ASSESSMENT OF SOME CARDIOVASCULAR RISK FACTORS IN PREDIALYSIS CHRONIC KIDNEY DISEASE PATIENTS IN UNIVERSITY OF BENIN TEACHING HOSPITAL, BENIN

A DISSERTATION SUBMITTED TO THE WEST AFRICAN COLLEGE OF PHYSICIANS IN PART FULFILMENT OF THE REQUIREMENTS FOR THE FELLOWSHIP IN INTERNAL MEDICINE
(SUB-SPECIALTY: NEPHROLOGY)

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DECLARATION

I hereby declare that this work is original and no part of it has neither been presented to any other college for a fellowship dissertation nor submitted elsewhere for publication.

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SUPERVISION

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DEDICATION

I humbly dedicate this work to the Almighty God, who has seen me through thick and thin and has provided the grace and strength to carry out this study.

I also dedicate this dissertation to millions of people with end stage renal disease all over the world and particularly to those in developing countries like ours, who presently suffer from inadequate care due to limited facilities.

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TABLE OF CONTENTS

Title Page	i
Declaration	ii
Supervision	iii
Certification	iv
Dedication	v
Acknowledgement	vi
Table of Contents	vii
List of Tables	viii
List of Figures	ix
List of Abbreviations	x
Abstract	1
CHAPTER ONE	
Introduction	2
Justification of Study	4
Aims and Objectives	5
CHAPTER TWO	
Literature Review	6
CHAPTER THREE	
Methodology	16
CHAPTER FOUR	
Results	24
CHAPTER FIVE	
Discussion	43
Conclusion	51
Limitations	52
Recommendations	53
References	54
Appendices	62
Appendix I: Questionnaire	62
Appendix II: Consent Form	66
Appendix III: Ethics and Research Committee Clearance Form	79

LIST OF TABLES

Table 1: Sociodemographic Characteristics of study population 25

Table 2: Clinical parameters of CKD and control groups..... 28

Table 3: Haematological and biochemical parameters of CKD and control groups 29

Table 4: Lipid profile of the CKD and control groups..... 30

Table 5: Echocardiographic left ventricular parameters of CKD and control groups..... 31

Table 6: Prevalence of cardiovascular risk factors in the study population 33

Table 7: Pattern of cardiovascular risk factors across CKD Stages..... 34

Table 8: Pattern of cardiovascular risk factors according to age groups 35

Table 9: Pattern of cardiovascular risk factors by aetiology of CKD …… 36

Table 10: Pattern of cardiovascular risk factors by gender..... 37

Table 11: Correlation between estimated GFR and some cardiovascular risk factors …… 38

Table 12: Multiple linear regression table of cardiovascular risk factors that correlated with estimated GFR in the CKD 39

LIST OF FIGURES

Figure 1: Aetiology of CKD in the Study Population..... 26

Figure 2: Stages of CKD in Study Population 27

Figure 3: Correlation between eGFR and Systolic Blood Pressure.....40

Figure 4: Correlation between eGFR and Diastolic Blood Pressure.....40

Figure 5: Correlation between eGFR and Pulse Pressure.....41

Figure 6: Correlation between eGFR and PCV.....41

Figure 7: Correlation between eGFR and Serum Phosphate.....42

LIST OF ABBREVIATIONS

ACEI:	Angiotensin converting enzyme inhibitor
ARIC STUDY:	Atherosclerosis Risk in Community Study
BMI:	Body mass index
CAD:	Coronary artery disease
CaxPP:	Calcium phosphate product
CCF:	Congestive cardiac failure
CGN:	Chronic glomerulonephritis
CHD:	Coronary heart disease
CKD:	Chronic kidney disease
CREATE:	Cardiovascular Reduction Early Anaemia Treatment
CRP:	C-reactive protein
CVD:	Cardiovascular disease
DBP:	Diastolic blood pressure
DM:	Diabetes mellitus
EF:	Ejection fraction
EPO:	Erythropoeitin
ESRD:	End stage renal disease
FGF:	Fibroblast growth factor
GFR:	Glomerular filtration rate
HDL-C:	High density lipoprotein cholesterol
HF:	Heart failure
HU:	Hyperuricaemia
IVSd:	Interventricular septal thickness in diastole
KDIGO:	Kidney Disease Improving Global Outcome
LDL-C:	Low density lipoprotein cholesterol

LVH:	Left ventricular hypertrophy
LVMI:	Left ventricular mass index
LVIDd:	Left ventricle internal diameter in diastole
MABP:	Mean arterial blood pressure
MI:	Myocardial infarction
NHANES:	National Health and Nutrition Examination Survey
NKF-K/DOQI:	National Kidney Foundation-Kidney Disease Outcome Quality Initiative.
PCV:	Packed cell volume
PP:	Pulse pressure
PTH:	Parathyroid hormone
PWd:	Posterior wall thickness in diastole
RAAS:	Renin angiotensin aldosterone system
RRT:	Renal replacement therapy
RWT:	Relative wall thickness
SBP:	Systolic blood pressure
SF:	Shortening fraction
TG:	Triglycerides
VLDL-C:	Very low density lipoprotein cholesterol
WHO:	World Health Organization

ABSTRACT

Introduction: Cardiovascular disease is the leading cause of death and hospitalization in chronic kidney disease (CKD) patients at all stages. Cardiovascular risk factors are also responsible for rapid progression of CKD to end stage renal disease. Prompt and comprehensive evaluation of these factors will reduce morbidity and mortality in pre-dialysis patients.

Objectives: The aim of this study was to determine the prevalence and pattern of some cardiovascular risk factors in pre-dialysis CKD patients in University of Benin Teaching Hospital, Benin, Nigeria.

Methodology: This was a cross-sectional analytical study that involved 78 consecutive pre-dialysis CKD patients and 78 age and sex matched controls without CKD over a one year period. Both groups were assessed for cardiovascular risk factors. The prevalence and pattern of these factors were determined. P –value of < 0.05 was taken as significant.

Results: The mean ages of the CKD vs control group were (47.46±15.45 vs 45.45±15.22 years). The M:F ratio was 1.7 for both groups. The common aetiologies of CKD in this study were hypertension in 38.5%, diabetes mellitus in 29.4% and chronic glomerulonephritis in 26.9%. There were 35.9% in CKD stage 3, 44.9% in CKD stage 4 and the remaining 19.2% in CKD stage 5. The common cardiovascular risk factors found in the CKD vs control were: hypertension (96.2%vs43.6%), anaemia (96.2%vs23.1%), LVH (76.9%vs25.6%), dyslipidae mia (76.9%vs48.7%), hypocalcaemia (75.6%vs29.5%), hyperphosphataemia (65.4% vs0%), hyperuricaemia (51.3%vs12%). Hyperphosphataemia, hypoalbuminaemia and LVH increased with CKD stage. Hypocalcaemia, tobacco use and anaemia were significantly commoner in males while dyslipidaemia was commoner in female CKD patients.

Conclusion: Cardiovascular risk factors are highly prevalent in pre-dialysis CKD subjects and are commoner in the males. The prevalence of some of these risk factors increased with severity of CKD.

CHAPTER ONE

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of hospitalization and death in CKD patients at all stages [1]and accounts for about 50% of mortality in this group of patients.[2] The prevalence of CVD among patients commencing renal replacement therapy (RRT) is high, indicating that the process of CVD commenced during the earlier stages of CKD.[3] United States renal data in 1998 showed that about 40% of patients starting dialysis already have evidence of coronary heart disease (CHD),[4] while Foley et al found that only 15% of end stage renal disease (ESRD) patients commencing therapy were considered to have normal left ventricular structure and function by echocardiographic criteria.[5] In dialysis patients, CVD mortality rate is about 9% per year, which is 10-30 times higher than in the general population.[6]

Adverse cardiovascular event rates remain high in patients with CKD after adjustment for conventional CVD risk factors such as hypertension, diabetes mellitus (DM), smoking, male sex and left ventricular hypertrophy (LVH). The progressive cardiovascular risk associated with worsening renal function may be explained by other factors that become increasingly important with decline in renal function. These factors are referred to as non-traditional risk factors and they include albuminuria, inflammation, anaemia, malnutrition, homocysteinaemia, calcium and phosphate abnormalities.

In a prospective cohort study in which 965 subjects were followed up for an average of 6.2 years, it was found that subjects with glomerular filtration rate (GFR) of 15-59 mls/min had an increased adjusted risk of atherosclerotic CVD compared with subjects with a GFR of 90-150mls/ min.[7] It was also established in the same study that for each 10mls/min/1.73m^2 decrease in GFR, there was an adjusted hazard ratio of 1.05, 1.07 and 1.06 for atherosclerotic CVD, de novo atherosclerotic CVD and recurrent atherosclerotic CVD respectively. Chronic

kidney disease is a risk factor for composite outcome of all cause mortality in the general population and this is more pronounced in blacks compared to whites.[8] It was hypothesized that these effects may be due to the more frequent and severe subclinical vascular disease secondary to hypertension or DM in blacks.

Individuals with CKD encounter the problems of inadequate risk factor modification and intervention, despite established awareness of their high cardiovascular risk.[9] This reduced use of proven therapies must be considered as a significant iatrogenic factor contributing to their increasing cardiovascular risk and mortality. Prompt and comprehensive evaluation of CVD risk factors with modification will reduce morbidity and mortality in pre-dialysis patients. This will also slow the progression of CKD to ESRD, hence reducing the huge financial burden on these patients especially in developing countries like Nigeria where RRT is not subsidized by the government and majority of patients cannot afford and sustain RRT.

1.1 JUSTIFICATION OF STUDY

The global burden of CKD is quite enormous even in developed countries where better health care services and insurance are available for the care of patients with renal disease.[10] The mortality of CKD is very high in developing countries including Nigeria. There is inadequate information on comprehensive cardiovascular risk assessment in pre-dialysis CKD patients especially in developing countries including Nigeria, despite the fact that it is the major cause of mortality in these patients. These cardiovascular risk factors also contribute significantly to the rapid progression of CKD. Cardiovascular disease accounts for up to 50% of mortality in pre-dialysis patients and almost all patients on RRT have well established CVD.[2, 4, 5]

Early identification and modification of these cardiovascular risk factors will slow the progression of these patients to ESRD. It will also reduce associated morbidity, mortality, huge economic burden and loss to the nation. Information from this study will also serve as a basis for making a rational guideline for control of these risk factors.

It is hoped that this study will contribute to filling part of the gap in the present knowledge, inspire further in-depth research especially in Africa on the impact of early recognition and control of cardiovascular risk factors on the outcome of pre-dialysis CKD patients.

1.2 AIMS AND OBJECTIVES

1.2.1 General Aim

To determine the prevalence and pattern of some cardiovascular risk factors in pre-dialysis CKD patients in University of Benin Teaching Hospital (UBTH).

1.2.2 Specific Objectives

1. To determine the prevalence of anaemia, LVH, dyslipidaemia, hypertension, DM, tobacco use, hyperuricaemia, hypoalbuminaemia, elevated C- reactive protein (CRP), calcium and phosphate abnormalities in pre-dialysis CKD patients.
2. To establish the correlation of these cardiovascular risk factors if any, with the degree of renal dysfunction.

CHAPTER TWO

LITERATURE REVIEW

Chronic Kidney disease has been defined by National Kidney Foundation- Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) as the presence of markers of kidney damage for 3 months with or without reduction in GFR or as the presence of GFR less than or equal to 60ml/min/1.73m^2 for 3 months with or without other signs of kidney damage.[11] Chronic Kidney Disease is divided into 5 stages; 1-5 by the NKF-KDOQI, however this has recently been modified by Kidney Disease Improving Global Outcome (KDIGO) into stages G1, G2, G3a and G3b, G4 and G5 based on the estimated GFR and stages A1, A2 and A3 based on albuminuria.[11]

The prevalence of CKD worldwide is on the increase with attendant huge financial burden, even in developed countries. The true prevalence of CKD in Nigeria is not known, however various community based studies from different parts of the country reported a prevalence of 11.4 – 26%.[12-14]

Cardiovascular disease is the commonest cause of morbidity and mortality in CKD patients [1] and includes CHD, stroke, congestive cardiac failure (CCF), peripheral vascular disease and arrhythmias. Renal dysfunction is associated with increased cardiovascular risk through mechanisms which are still being elucidated. Factors that have been found contributory include high proportion of coronary risk factors, co-morbidities, increasing expression of non-conventional risk factors, lack of appropriate risk factor modification and intervention.

The cardiovascular risk factors can be classified as traditional and non-traditional factors. Traditional risk factors include age, male sex, DM, hypertension, smoking, dyslipidaemia and LVH while the non-traditional risk factors include anaemia, albuminuria, homocysteinaemia, inflammation, wasting, sympathetic activation, oxidative stress, endothelial dysfunction,

abnormalities of calcium and phosphate metabolism. The traditional risk factors alone cannot solely explain the magnitude of CVD in CKD patients. The synergistic role of other non-traditional risk factors contributes significantly to the cardiovascular burden in CKD patients.[15]

2.1 HYPERTENSION

Hypertension has been established as a risk factor for CVD in the general population.[16] The prevalence of hypertension in CKD increases with declining GFR. The overall prevalence of hypertension in Nigeria is 11-46.4% [17] while the prevalence rate of hypertension in patients with CKD stages 3-5 is between 85-95%.[18] Hypertension and mortality risk in CKD patients have been shown to have a u-shaped relationship [19] It has also been established that widened pulse pressure is an independent predictor of CVD and all cause mortality in patients with CKD.[20] National Kidney Foundation has elucidated the importance of lowering blood pressure (BP) in order to slow the progression of renal disease and reduce cardiovascular morbidity and mortality.[21]

2.2 LEFT VENTRICULAR HYPERTROPHY

Left ventricular ~~V~~hH~~H~~ypertrophy represents a physiologic adaptation to long term increase in myocardial work~~—~~ as a result of either pressure or volume overload. As hypertrophy progresses, there is reduction in subendothelial perfusion with subsequent myocardial fibrosis. The death of cardiac myocytes becomes inevitable if these maladaptive forces are sustained.

Left v~~V~~entricular h~~H~~ypertrophy is defined as left ventricular mass index (LVMI) > 134g/m^2 in males and > 110g/m^2 in females.[22] Various studies have been done to assess LVH in predialysis CKD patients with a reported prevalence~~-~~ range of 27.6% -95.5%.[5, 23-25] Reported

prevalence however, varied according to the method of LVH assessment and stage of CKD patients used in the various studies. A lower prevalence of 27.6% was reported by Chijoke et al who used electrocardiography as a method of LVH assessment, which is not as sensitive as echocardiography used in some other studies that reported higher prevalence rates.[23] Ulasi et al reported a very high prevalence of 95.5% in black African patients with stages 4 and 5 CKD.[25] There is no consensus on the LVH geometric pattern predominant in CKD patients, some studies reported eccentric LVH as predominant [5,25] while Sambi et al reported concentric LVH as the predominant type.[26]

Left ventricular hypertrophy~~VH~~ evident on echocardiography is a predictor of morbidity and mortality from CVD. Levy et al found that there is progressive increase in risk of CVD as left ventricular mass increases.[27] Left ventricular hypertrophy~~VH~~ is a risk factor for development of arrhythmias, cardiomyopathy, sudden death and heart failure (HF). An increase in left ventricular mass predicts a higher incidence of clinical events including death attributable to CVD.[27] The prevalence of LVH increases as CKD progressively worsens.[24-25] The use of antihypertensive drugs that block the renin angiotensin activating system (RAAS) pathways have been shown to induce LVH regression compared to other antihypertensive medication.[28]

2.3 SMOKING

Cigarette smoking is an important and reversible risk factor for CVD. It is the single most important modifiable risk factor contributing to premature morbidity and mortality in the United States where it accounts for approximately 430,000 deaths annually.[29] The constituents of inhaled tobacco damage the cardiovascular system through various mechanisms including endothelial dysfunction, platelet dysfunction, increased coagulation and activation of the sympathetic nervous system.

Cigarette smoking has been recently implicated in the progression of renal disease in patients with severe hypertension.[30] Omoloja et al found that in a cohort of paediatric patients with CKD, second hand smoking was a predictor of nephrotic range proteinuria, hence it may be an important factor to consider in CKD progression.[31] A cross-sectional analysis of incident patients with ESRD from the Dialysis Morbidity and Mortality Wave 2 study showed that smokers had a 22% greater likelihood of having coronary artery disease (CAD) than nonsmokers.[32] There is also sufficient evidence to show that smoking cessation reduces progression in CKD patients.[32]

2.4 DYSLIPIDAEMIA

Dyslipidaemia is a common feature of CKD and a well recognized CVD risk factor.[33] There are limited studies on prevalence and pattern of dyslipidaemia among CKD patients in Nigeria. However, literature from a study done in Ilorin reported that the prevalence of hypercholesterolaemia was 90.8%, hypertriglyceridaemia was 81.7% and reduced decreased high density lipoprotein cholesterol (HDL-C). was 75.8% [34]. This was similar to the findings of Mshelia et al in Maiduguri [35]. Jisieike –Onuigbo et al in a study on lipid profile in patients with overt diabetic nephropathy found that 66.7% of the study population had hypertriglyceridemia, 62.5% had hypercholesterolemia, 45.8% had elevated low density lipoprotein cholesterol (LDL-C), and 58.3% had decreased HDL-C.[36]

A review of observational studies of dialysis patients established a reverse epidemiology between total cholesterol (TC) and risk of all cause mortality such that lower cholesterol levels were associated with higher mortality rate.[37]

Dyslipidaemia has been shown to predict a faster decline in GFR. A met-analysis of 12 trials in subjects with CKD on statins demonstrated a significantly lower monthly decline in GFR compared with controls who were not on statins.[38] In the Study of Heart and Renal

Protection (SHARP) trial, the use of a combination of simvastatin and ezetimibe reduced major atherosclerotic events such as coronary death, myocardial infarction (MI), non-haemorrhagic stroke only in the predialysis group and not the dialysis group.[39] Early detection of dyslipidaemia with appropriate institution of treatment will reduce CVD risk, rate of progression and hence mortality in these patients.

2.5 DIABETES MELLITUS

Diabetes Mellitus is the leading cause of ESRD worldwide but ranks after chronic glomerulonephritis and hypertension as aetiology of CKD in Nigeria.[10] It was established in the Copenhagen Heart Study that type 2 diabetics have a higher risk of developing MI, stroke and death compared to non-diabetics independent of other risk factors.[40] Previous studies in Nigeria have reported increased cardiovascular risk factors in diabetic patients without nephropathy [41,42.] Alebiosu et al found in a study done in southwest Nigeria, found a high prevalence of cardiovascular risk factors and events among subjects with clinical diabetic nephropathy compared with normal diabetic subjects. [43]

The National Cholesterol Education Program recognized DM as a high cardiovascular risk and hence, recommended that coronary risk factors like dyslipidaemia should be aggressively treated in diabetics.[44] Intensive glycaemic control has been shown to have long term benefits in reducing CVDcardiovascular disease in diabetics.[45]

2.6 ALBUMINURIA

Urinary albumin excretion rate is independently associated with the presence and severity of CVD in the general population.[46] Even low grade albuminuria below the current microalbuminuria threshold in middle aged non-diabetic and non-hypertensive individuals is associated with increased CVD risk.[46]

The pathophysiology of albuminuria is not completely understood, but it has been postulated that it may be the result of altered intra-renal haemodynamics with elaboration of widespread low level inflammatory processes in the body vasculature.[47] In hypertensive patients with or without DM, increasing urine albumin excretion is associated with elevated level of inflammatory markers like CRP ~~reactive protein~~, endothelial dysfunction and platelet activation.[48] Heavy proteinuria irrespective of the cause of the CKD is associated with faster rate of decline in renal function.[49] Reducing proteinuria using diet, angiotensin receptor blockers or ACEI predicts a better outcome.[50] Thus, prevention and treatment of albuminuria will reduce cardiovascular risk in affected individuals.

2.7 ANAEMIA

National Kidney Foundation- Kidney Disease Outcomes Quality Initiative ~~NKF KDOQI~~ defined anemia in adult men and women as haemoglobin < 13.5g/dl and < 12g/dl respectively [51] while World Health Organization defined it as haemoglobin < 13g/dl in men and <12g/dl in women.[52]

The causes of anaemia in CKD are multifactorial and include relative deficiency of erythropoietin, malnutrition, inflammation, uraemic toxins, bone marrow fibrosis and abnormal platelet function. There is progressive increase in the severity and incidence of anaemia with declining renal function. The reported prevalence of anaemia by CKD stage varies significantly and depends to a large extent on the definition of anaemia and aetiology of CKD. Data from National Health and Nutrition Examination Survey (NHANES) showed that haemoglobin levels starts to fall at an eGFR of less than 75 ml/min per 1.73 m^2 in men and 45 ml/min per 1.73 m^2 in women.[53] The prevalence of anaemia in CKD range between 77.5-93% in studies done in different parts of Nigeria.[54,55] The prevalence of anaemia in CKD was higher in blacks compared to whites.[56] The reasons are not fully understood, but may be related to genetics, environmental effects, rapid progression of CKD, malnutrition and

helminthic infections in blacks. The prevalence of anaemia in CKD patients increases as the GFR declines.[54] Atherosclerosis Risk in Communities (ARIC) study established that anaemia is an independent risk factor for CVD in a community cohort of subjects between ages 45-64 years.[57]

Erythropoeitin has several potential beneficial effects on the cardiovascular system independent of anaemia correction, including reduction in myocardial damage, pro-angiogenic and anti-apoptotic effects on endothelial cells. There has been considerable debate in recent times about the optimal target range of haemoglobin concentration in CKD patients. Correction of haemoglobin and outcome in renal insufficiency (CHOIR) study showed that the use of a target hemoglobin level of 13.5 g per deciliter as compared with 11.3 g per deciliter was associated with increased cardiovascular risk and no incremental improvement in the quality of life.[58]

2.8 CALCIUM AND PHOSPHATE ABNORMALITIES

Calcium is a major regulator of PTH secretion, hence persistent hypocalcaemia is a powerful stimulus for the development of hyperparathyroidism. Phosphate is increasingly retained as CKD progresses but hyperphosphataemia does not usually become evident until CKD stage 4 due to the compensatory effect of hyperparathyroidism and increased fibroblast growth factor (FGF-23) which increase renal phosphate excretion and maintain serum phosphate within the normal range.[59] Hyperparathyroidism has been established to contribute to diastolic dysfunction and LVH in hemodialysis patients. [60]

In an earlier study done in Benin, South- South Nigeria, the prevalence of hypocalcaemia, hyperphosphatemia and elevated CaxPP were found to be 71%,79% and 5% respectively.[61] Sanusi et al in a similar study done in Ile-Ife reported prevalence of hypocalcaemia, hyperphosphataemia and elevated CaxPP to be 59.3%, 79% and 12.5% respectively.[62]

It has been established that the presence of CaxPP greater than KDOQI target increases the all cause mortality risk in haemodialysis and peritoneal dialysis patients.[63]

There is also progressive worsening of renal function in CKD patients in the presence of hyperphosphataemia. Voormolen et al[60] studied 448 pre-dialysis patients and found that for every 1mg/dl rise in phosphate level, there is a mean decline in renal function by 0.154mls/min/month.

The use of active 1,25-dihydroxyvitamin D therapy has been found to be potentially antiproteinuric in CKD patients.[64] Sevelamer, a non calcium containing phosphate binder was found to correct chronic renal failure associated LV diastolic dysfunction, vascular abnormalities and also inhibited the development of LVH in murine chronic renal failure models.[65]

2.9 HYPOALBUMINAEMIA AND MALNUTRITION

Albumin is the single most abundant plasma protein accounting for 60% of the total plasma protein. The liver synthesizes 12 -14g/day of albumin. Albumin is a major source of sulph-hydryl groups and it scavenges free oxygen radicals, nitrogen radicals, and other toxins. Albumin binds toxic lipid moieties such as leukotoxin that contribute to increased vascular permeability.

Hypoalbulminaemia, a marker of malnutrition and underlying inflammation has come up as a powerful predictor of mortality in ESRD patients.[66] Hypoalbuminaemia is common in CKD patients and is associated with increased cardiovascular risk.[67] In a study by Shah et al involving 376 CKD patients in stages 2-4, it was established that low serum albumin was significantly associated with CVD irrespective of traditional risk factors like age, sex, DM and hypertension in a multivariate analysis.[67] Oral nutritional supplement use was associated with significantly lower hospitalization rates, but had no significant effect on mortality.[68] It

is worth noting that most of the studies on nutritional supplementation to treat protein energy malnutrition were done on dialysis dependent patients.

2.10 HYPERURICAEMIA

Uric acid is a weak acid that is composed of a pyrimidine and imidazole structure with oxygen molecules and is produced primarily in the liver, muscle and intestine. It is primarily excreted by the kidneys.

Hyperuricaemia contributes to endothelial dysfunction in CKD and this may be related to its effect on oxidative stress, inflammation and lipid peroxidation.[69] It also causes pre-glomerular arteriolar disease which impairs renal autoregulation thereby leading to glomerular hypertension. It is an independent cardiovascular risk factor for all cause mortality in the general population.[70]

Chun Liu et al found that in CKD stages 3-5, HU is a risk factor for all cause mortality and cardiovascular events, but not rapid progression of renal disease.[71] Uric acid is independently associated with LVMI. The combination of HU and LVH are independent and powerful predictors of CVD.[72]

Allopurinol is a xanthine oxidase inhibitor that decreases UA level and slows progression of renal disease in CKD. In addition, it reduced cardiovascular events substantially by 70% and the hospitalization risk in studied subjects.[73]

2.11 C-REACTIVE PROTEIN

C-reactive protein is an acute phase reactant that belongs to the protein family known as pentraxin. It is synthesized by the liver in response to factors such as interleukin-1, interleukin-6 released from macrophages and adipocytes.

The Center for Disease Control and Prevention in collaboration with American Heart Association in March 2002 agreed in a workshop on markers of inflammation, that highly sensitive CRP can be used in stratifying patients into low, average and high cardiovascular~~CV~~ risk based on the serum levels and this would be valuable in primary prevention.[74]

Chronic kidney disease ~~KD~~ is a chronic inflammatory state caused by the uraemic milieu, infection and exposure to dialyzer membrane. Consequences of inflammation in CKD include malnutrition, anaemia, hyporesponsiveness to erythropoietin, CVD and increased mortality. The levels of inflammatory markers like fibrinogen, homocysteine, CRP are increased in CKD patients with CHD more than those without CHD.[75] There is elevation of inflammatory and pro-coagulant biomarkers in the presence of renal insufficiency and it has been reported that a positive association exists between the presence of these biomarkers and CVD.[76] In the INVADE (Intervention Project on Cerebrovascular disease and Dementia in the community of Ebersberg, Bavaria) study, 3166 participants were followed up for 4 years and it was established that the incidence of CVD was higher in CKD patients with higher CRP level.[77] High CRP and low albumin were found to be independent risk factors for all cause mortality in pre-dialysis patients used in the Modification of Diet in Renal Disease study.[78]

CRP as a sensitive marker of inflammation can be used to identify CKD patients with a high cardiovascular risk, so that they can be closely monitored and aggressive risk factor modification instituted. ACEI and statins have anti-inflammatory properties and may have additional benefits apart from their direct effects on BP, proteinuria and lipids, in reducing CVD morbidity and CKD progression.

CHAPTER THREE

METHODOLOGY

3.1 Study Location

This study was carried out at the University of Benin Teaching Hospital (UBTH), a federal government owned tertiary hospital in Benin city, Edo state. It is a 700 bedded hospital located in the south-south geo-political region of Nigeria and receives referral cases from Edo state and neighboring states like Delta, Ondo, Ekiti and Kogi.

3.2 Study Design

This was a single centre, cross-sectional analytical study carried out over a one year period from January to December 2013. Consecutive pre-dialysis CKD patients in stages 3-5 attending the renal outpatient clinics and those receiving treatment in the medical wards of UBTH were recruited. Age and sex-matched controls that did not have CKD were recruited from among workers in UBTH. Cardiovascular risk factors were assessed in the two groups and a comparison done.

3.3 Study Population

The minimum sample size for this study was calculated using the Fischers formula;

$$N = \frac{z^2pq}{d^2}$$

where

Z= value of 95% significance (1.96)

P= prevalence of LVH in pre-dialysis CKD patients in a previous study which was

95.5% [25]

q= 1-p

d= margin of error

$N = \frac{(1.96)^2 \times 0.045 \times 0.955}{(0.05)^2}$

N = 66.04

With an attrition rate of 10% = 6.6

Minimum sample size = 73

3.4 Study Subjects

A total number of 80 subjects were recruited from consenting persons with stages 3-5 CKD in the renal clinic and medical wards.

3.5 Control Subjects

For every study subject selected, an age and sex-matched control subject was recruited from consenting workers of UBTH without CKD after screening for proteinuria using urinary dip stick and calculating their GFR from serum creatinine using Cockcroft-Gault formula.

3.6 Inclusion Criteria

a) Subjects with CKD stages 3-5 by KDOQI guideline [49]

b) CKD patients yet to commence dialysis

c) Those consenting to the study

3.7 Exclusion Criteria

a) CKD patients on dialysis

b) HIV- infected patients

c) Non-consenting pre-dialysis patients

d) Those with cardiomyopathy and valvular heart disease

e) Those with arteriovenous fistula

f) Those with gouty arthritis

3.8 Ethical Consideration

Ethical approval was sought from the Ethical and Research Committee of UBTH before the commencement of this study. A written informed consent was obtained from all subjects participating in the study.

3.9 Methods

All subjects were interviewed using a structured questionnaire (Appendix 1) and then physically examined. Demographic information such as age, sex, occupation, religion and educational status were obtained. History of renal symptoms, hypertension, DM and tobacco use was sought.

Weight was measured using a bathroom weighing scale made by U-MEC (model 98114) with subjects wearing light clothing. Height was measured using a stadiometer to the nearest centimeter with subjects not wearing shoes. The body mass index (kg/m^2) was calculated using the formula; Weight (kg) / Height ^{2} $(m)^2$

BP of subjects was measured in sitting position after 5 minutes rest, on the right arm using a mercury sphygmomanometer. The systolic and diastolic pressures were read to the nearest 2 mmHg. Systolic BP and diastolic BP were taken at phase 1 and phase 5 Korotkoff sound respectively. The average of 3 consecutive BP readings taken at 5 minutes interval was recorded.

3.10 Laboratory Investigations

Spot urine samples were tested for albumin-creatinine ratio. The principle of measurement of albuminuria was based on immunoturbidmetry and that of creatinine was based on colorimetry. The values were then used to determine the albumin: creatinine ratio (ACR).

About 20mls of venous blood was obtained from subjects after an overnight fast of 8-10 hours to perform biochemical tests which included fasting serum lipids, serum albumin, calcium, phosphate, uric acid and CRP. The packed cell volume (PCV) was determined by centrifugation method. Corrected calcium was calculated using the following formula;

Corrected Calcium (mg/dl) = 0.8 (40g/l - Serum Albumin) + Serum Calcium [mg/dl][79]

Fasting blood glucose was determined using an Accu check glucometer. Total serum cholesterol and triglyceride were determined by enzymatic estimation, while HDL-C was done by precipitation method. LDL-C was determined from the values of the aforementioned using the Friedewald formula.

Serum creatinine was measured using Jaffe's alkaline picrate method while the GFR was estimated using the Cockcroft and Gault formula. This formula has been validated in Nigerian subjects for predicting GFR.[80] The formula is as follows:

(140- Age in years) x weight (kg) x 0.85 (for females)

72 x serum creatinine (mg/dl)

These investigations were carried out in UBTH laboratory by a chemical pathologist.

Two dimensional motion mode echocardiogram was performed by a cardiologist on the study subjects -using ALOKA 400 ultrasound imaging system. Participants were placed in the left lateral position and measurements taken in the parasternal long axis view using leading edge to leading edge in accordance with American Society of Echocardiography's (ASE) recommendation. The left ventricular mass was calculated using the ASE formula modified by Devereux.[81]

Comment [EI1]: reframe this statement

LV mass (g) = 0.8(1.04(IVSd + LVIDd + PWTd)3 + 0.6

where IVSd= interventricular septal thickness in diastole, PWTd= posterior wall thickness in diastole, LVIDd= left ventricular internal diameter in diastole. Left ventricular mass was divided by the body surface area to determine the LVMI. The body surface area was determined using the formula;

Body surface area = (0.001) X (71.84) X Weight $(kg)^{0.425}$ X Height $(cm)^{0.725}$. [82]

The pattern of LVH was reported as eccentric or concentric hypertrophy based on the value of relative wall thickness (RWT). The RWT was derived from 2 X PWTd

LVIDd

3.11 Definition of Values

Hypertension was defined as BP greater or equal to 140/90mmHg or previous established diagnosis of hypertension.[83]

Diabetes mellitus was defined as FBS≥126mg/dl or previous established diagnosis of DM.[84]

Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2 [85]

Dyslipidaemia was defined as any or combination of the following[86]:

Total cholesterol > 200 mg/dl

HDL cholesterol< 50 mg/dl in females and < 40 mg/dl in males

LDL cholesterol > 100 mg/dl

TG > 150mg/dl

Anaemia was defined as PCV < 36% in females and < 39 % in males using WHO criteria[52]

Hyperuricaemia was defined as uric acid > 7.4mg/dl [87]

Normoalbuminuria was defined as ACR of < 30mg/mmol [11]

Microalbuminuria was defined as ACR OF 30-300mg/mmol [11]

Macroalbuminuria was defined as ACR of > 300mg/mmol [11]

Hypocalcaemia was defined as serum calcium < 8.2mg/dl [87]

Hyperphosphataemia was defined as serum phosphate > 4.8 mg/dl [87]

Hypoalbuminaemia was defined as serum albumin < 32g/l [87]

Elevated CaxPP was defined as CaxPP > 55mg^2/dl^2 [63]

Serum level of CRP of > than 3mg/dl defined high cardiovascular risk.[74]

Left ventricular hypertrophy was defined in absolute terms as LVMI >134 g/m2 in men and >110 g/m^2 in women. Eccentric hypertrophy was present if RWT was < 0.45 in presence of LVH. LVH with RWT > 0.45 was termed concentric hypertrophy.[82]

The estimated GFR was used in staging CKD as follows: [49]

GFR of 30-59 mls/min: Stage 3

GFR of 15-29 mls/ min: Stage 4

GFR < 15mls/min Stage 5

Aetiology of CKD was based on the following:

Diabetic nephropathy: A diagnosis of DM, features of microvascular complications, presence of large or normal sized kidneys on ultrasound in the absence of other possible aetiological factors.

Hypertensive nephropathy–: a history of long standing hypertension, presence of features of long standing hypertension such as -hypertensive retinopathy, thickened arterial wall, locomotor brachialis, loud aortic component of second heart sound, shrunken kidneys on renal scan-.

Sickle cell nephropathy: sickle cell disease patient with or without nephrotic range proteinuria, normal sized kidneys on ultrasound, absence of other aetiological factors like DM and hypertension.

Autosomal dominant polycystic kidney disease: presence of ≥ 3 cysts, which may be unilateral or bilateral in patients aged between 15-39 years, ≥ 2 cysts in each kidney for patients aged 40-59 and ≥ 4 cysts in each kidney for patients aged 60 and above

Chronic glomerulonephritis: bilaterally shrunken kidneys, active urinary sediments, absent -features of long standing hypertension, DM or other aetiological factors.

Obstructive uropathy: presence of oliguria or anuria, dilated pelvi-calyceal system, normal or enlarged kidneys on ultrasound in the absence of other aetiological factors.

Data Analysis

Data generated from this study were entered and analysed using the statistical package for social sciences (SPSS) version 17.0. Results ~~were presented~~were presented in tabular and graphical forms. Univariate analysis was used in description of socio-demographic characteristics of the study population. Continuous variables were– presented as mean and standard deviation for normally distributed data while median and interquartile range was used for skewed data. Discrete variables were presented as percentages. Chi-square test was

used to determine the significance of the observed differences for categorical variables while chi--square with trend was used where the categorical variable was ordinal. Student t-test was used to compare mean values of the sub-groups for those with unskewed data while Mann Whitney U was used to compare skewed data. Pearson's correlation was used to determine association between continuous variables with unskewed data and Spearman's correlation was used for skewed data. P values < 0.05 were considered significant.

CHAPTER FOUR

RESULTS

A total of 78 consecutive pre-dialysis CKD subjects and 78 age and sex-matched controls fulfilled the inclusion criteria and completed the study over a period of one year between January 2013 and December 2013.

4.1 SOCIO-DEMOGRAPHIC CHARACTERISTICS OF STUDY POPULATION

Table 1 shows the socio-demographic characteristics of the study population. The CKD and control groups were made up of 49 males (62.8%) and 29 females (37.2%) each. The male: female ratio was 1.7:1. The age range of the CKD group was 19-70 years with a mean age of 47.46 ±15.45 years while that of the control group was 20-66 years, with a mean age of 45.45 ± 15.22 years. There was no statistical difference in the age and sex of the studied groups. Thirty six (46.2%) of the CKD– patients were less than 45 years, thirty two(41%) were between 45 and 65years while the remaining 10 (12.8%) were more than 65 years. Most of the subjects in the two groups were married. Seventy six (97.4%) of the CKD patients were Christians while two (2.6%) were Muslims. All the control subjects were Christians. Only 7 (9%) in the CKD group and 2 (2.6%) in the control group did not have any formal education. Most of the study subjects had employment except 5 (6.4%) from the CKD group.

TABLE 1: Socio-demographic Characteristics of study population

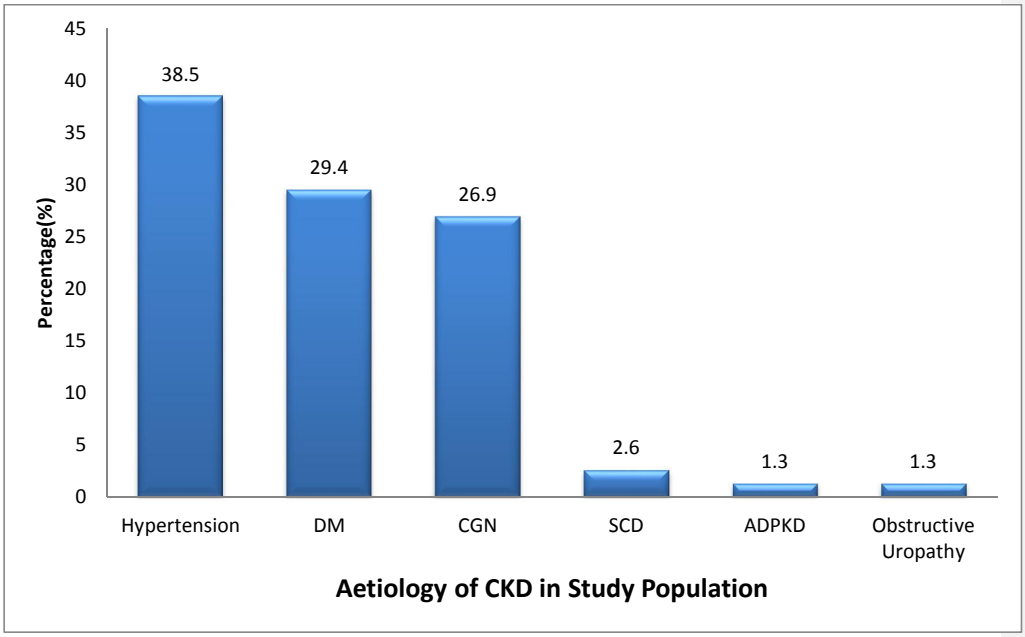
CHARACTERISTICS	CASES n = 78 (Mean ± S.D)	CONTROLS n = 78 (Mean ± S.D)	p-value
Age	47.46 ± 15.45	45.45 ± 15.22	0.41
≤ 45 years	36(46.2%)	36(46.2%)	1.00
46-65 Years	32(41%)	32(41%)	
> 65 years	10(12.8%)	10(12.8%)	
Sex			
Male	49 (62.8%)	49 (62.8%)	1.00
Female	29 (37.2%)	29 (37%)	
Marital status			
Single	16(20.5%)	17(21.8%)	
Married	56(71.8%)	55(70.5%)	
Divorced	2 (2.6%)	4(5.1%)	
Widowed	4(5.1%)	2(2.6%)	
Religion			
Christianity	76(97.4%)	78(100%)	
Islam	2(2.6%)	0(0%)	
Level of education			
No education	7 (9%)	2(2.6%)	
Primary	17 (21.8%)	6(7.7%)	
Secondary	21 (26.9%)	15(19.2%)	
Tertiary	33 (42.3%)	55(70.5%)	
Occupation			
Unemployed	5 (6.4%)	0(0%)	
Unskilled	8 (10.3%)	6(7.7%)	
Skilled	65 (83.3%)	72(92.3%)	

S.D= Standard deviation

4.2 AETIOLOGY OF THE CHRONIC KIDNEY DISEASE IN THE STUDY POPULATION

The common aetiologies of CKD in the study group were hypertension in 30 (38.5%), DM in 23 (29.4%) and chronic glomerulonephritis in 21 (26.9%). Other causes were sickle cell nephropathy in 2 (2.6%), autosomal dominant polycystic kidney disease in 1 (1.3%), and obstructive uropathy in 1 (1.3%). (Figure 1)

Figure 1: **Aetiology of CKD in the Study Population**

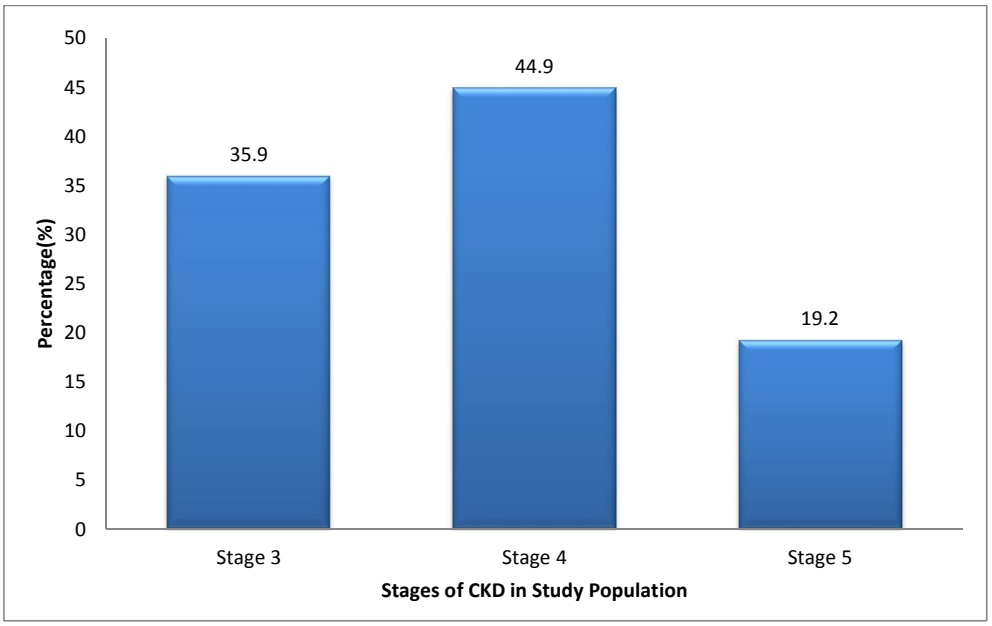


DM (diabetes mellitus), CGN (chronic glomerulonephritis), SCD (sickle cell disease), ADPKD (autosomal dominant polycystic kidney disease)

4.3 STAGES OF CHRONIC KIDNEY DISEASE IN THE STUDY POPULATION

Twenty-eight (35.9%) of the CKD subjects were in stage 3, thirty-five (44.9%) were in stage 4 and the remaining fifteen (19.2%) were in stage 5. (Figure 2)

Figure: 2 Stages of CKD in study population



4.4 CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

The mean body mass index was statistically lower in the CKD group compared to the control group with a p-value of 0.044 . The systolic blood pressure, diastolic blood pressure, pulse pressure and mean arterial blood pressure were all higher in the CKD group with a p-value of < 0.001 for each of these variables. (Table 2)

Table 2: Clinical parameters of CKD and control groups

	CKD (n=78) Mean ± S.D	**Control (n=78) Mean ± S.D**	**t**	**p-value**
Body Mass Index (kg/m2)	24.60±4.22	26.01±3.90	-2.177	0.044
Systolic BP (mmHg)	165.00±31.65	126.90±16.92	9.376	<0.001*
Diastolic BP (mmHg)	99.23±21.55	81.18±10.49	6.652	<0.001*
Pulse Pressure (mmHg)	65.77±19.71	45.72±12.94	7.512	<0.001*
Mean arterial BP (mmHg)	77.31±21.40	65.94±11.21	4.157	<0.001*

*(Significant p value<0.05)

BP (Blood pressure), S.D (Standard deviation), CKD (Chronic kidney disease)

4.5 HAEMATOLOGICAL AND BIOCHEMICAL PARAMETERS OF STUDY POPULATION

The mean packed cell volume, serum calcium, albumin were lower in the CKD group compared to the control group with a p value of <0.001 for each of these parameters. The mean serum phosphate, calcium phosphate product, uric acid were higher in the CKD group compared to the control group with a p value of < 0.001 for each of these parameters. There was no significant difference in the mean fasting blood glucose of both groups. The median value of ACR, C-reactive protein, serum creatinine were statistically higher in the CKD group while the median value of estimated GFR was statistically lower in the CKD group with a p-value of <0.001 for each of these parameters. (Table 3)

Table 3: Haematological and biochemical parameters of CKD and control groups

	CKD (n=78) Mean±Sd/Median(IQR)	**Control (n=78) Mean±Sd/Median(IQR)**	**t/u**	**p-value**
Packed cell volume (%)	25.69 ± 6.48	39.17 ± 6.11	-13.169	<0.001*
Serum Calcium (mg/dl)	7.79 ± 1.02	9.24 ± 1.01	-8.953	<0.001*
Serum Phosphate (mg/dl)	5.12 ± 0.89	4.04 ± 0.87	0.594	<0.001*
CaxPP (mg^2/dl^2)	46.68 ± 10.16	39.69 ±7.68	-4.825	<0.001*
Serum Albumin (g/l)	36.87 ± 6.33	45.73 ± 7.40	-7.928	<0.001*
ACR † (mg/mmol)	126.17(84.00)	25.06(26.92)	1881	<0.001*
FBS (mg/dl)	102.13±15.98	105.63±14.15	-1.448	0.150
Uric acid (mg/dl)	7.61 ± 3.34	5.20 ± 2.53	5.010	<0.001*
C-reactive protein† (mg/dl)	2.16(4.73)	0.08(0.27)	917.50	<0.001*
Serum Creatinine (mg/dl)	2.50 (1.80)	0.94(0 .21)	0.000	<0.001*
eGFR† (mls/min)	26.50 (20.84)	86.69(134.44)	14	<0.001*

*(Significant p value<0.05)

†Skewed data expressed in Median (IQR) and Man Whitney U test used. Sd(Standard deviation) IQR (Interquartile range), CaxPP (Calcium phosphate product), ACR (Albumin creatinine ratio), FBS (Fasting blood sugar), eGFR (estimated glomerular filtration rate).

4.6 LIPID PROFILE OF THE STUDY POPULATION

The median value of serum total cholesterol was higher in the CKD group than the control but the difference was not significant (p= 0.363). The median serum triglyceride was significantly higher in the CKD group than the control group (p= <0.001). The mean serum HDL-C was significantly lower in the CKD group than the control group (p= <0.001) while the serum LDL-C was significantly higher in the CKD group than control group (p=0.008) (Table 4)

Table 4: Lipid profile of the CKD and the control group

	CKD (n=78) Mean±Sd/Median(IQR)	Control (n=78) Mean±Sd/Median(IQR)	t/u	p-value
TC† (mg/dl)	179.50(50.80)	174.4(59.30)	2672	0.363
TG† (mg/dl)	104.50 (66.00)	63.4(54.8)	1599	<0.001*
HDL-C (mg/dl)	52.05±18.03	77.48±27.04	-6.823	<0.001*
LDL-C (mg/dl)	111.17±41.21	92.14±44.98	2.686	0.008*

*(Significant p value<0.05)

†Skewed data expressed in Median(IQR) and Man Whitney U test used
IQR (Interquartile range), HDL-C (High density lipoprotein- cholesterol), TG (Triglyceride), LDL-C (low density lipoprotein- cholesterol), TC (Total cholesterol) Sd (Standard deviation)

4.7 ECHOCARDIOGRAPHIC PARAMETERS OF THE STUDY POPULATION

The mean LVIDd, IVSd, PWd, RWT were significantly higher in the CKD group compared to the control group. The p-value of each of these parameters was < 0.001 except LVIDd that was 0.023. The median values of LVM and LVMI were significantly higher in the CKD group than the control group (p=<0.001).There was no statistical difference in the ejection and shortening fraction in both groups. (Table 5)

Table 5: Echocardiographic left ventricle parameters of the CKD and control groups

	CKD (n=78) Mean±Sd/Median(IQR)	**Control (n=78) Mean±Sd/Median(IQR)**	**t/u**	**p-value**
LVIDd	47.66±7.57	45.17±5.90	2.290	0.023*
IVSd	14.82±3.60	11.78±2.19	6.375	<0.001*
PWd	13.56±3.27	10.82±2.33	6.015	<0.001*
RWT (mm)	0.58±0.15	0.49±0.11	4.473	<0.001*
LVM† (g)	319.3(181.4)	218.6(80.8)	1321	<0.001*
LVMI † (g/m2)	184.3(99.9)	111.1(37.6)	1111	<0.001*
Ejection Fraction (%)	62.85±11.81	63.29±9.45	-0.256	0.798
Shortening Fraction (%)	35.21±10.08	35.36±5.09	-0.116	0.908

†Skewed data expressed in Median(IQR) and Man Whitney U test used. *(Significant p value<0.05)

IQR (Interquartile range). LVIDd (Left ventricle internal diameter in diastole), IVSd (Interventricular septal thickness in diastole), PWd (Posterior wall thickness in diastole), LVM (Left ventricular mass), LVMI (Left ventricular mass index), Sd (Standard deviation), RWT (Relative wall thickness)

4.8 PREVALENCE OF CARDIOVASCULAR RISK FACTORS IN STUDY POPULATION

The prevalence of hypertension, diabetes mellitus, tobacco use, dyslipidaemia, hypocalcaemia, hyperphospahataemia, hypoalbuminaemia, hyperuricaemia, elevated CRP and LVH were all higher and statistically significant in the CKD subjects compared to the control subjects with p value of < 0.001 for all these factors except DM that was 0.002. The prevalence of elevated CaxPP was higher in the CKD subjects compared to the control subjects, but was not statistically significant. Obesity was more prevalent in the control group, but this was not statistically significant. (Table 6)

Table 6: Prevalence of cardiovascular risk factors in the study population

Risk Factor	CKD group n=78	Control group n=78	χ^2	P-value
Hypertension	75(96.2%)	34(43.6%)	49.20	<0.001*
DM	32(41.0%)	14(17.9%)	9.99	0.002*
Tobacco use	19 (24.4%)	4 (5.1%)	11.47	<0.001*
Dyslipidaemia	60(76.9%)	38(48.7%)	13.28	<0.001*
Low HDL-C	30(38.5%)	8(10.8%)	16.84	<0.001*
Elevated LDL-C	45(57.7%)	26(33.3%)	9.33	0.002*
Elevated TG	17(21.8%)	8(10.2%)	3.86	0.049*
Elevated TC	23(29.5%)	22(28.2%)	0.03	0.869
Hypocalcaemia	59(75.6%)	23(29.5%)	33.32	<0.001*
Hyperphosphatemia	51(65.4%)	0(0%)	75.77	<0.001*
Anaemia	75 (96.2%)	18 (23.1%)	86.51	<0.001*
Hypoalbuminaemia	16(20.5%)	0(0%)	17.83	<0.001*
Hyperuricaemia	40(51.3%)	10(12.8%)	26.49	<0.001*
Macroalbuminuria	30(38.5%)	6(7.7%)	20.8	<0.001*
CRP				
High Risk	30(38.5%)	0(0%)	37.14	<0.001*
LVH	60(76.9%)	20(25.6%)	41.05	<0.001*
Concentric	48(61.5%)	18(31%)		
Eccentric	12(15.4%)	2(3.4%)		
Obesity	14(17.9%)	19(24.4%)	0.961	0.327
Elevated CaxPP	3(3.8%)	0(0%)	3.060	0.245

*Significant p value of <0.05

χ^2 (Chi square), LVH (Left ventricular hypertrophy), CaxPP (Calcium phosphate product), DM (Diabetes mellitus), CRP (C- reactive protein), HDL-C (High density lipoprotein-cholesterol), LDL-C (low density lipoprotein- cholesterol), TG (Triglyceride), TC (Total cholesterol)

4.9 PATTERN OF CARDIOVASCULAR RISK FACTORS ACROSS CKD STAGES

The prevalence of -hyperphosphataemia ~~and hypoalbuminaemia~~and hypoalbuminaemia significantly- increased across CKD stages 3 to 5 with a p-value of- 0.02 for each of the risk factor. The prevalence of LVH also increased across CKD stages 3 to 5, but did not reach statistical significance with a p value of 0.31.(Table 7)

Table 7: Pattern of Cardiovascular Risk Factors across CKD Stages

Risk factor	CKD stage 3 (n=28)	CKD stage 4 (n=35)	CKD stage 5 (n=15)	P values
Hypertension	26(92.6%)	35(100%)	14(93.3%)	0.69
Diabetes Mellitus	15(53.6%)	15(42.9%)	2(13.3%)	0.04*
Tobacco Use	9(32.1%)	9(25.7%)	1(6.7%)	0.05
LVH	20(71.4%)	26(74.3%)	14(93.3%)	0.31
Hypocalcemia	22(78.6%)	25(71.4%)	12(80%)	0.81
Hyperphosphatemia	11(39.3%)	30(85.7%)	10(66.7%)	0.02*
CaxPP	1(3.6%)	1(2.9%)	1(6.7%)	0.81
Dyslipidaemia	22(78.6%)	25(71.4%)	13(86.7%)	0.85
Hypoalbuminaemia	1(3.6%)	10(28.6%)	5(33.3%)	0.02*
Anaemia	27(96.4%)	33(94.3%)	15(100%)	0.63
Obesity	6(21.4%)	7(20.0%)	1(6.7%)	0.20
Macroalbuminuria	16(57.1%)	8(22.9%)	6(40%)	0.13
Hyperuricaemia	19(67.9%)	13(37.1%)	8(53.3%)	0.40
Elevated CRP	12(42.9%)	14(40%)	4(26.7%)	0.26

* Significant p value of <0.05

LVH(Left ventricular hypertrophy), CaxPP(Calcium phosphate product), CRP(C-reactive protein)

4.1O PATTERN OF CARDIOVASCULAR RISK FACTORS ACCORDING TO AGE GROUP

There was significant increase in the prevalence of diabetes mellitus in the older CKD patients compared with those who were less than 45 years with a p value of < 0.001. The prevalence of elevated CaxPP and macroalbuminuria were higher in patients below 45 years compared to other age groups with a p value of 0.03 for each of the risk factors. (Table 8)

Table 8: Pattern of Cardiovascular Risk Factors according to age group

Risk factor	<45 years (n=36)	45-65 years (n=32)	>65 years (n=10)	P value
Hypertension	33(91.7%)	32(100%)	10(100%)	0.21
Diabetes Mellitus	4(11.1%)	22(68.8%)	6(60%)	<0.001*
Tobacco Use	11(30.6)	5(15.6%)	3(30%)	0.67
LVH	30(83.3%)	22(68.8%)	8(80%)	0.35
Hypocalcemia	26(72.2%)	27(84.4%)	6(60%)	0.75
Hyperphosphatemia	25(69.4%)	18(56.2%)	8(80%)	0.86
CaxPP	3(8.3%)	0(0%)	0(0%)	0.03*
Dyslipidaemia	27(75%)	25(78.1%)	8(80%)	0.85
Hypoalbuminaemia	9(25%)	5(15.6%)	2(20%)	0.98
Anaemia	34(94.4%)	31(96.9%)	10(100%)	0.67
Obesity	4(11.1%)	9(28.1%)	1(10%)	0.62
Macroalbuminuria	20(55.6%)	6(18.8%)	4(40%)	0.03*
Hyperuricaemia	24(66.7%)	11(34.4%)	5(50%)	0.54
Elevated CRP	11(30.6%)	14(43.8%)	5(50%)	0.37

* Significant p value of <0.05

LVH(Left ventricular hypertrophy), CaxPP(Calcium phosphate product), CRP(C-reactive protein)

4.11 PATTERN OF CARDIOVASCULAR RISK FACTORS BY AETIOLOGY

The prevalence of macroalbuminuria was significantly higher in patients with CKD from CGN and DM compared to hypertension with a p-value of 0.02. (Table 9)

Table 9: Pattern of Cardiovascular Risk Factors by aetiology of CKD

Risk factor	CGN(n=21)	DM(n=23)	HTN(n=30)	Others(n=4)	p-value
Hypertension	20 (95.2%)	23 (100%)	30 (100%)	2 (50%)	<0.001*
Diabetes Mellitus	2 (9.5%)	21 (91.3%)	9 (30%)	0 (0%)	<0.001*
Tobacco Use	6 (28.6%)	3 (13%)	10 (33.3%)	0 (0%)	0.22
LVH	17 (81%)	16 (69.6%)	25 (83.3%)	2 (50%)	0.36
Hypocalcemia	18 (85.7%)	18 (78.3%)	19 (63.3%)	4 (100%)	0.17
Hyperphosphatemia	16 (76.2%)	12 (52.2%)	19 (63.3%)	4 (100%)	0.17
CaxPP	2 (9.5%)	0 (0%)	1 (3.3%)	0 (0%)	0.40
Dyslipidaemia	17(81%)	18(78.3%)	22(73.3%)	3(75%)	0.93
Hypoalbuminaemia	6(28.6%)	5(21.7%)	4(13.3%)	1(25%)	0.60
Anaemia	19 (90.5%)	22 (95.7%)	30 (100%)	4 (100%)	0.36
Obesity	1 (4.8%)	6 (26.1%)	7 (23.3%)	0 (0%)	0.17
Macroalbuminuria	12 (57.1%)	11 (47.8%)	5 (16.7%)	2 (50%)	0.02*
Hyperuricaemia	13 (61.9%)	9 (39.1%)	16 (53.3%)	2 (50%)	0.50
Elevated CRP	6(28.6%)	9(39.1%)	12(40%)	3(75%))	0.55

*** (**Significant p value of <0.05)

LVH(Left ventricular hypertrophy), CaxPP(Calcium phosphate product), CRP(C-reactive protein)

4.12 PATTERN OF CARDIOVASCULAR RISK FACTORS BY GENDER

The prevalence of tobacco use, hypocalcaemia and anaemia were significantly higher in the male CKD patients compared to the female CKD patients with p values of <0.001, <0.001 and 0.02 respectively. The prevalence of dyslipidaemia was significantly higher in the female CKD patients with a p value of <0.001. (Table 10)

Table 10: Pattern of Cardiovascular Risk Factors by gender

Risk factor	Male(n=49)	Female(n=29)	p-value
Hypertension	48 (98%)	27(93.1%)	0.28
Diabetes	20 (40.8%)	12 (41.4%)	0.96
Tobacco Use	18 (36.7%)	1 (3.4%)	<0.001*
LVH	41 (83.7%)	19 (65.5%)	0.07
Hypocalcemia	42 (85.7%)	17 (58.6%)	<0.001*
Hyperphosphatemia	31 (63.3%)	20 (69.0%)	0.60
CaxPP	2 (4.1%)	1 (3.4%)	0.89
Dyslipidaemia	33 (67.3%)	27 (93.1%)	<0.001*
Hypoalbuminaemia	9(18.4)	7 (24.1%)	0.54
Anaemia	49 (100%)	26 (89.7%)	0.02*
Obesity	6 (12.2%)	8 (27.6%)	0.09
Macroalbuminuria	13 (26.5%)	17 (58.6%)	0.37
Hyperuricaemia	26 (53.1%)	14 (48.3%)	0.68
Elevated CRP	15(30.6%)	15(51.7%)	0.18

*** (**Significant p value of <0.05)

LVH(Left ventricular hypertrophy), CaxPP(Calcium phosphate product), CRP(C-reactive protein)

4.13 CORRELATION BETWEEN ESTIMATED GFR AND SOME CARDIOVASCULAR RISK FACTORS.

There was significant negative correlation between estimated GFR and systolic BP (r= -0.361,p = <0.001), diastolic BP (r= -0.271,p = 0.016), PP (r= -0.284,p = 0.012) and serum phosphate (r= -0.280, p = 0.014). There was significant positive correlation between eGFR and PCV (r= 0.418,p = <0.001) (Table 11)

Table 11: Correlation between estimated GFR and some cardiovascular risk factors

PARAMETER	P value	R
Systolic BP	0.001*	-0.361
Diastolic BP	0.016*	-0.271
Pulse pressure	0.012*	-0.284
Mean arterial BP	0.944	-0.185
Packed cell volume	<0.001*	0.418
Serum calcium	0.248	0.133
Serum phosphate	0.014*	-0.280
Serum uric acid	0.112	-0.184
Serum albumin	0.207	- 0.146
ACR†	0.721	-0.041
CRP†	0.972	0.004
Serum LDL-C	0.417	0.094
Serum HDL-C	0.621	-0.58
Serum TG†	0.183	0.154
Serum TC†	0.604	0.060
LVMI†	0.646	-0.053

BP(Blood pressure), ACR (Albumin creatinine ratio), HDL-C (High density cholesterol) LDL-C (low density lipoprotein- cholesterol), TG (Triglyceride), TC (Total cholesterol)
*(Significant p value<0.05)

† Spearman correlation used for skewed data

4.14 MULTIPLE LINEAR REGRESSION OF CARDIOVASCULAR RISK FACTORS THAT CORRELATED WITH ESTIMATED GFR

Diastolic BP and PCV were found to be significant predictors of estimated GFR after multiple regression analysis. (Table 12)

Table 12: Multiple linear regression table of cardiovascular risk factors that correlated with estimated GFR in the CKD

Variable	Beta	t	p
Diastolic Blood Pressure*	-0.263	-2.650	0.010
Packed Cell Volume*	0.339	3.216	0.002
Serum Phosphate	-0.181	-1.771	0.081
Pulse Pressure (mmHg)	-0.156	-1.525	0.132
Constant		3.481	0.001

*Significant at 95% Confidence level

Figure 3: Correlation between eGFR and Systolic Blood Pressure

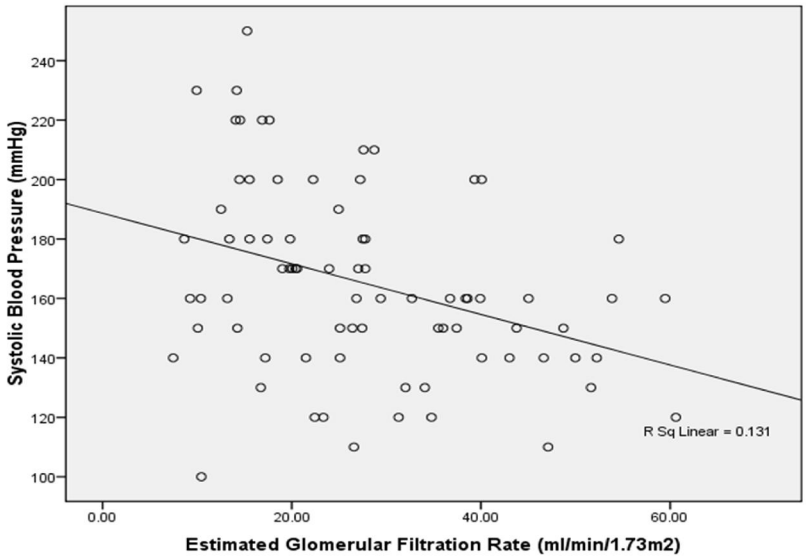


Figure 4: Correlation between eGFR and Diastolic Blood Pressure

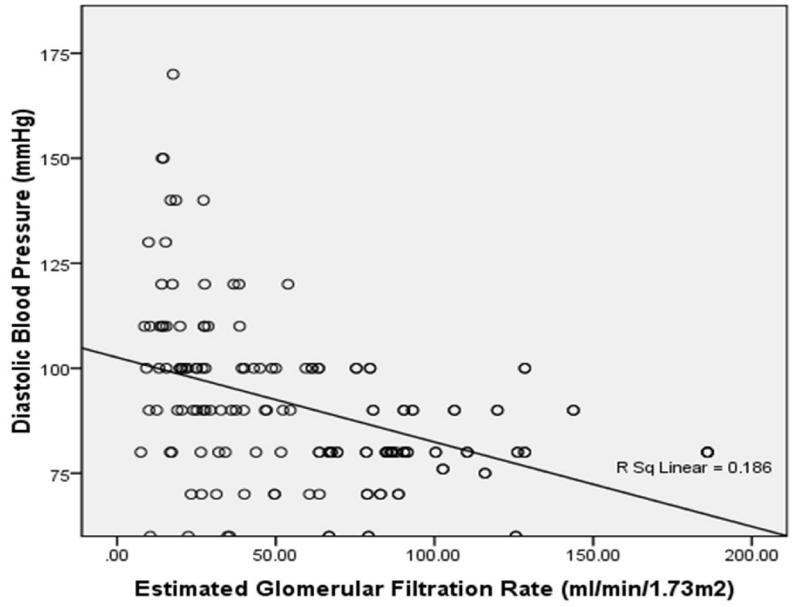


Figure 5: Correlation between eGFR and Pulse Pressure

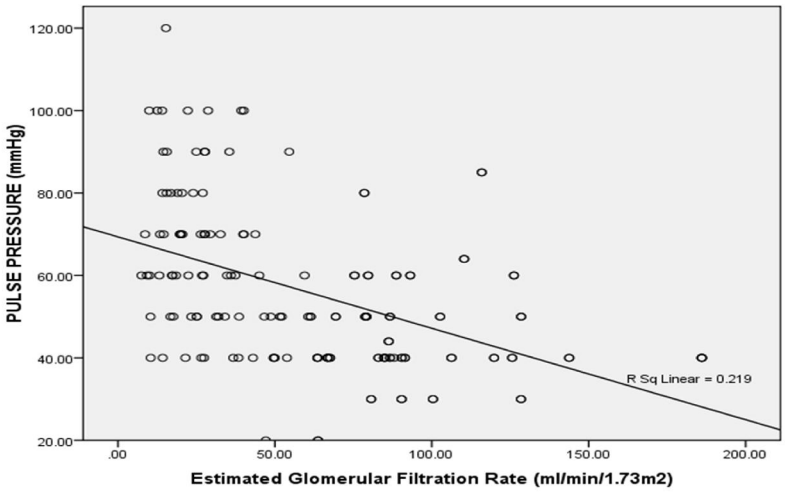


Figure 6: Correlation between eGFR and PCV

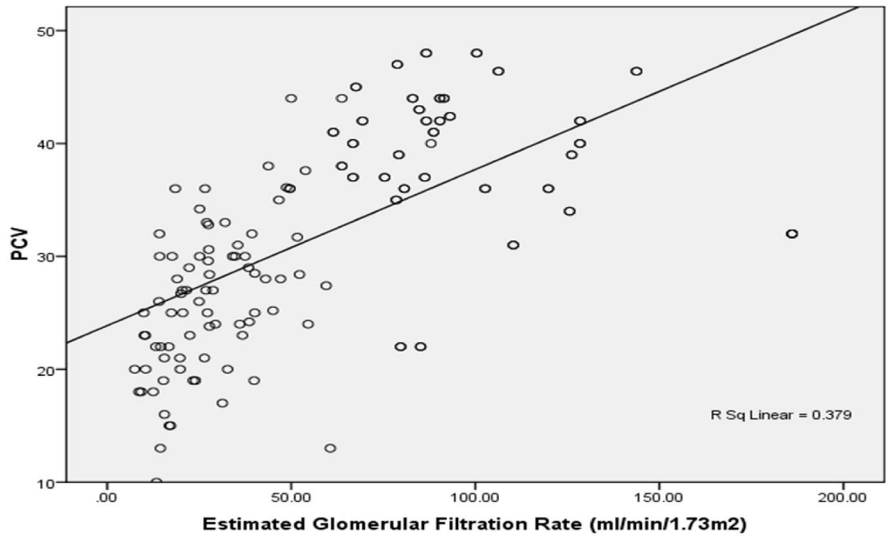
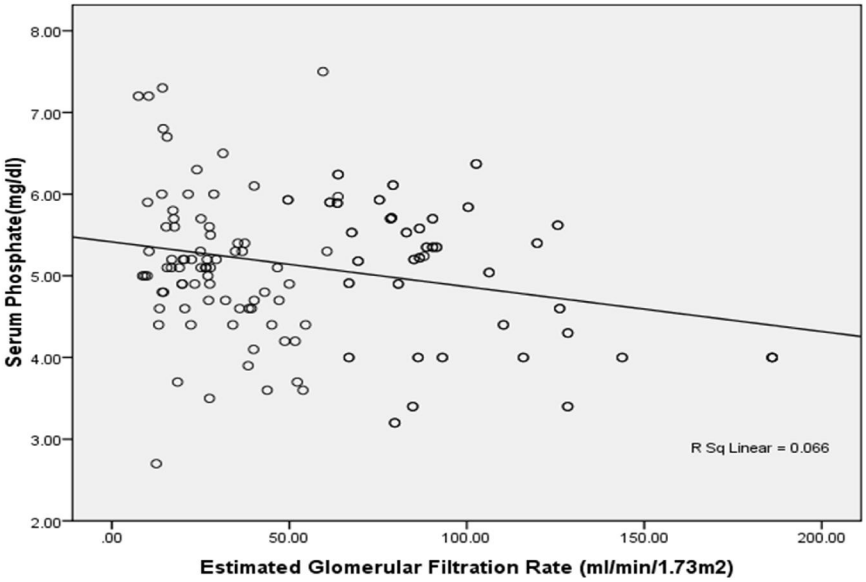


Figure 7: Correlation between eGFR and Serum Phosphate



CHAPTER FIVE

DISCUSSION

The mean age of the CKD group was 47.46±15.45 years while that of the control was 45.45±15.22. About 46% of these CKD patients were below 45 years. This study buttresses previous report that CKD commonly affects the younger population than the elderly in developing countries like Nigeria while the converse is seen in the developed countries. [10] There were more males than females in the CKD group with a ratio of 1:1.7. Majority of the study subjects were married and had at least primary level of education. Only two subjects in this study were Muslim, while others were Christians. This is because the predominant religion in Edo and Delta states where most of the study subjects are from is Christianity. Only 6.4% of the CKD patients were unemployed. The majority of the CKD patients were in stage 4, accounting for about 44.9%. The major causes of CKD in this study were hypertension, DM and CGN. Chronic glomerulonephritis~~GN~~ and hypertension have been reported to be commoner than ~~-~~DM as aetiology of CKD in Nigeria. [10]~~-~~ The high prevalence of DM as a cause of CKD found in this study may be as a result of the small sample size and a reflection of the rising prevalence of DM in Nigeria due to adoption of westernized culture.

Cardiovascular diseases~~VD~~ have been reported to account ~~-~~for about 50% of mortality in patients with CKD.[2] ~~-~~The burden of cardiovascular risk factors is enormous and is responsible for death in these patients because of inadequate risk assessment and management. This study showed a high prevalence of both traditional and non-traditional cardiovascular risk factors even in early stages of CKD.

The prevalence of obesity in the CKD group was 17.9% which was lower than 24.4% found in the control group, though this was not statistically significant. The mean BMI in the CKD group was significantly lower than that of the control group. The presence of malnutrition in

CKD patients that could be caused by anorexia, vomiting and chronic inflammation may account for the lower BMI in this study.

The prevalence of hypertension in the -CKD group was 96.2% which is significantly higher than 43.6% found in the control group. This prevalence is higher than 70.7% and 85.2% reported in previous Nigerian studies by Jesurobo and Ulasi et al respectively.[24,25] The higher prevalence of hypertension observed in this study may be partly due to the exclusion of patients with HIV associated nephropathy who do not commonly have hypertension and who were included in the other studies. However, the prevalence from this study was similar to 85-95% reported by Rao et al in a study in United States of America.[18]

The prevalence of hypertension in CKD patients in this study was quite high compared to the overall prevalence of hypertension in Nigeria which was reported as 11-46.4%.[21] This may be a pointer to the fact that CKD patients are more at risk of developing cardiovascular complications from hypertension compared to the general population. The prevalence of hypertension was slightly higher in the male and older CKD patients, though this was not statistically significant. Systolic BP, diastolic BP and PP significantly correlated with estimated GFR negatively in this study. These findings are similar to reports from other studies which reported that the prevalence of hypertension increased as CKD progressed.[18,25]

The prevalence of DM in the CKD group was 41% and this was significantly higher than 17.9% in the control group. The high prevalence of DM and diabetic nephropathy in this study may be a reflection of the increasing prevalence of DM worldwide due to adoption of westernized lifestyle and physical inactivity. There was no significant difference in the mean value of fasting blood glucose of the CKD and the control groups. It has been established that as CKD progresses, glycaemic control may be better achieved due to prolonged half life of insulin from reduced renal clearance. This usually warrants adjustment of the dose of the

glucose lowering agent or even discontinuation in order to avoid hypoglycaemia. There was no significant difference in the prevalence of DM in the male and female CKD patients but the prevalence of DM significantly increased with increasing age.

History of tobacco use was present in 24.4% of the study group and this was higher than 5.4% in the control group; this difference was statistically significant. The prevalence of tobacco use was significantly higher in males than female. This is not surprising because tobacco use is more culturally acceptable in males than females in Nigeria.

The prevalence of macroalbuminuria in the CKD group was 38.5% which was significantly higher than 7.7% in the control group. The prevalence of macroalbuminuria was significantly higher in patients with CKD from CGN and DM compared with hypertension though the difference did not reach statistical significance. This is because both CGN and DM primarily cause glomerular disease which is characterized by marked proteinuria. Proteinuria has been associated with rapid progression of both proteinuric and non-proteinuric CKD. The control of proteinuria using diet and RAAS blockers has been shown to slow disease progression and reverse LVH if treatment is instituted early.[28] These therapeutic strategies should be instituted early in our CKD patients.

The prevalence of anaemia was 96.2% in the CKD group and was significantly higher than 23.1% in the control group. The prevalence of anaemia in the CKD group was higher than 77.5% in a previous Nigerian study, [54] but comparable with 93% reported in Ilorin, Nigeria.[55] The high prevalence of anaemia in this study may be due to the fact that the World Health Organization definition of anaemia [52] used in this study is higher than that used in the study referred to above. CKD patients in stages 1 and 2 who do not commonly present with anaemia were not included in this study and this might have also contributed to the high prevalence of anaemia in this study. Malnutrition, inflammation and helminthic infections are

commoner in people from developing countries like Nigeria and this may also be contributory to higher prevalence of anaemia in this study compared to 45% reported in United States of America.[88] The prevalence of anaemia was higher in the CKD stage 5 patients compared to other stages. There was also a significant positive correlation between estimated GFR and PCV in this study. This is in agreement with previous reports that have established worsening anaemia with progressive decline in renal function.[53,54]

The prevalence of anaemia in male CKD patients was 100% and this was significantly higher than ~~-~~89.7% ~~-~~in female CKD patients. This could be due to the higher PCV cut off value of less than 39% used in definition of anaemia in male subjects compared to a lower cut off value of less than 36% used in female subjects. The prevalence of anaemia also increased with increasing age. Anaemia contributes significantly to development of CVD in CKD patients by causing LVH and subsequently left ventricular dilatation, if corrective measures are not promptly instituted. The NKF-KDIQO recommended that erythropoietin stimulating agent should be commenced once haemoglobin concentration falls below 10mg/dl with a therapeutic target that is not above 12g/dl.[51]

The prevalence of LVH in the CKD group was 76.6% and this was significantly higher than 25.6% observed in the control group. The prevalence of LVH in earlier reports range between 27.6-95.5%.[5,23-25] The prevalence of LVH also depends on the mode of diagnosis. Studies that used echocardiographic criteria had higher values than those that used electrocardiography due to higher sensitivity of the former. The prevalence of LVH in the CKD group in this study was lower than 95.5% reported by Ulasi et al [25] in a similar study; however, majority of participants in this study were in stages 3 and 4 unlike the latter study that evaluated stages 4 and 5 CKD patients. The prevalence is similar to 76% reported by Jesurobo et al [24] but very high when compared to 27.6% reported by Chijoke et al respectively.[23] The low prevalence reported by Chijoke et al may be ~~because~~

~~electrocardiography~~because electrocardiography criteria used in the study is~~-~~ a less sensitive tool to diagnose LVH. LVH was more prevalent in male CKD patients in this study which may be related to the contribution of testosterone on hypertrophy of the heart in the male subjects. Hypertension contributes significantly to LVH and this may explain while LVH was more prevalent in patients with CKD from hypertension compared to other aetiologies.

Concentric LVH was the predominant geometric pattern in this study and this is similar to previous report by Sambi et al.[36] The predominance of concentric LVH may be explained by the high prevalence of hypertension and hyperphosphataemia in the CKD subjects recruited in this study. Some authors however, reported eccentric LVH as the predominant geometric pattern in CKD patients.[5,25] The prevalence of LVH increased across CKD stages 3 to 5, but did not reach statistical significance. The lower sample size used in this study may account for this finding. Earlier studies have reported similar finding of increasing prevalence of LVH across CKD stages. [24,25] This study showed that LVH occurs early in CKD, which buttresses the fact that even CKD patients in early stages are at high risk of cardiovascular death since LVH has been shown to be a predictor of mortality.[27] Optimal BP control in CKD patients with use of drugs that block the RAAS have been shown to reverse LVH and prevent attendant associated CVD mortality.[28]

The prevalence of dyslipidaemia in the CKD group was 76.9% and this was significantly higher than 48.7% present in the control group. The serum TG and LDL-Cholesterol were significantly higher while serum HDL-Cholesterol was lower in the CKD group. In the CKD group, prevalence of elevated TC was 29.5%, hypertriglyceridaemia was 21.8%, elevated LDL-C 57.7% and reduced HDL-C was 38.5%. The commonest ~~pattern of dyslipidaemia in the CKD group were~~patterns of dyslipidaemia in the CKD group were elevated LDL-C and reduced HDL-C which are the major contributors to atherosclerosis and attendant CVD morbidity and mortality. Msheila et al[54] reported elevated TG and elevated HDL as the

commonest pattern of dyslipidaemia while others have reported elevated TG and TC.[34, 36] The varied pattern of dyslipidaemia in the different studies may be due to different criteria used for the definition of dyslipidaemia. The prevalence of dyslipidaemia was significantly higher in female CKD compared with male CKD patients. There was no association between the severity of dyslipidaemia and the stages of CKD in this study. Dyslipidaemia was commoner in patients with CKD from CGN and DM compared to other aetiologies. The prevalence of dyslipidaemia also increased with age of the CKD population. Studies have shown that treatment of dyslipidaemia reduces major atherosclerotic events and rate of progression in CKD.[38,39] Antilipidaemic drugs like statins have both anti-inflammatory and anti-proteinuric effects in addition to their primary lipid lowering effects.

Hypocalcaemia was present in 75.6% of the CKD group and this was significantly higher than 29.5% that was present in the control group .This was similar to the findings of Onyemekeiha et al [61] who reported a prevalence of 71% in an earlier study done in Benin, South -South Nigeria, but higher than 59.3% reported by Sanusi et al [62] in Ile-Ife, South-West Nigeria. Hyperphosphataemia was present in 65.4% of the CKD group but absent in the control group. The prevalence was however, lower than 75% and 79% reported in previous similar studies.[61,62] The lower prevalence of hyperphosphataemia in this study may be due the fact that the other studies were carried out in stage 5 CKD patients while this study involved mainly stages 3 and 4 CKD patients. There was a significant negative correlation between estimated GFR and serum phosphate in this study. The prevalence of hyperphosphatemia increased significantly across the CKD stages. Hypocalcaemia was significantly higher in males than females in the CKD group. Elevated CaxPP was present in only 3.5% of the CKD group and absent in the control group. This was lower than 12.5% reported in Ile Ife.[62] This is however not surprising, because the researchers in Ile-Ife studied

only stage 5 CKD patients. There are established therapeutic agents that can reverse these abnormalities when instituted early.[64,65]

Hypoalbuminaemia was present in 20.5% of the CKD group, while none of the controls had hypoalbuminaemia. The prevalence of hypoalbuminaemia increased significantly from CKD stage 3 to 5 in this study and this may be explained by progressive malnutrition that occurs from the effect of uraemic toxins with declining renal function. The prevalence was higher in CKD patients from DM and CGN than hypertension possibly because they are associated with significant proteinuria. Hypoalbuminaemia, being a surrogate marker of malnutrition and inflammation tend to worsen with deteriorating renal function. It has been shown that CKD with hypoalbuminaemia is associated with faster decline in GFR, poor cardiovascular outcome and increased mortality after commencement of RRT.[89] Some studies have established that the use of oral nutritional supplements improve outcome in ESRD patients on dialysis.[68]

The prevalence of asymptomatic HU was 51.3% in the CKD group which was significantly higher than 12.8% in the control group. Hyperuricaemia was commoner in patients with CGN compared to others. The value of treatment of asymptomatic HU in CKD is presently still a subject of debate. Treatment of asymptomatic HU using allopurinol has been shown to reduce cardiovascular events, hospitalization, achieve better BP control and reduce the progression of renal disease.[64,73] Febuxostat is a hypouricaemic drug that has been found to be safe in patients with renal disease and is not associated with adverse drug reactions like allopurinol. The use of this drug is however limited by its unavailability and high cost in countries like Nigeria. Allopurinol could still be cautiously used with dose adjustment and close monitoring for any adverse drug reaction.

The median value of CRP was significantly higher in the CKD group compared to the control group. It was also established that 38.5% of the CKD patients had high cardiovascular risk compared to none in the control group based on the serum CRP level.

Uric acid and CRP as inflammatory –markers– may be used in risk stratification of CKD patients so as to identify those that will require aggressive intervention and close monitoring for cardiovascular events. Statins and ACEIs have additional anti-inflammatory effects in addition to their primary actions.

CONCLUSION

Both traditional and non-traditional cardiovascular risk factors are highly prevalent in pre-dialysis CKD subjects. These risk factors are commoner in CKD patients compared to control subjects in this study. The prevalence of some of these risk factors like -hyperphosphataemia, hypoalbuminaemia and LVH increased across the CKD stage. Hypocalcaemia, tobacco use and anaemia were significantly commoner in males while dyslipidaemia was commoner in female CKD patients.

Most of these risk factors are also known to be responsible for rapid progression to ESRD and are potentially reversible if they are identified early with institution of appropriate treatment measures. This will go a long way to reduce the rate of progression of CKD, cardiovascular morbidity and mortality in these patients.

LIMITATION OF STUDY

The long term effect of established cardiovascular risk factors on morbidity and mortality in pre-dialysis CKD patients could not be assessed in this study. Also, all cardiovascular risk factors especially the non-traditional risk factors like homocysteine, parathyroid hormone could not be assessed in this study due to cost.

RECOMMENDATIONS

A large prospective multi-centre study that will assess the long term effect of cardiovascular risk factors and their modification on the overall mortality in CKD patients is recommended. Comprehensive evaluation of all pre-dialysis patients should be done for cardiovascular risk factors and diseases with the aim of aggressive modification of these risk factors with both lifestyle modification and therapeutic interventions. This will go a long way in retarding CKD progression, reducing both cardiovascular morbidity and mortality in these patients. CKD patients should be considered as high risk group for CVD, hence this should be taken into account when management guidelines and research priorities are being defined.

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APPENDIX I

Questionnaire on Cardiovascular Risk Assessment in Predialysis CKD patients in University of Benin Teaching Hospital, Benin City

A. Demographic Information

Name (Initials): **Serial No.:**

Hospital No. **Contact Phone No:**

Tribe:

1. Sex: M [ ] F [ ]

2. Age: _____years

3. Marital status: Single [ ], Married [ ], Divorced [ ], Widowed [ ], Separated [ ]

4. Religion: Christian [ ], Muslim [ ], Others _____

5. Occupation: _____

6. Educational status: Primary [ ], Secondary [ ], Tertiary [ ], None [ ]

B. History

Symptoms:

Facial swelling	Yes / No
Leg swelling	Yes/ No
Orthopnoea	Yes/No
Cough	Yes/No
PND	Yes / No
Nocturia	Yes / No
Frothiness of urine	Yes / No
Reduction in urine output	Yes / No
Weakness	Yes / No
Bone Pain	Yes / No

C. Medical History

Diabetes mellitus	Yes / No
If yes, for how long?	……
Hypertension	Yes / No
If yes, for how long?	……

Previous CVA Yes/ No

Previous CCF Yes/No

Previous MI Yes/ No

D. Social History

Cigarette use Yes/ No

If yes, how many pack years ……

E. Drug History

Antihypertensive use Yes / No

If yes:

Are you regular? Yes / No

For how long have you been on antihypertensive drugs?

Glucose lowering agent use Yes / No

If yes:

What type ?

Are you regular? Yes/ No

For how long have you been on it?

Lipid lowering agent use Yes/ No

If yes:

What type? .....

Are you regular? Yes/ No

For how long have you been on it?

ACEI or ARB use Yes/ No

If yes:

What type?

Are you regular?

For how long have you been on it?

F. Physical Examination:

1. Anthropometry

Weight: _____kg

Height: _____m

BMI: _____kg/m^2

Waist Circumference: _____cm

Hip Circumference: _____cm

Waist-Hip Ratio

2. Physical Examination

Pallor Yes / No

Dehydration Yes / No

Facial swelling Yes / No

Leg swelling Yes / No

Blood Pressure: Systolic [ ]mmHg

Diastolic [ ]mmHg

Pulse Pressure: ----------

D. Laboratory Evaluation

1. Serum Electrolyte, Urea and Creatinine

a. Urea: _____mg/dl Normal [ ] Abnormal [ ]

b. Creatinine: _____mg/dl Normal [ ] Abnormal [ ]

c. Sodium: _____mmol/L Normal [ ] Abnormal [ ]

d. Potassium: _____mmol/L Normal [ ] Abnormal [ ]

e. Chloride: _____mmol/L Normal [ ] Abnormal [ ]

f. Bicarbonate: _____mmol/L Normal [ ] Abnormal [ ]

eGFR: _____ml/min

2. Fasting Blood Glucose [ ]mg/dl Normal [ ] Abnormal [ ]

3. Serum Lipid Profile

a. Total cholesterol _____mg/dl Normal [ ] Abnormal [ ]

b. HDL-Cholesterol_____mg/dl Normal [ ] Abnormal [ ]

c. LDL-Cholesterol_____mg/dl Normal [ ] Abnormal [ ]

d. Triglycerides_____mg/dl Normal [ ] Abnormal [ ]

4. Serum Calcium and Phosphate

a. Serum Calcium ……..mg/dl

b. Serum Phosphate ……..mg/dl

c. Corrected Serum Calcium ……. mg/dl

d. CaXP product ……. mg^2/ dl^2

6. Packed Cell Volume (PCV) _____%

7. **CRP Value** …….

8. Serum Uric Acid ----------

9. Left Ventricle Dimension on Echocardiography

LVIDd: ……

IVSd: ……

PWd: ……

RWT: ……..

LVM: …….

LVMI: ……

EF: ……..

SF: ……

10. Evidence of LVH on Echocardiography Yes/No

APPENDIX II

INFORMED CONSENT FORM

TITLE OF STUDY: ASSESSMENT OF SOME CARDIOVASCULAR RISK FACTORS IN PRE-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS IN UNIVERSITY OF BENIN TEACHING HOSPITAL (UBTH), BENIN

INVESTIGATOR: DR. ADEJUMO, OLUSEYI ADEMOLA; DEPARTMENT OF MEDICINE, UBTH

FINANCIAL SPONSORSHIP: This research is self- sponsored.

PURPOSE OF RESEARCH

There is a high prevalence of cardiovascular risk factors in predialysis chronic kidney disease patients. This is associated with rapid progression of chronic kidney disease. This also, increases the morbidity and mortality in these patients.

The purpose of this study is to determine the prevalence and pattern of cardiovascular risk factors in predialysis chronic kidney disease patients.

PROCEDURES INVOLVED IN STUDY

You will be asked some questions concerning your symptoms, past medical history, social history and drug history. Anthropometric measurements will also be done. Blood and urine samples will be taken to run some biochemical parameters for you.

COMPENSATION

There shall be no financial compensation for participating in this study.

VOLUNTARY PARTICIPATION

Please note that your participation in this research is entirely voluntary. No form of discrimination will be meted to you should you decide not to participate in this study. You are entirely free to change your mind and stop participating at any point in time even if you agreed earlier.

RISKS

There is a little measure of painful discomfort associated with the blood collection procedure. No other adverse effect or risk is expected to be associated with participation in this study. However, any adverse effect experienced will be taken care of by me.

BENEFITS

Participants with high cardiovascular risk will be identified very early and corrective measures will be put in place to forestall further disease progression. Information from this study will guide physicians to seek cardiovascular risk factors in chronic kidney disease patients early to enable them institute appropriate treatment.

CONFIDENTIALITY

All information obtained in the course of this study will be treated confidentially. The name of participants will not be written in full on the questionnaire. All information obtained with the questionnaire will be encoded in a file in my personal computer and protected with a pass word. The questionnaire will afterward be locked up in my study. The samples will neither be stored for any future studies nor given out to other investigators for another study.

CONTACT INFORMATION

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Chairman, Ethics and Research Committee

University of Benin Teaching Hospital

Phone number: 052-600418

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Telex: 41120 NG

CERTIFICATE OF CONSENT

I have read the above information (or it has been read and translated to me). I have had the opportunity to ask questions about the study and my questions have been answered to my satisfaction.

(A) I consent to voluntarily take part as a participant in this research.

(B) I do not consent to participate in this research.

Name of participant: _____

Signature of Participant: _____

Date: _____