

PREVALENCE OF PERIPHERAL ARTERIAL DISEASE
AMONG CHRONIC KIDNEY DISEASE PATIENTS AT
KENYATTA NATIONAL HOSPITAL

BY

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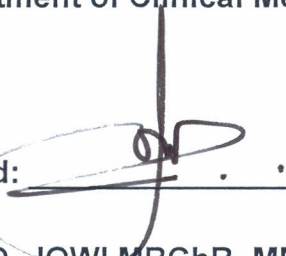
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ABBREVIATIONS

ABI	-	Ankle-Brachial Index
BMI	-	Body Mass Index
BSA	-	Body Surface Area
CAD	-	Coronary Artery Disease
CAPRIE	-	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events
CHD	-	Coronary Heart Disease
CKD	-	Chronic Kidney Disease
CI	-	Confidence Interval
CrCl	-	Creatinine clearance
CRI	-	Chronic Renal Insufficiency
CRP	-	C - reactive protein
CV	-	Cardiovascular
CVD	-	Cardiovascular Disease
DBP	-	Diastolic Blood Pressure
DCCT	-	Diabetes Control and Complications Trial
ESRD	-	End-Stage Renal Disease
FPG	-	Fasting Plasma Glucose
GFR	-	Glomerular Filtration Rate
HDL	-	High Density Lipoprotein
HEMO	-	Hemodialysis
IFG	-	Impaired Fasting Glucose
K/DOQI	-	Kidney/Disease Outcome Quality Initiative
KNH	-	Kenyatta National Hospital
LDL	-	Low Density Lipoprotein
MHz	-	Megahertz
MI	-	Myocardial Infarction
ml/min	-	millilitre/minute
Min	-	Minute
mls	-	millilitres
NCEP/ATPIII	-	National Cholesterol Education Program/ Adult Treatment Panel III
NHANES	-	National Health and Nutrition Examination Survey
NKF	-	National Kidney Foundation
OR	-	Odds ratio
PAD	-	Peripheral Arterial Disease
PAOD	-	Peripheral Arterial Occlusive Disease
SBP	-	Systolic Blood Pressure
UKPDS	-	United Kingdom Prospective Diabetes
WHO	-	World Health Organization

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ABSTRACT

Background

Chronic kidney disease (CKD) is a worldwide public health problem. There is a high prevalence of cardiovascular disease (CVD) in patients with CKD contributed to by presence of both traditional and non-traditional cardiovascular (CV) risk factors. Peripheral arterial disease (PAD) is a distinct atherothrombotic syndrome that is associated with an elevated risk of cardiovascular and cerebral events including myocardial infarction, stroke and death. The ankle-brachial index (ABI) is a simple, non-invasive, inexpensive and reliable measurement to assess the patency of the lower extremity arterial system with a sensitivity of 95% and specificity of 100%.

Objectives

The aim of the study was to determine the prevalence of PAD and the associated cardiovascular risk factors among patients with CKD at the Kenyatta National Hospital.

Design /methods

Hospital based cross-sectional prevalence study

Setting

Kenyatta National Hospital Renal Clinic.

Subjects

Adult patients ≥ 30 years with chronic kidney disease defined as proteinuria for ≥ 3 months and or a GFR ≤ 60 ml/min/1.73 m².

Outcome measures

- Prevalence of PAD.
- Prevalence of selected CV risk factors in patients with CKD and PAD: - age, male gender, hypertension, cigarette smoking, dyslipidemia and diabetes mellitus.
- Relationship between the selected CV risk factors and PAD.
- Proportion of patients with symptomatic PAD.

Results

Between January and October 2006, 194 patients with CKD were studied, 111 males and 83 females. The underlying aetiology of CKD was diabetes in 34%, hypertension in 29%, chronic glomerulonephritis in 29%, obstructive uropathy in 6% and polycystic kidney disease in 2%. The mean GFR was 36 ± 24.7 (range 1.9 - 110.1 ml/min/1.73m²) with 81.4% of the patients having advanced CKD.

Twenty-three patients had ABI <0.9 computing to a PAD prevalence of 11.9%(95% CI, 7.3- 16.4). The mean age of PAD patients was significantly higher than non-PAD counterparts (67.7 ± 14.3 yrs versus 50.5 ± 13.6 ; $p=0.000$). PAD patients had a worse renal function compared to non-PAD patients (GFR 27.2 ± 21 versus 37.3 ± 25 ml/min/1.73m², $p=0.04$). All but five of the PAD patients were male and all females were aged over 55yrs.

All the PAD patients demonstrated presence of traditional CV risk factors with the majority having more than two risk factors. The commonest risk factor was age occurring in 87% followed by male gender 78%, hypertension 74%, diabetes mellitus 56%, cigarette use 47% and dyslipidemia 43%.

The odds ratios for cigarettes use, male gender, diabetes mellitus and CKD stage ≥ 3 versus CKD stage <3 were on average two fold, however only the male gender and diabetes mellitus attained statistical significance. Hypertension and dyslipidemia in this data set were not associated with the presence of PAD.

On basis of the Edinburgh Claudication Questionnaire, 47.8% of PAD patients exhibited intermittent claudication.

Conclusions

The prevalence of PAD in CKD patients at KNH was 11.9%. All the selected CV risk factors were prevalent in the PAD population in varying proportions. Of the CV risk factors assessed, male gender and diabetes mellitus were independently associated with PAD. More than half of the patients with PAD were asymptomatic.

1. LITERATURE REVIEW

1.1 CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is a worldwide public health problem.¹ In 2002, the National Kidney Foundation (NKF) published clinical practice guidelines on evaluation, classification, and risk stratification in CKD.² In these guidelines, CKD is defined as either (1) kidney damage for ≥ 3 months, as confirmed by kidney biopsy or markers of kidney damage with or without a decrease in glomerular filtration rate (GFR), or (2) GFR < 60 ml/min/1.73m² for ≥ 3 months, with or without kidney damage. Kidney damage is ascertained by either kidney biopsy or markers of kidney damage, such as proteinuria, abnormal urinary sediment or abnormalities on imaging studies. The finding of proteinuria is associated with a worse prognosis for both kidney disease progression and the development of cardiovascular disease (CVD).

GFR < 60 ml/min/1.73m² is the cut-off value for the definition of CKD². It represents a reduction by more than half of the normal value of 125 ml/min/1.73m² in young men and women. This level of GFR is associated with onset of laboratory abnormalities characteristic of uraemia, including increased prevalence and severity of several CVD risk factors. Kidney failure is defined as GFR < 15 ml/min/1.73m² or treatment by dialysis.²

In the United States, there is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost. The number of individuals with kidney failure treated by dialysis and transplantation exceeded 320,000 in 1998 and is expected to surpass 650,000 by 2010.¹ There is an even higher prevalence of earlier stages of CKD. (Table1)²

TABLE 1. Stages of CKD

Stage	Description	GFR, mL · min ⁻¹ per 1.73 m ²	US Prevalence, 1000s	US Prevalence, %
1	Kidney damage with normal or increased GFR	≥ 90	5900	3.3
2	Kidney damage with mildly decreased GFR	60–89	5300	3.0
3	Moderately decreased GFR	30–59	7600	4.3
4	Severely decreased GFR	15–29	400	0.2
5	Kidney failure	< 15 or dialysis	300	0.1

Kidney failure requiring treatment with dialysis or transplantation is the most visible outcome of CKD. However, individuals with CKD are more likely to die of CVD than to develop kidney failure.³

1.2 CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR DISEASE

The significant burden of CVD in CKD was recognized by Lindner et al more than 30 years ago.⁴ Their study on the long-term outcomes of maintenance haemodialysis noted, "As the patient survival has approached the 10 year mark, there has been increasing indication that accelerated atherosclerosis may become the major unresolved problem threatening the longevity of the patients on regular maintenance dialysis".

In 1998, the NKF Task Force on Cardiovascular Disease in Chronic Renal Disease issued a report emphasizing the high risk of CVD in CKD.⁵ This report showed that there is a high prevalence of CVD in CKD and that the mortality due to CVD was 10 to 30 times higher in dialysis patients than in the general population. The task force recommended that patients with CKD be considered in the 'highest risk group' for subsequent CVD events and that treatment recommendations based on CVD risk stratification should take into account the highest -risk status of the patients with CKD. The primary types of CVD in CKD include cardiomyopathy and arterial vascular disease consisting of 2 subtypes namely atherosclerosis and arteriosclerosis (large vessel remodelling).

Atherosclerosis is an intimal disease characterized by the presence of plaques and occlusive lesions.⁶ There is a high prevalence of atherosclerosis in CKD.⁷ Surrogates of atherosclerosis include both intima-media thickness of the carotid wall that is detectable by ultrasound and inducible myocardial ischemia that is detectable by coronary stress tests. Clinical presentations of atherosclerosis include peripheral arterial disease, ischemic heart disease (angina, myocardial infarction and sudden cardiac death) which is common in CKD, cerebrovascular disease or heart failure.

'Traditional' and 'non-traditional' cardiovascular (CV) risk factors contribute to the increased prevalence of CVD in patients with kidney disease.⁸ Traditional CV risk factors are those derived from studies of the Framingham population while the non-traditional risk factors (also called uraemia-related risk factors) are those that increase in prevalence or severity as renal function declines. (Table 2)

TABLE 2. Traditional and non-traditional CV risk factors in CKD

Traditional Risk Factors	Nontraditional Factors
Older age	Albuminuria
Male sex	Homocysteine
Hypertension	Lipoprotein(a) and apolipoprotein(a) isoforms
Higher LDL cholesterol	Lipoprotein remnants
Lower HDL cholesterol	Anemia
Diabetes	Abnormal calcium/phosphate metabolism
Smoking	Extracellular fluid volume overload
Physical inactivity	Electrolyte imbalance
Menopause	Oxidative stress
Family history of CVD	Inflammation (C-reactive protein)
LVH	Malnutrition
	Thrombogenic factors
	Sleep disturbances
	Altered nitric oxide/endothelin balance

In his study in 2002, Sheikh found a high prevalence of multiple CV risk factors among patients with chronic renal insufficiency (CRI) at the Kenyatta National Hospital (KNH). These factors were left ventricular hypertrophy, anaemia, hypertension and hyperhomocysteinemia in 47-77% of the patients.⁹

1.3 PAD DEFINITION / CLASSIFICATION

Peripheral arterial disease (PAD) is a distinct atherothrombotic syndrome that is associated with an elevated risk of cardiovascular and cerebrovascular events including death, myocardial infarction (MI) and stroke.

PAD can be defined on the basis of anatomical or functional considerations. Anatomically it is defined as atherosclerotic arterial disease, while functionally it is defined as arterial narrowing, causing a mismatch between the oxygen supply and demand resulting in symptoms of intermittent claudication, exercise limitations or tissue loss.

These two definitions help divide PAD into asymptomatic and symptomatic disease states. Symptomatic PAD ranges in severity from intermittent claudication to critical limb ischemia. Intermittent claudication presents as reproducible limb discomfort during exercise, which is invariably relieved within minutes by rest. Critical limb ischemia is a severe form of PAD, which if left untreated can lead to non-healing wounds, gangrene and eventual amputation.

Most cases of PAD are asymptomatic.¹⁰ Asymptomatic PAD just like symptomatic PAD is associated with an increased risk of atherothrombotic events including MI and stroke,¹¹ impaired lower extremity functioning¹² and carotid artery stenosis.¹³

The Limburg Peripheral Arterial Occlusive Disease (PAOD) Study, a cross-sectional survey of 3650 patients aged 40 to 78 years found that symptomatic and asymptomatic PAD patients had a comparable risk factor and co-morbid profile.¹⁴

1.4 PAD IN THE GENERAL POPULATION

Based on current epidemiological projections, 27 million people in Europe and North America (16% of the populations 55 years and older) have PAD: an estimated 10.5 million people are symptomatic while the majority, 16.5 million are asymptomatic.¹⁵ Atherosclerotic PAD affects nearly 10% of men 65 years of age, increasing to 20% of men and women ≥ 75 years.¹⁶

In North American patients with systolic hypertension aged >60 years, approximately 25% have ankle-brachial indices (ABIs) ≤ 0.90 .¹⁷ Intermittent claudication, the earliest symptom of PAD, has an overall prevalence of 4.5% for those aged >55 years.¹⁸

Locally, prospective study by Awori in 2004 on lower limb amputations at KNH found a significant contribution of peripheral vascular disease. 55% of the amputations were due to PVD confirmed by arteriography, of which 17.6% were related to diabetes mellitus. Majority of these patients were in the age group 31-45 years.¹⁹

1.5 PERIPHERAL ARTERIAL DISEASE AND CVD RISK

Patients with PAD, even in the absence of a history of myocardial infarction or ischemic stroke, have approximately the same relative risk of death from cardiovascular causes as do patients with a history of coronary or cerebrovascular disease.²⁰

Epidemiological and clinical studies of the general population have clearly shown that PAD is a strong predictor for subsequent cardiovascular and overall mortality.^{17 21} PAD is associated with high mortality, 3 times higher than that of the general population²² even in patients without CKD and its prevalence appears to be much higher among end-stage renal disease patients as evidenced by the high amputation rates in this group compared to the general population.²³ PAD has not been as extensively studied as has other atherosclerotic diseases such as coronary artery disease and cerebrovascular disease especially among CKD patients.

1.6 PAD IN CKD POPULATION

PAD confers substantial risks for both morbidity and mortality in the end-stage renal disease (ESRD) population. The incidence of non-traumatic lower extremity amputation among the United States ESRD population is approximately 10 times higher than that among non-ESRD patients, even controlling for diabetes mellitus.²⁴ Dialysis patients with PAD are at increased risk for hospital admission²⁵, death within six months after initiation of dialysis²⁶, and death after acute myocardial infarction.²⁷ In the post-renal transplant population, PAD has been recognized as a risk factor for poor outcomes including prolonged hospitalization,²⁸ poor allograft survival rates²⁹ and increased mortality rates especially among diabetic recipients.³⁰ Amputation is the most common vascular complication after renal transplantation, occurring in 13-25% of renal allograft recipients within 5 years after transplantation.³¹

According to 1999 US Renal Data System data, the overall prevalence of PAD among incident ESRD was 14.9%.³² The Hemodialysis (HEMO) study reported a PAD prevalence of 23% among a sample of established hemodialysis patients.³³ Webb et al reported a 19% prevalence of intermittent claudication among a population of 325 British patients undergoing hemodialysis.³⁴ Estimates for prevalence of PAD among renal transplant recipients range from 15 to 30%.³⁵ In these aforementioned studies, the estimation of prevalence was based on history and physical findings.

Several other studies have measured the prevalence of PAD among ESRD on the basis of ABI <0.9 and found a prevalence ranging from 16 to 38%. (Table 3)

TABLE 3. PAD: ABI-based prevalence among patients with ESRD.

Author	No. of Patients	Population	Prevalence ABI < 0.9 (%)
Fishbane et al ³⁶	132	Hemodialysis (USA)	35
Al Zahrani et al ³⁷	60	Hemodialysis (Saudi Arabia)	38.3
Testa and Ottavioi ³⁸	226	Hemodialysis (France)	33
Ono et al ³⁹	774	Hemodialysis (Japan)	16.6

Few studies have been done to determine the prevalence of PAD in early stages of pre-dialysis CKD. A recently published study based on data from the National Health and Nutrition Examination survey (NHANES) 1999 to 2000 confirmed the high prevalence of PAD, 24%, defined by an ABI <0.9 among 211 patients aged 40 years and above with renal insufficiency in CKD stages 3 and 4.⁴⁰ This prevalence was much higher than that found in the general adult population using the NHANES 1999 to 2000 data where the prevalence was found to be 4.3%.⁴¹

Leskinen et al studied the prevalence of PAD using ABI in a Finnish population of 136 patients with chronic renal failure, which included 59 non-dialyzed non-transplanted patients with plasma creatinine >202mmol/L and creatinine clearance 30 ± 25 ml/min. The prevalence of PAD was 22%⁴² compared to only 1.7% in the control group with normal renal function.

Garcia et al found a PAD prevalence of 32%, in a Spanish population of 102 non-dialyzed patients with CKD and CrCl <60 ml/min.⁴³ This contrasted with data published for a Spanish population of 130 essential hypertensive patients without renal insufficiency, in which only 6.9% of the sample had PAD.⁴⁴

1.7 RISK FACTORS FOR PAD DEVELOPMENT

Atherosclerotic disease is diffuse in nature and there is considerable territorial overlap between cerebral, coronary and peripheral atherosclerotic disease as demonstrated by the CAPRIE study.⁴⁵

Data from several surveys have been used to successfully identify and document a clinical profile of the population at risk for PAD, in whom direct screening is beneficial. Framingham Heart Study data have defined age, sex, serum cholesterol level, hypertension, tobacco use, diabetes mellitus, and coronary heart disease as factors associated with an increased risk for PAD and intermittent claudication.⁴⁶

Among patients in CKD stage 5, the contribution of other non-traditional CVD risk factors such as hyperparathyroidism, chronic inflammation, hyperhomocysteinemia and apolipoprotein (a) levels has been associated with the development or progression of PAD.⁴⁷

1.7.1: Age

The prevalence of PAD increases sharply with age, from 3% in patients younger than 60 years of age to 20% in patients older than 75%.⁴⁸ Data from the Framingham study revealed that the prevalence of PAD increased 10-fold from men aged 30-44 to men aged 65-74 and almost 20-fold in women in the same age groups.⁴⁶

1.7.2: Male Gender

Analysis of the Framingham Heart Study demonstrated that male gender is a significant risk factor for the development of symptomatic PAD, although not all studies have found a similar association.⁴⁶

1.7.3: Hypertension

The role of hypertension as a major risk factor for the development and progression of PAD is well demonstrated in the Framingham Offspring Study and the German Epidemiological Trial in ABI.^{49 50} The Appropriate Blood Pressure Control study demonstrated a marked reduction in cardiovascular events in hypertensive PAD patients with diabetes when treated with an intensive blood pressure-lowering strategy compared with standard anti-hypertensive therapy.⁵¹ In the most recent guidelines from the Joint National Committee on the Detection, Evaluation, and Treatment of

Hypertension, PAD is considered equivalent in risk to ischemic heart disease, which supports the use of aggressive blood pressure control.⁵²

1.7.4: Tobacco Use

The amount and duration of tobacco use correlates directly with the development and progression of PAD.⁵³ Multiple factors seem to be involved in the atherogenic effect of tobacco use: activation of the sympathetic system with resultant vasoconstriction, oxidation of low-density cholesterol, inhibition of tissue plasminogen activator release from the endothelium, increased blood fibrinogen concentration, increased platelet activity, increased expression of plaque tissue factor, and endothelial dysfunction.⁵⁴

Tobacco cessation results in improved ankle pressure and exercise tolerance in patients with intermittent claudication as early as 10 months after tobacco cessation.⁵⁵ In addition, tobacco cessation is associated with improved postoperative arterial bypass graft patency rates.⁵⁶

1.7.5: Diabetes Mellitus

Diabetes increases the risk for atherogenesis via deleterious effects on the vessel wall (derangement of nitric oxide bioavailability in endothelial cells, stimulation of proatherogenic activity in vascular smooth muscle cells via reductions in phosphatidylinositol-3 kinase, and increases in oxidative stress and up-regulation of protein kinase C receptor for advanced glycation end-products and nuclear-kB), effects on blood cells (hypercoagulable state, enhanced platelet aggregation) and rheology (increased blood viscosity and fibrinogen levels).⁵⁷

A survey of patients with diabetes 50 years of age or older demonstrated a prevalence of PAD of 29%.⁵⁸ In the Rotterdam study,⁵⁹ diabetes was present in 11.9% and 16% of male and female patients with abnormal ABI, versus 6.7% and 6.3% of those without PAD. In the Cardiovascular Health Study⁶⁰ diabetes was associated with a 3.8 fold increased prevalence of PAD in patients older than 65 years.

The Diabetes Control and Complications Trial (DCCT) compared intensive and conventional insulin therapy in 1441 patients with type 1 diabetes. Intensive therapy was associated with a trend toward a reduction in cardiovascular events ($P=0.08$) but had no effect on the risk of peripheral arterial disease.⁶¹ The results were similar in 3867 patients with type 2 diabetes in the United Kingdom Prospective Diabetes Study, which compared intensive drug treatment using sulfonylurea or insulin with dietary therapy. Intensive drug therapy was associated with a trend toward a reduction in myocardial infarction ($P=0.05$) but had no effect on the risk of death or amputation due to peripheral arterial disease (relative risk 0.6; 95% confidence interval, 0.4 to 1.2).⁶² The data suggests that intensive blood glucose control in patients with either type 1 or type 2 diabetes may not favourably affect peripheral arterial disease.

1.7.6: Hyperlipidemia

The Lipid Research Clinics Prevalence Study⁶³ confirmed the association of dyslipoproteinemia (specifically low levels of high-density lipoprotein cholesterol and elevated low-density cholesterol) with symptoms and signs of PAD. In the National Cholesterol Education Program Adult Treatment Panel III report on detection, evaluation and treatment of high blood cholesterol in adults,⁶⁴ PAD was considered a coronary artery risk equivalent. Data from the Scandinavian Simvastatin Survival Study of 4,444 patients with known cardiovascular disease revealed that the use of simvastatin reduced the episodes of new or worsening intermittent claudication by 38%.⁶⁵

1.7.7: Hyperhomocysteinemia

Homocysteine appears to promote atherogenesis by oxidative damage to vascular endothelial cells and increased proliferation of vascular smooth muscle cells. In a prospective study of patients with symptomatic PAD, for each 1.0 $\mu\text{mol/L}$ increase in plasma homocysteine level, there was a 3.6% increase in the risk of all-cause mortality at 3 years and a 5.6% increase in the risk of cardiovascular-related death.⁶⁶

Kidney patients present with hyperhomocysteinemia as a result of delayed elimination and altered metabolism. While the prevalence of hyperhomocysteinemia (plasma homocysteine levels $>15 \mu\text{mol/L}$) in the general population is approximately 5%, in

dialysis patients it reaches 80% to 90%.⁶⁷ Studies have shown that dialysis patients with the highest homocysteine levels exhibit a higher prevalence of PAD compared with patients with the lowest homocysteine levels.⁶⁸

1.7.8: C - reactive protein

Ridker et al directly evaluated the relationship between C-reactive protein (CRP) levels and PAD. In the Physician's Health Study, 144 healthy men who subsequently developed symptomatic PAD were noted to have significantly higher baseline CRP than a group of control subjects who did not develop PAD.⁶⁹ An association between carotid artery atherosclerosis and CRP levels among patients with chronic renal insufficiency has been demonstrated.⁷⁰

1.7.9: Lipoprotein (a)

Lipoprotein (a) is a risk factor for PAD in the general population. It is genetically determined. Dialysis patients have significantly higher levels of lipoprotein (a) isoforms than do individuals with normal renal function. Low molecular weight apolipoprotein (a) isoforms are associated with the presence of carotid artery plaques among hemodialysis patients.⁶⁹

1.7.10: Hyperparathyroidism

Vascular calcification is extremely common among dialysis patients⁷¹ and perhaps contributes to the development of PAD. Among patients with ESRD, abdominal aortic calcification seems to be correlated with increased calcium-phosphorus product level⁷² while hyperphosphatemia and hyperparathyroidism have been demonstrated to be correlated with coronary, carotid and femoral artery atherosclerosis among dialysis patients.^{73 74}

1.8 PAD DIAGNOSIS

There are a number of non-invasive options that accurately diagnose PAD, including:

- Ankle-brachial index (ABI) is the gold standard to establish diagnosis and serve as a baseline measure for patient follow-up. Measurements may be taken before and after exercise to assess the dynamics of intermittent claudication.
- Toe-brachial index (TBI) may be particularly helpful in diabetics, whose disease tends to be more severe and frequently involves calcification of the media, making ABI measurements inaccurate due to the inability to compress the ankle vessels. It is technically more difficult to perform and requires use of a vascular laboratory.
- Segmental pressures and pulse volume recordings are used to measure pressures at levels in the ankle, calf, above the knee, and thigh. These are useful in diabetics with medial arterial calcification.
- Duplex and colour flow ultrasound scanning, normally reserved for patients who are scheduled for balloon angioplasty or other interventions, enables stenotic segments to be localized for treatment planning.
- MR angiography is an evolving imaging modality that is useful as a diagnostic tool, particularly in patients who cannot receive iodinated contrast agents due to renal disease.

1.9 THE ANKLE-BRACHIAL INDEX IN PAD DETECTION

The ankle-brachial index (ABI) is a simple, inexpensive, reproducible, non-invasive measurement to assess the patency of the lower extremity arterial system.⁷⁵

The ABI is measured by having the patient lie in the supine position with subsequent performance of the ankle and brachial blood pressure measurement using a 5 to 10 MHz hand-held Doppler device to identify the systolic blood pressure.

An appropriately sized blood pressure cuff is required. The posterior tibial and dorsalis pedis artery systolic pressures are both measured and compared with the arm pressure. The ABI value is calculated by dividing the higher of the ankle systolic pressures by the higher of the 2 systolic brachial pressures.

The impact of both inter-observer and intra-observer error on reproducibility has been quantified in a Dutch general practice based study.⁷⁶ The difference between two sequential ratios had to be at least 19% in order to exclude an intra-observer error.

A diagnosis of PAD is based on the presence of limb symptoms or an ABI measurement less than 0.9. A resting ABI value of 1.0 is considered normal while a resting ABI value less than 0.9 approaches 95% sensitivity in detecting angiogram positive disease, and is associated with the presence of 50% or greater stenosis in one or more major vessels. It is almost 100% specific in excluding healthy individuals.⁷⁷

The ABI allows for detection of PAD at all stages of the disease process and can stratify the severity of both asymptomatic and symptomatic disease with a numerical value that can assist in guiding a treatment approach:

0.91-1.30	Normal
0.71-0.90	Mild PAD
0.41-0.70	Moderate PAD
≤0.40	Severe PAD ⁷⁸

Individuals with an ABI <0.9 are twice more likely to have coronary heart disease (CHD) than those with a normal ABI and have an increased risk of fatal and non-fatal MI, stroke and death from cardiovascular causes, as well as all-cause death.²¹

In a study to determine the relationship between ABI and morbidity and mortality in patients with PAD, the 5-year cumulative survival rates were 63% for ABI <0.50, 71% for ABI 0.50-0.69 and 91% for ABI 0.70- 0.89.⁷⁹

There are some limitations of the utility of ABI in diagnosis of PAD. Firstly, older patients and those with diabetes may have stiff, calcified, non-compressible vessels and may have an ABI >1.30, even in the presence of PAD. Despite this shortcoming, the American Diabetes Association (ADA) recommends use of ABI as a screening tool in diabetics⁵⁷ and those with ABI >1.30 can be subjected to other diagnostic modalities.

Secondly, patients with high-grade aorto-iliac arterial stenoses or occlusions may occasionally present with a normal ABI at rest due to the presence of a rich collateral arterial network. These patients require other diagnostic tests.

Thirdly, congenital absence of pulses may limit the use of the ABI. The dorsalis pedis pulse is congenitally absent in approximately 10% of the population and the posterior tibial pulse is absent in less than 10% of the population.^{80 81} Congenital absence of these pulses are commoner in Caucasians than in blacks.⁷⁸ An abnormal posterior tibial pulse is 71.2% sensitive and 91.3% specific for PAD, whereas an abnormal dorsalis pedis pulse is only 50% sensitive and 73.1% specific.⁸² If no posterior tibial or dorsalis pedis pulse are found then the anterior tibial and/ or peroneal artery pulses are used for ABI measurement.

Finally, despite its usefulness in diagnosis of PAD, the ABI is unable to measure effectiveness of preventive treatment. Therefore it has a limited role in follow-up of patients with PAD.

In spite of these limitations, the ABI is the most practical, effective and accurate method of PAD detection especially in asymptomatic at risk population.

1.10 INTERMITTENT CLAUDICATION

This is the earliest symptom of PAD. It is usually diagnosed by a history of leg pain on exercise that is relieved by rest. Questionnaires have been developed for epidemiological use to diagnose intermittent claudication.

The WHO/Rose Questionnaire designed in 1962 by Rose⁸³ and adopted by the WHO, has a specificity of 99.8% in excluding healthy individuals and a sensitivity of 67.5% in detecting those with claudication compared with physician assessment of symptoms.

The Edinburgh Claudication Questionnaire⁸⁴ was validated in a study of approximately 300 patients older than 55 years who consulted their general practitioner. When compared with the independent assessment of two blinded clinicians, the questionnaire showed a sensitivity of 91% and a specificity of 99% for the diagnosis of intermittent claudication.

2. JUSTIFICATION OF THE STUDY

CKD patients are at risk of CVD. A previous study by Sheikh showed increased prevalence of multiple CV risk factors in the patients with CRI at KNH ⁹.

PAD is a marker of generalized atherosclerosis and is a strong predictor for subsequent cardiovascular and overall mortality. PAD prevalence among dialysis patients is high in the West as evidenced by high rates of amputations. There is no local data on the prevalence of PAD among our CKD patients.

Relative to methods of detecting other forms of atherosclerotic cardiovascular disease such as coronary angiography, ABI measurement is a simple, non-invasive procedure that can be performed easily in the outpatient setting to diagnose sub clinical atherosclerotic disease.

This study proposed to determine the prevalence of PAD in patients with CKD and the associated cardiovascular risk factors. The data generated from this study will sensitise clinicians on the magnitude of PAD in this high-risk group and the need to look out for it by measurement of the ABI. Those found to have PAD benefited from secondary prevention strategies as well as evaluation for atherosclerosis in other vascular beds – coronary and cerebral.

2.1 RESEARCH QUESTIONS

1. What is the prevalence of PAD using ABI in CKD patients at KNH?
2. What is the prevalence of selected CV risk factors in patients with CKD and PAD?
3. What is the relationship between these selected CV risk factors and PAD?
4. What proportions of the patients with PAD are symptomatic?

3. OBJECTIVES

3.1 Broad Objective:

To determine the prevalence of PAD and the associated CV risk factors in CKD patients.

3.2 Specific Objectives:

1. To determine the prevalence of PAD using the ABI among patients with CKD at KNH.
2. To determine prevalence of selected CV risk factors in patients with CKD and PAD at KNH: -
 - Diabetes mellitus
 - Hypertension
 - Dyslipidemia
 - Smoking
 - Gender
 - Age
3. To determine the relationship between the selected CV risk factors and PAD.
4. To determine the proportion of patients with symptomatic PAD using the Edinburgh Claudication Questionnaire.

4. METHODOLOGY

4.1 Study Design

Hospital-based, cross-sectional prevalence survey.

4.2 Study Site

Kenyatta National Hospital Renal Clinic.

4.3 Study Population

Adult males and females ≥ 30 years presenting at KNH Renal Clinic with CKD.

4.4 Case Definition

CKD was defined as proteinuria for ≥ 3 months and or a GFR ≤ 60 ml/min/1.73 m².

Proteinuria was defined by a positive dipstick urinalysis ≥ 1 plus +.

GFR was calculated from serum creatinine using the Cockcroft-Gault formula and corrected to body surface area

4.5 Patient Selection

4.5.1 Inclusion Criteria

1. Adult patients aged ≥ 30 years of both sexes with a diagnosis of CKD
2. Signed informed consent to participate in the study.

4.5.2 Exclusion Criteria

1. Patients on renal replacement therapy (hemodialysis or peritoneal dialysis).
2. Patients with leg ulcers, plaster casts, bandages or massive limb oedema that precluded ABI measurement.

4.6 Sampling Technique

Consecutive patients who satisfied the inclusion criteria during the study period were recruited into the study. Sampling continued until desired sample size was attained.

4.7 Sample Size

The minimum sample size (n) required to determine the prevalence of PAD was calculated using the formula⁸⁵: -

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

- Whereby Z value is the upper $\alpha / 2$ point of the normal distribution, 1.96.
- π is the assumed prevalence. Based on the Finnish study and the NHANES survey where prevalence of 22% and 24% were obtained respectively, an estimated prevalence of 24% was utilised.
- d is the precision, 0.05, with which to determine the prevalence.

Therefore n = 280 patients.

4.8 Study Period

Patients were recruited over a ten-month period, between January and October 2006.

4.9 Screening and Recruitment

The Principal Investigator (MM) recruited patients from KNH Renal clinic. The files for all the patients booked for the once weekly clinic were scrutinized specifically looking at the serum creatinine (screening serum creatinine) and urinalysis, done in the preceding 3 to 6 months.

Patients with a prior urinalysis result showing proteinuria and those with calculated GFR $<60\text{ml}/\text{min}/1.73\text{m}^2$ were assessed for eligibility into the study using the screening proforma. A repeat serum creatinine and urinalysis was done on the morning of the clinic. The creatinine result was used to calculate GFR using the Cockcroft-Gault formula as follows⁸⁶: -

$$\text{GFR} = \frac{(140 - \text{Age})(\text{years}) \times \text{body weight in kilogrammes} \times K}{\text{Serum creatinine (umol/L)}}$$

K = constant 1.23 men, 1.04 women

Calculated GFR was expressed per 1.73m² of body surface area by multiplying calculated values by 1.73/body surface area.

Those fulfilling the criteria for the case definition were recruited as cases if they signed the consent form administered by PI to participate in the study.

CKD staging was done using the calculated GFR/ proteinuria as shown in table 4:

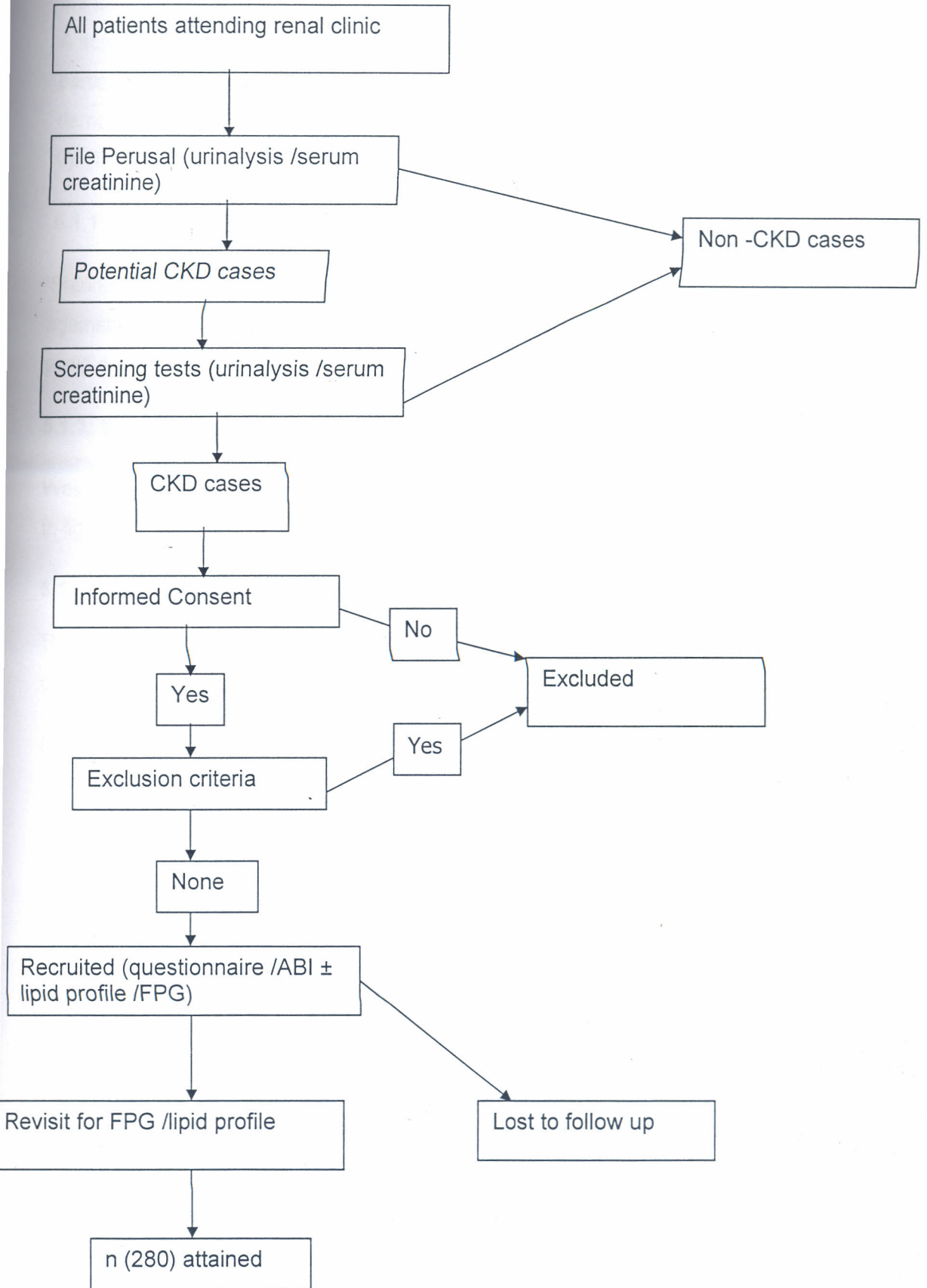
Table 4: NKF/ DOQI stages of CKD ²

Stage	Description	GFR (ml/min/1.73m ²)
1	Kidney damage with normal or ↑ GFR	>90
2	Kidney damage with mild ↓ GFR	60 - 89
3	Moderate ↓ GFR	30 - 59
4	Severe ↓ GFR	15 - 29
5	Kidney failure	<15

Demographic data was obtained for all the patients who had CKD as defined above (including those excluded for various reasons).

Once recruited, 2-research assistants administered the questionnaire (appendix II) under supervision by the PI. The PI performed the physical examination and ABI measurement on all the patients on the same day. Those patients who were appropriately fasted (10 -12hr overnight fast) on the day of recruitment had their blood withdrawn for measurement of fasting plasma glucose and lipid profile. Those not fasted were asked to return the following Friday to Renal clinic for withdrawal of blood samples. The cost of the all the laboratory tests as well as reimbursement of transportation cost for the revisit was met by PI.

Figure 1: Flow chart of Screening and Recruitment



5. DATA COLLECTION

5.1 Clinical Methods

A screening proforma was used to obtain demographic data and to assess eligibility of participation in the study (Appendix I). A study proforma was used to obtain demographic data and a complete medical history from the enrolled patients (Appendix II). The PI undertook comprehensive physical examination using standard procedures:-

5.1.1: Height

Standing height was measured once to the nearest 0.5cm barefoot, the back square against the wall tape, eyes looking straight ahead, with a set square resting on the scalp and against the wall.

5.1.2: Weight

Weight was measured once to the nearest 100 grams using a lever balance, barefoot, in light garments.

5.1.3: Body Mass Index

The body mass index (BMI) was calculated using the World Health Organization (WHO) criteria as weight (in kilograms) divided by height (in meters) squared.

5.1.4: Body Surface Area

The body surface area (BSA) was calculated using height and weight.⁸⁷

5.1.5: Blood Pressure

Blood pressure was measured as per WHO recommendation,⁸⁸ with patient in a sitting position and using a standard adult cuff and a manual mercury sphygmomanometer, after an initial rest period of 15 minutes. The systolic blood pressure was determined by the first audible perception of the Korotkoff Sound (phase I). Diastolic blood pressure was determined by the perception of disappearance of fifth Korotkoff sound (Phase 5) or if the sound did not disappear the point at which it was muffled was used. Two measurements were undertaken at 5-minute intervals and the average of these two readings recorded.

5.1.6: Ankle-Brachial Index

All patients were subjected to ABI measurement as per standard protocol. The ABI measurement was done by the PI throughout the study with training and supervision by one of the supervisors (JOJ), well trained and experienced in ABI measurement. Patients were asked to lie supine on the examination couch for at least 5 minutes before blood pressure measurement. Appropriate size blood pressure cuffs were applied to bare ankles with the midpoint of the rubber cuff over the posterior tibial artery, approximately 3 centimetres above the medial malleolus. Ankle systolic blood pressure was taken with an 8-megahertz hand-held Doppler device (Lifedop 250R-Summit Doppler) using both the dorsalis pedis and posterior tibial arteries. The maximum sound impulse determined the location of the artery. If both pulses were absent then the anterior tibial and/ or peroneal artery were used for ankle systolic pressure measurement. The brachial systolic blood pressure was taken at the cubital fossa using the brachial artery in each arm. The higher of the two arm pressures was selected as the denominator while the higher of the two pressures in each ankle was the numerator. The right and left ABI were calculated as: -

Higher ankle systolic blood pressure

Higher brachial systolic blood pressure

The worst of the 2 values calculated was used to define ABI for each individual.

5.2 Laboratory Methods

5.2.1 Specimen collection and handling during screening

- 2 mls of venous blood was drawn aseptically from the antecubital fossa into a plain tube.
- 5-10 mls mid-stream urine was collected in a universal bottle.

Specimens were taken to the renal laboratory of the KNH.

Blood specimens were allowed to clot then centrifuged at 3000 rpm for 15 minutes. 1ml of serum was put into a transfer vial for creatinine estimation.

Serum creatinine was measured by the alkaline picrate method ⁸⁹ on an auto analyser (Technicon RA 1000).

Urine specimen was mixed by gently shaking the bottle. Dipstick urinalysis was done using multistix 10SG (Bayer) throughout the study period to assess for proteinuria.

5.2.2: Follow-up visit

Study subjects were instructed to observe overnight fasts (10-12 hours) before specimens were collected.

5 mls venous blood was drawn aseptically from the antecubital fossa into a lithium heparin tube. Specimens were transported to the main Biochemistry laboratory immediately.

Specimens were centrifuged at 3000rpm for 15 minutes. 1ml of plasma was collected into 3 transfer vials for biochemical analyses.

- Plasma glucose (fasting) was measured by the glucose oxidase method ⁹⁰ on the autoanalyser (Technicon RA 1000).

Fasting lipid profile was done on the Humalyzer 3000 auto-analyser.

- Total cholesterol was estimated colorimetrically using the enzymatic hydrolysis and oxidation method.⁹¹
- Triglycerides was determined using the enzymatic hydrolysis with lipases method.⁹¹
- HDL-cholesterol was estimated using the phosphotungstic acid/ magnesium chloride precipitation method.⁹¹
- LDL-cholesterol level was calculated using the Friedewald-Fredrickson formula.⁹²

5.2.3: Quality Assurance

Commercial reagent kits were used for all biochemical assays. All analyses were performed according to manufacturer's specifications by competent technologists.

Commercial quality control materials were included in all analytical runs. Results were only accepted if control samples were within acceptable limits.

6. DEFINITION OF STUDY VARIABLES

6.1 DEPENDENT STUDY VARIABLE

PAD was defined by an ABI <0.9 . PAD severity was classified based on the ABI ⁷⁸ as follows:

>1.30 Noncompressible

$0.91 - \leq 1.30$ Normal

$0.71 - 0.90$ Mild PAD

$0.41 - 0.70$ Moderate PAD

<0.40 Severe PAD.

6.2 INDEPENDENT STUDY VARIABLES

6.2.1: Diabetes and Impaired Fasting Glucose

Study participants were considered diabetic if: -

- Self report of diabetes, or
- Use of hypoglycaemic medication, or
- Fasting plasma glucose (FPG) ≥ 7.0 mmol/L ⁹³

Impaired fasting glucose (IFG) was defined as FPG ranging from 6.1 mmol/L to 6.9 mmol/L. ⁹³

6.2.2: Hypertension

Study participants were considered hypertensive ⁵² if they had a SBP ≥ 140 mmHg or a DBP ≥ 90 mmHg or if they were taking antihypertensive medication.

6.2.3: Dyslipidemia

Study participants were classified as per NCEP/ATP III guidelines.⁶⁴

Total Cholesterol	<5.17 mmol/L - Desirable
	5.17 - 6.18 mmol/L - Borderline high
	>6.21 mmol/L - High
LDL Cholesterol	<2.59 mmol/L - Optimal
	2.59 - 3.34 mmol/L - Near Optimal
	3.36 - 4.11 mmol/L - Borderline high
	4.14 - 4.89 mmol/L - High
	≥4.91 mmol/L - Very high
HDL Cholesterol	<1.03 mmol/L - Low
	<1.29 mmol/L - Optimal
	≥1.55 mmol/L - High
Triglycerides	<1.69 mmol/L - Normal
	1.69 - 2.25 mmol/L - Borderline high
	2.26 - 5.64 mmol/L - High
	≥5.65 mmol/L - Very high

Dyslipidemia was defined by any one of the following: - total cholesterol ≥5.17 mmol/l or LDL cholesterol ≥2.6 mmol/l or, HDL cholesterol ≤1.03 mmol/l, or triglycerides ≥2.26 mmol/l.

6.2.4: Cigarette Smoking

Study participants were classified according to their smoking status: ⁻⁹⁴

- Current smokers were defined as those who had 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 had smoked at least 100 cigarettes in their lifetime but would have quit smoking more than one year earlier.
- Non-smokers were those who had smoked less than 100 cigarettes in their lifetime or who had never smoked.

6.2.5: Age as a CV Risk Factor

Men \geq 45 years; women \geq 55 years

7. DATA MANAGEMENT AND STATISTICAL ANALYSIS

All data emanating from the study was verified cleaned and entered into data entry sheets. Statistical analysis was performed using Statistical Package for Social Sciences, version 10.0 software for windows.

Analysis involved descriptive statistics such as means, medians and standard deviation for continuous variables and frequency distributions for categorical variables, with their corresponding 95% confidence intervals. Comparisons for continuous data were made using the t test, and of categorical data using the chi-square test.

Prevalence was calculated as number of patients with PAD divided by the total number of patients and expressed as a percentage with 95% confidence interval.

Prevalence rates of risk factors were calculated as percentages with 95% confidence intervals.

Multivariate analysis was performed in order to investigate independent associations between risk factors (hypertension, smoking, age, and diabetes mellitus) and PAD.

The level for statistical significance was $P \leq 0.05$.

8. ETHICAL CONSIDERATIONS

The study was conducted after approval by the Department of Clinical Medicine and Therapeutics, University of Nairobi, and the Kenyatta National Hospital Scientific and Ethical Review Committee.

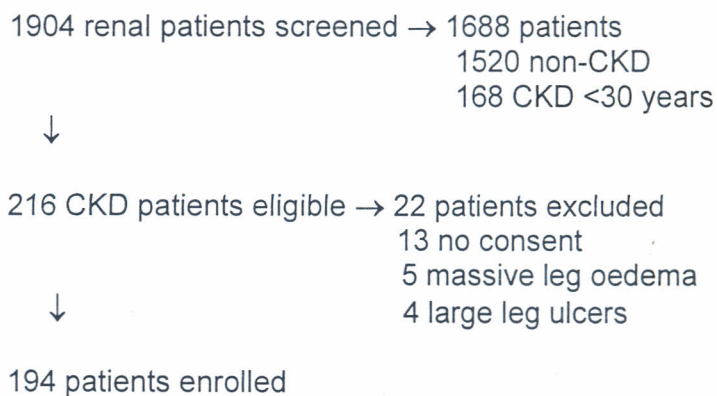
A detailed written (and verbal) consent explanation was given to the study subjects (Appendix III)

In the event of a favourable response, the patient was requested to sign an informed consent form (Appendix IV)

9. RESULTS

1904 outpatients attending KNH Renal Clinic were screened over a 10-month duration between 3rd January and 5th October 2006, of which 216 (11.3 %) met study inclusion criteria; 22 (10.1%) were excluded and thus 194 included. Majority (90%) of the 1688 patients who did not meet inclusion criteria were non-CKD while the rest were CKD under 30 years. The desired sample size was 280 CKD patients to identify at least 70 PAD patients. Sample size calculation was predicated on PAD prevalence with an estimated prevalence of 24 % (from the literature). There was a shortfall in desired sample' occasioned by an enrolment rate that was a third of the anticipated. KNH Registry data for January to December 2005 indicated that 199 patients had a diagnosis of chronic renal failure. Over a 10-month period 216 patients were found to have CKD (Figure 2).

Figure 2: Flow chart of enrolment



9.1 DEMOGRAPHICS OF EXCLUDED PATIENTS

Of the 22 patients excluded, 13 males (59.1%) and 9 females (40.9%) and their mean age was 52.05 ± 13.3 (range 30 –84) years. 13 (59%) were excluded for non-consent, 9 (41%) due to ABI measurement technicalities (massive oedema in 5 and large leg ulcer in 4 patients).

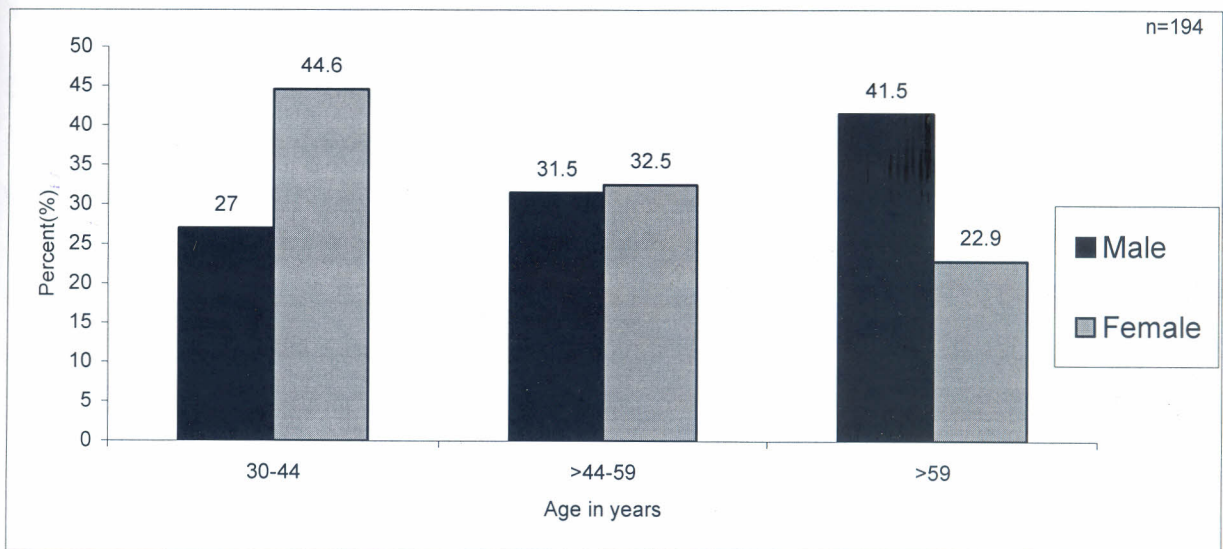
The excluded patients did not differ from included patients with regards to age and gender.

9.2 DEMOGRAPHICS OF STUDY PATIENTS

Mean age of study subjects was 51.96 ± 14.18 (range 30-84) years and 111 (57.2%) males and 83 (42.8%) females. 78.9% of study patients were married, 53.1% had at least primary education and 61.8% had no source of income, as they were retired or unemployed.

The study patients were grouped into 3 age-by-gender groups. The study patients were equally distributed in the 3 age categories. Females however predominated the 30 - 44 year age group, while males predominated in the >59 year age group. The male to female ratio in age group >44 - 59 years was 1:1 (Figure 3)

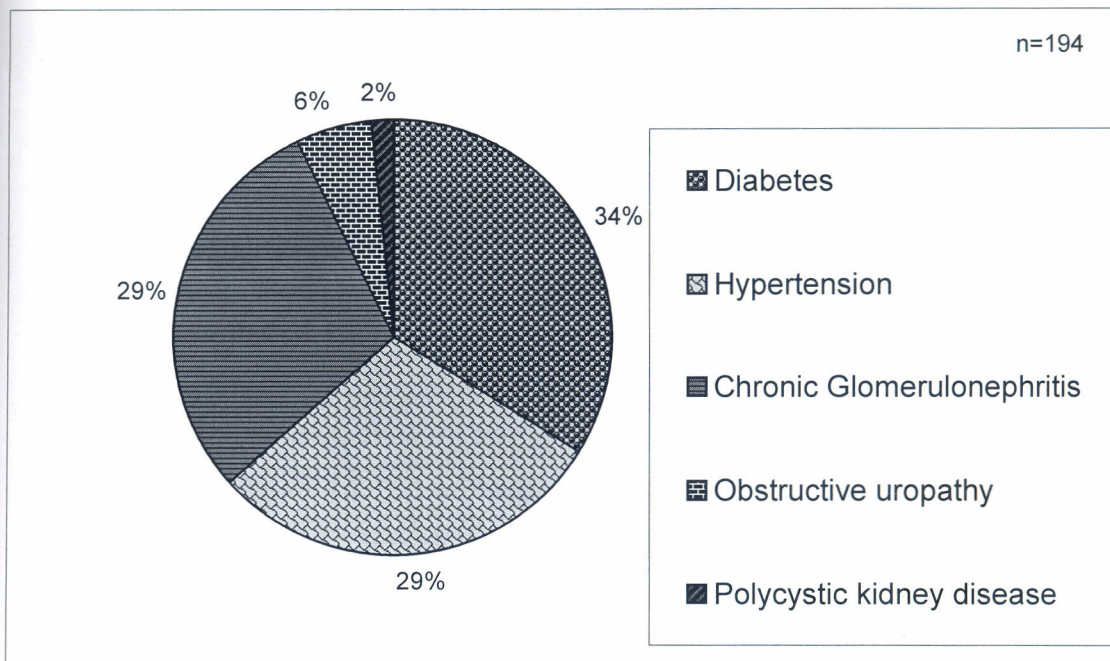
Figure 3: Age by gender distribution of study population



9.3 AETIOLOGY OF CKD

The cause of CKD was obtained from patients case records. Majority (34%) had diabetes mellitus. Hypertension and chronic glomerulonephritis were equally distributed and contributed to 29% of CKD each. (Figure 4)

Figure 4: Aetiology of CKD



9.4 DISTRIBUTION OF PATIENTS ACCORDING TO CKD STAGE

Study patients were classified into CKD stage 1 - 5 as per NKF/ DOQI classification² on the basis of the calculated GFR corrected to body surface area and this is depicted in table 5. The frequency distribution of study subjects by CKD stage was 2.1%, 16.5%, 34.5%, 22.2% and 24.7% in stage 1,2,3,4 and 5 respectively; with 80% having advanced CKD stage ≥ 3 (GFR ≤ 60 ml/min/1.73m²). The mean GFR of the study population was 36 ± 24.7 (range 1.9 - 110.1 ml/min/1.73m²)

Table 5: CKD stage of study patients

CKD stage	Description	GFR (ml/min/1.73m ²)	No	%
1	Kidney damage with normal or ↑ GFR	>90	4	2.1
2	Kidney damage with mild ↓ GFR	60-89	32	16.5
3	Moderate ↓ GFR	30-59	67	34.5
4	Severe ↓ GFR	15-29	43	22.2
5	Kidney failure	<15 or dialysis	48	24.7
Total			194	100

9.5 ABI RESULTS

9.5.1 ABI measurement

All the study patients underwent successful ABI measurement, however. Two (1%) patients had ABI>1.3 and therefore could not be classified as having or not having PAD and were subsequently excluded from all subsequent analysis. 23 patients had ABI < 0.9, computing to a PAD prevalence of 11.9% (95% CI, 7.3 – 16.4). Mean age of PAD patients was significantly higher than non-PAD counterparts (67.7 ± 14.3yrs versus 50.5 ± 13.6; p=0.000).

All but five of the PAD patients were male and all females were aged over 55yrs.

9.5.2 PAD severity

The study patients were classified into PAD severity categories on basis of the ABI measurements. (Table 6) 3 (1.5%) had severe PAD, 10 (5.2%) moderate PAD and 10 (5.2%) mild PAD.

Table 6: PAD severity by ABI classification

PAD severity by ABI	No.	%
Severe PAD (ABI ≤ 0.40)	3	1.5
Moderate PAD (ABI 0.41-0.70)	10	5.2
Mild PAD (ABI 0.71-0.90)	10	5.2
Normal (ABI 0.91- ≤ 1.30)	169	87.1
Incompressible (ABI > 1.3)	2	1
Total	194	100

9.5.3 PAD and CKD stage

Majority of PAD patients had advanced CKD disease, with 74% in stage 4 and 5, and 90% in stage 3 and above as depicted in (Table 7). PAD patients had a worse renal function compared to non-PAD patients (GFR 27.2 ± 21 versus 37.3 ± 25 ml/min/1.73m², p=0.04).

Table 7: PAD Frequency by CKD stage

CKD stage	No	%
1	0	0
2	2	8.7
3	4	17.4
4	11	47.8
5	6	26.1
Total	23	100

9.5.4: CV RISK FACTORS IN PAD

Excluding the presence of CKD, all patients with PAD demonstrated presence of selected CV risk factors with the majority having more than two risk factors. The frequency of risk factor occurrence is depicted in table 8. The commonest risk factor was age occurring in 87% followed by male gender 78%, hypertension 74%, diabetes mellitus 56%, cigarette use 47% and dyslipidemia 43%.

Table 8: PAD and CV risk factors

Risk factors	Frequency	%
Female \geq 55 years	5	86.95
Male \geq 45 years	15	
Male gender -	18	78.3
Hypertension	17	73.9
Diabetes	13	56.5
Cigarette smoking	11	47.8
Dyslipidemia	10	43.5
Total	89	100

9.5.5: PAD Risk Factor Odds Ratio

As a measure of the magnitude of the relationship between PAD and the risk factors, the probability of risk factor presence in PAD patients relative to the converse probability was determined on univariate analysis using the odds ratio (OR) estimation and chi-square test. These results are depicted in (Table 9)

Table 9: PAD risk factor odds ratio

Risk factor	Odds ratio (95% CI)	P value
Male/ female	3.02 (1.07 – 8.5)	0.03
DM/ no DM	2.41 (0.99 – 5.8)	0.046
Cigarette smoking/ no cig. Smoking	2.04 (0.85 – 4.92)	0.107
Age male ≥ 45 years/ < 45 years	2.3 (0.61 – 8.44)	0.213
HTN/ no HTN	0.9 (0.35 – 2.57)	0.922
Dyslipidemia/ no dyslipidemia	0.6 (0.27 – 1.55)	0.325
CKD stage ≥3/ CKD stage <3	2.61 (0.58 – 11.66)	0.195

The odds ratios for cigarettes smoking, male gender, diabetes mellitus and CKD stage ≥3 versus CKD stage <3 were on average two fold, however only the male gender and diabetes mellitus attained statistical significance (Tables 10 and 11). Hypertension and dyslipidemia in this data set were not associated with the presence of PAD.

Table 10: 2x2 table for PAD and male gender

	PAD		
	Yes	No	
Gender Male	18 (78.3%)	93 (54.4%)	111 (57.2%)
Female	5 (21.7%)	78 (45.6%)	83 (42.8%)
Total	23	171	194

$\chi^2 = 4.721$

df = 1

p = 0.03

OR = 3.019 (1.072 - 8.504)

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Table 11: 2x2 table for PAD and diabetes

		PAD		
		Yes	No	
Diabetes	Yes	13 (56.5%)	60 (35.1%)	73 (37.6%)
	No	10 (43.5. %)	111 (64.9%)	121 (62.4%)
Total		23	171	194

$\chi^2 = 3.968$

df = 1

p = 0.046

OR=2.405(0.995-5.811)

9.5.6 Multivariate analysis

Multivariate analysis was carried out to determine risk factors independently associated with the presence of PAD among those that were significant at univariate analysis, namely male gender (p = 0.03) and diabetes (p = 0.046). Male gender and diabetes were found to be independently associated with PAD, p = 0.035 and p = 0.05 respectively with unaffected odds ratios 3.0 and 2.5 respectively. (Table 12)

Table 12: Multivariate analysis for male gender and diabetes

Variables in the Equation

	B	S.E.	Wald	df	Sig.	Exp(B)
Step 1 ^a DIAB	.896	.456	3.853	1	.050	2.450
GENDER	1.122	.533	4.431	1	.035	3.070
Constant	-.868	.984	.777	1	.378	.420

a. Variable(s) entered on step 1: DIAB, GENDER.

9.6 SYMPTOMATIC PAD

On basis of the Edinburgh Claudication Questionnaire 52% (12) were asymptomatic and 11(47.8%) of PAD patients exhibited intermittent claudication.

10. DISCUSSION

Knowledge on the prevalence of PAD in patients with pre-dialysis CKD is limited because of the previous lack of uniformity in CKD definition and recognition. In 2002, the NKF issued new guidelines on definition and classification of CKD², which are currently in use. This study set out to determine the prevalence of PAD in CKD using this new classification.

In this study, 194 CKD patients were enrolled. Males comprised 57.2% and the male to female ratio was 1.3:1. A study by Sheikh⁹ looking at CV risk factors among CRI patients at the hospital found similar gender predominance. In his study, males were 71% and the male to female ratio was 2.5:1. Reasons for this gender predominance may be related to gender bias in health-seeking behaviour, socio-economic variability affecting access to healthcare in a tertiary hospital as well as gender bias in aetiological background to the CKD. Male gender has been shown to be a risk factor for development of CKD.⁸ The implication of finding is that over 50% of the study population had male gender as a non-modifiable CV risk factor.

The mean age of the overall CKD population was 51.96 years. This was similar to that found by Sheikh⁹ where the mean age was 52.7 years. On the whole, the average age of the patients was significantly younger than that seen in European and American studies in CKD population.^{40 42 43} This difference in age could be explained by the fact that our CKD population is significantly younger than the western population. Life expectancy and quality of healthcare in developed countries also contributes to this observed difference. Among the Caucasian population, CKD mainly develops as a complication of diabetes and hypertension⁹⁵ while in Africa CKD is mainly due to post-infectious chronic glomerulonephritis, which affects the younger age group.

There were 3 main aetiologies of CKD in the study population – diabetes (34%), chronic glomerulonephritis (29%) and hypertension (29%) with diabetes dominating the other two aetiologies. This distribution of aetiologies is in contrast to that described in 2 local studies. Sheikh⁹, studying a similar population found the causes to be chronic glomerulonephritis in 36.1%, hypertension in 31.3% and diabetes in 28.9%. Sheikh's findings were similar to that described earlier by Kayima⁹⁶ where chronic

glomerulonephritis was 36%, hypertension was 23% and diabetes was 23%. The main reason for this difference is that patients younger than 30 years were excluded from our study. Post-infectious chronic glomerulonephritis is a common cause of renal failure in the younger patients who were excluded. The older patients develop renal failure as complications of longstanding hypertension or diabetes and these were the patients enrolled into the study. There is an increasing prevalence of diabetes mellitus in the developing world⁹⁷ and this could partly explain the predominance in this study. Majority (63%) of the study population had both diabetes and hypertension as a cause of the CKD as well as contributing adversely to their CVD risk.

ABI measurements were obtained for all the enrolled patients. 23 patients had ABI <0.9 giving a PAD prevalence of 11.9% in patients with CKD stage 1-5. This is relatively much lower than that described in other studies done in the west in patients with advanced pre-dialysis CKD (GFR < 60 ml/min/1.73m²). One of these studies recently published from Spain,⁴³ included 102 CKD patients in stage 3 –5, referred for the first time to a nephrology clinic, and without a prior diagnosis of PAD. ABI revealed that 32% of the patients suffered from PAD. This prevalence is similar to that observed in dialysis patients²³ but is much higher than in our study population. Using a subgroup of 2229 patients of NHANES, a 24% PAD prevalence rate was observed in patients with estimated GFR < 60ml/min/1.73m² versus a prevalence rate of 3.7% in patients with GFR > 60ml/min/1.73m²⁴⁰ These results could differ from our study because of patient characteristics, such as age, that contribute to PAD. The mean age of the patients was 70± 11 years in the Spanish study⁴³ and 76.1± 1.1 years in the NHANES survey,⁴⁰ therefore, the patients were older than in our population (51.96± 14.18 years). Another study⁴² that included younger patients (55.7± 11.4 years) and a mean GFR of 30 ml/min reported a prevalence rate of 22% that was slightly lower than for the 2 other studies. Another possible explanation for the difference in PAD prevalence is that these other studies enrolled patients with advanced CKD. These are patients with increased prevalence and severities of several adverse CVD risk factors that include both the traditional and non-traditional factors (uraemia-related factors). Sheikh's study⁹ documented a high prevalence of these non-traditional risk factors among patients with advanced CRI at KNH. Our study included patients in non-advanced CKD stage 1 and 2 where these non-traditional factors may have been absent and this may explain the difference in the prevalence. Finally, the duration of CKD and quality of interventions may influence the development and prevalence of PAD. It is known that

CKD progresses faster in black patients than their white counterparts as a result there are shorter exposure to adverse risk factors. This may contribute to the relatively low prevalence. Longer survival of patients with CKD in the west⁹⁵ results in more comorbid hypertension and diabetes, which are adverse CV risk factors. Older age, male gender, diabetes, hypertension and proteinuria have been shown to be risk factors for both CVD and CKD.⁸

2(1%) patients had ABI >1.3 (incompressible). This suggests the presence of medial arterial calcification (MAC) also described as Monckeberg arteriosclerosis. This could slightly affect the sensitivity but not specificity to detect PAD.

PAD severity was determined using ABI categories. Of the 23 patients with PAD, 43.5% had mild PAD (ABI 0.71 - 0.90), 43.5% had moderate PAD (ABI 0.41 - 0.70) and 13% had severe PAD (ABI \leq 0.40). In a study by Sikkink⁷⁹ to determine the relationship between ABI and morbidity/mortality in patients with PAD, the 5-year cumulative survival rates were 63% for ABI <0.50, 71% for ABI 0.50 - 0.69 and 91% for ABI 0.70 - 0.89. These data therefore suggest that 43.5% of our patients with ABI 0.71 - 0.90 have a presumptive 5-year cumulative survival rate of 91% while those with ABI below this have a presumptive 5-year cumulative survival rate of 63 - 71%. A recent study⁹⁸ studied mortality 1 year after diagnosis of severe PAD in 5787 patients with diverse degrees of renal function. In patients with an estimated GFR < 30 ml/min, the 1-year mortality was 44%. After adjusting for age, diabetes mellitus and previous cardiovascular events the risk of death in patients with similar degrees of PAD was 2.9 times higher than in patients with GFR < 60 ml/min versus the group with GFR > 60 ml/min. This confirms the great mortality rate among renal patients that suffer PAD.

The 23 PAD patients were classified into CKD stage 1 - 5 and 91.3% had advanced CKD (stage 3 - 5). PAD patients had a worse renal function compared to non-PAD patients (GFR 27.2 ± 21 versus 37.3 ± 25 ml/min/1.73m², p=0.04). This may be explained by the clustering of CV risk factors as well as the contribution of non-traditional (uraemia-related) risk factors. Potential pathophysiologic mechanisms by which decreased creatinine clearance might predispose to PAD include altered calcium-phosphate product, homocysteine, and lipoprotein (a) metabolism and alterations in inflammatory and coagulation pathways⁴⁷.

All the PAD patients demonstrated presence of traditional CVD risk factors with the majority having more than two risk factors. The commonest risk factor was age occurring in 87%, followed by male gender 78%, hypertension 74%, diabetes mellitus 56%, cigarette use 47% and dyslipidemia 43%. The odds ratio for cigarette use, male gender and diabetes mellitus were on average two fold while that for male gender as a risk factor was three fold. Of the traditional risk factors assessed, male gender and diabetes mellitus were independently associated with PAD. Hypertension and dyslipidemia were not associated with presence of PAD.

The proportion of PAD patients with diabetes mellitus was 56.5%. In the Spanish study⁴³, 26% of the patients with PAD had diabetes mellitus. An association was found between diabetes mellitus and PAD. It is known that diabetics have a greater burden of other atherogenic risk factors than non-diabetics, including hypertension, hypertriglyceridemia, increased total-to-HDL cholesterol ratio, and elevated plasma fibrinogen. A local study on diabetics described the prevalence of hypertension at 64.8%, dyslipidemia at 93.5%, and a clustering of at least two cardiovascular risk factors (excluding the diabetes itself) in all patients.⁹⁹

This study did not show significant association of PAD with cigarette use. The literature has shown that smoking is associated with both development and progression of PAD.¹⁰⁰ Patients with PAD who continue to smoke have a higher risk of disease progression than patients who stop smoking. It is also equally important to note that smoking is reported as a habit rather than the magnitude of cigarette smoking. A higher risk of vasculopathy certainly occurs with a larger number of cigarettes smoked.¹⁰⁰ The study design did not capture quantitative aspects of cigarette smoking. Possible explanations for the negative association in this study include a chance finding occasioned by a small sample size.

Traditionally, elevated LDL has been the main dyslipidemia associated with atherosclerosis⁶⁴, with widespread response to therapy⁶⁵. This apparent lack of association of dyslipidemia with PAD is probable on the generalization of dyslipidemia. CKD is more associated with hypertriglyceridemia¹⁰¹, which has not been conclusively associated with PAD. The predominant dyslipidemia in this study was hypertriglyceridemia in 51.3% of the patients. The negative association was occasioned by a small sample size.

The proportion of PAD patients with hypertension was 73.9%. This study did reveal a high prevalence of hypertension among all the CKD patients, 74.7%. Majority of these patients were on optimal treatment. Hypertension is a well-established risk factor for PAD. This negative association in this study was occasioned by the small sample size. Intervention in form of treatment of hypertension probably contributed to the lack of association.

Of the patients with PAD, 47.8% presented a clinical picture compatible with intermittent claudication. In the Spanish study ⁴³ 30% of the PAD patients had intermittent claudication. Several epidemiological studies have shown that majority of PAD patients are asymptomatic therefore symptoms alone are not useful in excluding PAD. In our study, more than half of the patients with PAD were asymptomatic. It is known that asymptomatic PAD just like symptomatic PAD is associated with an increased risk of atherothrombotic events including MI and stroke ¹¹, impaired lower extremity functioning ¹² and carotid artery stenosis ¹³. Painful neuropathy (common in diabetes and uremia) is a cause of "pseudoclaudication" hence the symptom of calf pain may not be a useful aspect to emphasize on. ABI measurement is a non-invasive, simple, inexpensive, reproducible and reliable tool for subclinical PAD and as shown in our study it improved the pick up rate for PAD by 50%.

11. CONCLUSIONS

1. There was a low prevalence of PAD among CKD patients aged 30 years and above at KNH.
2. Majority of the PAD patients had mild to moderate PAD and were in advanced CKD stage 3 - 5.
3. All the selected CV risk factors were prevalent in the PAD population with most patients having more than two risk factors.
4. Male gender and diabetes mellitus were independently associated with PAD.
5. More than half of the patients with PAD were asymptomatic.

12. LIMITATIONS

1. Failure to achieve the desired sample size.
2. The ability to discern association between PAD and risk factors was limited by a small number of patients with PAD.
3. Cross-sectional study may not bring out associations in on-going disease process.

13. RECOMMENDATIONS

1. There is need to actively look for PAD using ABI in patients with CKD without relying on symptoms as more than half are asymptomatic.
2. Patients with diabetes, male gender and those with CKD stage 3 – 5 should have regular ABI measurement as they are of the highest risk for PAD. Early aggressive management including risk factor modification should be done to improve outcome in this high-risk group. Other traditional CV risk factors though *not demonstrated in this study to be associated with PAD, should be modified.*
3. Further population-based studies are required to determine the prevalence of PAD in the general population in view of the relatively low prevalence rate found in this study among high-risk patients.

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15. APPENDIX I - SCREENING PROFORMA

Study No:

Name:

Age (Years):

Hospital No.:

DOB:

Contact Details: P.O. Box

Tel. No.:

Place of work:

Year of diagnosis of renal dysfunction

Aetiology of renal dysfunction

DEMOGRAPHICS

1. Gender 1 = Male 2 = Female

2. Marital status

1=Single 2=Married 3=Divorced 4=Widowed 5=Separated

3. Usual residence

4. Usual occupation

1 = self employed 2 = employed 3 = unemployed 4 = retired

5 = training/student

5. Level of education

1 = None 2 = Primary school 3 = Secondary school 4 = Tertiary level

5 = other (specify)

ELIGIBILITY

1. Are you willing to participate in the study:

THE PREVALENCE OF PERIPHERAL ARTERIAL DISEASE USING THE ANKLE-BRACHIAL INDEX AMONG PATIENTS WITH CHRONIC KIDNEY DISEASE AT THE KENYATTA NATIONAL HOSPITAL?

1 = YES 2 = NO

2. Have you ever been told by a doctor that you have any one of the following?

1 = YES 2 = NO

- Blockage of lower limb arteries legs confirmed by arteriography or vascular Doppler

- Surgery- stenting or amputation for blocked limb arteries.

3. Are you willing to return on a different day when you are fasted for blood tests? 1 = YES 2 = NO

Laboratory Tests

Previous serum creatinine (umol/L)

Previous creatinine clearance (ml/min)

Current serum creatinine (umol/L)

Calculated creatinine clearance (ml/min)

Previous urinalysis (proteinuria)

Current urinalysis (proteinuria)

CKD Stage

FOR OFFICIAL USE

Recruited 1 = YES 2 = NO

15. APPENDIX II - STUDY PROFORMA

Name: Study No.
Date:
DOB (month, year)
Age (years)
Year of diagnosis of renal dysfunction
Aetiology of renal dysfunction

- 1 = Diabetic nephropathy
- 2 = Hypertensive nephropathy
- 3 = Chronic glomerulonephritis
- 4 = Obstructive uropathy
- 5 = Polycystic kidney disease
- 6 = Other (specify)

DEMOGRAPHICS

- 1. Gender 1 = Male 2 = Female
- 2. Marital status
1=Single 2=Married 3=Divorced 4=Widowed 5=Separated
- 3. Usual residence
- 4. Usual occupation
1 = self employed 2 = employed 3 = unemployed 4 = retired
5 = training/student
- 5. Level of education
1 = None 2 = Primary school 3 = Secondary school

4 = Tertiary level 5 = other (specify)

CHRONIC ILLNESS

6. Diabetes

1 = YES 2 = NO

Duration Years

7. Hypertension

1 = YES 2 = NO

Duration Years

PAST MEDICAL HISTORY

8. Have you ever had any of the following? (Tick response)

1 = Been told by a doctor that you have coronary heart disease?

2 = Heart attack

3 = Angina pectoris (chest pain due to insufficient blood flow to
the heart)

4 = Coronary bypass surgery

5 = Coronary angioplasty (ballooning)

6 = Been told by a doctor that you have abdominal aortic aneurysm

7 = Transient ischemic attacks (transitory strokes)

8 = Blockage of carotid artery

9 = Stroke

FAMILY HISTORY

9. Did or does any of your relatives suffer from diabetes?

1 = YES 2 = NO

Father Mother Brother/sister Children

Other (specify)

10. Did or does any of your relatives suffer from hypertension?

1 = YES 2 = NO

Father Mother Brother/sister Children

Other (specify)

11. Did or does any of your relatives suffer from kidney disease?

1 = YES 2 = NO

Father Mother Brother/sister Children

Other (specify)

12. Did any of your first-degree relatives (father, mother, brothers, sisters or children) suffer from heart attack, stroke or sudden death? If a male relative before 55 years / female relative before 65 years.

1 = YES 2 = NO

CLAUDICATION QUESTIONNAIRE

13. Do you get a pain or discomfort in your leg(s) when you walk?

1 = YES 2 = NO

If 'NO', stop here

14. Does this pain ever begin when you are standing still or sitting?

1 = YES 2 = NO

15. Do you get it if you walk uphill or hurry?

1 = YES 2 = NO

16. Do you get it if you walk at an ordinary pace on the level?

1 = YES 2 = NO

17. What happens to it if you stand still?

1 = usually continues for more than 10 minutes

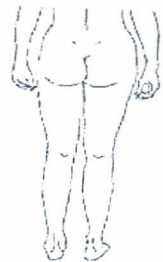
2 = usually disappears in 10 minutes or less.

18. Where do you get this pain or discomfort? Mark the place(s) with an X on the diagrams below:

Front



Back



Intermittent claudication 1 = YES 2 = NO

SMOKING HABITS

19. Do you smoke cigarettes now?

1 = YES, regularly 2 = NO

20. On average how many cigarettes do you smoke per day?

Cigarettes /day.

21. Did you ever smoke cigarettes regularly in the past?

1 = YES, regularly 2 = NO

a) When did you stop smoking cigarettes regularly? Year

If in the last 12 months

1 = less than 1 month ago

2 = 1-6 months ago

3 = 6-12 months ago

22. What is the highest average daily number of cigarettes you have ever smoked for as long as a year? Cigarettes /day.
23. For how many years have you been smoking cigarettes? Years.

24. Smoking status

1=Current Smoker

2= Former Smoker

3= Non –Smoker

ALCOHOL INTAKE

25. Do you drink alcohol?

1 = YES 2 = NO

CURRENT MEDICATIONS

Are you currently on any of the following medications?

26. Drugs to lower blood sugar (oral/injectable).

1 = YES 2 = NO

Drug _____ Dose _____ Duration _____

27. Blood pressure lowering drugs

1 = YES 2 = NO

Drug _____ Dose _____ Duration _____

28. Blood lipid-lowering drugs.

1 = YES 2 = NO

Drug _____ Dose _____ Duration _____

29. Anti-platelet drugs (aspirin/clopidogrel)

1 = YES 2 = NO

Drug _____ Dose _____ Duration _____

PHYSICAL EXAMINATION

30. Height (cm)

31. Weight (kg)

32. BMI (kg/m²)

33. BSA (m²)

34. 1st BP reading _____ mmHg 2nd BP reading _____ mmHg

Average of 2 BP readings _____ mmHg.

35. ABI results

ABI Results

Right Arm

_____ mmHg



Left Arm

_____ mmHg

Left ABI

Left Ankle Pressure = _____ mmHg = _____
 Higher Arm Pressure _____ mmHg

Right Ankle

_____ mmHg

Left Ankle

_____ mmHg

Right ABI

Right Ankle Pressure = _____ mmHg = _____
 Higher Arm Pressure _____ mmHg

36. Neck
 Carotid bruit 1 = YES 2 = NO

37. Pulses

Brachial	1 = Present	2 = Absent	<input type="text"/>
Femoral	1 = Present	2 = Absent	<input type="text"/>
Posterior tibial	1 = Present	2 = Absent	<input type="text"/>
Dorsalis pedis	1 = Present	2 = Absent	<input type="text"/>

38. Abdomen
 Abdominal bruits 1 = Present 2 = Absent
39. Feet
 Ulcers/gangrene 1 = YES 2 = NO
40. Neurological Exam
 Stroke 1 = YES 2 = NO

LAB. RESULTS

Creatinine (umol/L)

Creatinine clearance (ml/min)

Corrected creatinine clearance (ml/min/1.73m²)

Fasting blood sugar (mmol/L)

Serum lipid profile

Total cholesterol (mmol/L)

HDL-cholesterol (mmol/L)

LDL-cholesterol (mmol/L)

Triglycerides (mmol/L)

Urinalysis

Protein

CKD Stage

15. APPENDIX III - CONSENT EXPLANATION

My name is Dr Maritim. I am a postgraduate student in Internal Medicine. I am conducting a study: -

1. To assess the prevalence of peripheral arterial disease in patients with chronic kidney disease using the ankle-brachial index.
2. To assess the cardiovascular risk factors associated with peripheral arterial disease in patients with chronic kidney disease.

If you agree to join in this study, we expect the following: -

1. Sign a consent form.
2. Be required to answer several questions as shown in the study proforma.
3. Undergo a general physical, cardiovascular and neurological exam including measurement of your blood pressure, weight and height.
4. Be done measurement of brachial and ankle systolic blood pressure using a hand-held Doppler device. It is safe and painless.
5. Be required to give 10 ml of a mid-stream specimen of urine.
6. Be required to come fasted on a follow-up visit for blood tests.
7. Be withdrawn 10 ml of blood by venepuncture. They will feel slight pain by the needle prick.

By participating in the study you will benefit by: -

1. Having all the above examinations and procedures done free of charge.
2. *A copy of the results of these tests done shall be availed in your file and the doctor will be informed of these results.*
3. You will receive free interventional advice and appropriate management.

You can withdraw from this study without losing any benefits or quality of management of your medical problem being affected.

In case you have any questions related to this study you can contact the following: -

Dr Maritim (Principal Investigator)

Tel 0733-729963.

15. APPENDIX IV - CONSENT FORM

I, after reading the consent explanation form and having been explained to by Dr. Maritim (The Principal Investigator) do voluntarily agree to take part in this research study on THE PREVALENCE OF PERIPHERAL ARTERIAL DISEASE USING THE ANKLE-BRACHIAL INDEX AMONG PATIENTS WITH CHRONIC KIDNEY DISEASE AT THE KENYATTA NATIONAL HOSPITAL. I am also aware that I can withdraw from this study without losing any benefits or quality of management of my medical problem being affected.

SIGNED:

THUMBPRINT.....

WITNESS

DATED

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MEDICAL LIBRARY