask some questions which the patient; parent/guardian will be expected to respond appropriately. He/She may choose not to answer the questions or refuse to be included in this study. This will however not affect or influence or compromise subsequent medical care given to the patient. Acceptance to be included in the study will not accord the patient any special favors, or treatment nor monetary gain.

There are no risks to the patient acceptance to be included in the study will however be beneficial. It will outline the modifiable risk factors specific to the patient of which specific intervention can be offered. This may mean that the patient will take longer to enter in RRT program.

The investigator will bear the cost of the study. Data obtained will be confidential and communicated to primary clinician for relevant action or where possible the patient will be referred to appropriate clinic/unit center.

Signature of investigator.....

Date:.....

APPENDIX II

CONSENT FORM

Dr Mbogo has explained the purpose and conditions of this study clearly to me.

I ---------- therefore agree to the above and give consent to be included in the study/ I agree to the above and give consent for ---------- --- to be included in the study

Name _____ **Witness**_____

Signature _____ **Signature**_____

Date _____ **Thump print** ----------

APPENDIX III

STUDY PROFOMA

Name (initials).....

Study ID number.....

Date of Examination.....

Date of Birth month, year.....

Date of Diagnosis of Diabetes.....

SOCIO DEMOGRAPHIC CHARACTERISTICS

1. Gender 1=Male 2=Female
2. Race/ethnic group
3. Usual residence
4. Usual occupation
5. Level of formal education

1=none 4= tertiary level

2= primary school 5= adult education

3= secondary school

6. Marital status

1=single 4=widowed

2=married 5=separated

3=divorced

PAST MEDICAL HISTORY

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

1 = Yes 2 = No

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

8. Have you ever been told by a health-worker that you have kidney disease?

1 = Yes 2 = No

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

9. Were you referred to the renal clinic or to a nephrologist (kidney specialist)?

10. Have you ever suffered from any other serious illness in the past?

1 = Yes 2 = No

If so, specify.....

FAMILY HISTORY

11. Did, or do any of your relatives suffer from diabetes?

1 = Yes 2 = No

If yes, specify.

1 = 1 parent

2= both parents

3= sibling

4= others (specify)

12. Did or do any of your relatives suffer from hypertension?

1 = Yes 2 = No

If yes, specify:

1 = Parent

2 = both parents

3 = sibling

4 = other, specify

13. 13. Did, or do any of your relatives suffer from kidney disease?

1=yes 2=no

If yes, specify.....

1 = Parent

2 = both parents

3 = sibling

4 = other, specify

SMOKING HABITS

14. What is your current smoking status?

1 = never been a smoker

2 = former smoker

3 = current smoker

15.

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

Are you currently on any of the following medications?

1= Yes 2 = No

If yes, what are they?

16. Oral hypoglycemic agents (specify drug and dose)

a. E.g. Chlopropamide

b. Glibeclamide

c. Metformin

d. Others, specify

17. Insulin treatment (specify formulation and dose)

18. Blood pressure lowering drugs (specify drug and dose)

a. e.g. Captopril

b. Lisinopril

c. Enalapril

d. Others, specify

19. Drugs for any cardiac condition (specify drug and dose)

20. Oral contraceptives or estrogens (specify drug and dose)

21. Cortisone or related steroids (specify drug and dose)

22. Blood lipid lowering drug (specify drug and dose)

23. Haematinics and / or erythropoieitin

24. Calcium supplements e.g. Calcium Ssandoz

25. Phosphate binders e.g. Calcium carbonate (Actal Tums)

26. Any other drug(s) taken regularly (at least once a day)

Physical Examination

Height cm.....

Weight kg.....

BMI (kg/cm^2.....

Waist circumference cm.....

Hip circumference cm.....

WHR.....

Sitting Blood pressures (mmHg)	Systolic	Diastolic
1st reading	.....	.....
2nd reading	.....	.....
Average BP	.....	.....

LABORATORY DATA

Fasting blood sugar	.....	mmol/l
Glycated Haemoglobin (HbAic)	.....	%
Haemoglobin	.....	mg/dl
Total cholesterol	.....	mmol/l
HDL – C	.....	mmol/l
Triglycerides	.....	mmol/l
Calculated LDL –C	.....	mmol/l
Serum creatinine	.....	*u*mol/l
Calculated GFR	.....	mls/min
Serum urea	.....	mmol/l
Serum sodium	.....	mmol/l
Serum potassium	.....	mol/l

Serum Calcium	.....	mmol/l
Serum albumin	.....	mmol/l
Corrected Calcium	.....	mmol/l
Serum Phosphate	.....	mmol/l
Calcium X phosphate product	.....	$mmol^2/l^2$
Urine protein:	.....	measured by dipstix