ANAEMIA IN CHRONIC KIDNEY DISEASE IN LASUTH: IMPACT ON QUALITY OF LIFE AND LEFT VENTRICULAR MASS INDEX

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DECLARATION

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Abstract

Anaemia is a common complication of chronic kidney disease(CKD), and has been shown to worsen as CKD advances. It has also been identified as an independent predictor of left ventricular hypertrophy (LVH) among CKD patients, and worsens their cardiovascular outcome, and impacts negatively on their quality of life.

The aim of this study was to assess the prevalence and geometric pattern of LVH among anaemic CKD patients, and the relationship between the severity of anaemia and its impact on the quality of life of anaemic CKD patients attending nephrology clinic at Lagos State University Teaching Hospital.

Methods: A cross sectional analytical study was carried out within a 10 month period (April 2016 to January 2017). A total of one hundred and sixty three subjects were recruited which included one hundred and two anaemic CKD subjects and sixty one CKD subjects without anaemia as controls. Karnofsky structured questionnaire was used to assess quality of life, echocardiogram was used to determine the presence of LVH, the left ventricular geometric pattern (L.V geometry) and the left ventricular systolic function, while the packed cell volume was used to categories subjects into severity of anaemia.

Result: The mean age of anaemic CKD subjects was 54.04 ± 14.47 years, while those of controls was 54.92 ± 15.67 years, with t = -0.364, p = 0.717. The duration of CKD among anaemic CKD subjects was 3.41 ± 5.22 years and controls was 3.09 ± 2.57 years, with t = 0.442 and P = 0.659. The prevalence of anaemia among CKD subjects was 102(62.6%), and it significantly worsens as CKD advances, which ranged from 42.3% in stage 3 to 93% in stage 5 ($X^2 = 29.69$, $p < 0.001$). The mean physical performance score was significantly lower among anaemic CKD

subjects than controls, which was 73.17 ± 12.95 and 84.59 ± 11.04 respectively, with t = -5.739 and P < 0.001. Furthermore, the mean physical performance score decreases significantly with advancing CKD among both study groups. The prevalence of LVH among anaemic CKD subjects was 64(68.8%), and was not significantly different among CKD subjects without anaemia was 33(57.9%), X^2 = 1.845, p = 0.174, O.R = 1.61, and 95% C.I was 0.81 – 3.17. The most frequent pattern of LVH seen among both groups was concentric LVH which was 50 (53.8%), and 25(43.9%) among both anaemic CKD subjects and controls respectively, X^2 = 2.385, and p = 0.497. The overall prevalence of left ventricular systolic dysfunction among subjects was 68(45%), with significantly higher frequency among anaemic CKD subjects 58(61.7%), than controls 10(17.5%), with X^2 = 27.952 and p < 0.001, O.R = 7.57, and 95% C.I = 3.43 – 16.73. Also there was a strong negative correlation between packed cell volume and left ventricular mass index with correlation coefficient (r = -0.345, p = 0.001) among anaemic CKD subjects, but weak positive correlation among controls (r = 0.001, p = 0.993).

Conclusion: This study showed that CKD patients with anaemia had significant impairment in their physical ability than CKD patients without anaemia, and high prevalence of LVH and poor left ventricular systolic function among them.

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1.1 Introduction

Cardiovascular disease (CVD) is highly prevalent among end-stage renal disease (ESRD) patients and is the main reason for their high mortality and morbidity rates(1). A large proportion of patients starting renal replacement therapy (RRT) also have CVD, suggesting that the pathogenic factors leading to cardiac dysfunction begin in the early stages of chronic kidney disease (CKD). This is of major importance, as it has been widely demonstrated that cardiovascular status at the beginning of dialysis strongly affects patients' outcome (2). Many factors account for the strong relationship between CKD and CVD, but the contribution of anaemia and hypertension to the development of cardiac abnormalities have been proven to be substantial (3).

Anaemia is an important pathogenic factor responsible for cardiovascular abnormalities such as heart failure and in particular left ventricular hypertrophy (LVH), which significantly worsens the prognosis of CVD morbidity, mortality and the quality of life outcome among CKD patients(1). This could explain the association between anaemia with both hospitalization and mortality rates in such patients and leads to the expectation that correction of anaemia may improve cardiovascular status and long-term prognosis.

A partial regression of LVH after partial correction of anaemia has been observed in several studies(4,5), but it is still unclear whether normalizing haemoglobin concentrations produces additional cardiac advantages. Indeed, no significant differences between partial and complete correction of anaemia in inducing regression of established LVH have been demonstrated so far,

but further investigation is needed. Furthermore, because anaemia affects the quality of life of CKD patients, normalization of anaemia improves quality of life and physical function of selected categories of patients(6). Also keeping in mind the potential risks of haemoglobin normalization in haemodialysis patients such as stroke, hypertension, vascular access thrombosis with severe heart disease and grafts, individualising the target haemoglobin concentration to the characteristics of the patient is the most important approach in the management of such patients(6).

Chronic Kidney Disease has a significant impact on Quality of Life (QoL)(7), and this impact may vary from one stage of CKD to another, as well as from one domain of Quality of life to another; with some domains being more affected than others(8). Furthermore, complications of CKD such as anaemia, cardiovascular diseases, mineral bone disease, malnutrition, and other co-morbid conditions, such as hypertension, diabetes and dyslipidaemia negatively affect physical functioning and well-being. Therefore early recognition of these complications with overall quality of life assessment helps to improve the burden and well-being of CKD patients.

1.1.1 Burden of disease

According to the United States Renal Data System(USRDS) report of 2015, the estimated prevalence of CKD was reported to be 13.6% in the general population(9). The prevalence has been higher among the elderly population (above 65 years), which has peaked at a prevalence of 10.7% in 2013(9). However, mortality from CKD especially stages 4 to 5, has been estimated to be 60% from 2008 to 2013(9).

There have been advances in medical care of dialysis treatment over recent years, despite such, mortality and morbidity among end-stage renal disease (ESRD) patients still remains significantly higher when compared with the general population, mainly due to an excess of

cardiovascular disease (CVD). As evidenced by the United States Renal Data System, cardiovascular mortality in dialysis patients is approximately 10 to 20 times higher than that of the general population(10). CVD is the leading cause of death in these patients, accounting for more than 50% of deaths, and is also responsible for 30% of hospitalisations(10), therefore, the prevalence of CVD is already very high at the start of RRT.

However, in a Canadian study(11), in which CVD was assessed among CKD patients, CVD was found to be highly prevalent in patients starting RRT, and 14% of the patients had coronary artery disease, 19% had angina pectoris, 31% had cardiac failure and 7% had dysrhythmia; whereas on echocardiographic evaluation 15% of the patients had systolic dysfunction, 32% had left ventricular dilatation and 74% had left ventricular hypertrophy (LVH)(11). Similar results were reported from data from the Lombardy Registry(2).

Large studies have found an inverse relationship between haematocrit level, morbidity and mortality in dialysis patients. In an analysis of more than 75,000 haemodialysis patients with different haematocrit levels, improved survival rates were associated with increasing haematocrit; patients with haematocrit less than 27% and between 27% and 30% showed a relative risk for all-cause death of 1.51 and 1.20 respectively, compared to a reference group with haematocrit between 30% to 33%, whereas for patients with haematocrit in the range 33% to 36% the relative risk was 0.90(12). In another analysis of the same population, the adjusted risk for all-cause hospitalization was also correlated to haematocrit level, and a relative risk of future hospitalization of 1.30, 1.14 and 0.89 was demonstrated for patients with haematocrit levels less than 27%, 27% to 30% and 33% to 36%, respectively(13).

The impact of anaemia and LVH on cardiovascular status of CKD patients was well revealed in a multi centre community based longitudinal study which reported that LVH increases the

composite risk of myocardial infarction, stroke and death by 74% with a hazard ratio of 1.67, while anaemia increased the risk by 63.1% with hazard ratio of 1.51, and the combination of anaemia and LVH increased the risk for cardiovascular disease mortality by 80% with hazard ratio of 3.30(14).

Moreover, the benefit of correcting anaemia also persists for higher levels of haematocrit; haemodialysis patients with haematocrit levels >33% had a 16-22% lower risk of hospitalization and death compared with all the other patients(15). Further studies, like the analysis of data from the Lombardy Registry showed that all cause mortality significantly decreased with the increase in haematocrit levels (odds ratio 0.95 per unit of haematocrit) among dialysis patients; the same trend was observed for hospitalization rate(16). Other studies have shown that higher haemoglobin among CKD patients was associated with a decreased relative risk for both mortality and hospitalization(17,18), and anaemia has been shown to be an independent predictor of non-elective hospitalization (risk ratio 0.987, P = 0.0004)(18). Therefore, these studies have revealed the high prevalence of morbidity and mortality associated anaemia among CKD patients, and better outcome when haemoglobin level is higher.

1.1.2 Justification

Cardiovascular disease (CVD) is highly prevalent among CKD patients with high morbidity and mortality(1). Also CKD patients tend to develop these cardiovascular disease prior to onset of ESRD, in addition such patients die from CVD more rather than progression to ESRD(1). LVH is considered an important risk factor for progression of CVD and an independent predictor for adverse cardiovascular outcomes among CKD patients(19). The adverse cardiovascular outcome associated with LVH include, congestive cardiac failure, ischemic heart disease, stroke and sudden cardiac death among CKD patients, which accounts for the high mortality among CKD

patients. Furthermore, haemoglobin level has been found to predict the degree of LVH(19), and both LVH and anaemia are determinants of cardiovascular outcomes(20). Correction of anaemia with erythropoietin therapy has been shown to influence the regression of left ventricular mass(4,21–23).

Two studies in Nigeria(24,25) that have determined the prevalence and geometric pattern of LVH and anaemia among CKD patients in Nigeria, and these studies have reported a high prevalence of both LVH and anaemia, and a significant correlation between them among CKD patients. However, these studies were not primarily focused on anaemic CKD patients, but focused more on hypertensive patients. This is evidenced in the inclusion criteria which recruited hypertensive patients who had stopped there antihypertensive medications for many years before presenting with CKD, while CKD patients who were on any antihypertensive medications or any medications that could affect their blood pressure were excluded from the study(24). Furthermore, these studies were not aimed at assessing for left ventricular mass regression after correction of anaemia with erythropoietin therapy; neither did these studies compare the degree of left ventricular mass with the severity of anaemia.

Evidence based studies have shown that anaemia reduces the QoL among CKD patients, with significant correlation between the level of anaemia and physical activity, vitality, fatigue emotional status, sexual activity and cognitive functions(26–28). Also, CKD progression has been associated with reduced QoL(29). It has been shown that all QoL dimensions deteriorated significantly across CKD stages with the lowest scores in CKD 5. Therefore, assessment of quality of life in CKD has become a vital tool not only in the monitoring of treatment outcomes, but also because it has been established to significantly influence morbidity and mortality(30).

Therefore, this study aims to add to the pool of knowledge on the prevalence and geometric pattern of left ventricular mass among anaemic CKD patients, and to correlate the level of anaemia with left ventricular mass index and their quality of life (physical function).

1.1.3 RESEARCH QUESTIONS

1. What is the prevalence of left ventricular hypertrophy among anaemic CKD patients?
2. What is the geometric pattern of left ventricular hypertrophy among anaemic CKD patients?
3. Is there any correlation between the severity of anaemia and the quality of life (physical performance) among anaemic CKD patients?

1.1.4 GENERAL AND SPECIFIC OBJECTIVES

1.1.5 AIM:

This study aims to assess the prevalence and geometric pattern of left ventricular hypertrophy among anaemic CKD patients, and the relationship between the severity of anaemia and its impact on their quality of life (physical performance).

1.1.6 SPECIFIC OBJECTIVES:

1. To determine the prevalence of left ventricular hypertrophy among anaemic CKD patients as compared to CKD patients without anaemia.
2. To determine the geometric pattern of left ventricular hypertrophy among anaemic CKD patients as compared to CKD patients without anaemia.
3. To correlate the severity of anaemia with left ventricular mass index.

4. To correlate the severity of anaemia and quality of life (physical performance) among CKD subjects.

1.1.7 Hypothesis

1. There is difference in the prevalence and geometrical pattern of left ventricular hypertrophy in anaemic CKD patients when compared to CKD patients without anaemia.

2. There is a correlation between the severity of anaemia and the quality of life score (physical performance).

Literature Review

Epidemiology of cardiovascular disease in chronic kidney disease patients

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function present for more than 3 months with implication for health(31). Criteria for CKD assessment include any of the following persisting for more than 3 months. Decreased GFR < 60ml/min/1.73m^2 or albuminuria defined as albumin excretion rate ≥ 30mg/24 hours or albumin creatinine ratio ≥ 30mg/g (≥ 3mg/mmol), urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, and history of kidney transplantation. Stages of CKD are categorized based on estimated glomerular filtration rate (eGFR) defined as follows: stage 1 eGFR ≥ 90ml/min/ 1.73m^2, stage 2 eGFR of 60 – 89 ml/min/1.73m^2, stage 3a eGFR of 45 – 59 ml/min/1.73m^2, stage 3b eGFR of 30 – 44 ml/min/1.73m^2, stage 4 eGFR of 15 – 29 ml/min/1.73m^2, stage 5 eGFR of < 15 ml/min/1.73m^2 (31).

CKD prevalence is estimated to be 8-16% worldwide. This prevalence has been observed to be increasing in many populations. For instance, the United State Renal Data Registry (USRD)(10) data shows that the prevalence of CKD in the USA is increasing. The prevalence of stage 3–4 CKD increased from ~5.5% in the 1988–1994 survey to >8% in the 1999–2004 survey. The prevalence of end-stage renal disease (ESRD) has steadily increased by 18% between 2000 and 2007; in 2010, ESRD was estimated to affect 1,699 per 1 million US individuals(10).

The New Opportunities for Early Renal Intervention by Computerized Assessment (NEOERICA) study(32) which reported the prevalence of CVD among CKD patients to be 19.9%, and revealed that CVD prevalence increases as CKD advances, with early CKD (eGFR >

60ml/min/1.73m^2) having a CVD prevalence of 14.8%, while advanced CKD (eGFR < 30ml/min/1.73m^2) have a CVD prevalence of 50.7%.

According to National Health and Nutrition Examination Survey (NHANES) survey(33) in 2007 to 2010, CVD was present among 29.6% and 13.0% of adults with CKD Stages 3-5 and Stages 1-2, respectively, compared to 5.5% of those without CKD. However, coronary artery disease (CAD) had a prevalence of 8.7% in stage 1-2, and 17.6% in stage 3-5, while only 3.7% was reported in patients without CKD. Stroke was reported to be 5.3% in stage 1-2, 12% in stage 3-5, and 1.9% among patients without CKD. Congestive heart failure was reported as 3.9%, 11.1%, and 1.3% among stage 1-2, stage 3-5 patients with CKD and those without CKD respectively.

Aetiopathogenesis of anaemia in CKD

Anaemia is common among CKD patients and prevalence worsens as CKD advances(34). The postulated aetiopathogenesis for anaemia in CKD includes erythropoietin (EPO) deficiency, haemolysis, absolute and functional iron deficiency, folic acid deficiency, carnitine deficiency, chronic inflammation, aluminium intoxication, hyperparathyroidism with myelofibrosis, external blood loss either through haemodialysis, bone-marrow suppression induced by retained toxic metabolites and drugs(34).

Although the anaemia of chronic renal failure is a complex disorder in which many factors may play a role as previously stated, the main defect is absolute or relative EPO deficiency. In most patients with substantially impaired renal function, EPO production is impaired at any given hematocrit concentration(35). Erythropoietin stimulates terminal differentiation of committed erythroid progenitors in the marrow, increases cellular haemoglobin synthesis, and causes marrow reticulocytes to shift into the circulation prematurely. The normal response to anaemia is an orderly sequence of EPO production that leads to increased marrow erythropoiesis. Renal

disease usually disrupts this orderly sequence and results in a sub-maximal EPO response to an anaemic stimulus(36).

Iron is a critical body substance, transporting oxygen to tissues via haemoglobin and functioning as a cofactor in a number of enzyme systems. The most common factor that confounds renal anaemia is iron deficiency, whether it is related to or independent of blood loss from repeated laboratory testing, needle punctures, or blood retention in the dialyzer and tubing at the end of each dialysis treatment(37). It has been estimated that 1 to 3 g of iron are lost annually from these causes, and uptake of iron by intestinal mucosal cells and iron retention also may be impaired in dialysis patients(38). Moreover, iron deficiency and chronic inflammation have interplay in contributing to anaemia in chronic kidney disease patients.

Uremia is a chronic inflammatory state, and thus patients with renal failure may develop anaemia and become refractory to EPO because of mechanisms associated with chronic inflammation(39). A significant association has been shown between hyporesponsiveness to EPO and high levels of inflammatory markers in HD patients(40). Hyporesponsiveness to EPO in patients with chronic inflammation often can be explained by functional iron deficiency. This is characterized by apparently insufficient available iron to keep up with the demands of erythropoiesis. The mechanisms of functional iron deficiency may involve increased levels of circulating cytokines that are capable of inducing macrophages of the reticuloendothelial system to more avidly take up and hold on to iron. Cytokines also may decrease endogenous EPO production or decrease the responsiveness of erythroid precursor cells to endogenous or exogenous EPO. In particular, interleukin-1 and tumor necrosis factor have been shown to have both of these effects(41). Recent studies have indicated a potential contribution of hepcidin in dysregulation of iron metabolism in patients with kidney disease(42,43). Hepcidin evolves as a

potent regulator of the body's iron distribution, piloting the flow of iron via, and directly binding to, the cellular iron exporter ferroportin(43). Hepcidin is expressed in the liver, distributed in blood, and excreted in urine. The hepcidin-ferroportin axis dominates the iron egress from all cellular compartments that are critical to iron homeostasis. The gene that encodes hepcidin expression is subject to regulation by proinflammatory cytokines, such as interleukin-6 and interleukin-1, and excessive hepcidin production contributes to the functional iron deficiency and associated anaemia during inflammatory states. Other factors as earlier listed all contribute significantly to anaemia in CKD patients.

Effect of anaemia on cardiac function

Anaemia and hypertension are two major factors contributing to the development of LVH in CKD patients. There are distinctions between the pathophysiology of hypertension and anaemia resulting in LVH. If hypertension is the primary stimulus, LVH arising as a result of hypertension has a direct relationship to systolic or pulse pressure, which is determined by arterial stiffness. This results in increased peripheral resistance and pressure overload which engenders parallel addition of new sarcomeres with a disproportionate increase in ventricular wall thickness and normal chamber radius, thus classified as concentric hypertrophy(44).

However, if the primary stimulus is anaemia, it results in reduced blood viscosity and reduced peripheral resistance which leads to increased venous return and increased cardiac output, and the resulting vicious cycle leads to volume overload. This results in increased diastolic pressure and stress on the myocardium, which in turn leads to increased cardiac chamber and radius with relative increase in wall thickness termed eccentric hypertrophy(44).

Physiologically, left ventricular hypertrophy is primarily an adaptive remodelling process, compensating for an increase in workload placed on the heart with the aim of minimizing ventricular wall stress. Two contrasting models of adaptation may develop depending on the patterns of stress imposed. Pressure overload, caused, for example, by hypertension or aortic stenosis, requires the generation of greater intra-cardiac pressure during ventricular contraction. This is achieved by arraying contractile protein units in parallel. Relatively, an increase in wall thickness and a fall in cavity volume take place. Concentric hypertrophy, as this process is known, leads to decreased diastolic compliance and may place the myocardium at risk of ischemia, even without coronary artery disease. In conditions of volume overload, such as anaemia or aortic incompetence, lengthening of contractile units leads to a physiologically useful increase in systolic stroke volume, according to Starling's Law. Unopposed, this process of left ventricular dilation leads to increased wall tension, a state known to increase oxygen requirements, and myocyte burnout. According to the Law of Laplace, the wall tension of a hollow spherical body is directly proportional to radius and pressure, and inversely proportional to wall thickness. Thus, in states of left ventricular dilation, wall thickening and left ventricular hypertrophy are useful secondary order adaptations that tend to decrease wall tension(45,46).

Subtle signalling changes can lead from physiologic adaptation to pathologic mal-adaptation. With continuing pressure and volume overload, cardiac myocyte apoptosis accelerates. In addition, fibrosis accelerates. Hypertrophy, apoptosis, and fibrosis are influenced by constitutional and genetic factors, hormones, growth factors, and cytokines such as endothelin 1, angiotensin II, insulin-like growth factor, and tumour necrosis factor α. The balance of these

factors and downstream intracellular signals can alter the balance among hypertrophy, apoptosis, and fibrosis(47).

The effects of anaemia on the development of LVH are probably mainly due to the haemodynamic adaptations occurring in anaemic patients. These adaptations, which are thought to begin at higher haemoglobin concentrations in CKD patients than in non-nephropathic patients, include an increased cardiac pre-load and a decreased systemic vascular resistance, namely a decreased cardiac after-load, both of which are responsible for an increase in cardiac output. These cardiovascular responses are appropriate and compensate the inadequate tissue oxygenation secondary to anaemia in the first phase.

However, in the long term, maintenance of a high cardiac output state could lead to remodelling of the left ventricle, including dilation of the ventricle in response to chronic volume overload and thickening of the left ventricular wall aimed at decreasing the high wall tension of the dilated ventricle. Nevertheless, other potential factors, together with anaemia, are likely to contribute to the development of LVH in CKD patients. Hypertension, leading to increased cardiac afterload, is probably a major contributor to the development of LVH, whereas volume overload can also be caused by vascular accesses for haemodialysis. Furthermore, additional potential factors, such as older age, diabetes, hyperparathyroidism and uraemia per se, can all further contribute to the high occurrence of LVH in CKD patients(1).

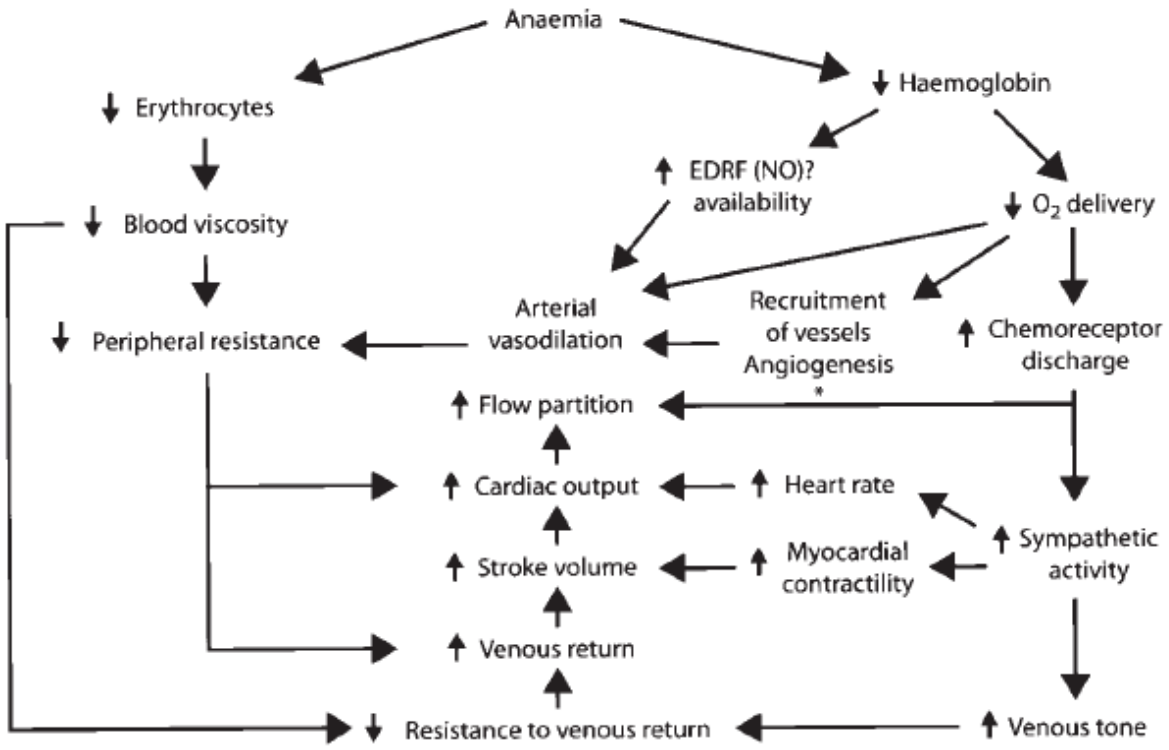

Figure 1: Pathophysiology of Anaemia on cardiac function(44)**. Reproduced by permission.**

<u>Prevalence and pattern of LVH in CKD patients and impact on morbidity and mortality</u>

A study in Enugu(24) which assessed left ventricular hypertrophy in African black patients with CKD reported the prevalence of anaemia to be 98.86%, while prevalence of LVH among CKD patient was 95.5%, and pattern of hypertrophy revealed eccentric dilatation to be commoner with a prevalence of 54.6%, followed by concentric LVH as 40.9%, and concentric remodelling as 1.1%. The strong predictors for LVH in this study were systolic hypertension and male gender(24). However, this study was not focused on anaemic CKD patients, and also patients on antihypertensive were excluded, also the echocardiographic method for assessing LVH used was Penn conventional method which underestimates LV mass(48). Therefore, this study may not have accurately estimated the prevalence of LVH, and its geometric pattern. Furthermore,

another study in Port Harcourt(25) which also assessed LVH among CKD patients reported the prevalence LVH to be 76%, and the prevalence increased from 56% in early stages of CKD to 90% at stage 5 CKD, while anaemia was also common with a prevalence of 81.3%, and was reported to be higher in ESRD patients (87%). This study was also not focused on anaemic CKD patients, and the geometric pattern of LVH was not evaluated.

In the Canadian Multi-Centre cohort study(17) which assessed LV mass and impact of anaemia amongst CKD patients reported the prevalence of LVH to be 36% at the early stage of CKD, and LV mass at baseline was 20% above the general population , while a 12 month follow up revealed a significant increase of 25% above the general population and prevalence of LVH increased to 74% at ESRD, 32% of patients had left ventricular dilation, and 15% had systolic dysfunction(11,17). Furthermore, there was a significant haemoglobin level at which 0.5g/dl decrease in haemoglobin predicted a $10g/m^2$ rise in LV mass, although systolic hypertension was also identified as one of the predictors of LVH, but concluded that decline in haemoglobin level was a stronger predictor. Foley et al(49) also predicted haemoglobin level to correlate with LVH in dialysis patients with each 1g/dl decrease in haemoglobin being associated with 50% increase risk of left ventricular dilatation and systolic dysfunction, this has been corroborated in another study(50).

However, the development, severity, and persistence of LVH are strongly associated with mortality risk and cardiovascular events in CKD and in ESRD. Zoccali et al.(51) reported a 50% mortality risk and more than 85% risk in cardiovascular event at 3 year in patients in the highest percentiles of change in LV mass treated with conventional haemodialysis. While London et al.(52) reported a 10% decrease in LV mass (approximately 29 g) translating into a 28% decrease in mortality risk from cardiovascular events over a 5-yr follow-up of a cohort of patients treated

with haemodialysis (1.0g decrease in LV mass translated to a 1.0% decrease in CV mortality risk). Other literatures have also indentified LVH has as an independent risk factor for mortality in dialysis patients with a relative risk of 2.9 for all-cause mortality, and 2.7 for cardiac mortality(53).The predictors of LVH regression reported in this study included adequate control of systolic BP, a lower pulse wave velocity (a surrogate measure or aortic distensibility), and a greater rise in haemoglobin levels(52). Worthy of note is that failure to regress LVH over time was related to unchanged aortic distensibility and to severe anaemia(52).

LVH and fibrosis, could play an important role in the triggering of lethal arrhythmia(54). It must be mentioned that sudden cardiac death (SCD) can be caused by ventricular arrhythmias (primarily ventricular fibrillation), which can arise spontaneously from abnormal electrical conduction and/or sudden ischemic events, such as a coronary thrombotic occlusion resulting from rupture of a "vulnerable" lipid-rich atheromatous plaques. The presence of LVH almost doubled the risk of sudden cardiac death in the group of patients enrolled in the 4D trial, which assessed the effect of artovastatin in diabetic patients on haemodialysis(55). Potential additional substrates for genesis of fatal ventricular arrhythmias in CKD patients include metabolic (*e.g.*, hyperphosphatemia, hyperparathyroidism) and electrolyte (potassium, pH) alterations, sympathetic over activity, autonomic nerve dysfunction, concomitant obstructive sleep apnea, acquired or hereditary QT interval prolongation, systolic and/or diastolic dysfunction, acute volume overload, and acute myocardial ischemia(54). Therefore, it is of primary importance to define, and possibly even correct, any reversible risk factor for the development of LVH as early as possible in the course of CKD.

Diagnosis of left ventricular hypertrophy

Left ventricular hypertrophy is a histologic entity. Myocardial biopsy is rarely performed, so it is rarely possible in practice to prove that maladaptive pathologic features, especially fibrosis, are present. Instead, LVH is diagnosed using measurements of left ventricular size, geometry, and function.

Echocardiography is non-invasive and provides an accurate assessment of each of these parameters. For each parameter, superior techniques exist but are not routinely used because of cost, unavailability, or invasiveness. Therefore, magnetic resonance imaging seems to be a superior technique to assess left ventricular mass and cavity volume in patients with end-stage renal disease (ESRD)(56). Similarly, cardiac function is measured better with invasive techniques. In practice, echocardiography is a reasonable overall tool and is highly suited for longitudinal research studies.

Left ventricular mass as been shown to increase with age, and also influenced by gender (male gender) and body size(57). Therefore, for comparative purposes, left ventricular mass usually is normalized to some index of body size(57). However, normalization to body surface area is the most commonly used method. In the healthy, adult, according to American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACI), the upper limits of normal are 115 g/m^2 for males and 95 g/m^2 for females(57). Left ventricular hypertrophy is defined as left ventricular mass index (LVMI) more than 115g/m^2 in males and greater than 95g/m^2 in females(57). It is classified into 3 groups based on left ventricular mass index and relative wall thickness (RWT) and it includes concentric hypertrophy where there is increased LVMI and RWT > 0.42, eccentric hypertrophy in which there is increased LVMI and RWT< 0.42, and concentric remodelling has normal LVMI and RWT is > 0.42(57).

Anaemia correction and impact on left ventricular mass

Anaemia is known to be an important, potentially modifiable, risk factor for the development of LVH in patients with CKD; its correction should improve cardiovascular status, and consequently long-term survival in this population (58). A number of small, non- randomized studies have analyzed changes in cardiac morphological parameters after correction of anaemia with recombinant human erythropoietin in CKD patients prior to dialysis and have found that at least partial regression of LVH is possible.(58) Portoles et al(21), first documented that partial correction of anaemia with recombinant human erythropoietin can induce a significant decrease in LVH. In a cohort of 11 pre-dialysis patients prospectively studied over a 3 month follow-up; result of the study showed a decrease in mean left ventricular mass index from 178.2 g/m2 to 147.3 g/m2 after partial correction of anaemia (while haematocrit levels increased from 26.3% to 34.7%)(21).

Furthermore Hayashi et al.(22) also documented a decrease in LV mass index among 9 pre-dialysis patients with a mean haematocrit level of 23.6% at base line (from a mean LV mass index baseline value of 140.6 g/m^2 to 126.9 g/m^2) after partial correction of anaemia (achieved haematocrit 32.1%) at 4 months, and there was a further significant decrease (111.2 g/m^2, P = 0.0108) after normalisation of haematocrit (achieved haematocrit 39.1%) following a 12 months(22). Similar result was reported by Ayus et al.(4) which recruited 40 anaemic patients in stage 4 and 5 CKD with a control arm, who were placed on erythropoietin and were followed up for 6 months revealed a significant decline in LV mass index(4)**.** A meta-analysis(23) of CKD patients with severe anaemia have confirmed a significant reduction in LV mass among pre-dialysis patients even when lower target of haemoglobin (<12g/dl) with lesser cardiovascular complications from erythropoietin as compared to higher target (>13g/dl)(23).

In dialysis patients, studies analysing the effectiveness of anaemia correction in inducing LVH regression have shown different results, mostly depending on the characteristics of the studied populations. Although small-sized, prospective studies have shown partial regression of LVH after partial correction of anaemia with recombinant human erythropoietin (59–60). The Canadian Normalization of Haemoglobin Study(61) failed to confirm these findings. This was a multicentre trial of 146 haemodialysis patients with LVH but without clinical evidence of symptomatic heart disease, who were randomly assigned to achieve different target haemoglobin levels; even the complete correction of anaemia failed to induce a significant regression of well established LVH (61).

Similar results was reported in the CREATE study (Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin Beta)(62). Although these studies were focused on ESRD patients on maintenance haemodialysis, such patients may not have achieved significant regression of left ventricular mass because they are prone to other attendant risk of volume overload from repeated blood transfusion, and other haemodynamic disturbance from arteriovenous fistula which result in large volume flow return to the heart.

Therefore, taken together, these results suggest that anaemia correction can give the maximum benefit in reducing LVH if it is performed as early as possible in the course of CKD. The low incidence of LVH regression in the uremic patient may be due to long-term exposure to a number of co-morbid conditions, other than chronic volume and pressure overload, contributing to the development of myocardial fibrosis, calcium deposition, increased left ventricular stiffness and atherosclerosis, which are all factors implicated in preventing the reversibility of well-established LVH(1). In other words, it is better to prevent the development of severe cardiac damage rather than trying to reverse it once it is well established(1).

However, it has been established that the recommended target haemoglobin of 11 to 12g/dl among anaemic CKD patients will provide better benefits (on cardiovascular status and improved quality of life), while higher targets has been associated with higher cardiovascular complications such as stroke, vascular access thrombosis and hypertension(6,63)

Anaemia and Quality of Life Among CKD Patients

WHO defines Quality of Life (QoL) as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment(64).

Anaemia is highly prevalent in patients with CKD(65) and several studies have indicated the significant negative impact of anaemia in patients with CKD on QoL(66,67). Anemia in CKD is associated with reduced quality of life and increased cardiovascular disease, hospitalizations, cognitive impairment, and mortality(68). This impact of anaemia on Health-related QoL has been found to improve on therapy with erythropoetin stimulating agents (ESAs)(69). Decline in haematocrit level have also been associated with deterioration in mental, emotional and physical activity, and are significantly worse in anaemic CKD patients compared to patients without anaemia(27,28). Moreover, association between changes in haemoglobin and changes in QoL in patients treated with darbepoetin alfa revealed that improvements in haemoglobin concentration in CKD patients not on dialysis were associated with QoL improvements on scales measuring physical activity, vitality and fatigue(26).

Cardiovascular disease has been shown to be significantly associated with impaired quality of life; specifically in patients with history of congestive heart failure, myocardial infarction and

increased left ventricular mass. These patients reportedly have a worse physical component summary (PCS) as compared to their respective counterparts(7). Therefore early screening for CV risk factors with possible treatment and secondary prevention will contribute to improved quality of life (well-being and functioning)(7,8).

Tools for Assessment of Quality of Life

Several tools have been used to assess health related quality of life (HRQoL) and related concepts of functional status. Among them are the medical outcomes study short form (SF-12 and SF-36), Karnofsky Performance Scale (KPS), The Sickness Impact Profile (SIP), EuroQol and the Quality of Well being Scale (QWB).

Short Form Health survey (SF-36 Questionnaire)

SF-36, looks at quality of life as a multidimensional model, assessing eight different perspectives of HRQOL namely physical functioning; role limitations due to physical health problems; bodily pain; general health; vitality (energy/ fatigue); social functioning; role limitations due to emotional problems; and mental health, which implies psychological distress and psychological well-being(70). It utilizes a 36-item questionnaire, which was constructed as an improvement on the older SF-8 and SF-20 scales(71). This scale has internal consistency reliability of between 62% and 90% for the different domains in haemodialysis patients(72). It also has test-retest reliability of between 60% and 81% for the different domains(73). However, because most domains are subjective, symptoms scoring can be easily exaggerated by the patients.

Karnofsky Performance Status Scale (KPS)

The Karnofsky performance status scale (KPS) focuses on overall physical Quality of Life. It allows patients to be classified based on their functional impairment; it comprises an 11-point scale correlating to percentage values of 0 to 100. The scale ranges from scores of 0 (at death) to 100 which imply full-functional capability to carry out normal daily activities without clinical evidence (symptoms or signs) of disease. A score below 70 represents a functional capacity that requires some assistance, but the patient could still care for most personal needs while that below 50 represent incapacitation that requires hospitalization or institutionalization(71,74). Some of its demerits are the fact that it is independent of the patient's judgment and the fact that psychological state is downplayed.

However, Karnofsky performances scale is the most commonly used health related quality of life instrument for assessment of patients functional capacity(71,74,75). Furthermore, studies in Africa have shown excellent correlation between KPS and SF – 36 in the assessment of health related quality of life among CKD patients(30).

CHAPTER 3

MATERIALS AND METHODS

3.1 STUDY DESIGN

The study was a cross sectional analytical study designed to assess the prevalence and geometric pattern of LVH among anaemic CKD subjects, and the relationship between the severity of anaemia and its impact on their quality of life (physical performance), within a 10 month period (April 2016 to January 2017).

3.2 STUDY POPULATION

The study population were patients with CKD attending the nephrology clinic at Lagos State University Teaching Hospital, which attends to at least 20 CKD patients at each clinic visit and runs two clinics every week.

3.3.1 Inclusion Criteria:

- CKD patients within stages 3 to 5 with anaemia who were within the age range of 18 to 75 years. The patients have been attending nephrology clinic for at least 3 months prior to the study.

3.3.2 Inclusion Criteria for controls:

- CKD patients within stages 3 to 5 without anaemia who were on erythropoietin or blood transfusion within the age range of 18 to 75 years. The patients have been attending nephrology clinic for at least 3 months prior to the study.

3.3.3 Exclusion Criteria are:

- Patients with underlying cardiac disease such as valvular heart disease, congenital heart disease and cardiomyopathy.
- Arteriovenous fistula.
- Patients with features of volume overload (pulmonary oedema, peripheral congestion and congestive cardiac failure).

3.4 SAMPLE SIZE DETERMINATION

The sample size was determined using this formula(76,77):

$$N = \frac{Z^2 \times Pq}{d^2}$$

Z - Standard normal deviate = 1.96 at 95% C.I

P - Proportion of disease (anaemia) in the population (CKD)(24) = 0.9886 which is 98.86%

q - 1-prevalence = 1- 0.9886 = 0.0114

d - Precision = 0.025

$$N = \frac{(1.96)^2 \times 0.9886 \times 0.0114}{(0.025)^2}$$

N = 70,

Also considering 10% of attrition calculation with a total sample size = 78

However, a total sample size of 102 anaemic CKD subjects was used, and controls were 61 CKD subjects without anaemia; with a case: control ratio of approximately 3:2. Control subject were matched for age, gender, and hypertension status, while participants were within the age range of 18 years to 75 years. However, case: control ratio approximately 3:2 was used because of the cost of completing the study.

3.5 SAMPLING TECHNIQUE

A stratified systematic sampling technique was used for the selection of subjects. Patients were stratified into different stages of CKD 3 to 5 based upon their eGFR. A systematic random sampling technique was used to recruit patients, in which every 3rd patient that qualified were recruited into CKD subjects with anaemia group until the sample size was achieved. This also involved recruitment of at least 26 patients into each stages of CKD 3 to 5.

However, CKD subjects without anaemia were recruited using stratified random sampling technique into CKD stages 3 to 5, and simple random sampling technique was used to recruit them into each of the stages, and they were matched for age and gender. This technique was employed because of the challenges of achieving equal proportion of subjects in each of the stages especially in stage 5 CKD.

3.6 STUDY INSTRUMENTS

Mercury sphygmomanometer (Accoson's brand)

Echocardiography machine (General Electric Vivid Q)

Hansen's weighing scale

Stadiometer

Karnofsky Performance scale

Erba XL 600 Automated analyzer

3.7 STUDY PROCEDURE

Recruited subjects were stratified into appropriate CKD stages 3-5, in accordance with their eGFR (MDRD). Clinical history was obtained using a structured questionnaire, and this included subjects bio-data (age, sex), history of hypertension with duration, history of CKD with duration. Past medical history of coronary artery disease, cardiac dysrrhythmia, and congestive cardiac failure was sorted. Social history included intake of alcohol, smoking habit, and family history of cardiovascular disease was enquired from participants. Drug history entailed use of antihypertensive, erythropoietin therapy and duration, antiplatelet, vitamin D supplement, calcium and phosphate binders and lipid lowering agents was documented in the questionnaire.

BMI assessment

Examination involved weighing of subjects using a Hansen's weighing sale. Subjects wore light clothes with no footwear and measurements were approximated to the nearest 0.1kg. Height was measured with seca stadiometer with the subject standing erect backing the stadiometer such that the occiput, back and heel makes contact with the stadiometer and measurement was to the nearest 0.1meters. Body mass index (BMI) was calculated using the formula: weight (kg)/ Height^2 (m^2). Body surface area (BSA) was calculated using Dubois formula BSA = $(0.0001)\times(71.84)\times(\text{weight}^{0.425})\times(\text{height}^{0.725})$, with weight in kilograms and height in centimeters(79).

Blood pressure assessment

The blood pressure was measured after five to ten minutes of rest using the Accoson's sphygmomanometer with appropriate cuff size (80% encircling the arm). Subjects were seated comfortably, and the arm was supported at the level of the heart. Blood pressure was measured in both arms, and the average of two blood pressure reading in the arm with the higher blood pressure was recorded as the subject's blood pressure. Cardiovascular, respiratory, abdominal and central nervous systems were assessed as documented in the questionnaire.

Quality of life assessment

The Karnofsky Performance Status (KPS) questionnaire was used for the assessment of quality of life. This questionnaires was administered by trained interviewers.

Echocardiography

Transthoracic echocardiography (M-mode, two dimensional and Doppler) was performed with the General electric vivid Q echocardiographic machine, using 3.5 MHz phased array probe (cardiac probe) transducer. All patients underwent two dimensionally guided 2D, M-mode echocardiogram and Doppler recording. Linear internal measurements of the left ventricular wall and chamber size was measured through the two dimensional mode which was translated to the M-mode echograms, perpendicular to the left ventricular long axis, and measured at the level of the mitral valve leaflet tips, and images were frozen to take measurement. Electronic callipers was positioned on the interface between myocardial wall and cavity and the interface between wall and pericardium following the American Society of Echocardiography and the European Association of Cardiovascular Imaging convention (ASE/EACI)(57).

Two cardiologists read the echocardiograms to reduce intra-observer bias. Left ventricular mass was calculated by using an anatomically validated formula American Society of Echocardiography and the European Association of Cardiovascular Imaging convention (ASE/EACVI)(57):

LV mass (g) = $0.8(1.04(IVS + LVID + PWT)^3 – LVID^3) + 0.6g$.

(Where IVS= interventricular septal thickness, PWT= posterior wall thickness in diastole LVID= left ventricular internal diameter, all measurement taken in diastole).

Left ventricular mass index (LVMI) was calculated by dividing the left ventricular mass in grams by body surface area(57).

Relative wall thickness (RWT) was calculated with the formula(57):

(2 × posterior wall thickness)/(LV internal diameter at end diastole).

Left ventricular systolic function (ejection fraction) was determined using Simpson's biplane method(57) = (End Diastolic Volume(EDV) – End Systolic Volume (ESV))/ End Diastolic Volume(EDV) × 100

3.7.1 Sample Collection

A total of 10mls of venous blood was collected from the antecubital fossa of each subject. Samples for fasting lipid profile was 4mls which was collected while the patient fasting overnight for at least 8 hours into a plain bottle, while blood for random blood glucose of 1ml was collected in fluoride oxalate bottles, blood for haemoglobin was 2mls collected into ethylenediaminetetraacetic acid (EDTA) bottle, and sample for creatinine was 3mls, which was collected into lithium heparin bottle.

Investigations done included: haemoglobin, random blood sugar, fasting lipid profile (total cholesterol- TC, high density lipoprotein- HDL, low density lipoprotein- LDL, and triglycerides- TG), serum creatinine and echocardiography

3.7.2 Biochemical Analysis

Samples were separated and stored at freezing point (0^0C) in a freezer until all batches of samples were collected. Samples were centrifuged at 350rpm for 5 minutes, the serum separated and analyzed.

3.7.3 Laboratory Analysis

- Serum Creatinine was determined by the modified Jaffe reaction using alkaline picrate and standardized with the National Kidney Disease Education Program (NKDEP) Laboratory Working Group protocol using Erba XL 600 Automated analyzer(80).
- Urea was determined by enzymatic (urease) colorimeteric method was analyzed using Erba XL 600 Automated analyzer(81).
- Electrolytes were analyzed by ion selective electrodes SFRI Park ISE 6000 automated analyzer(82).
- Serum cholesterol was analysed using enzymatic (cholesterol oxidase) colorimetric method(83).
- Serum triglyceride was analysed using enzymatic (glycerol kinase) colorimetric method(84).

3.8 MAIN OUTCOME MEASURES/ DEFINITION OF TERMS

Hypertension was defined as blood pressure greater than or equal to 140/90 mmHg, taken on at least two occasions and/ or use of antihypertensive therapy(85).

Estimated glomerular filtration rate was estimated using Modification of Diet in Renal Disease (MDRD-4) formula which is accurate for GFR estimation(31) which is as follows

GFR (mL/min/1.73 m^2) = 175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if black).

Chronic kidney disease was defined as abnormalities of kidney structure or function present for more than 3 months with implication for health(31). And was classified into the different stages 3 to 5 of chronic kidney disease as follows: stage 3 with eGFR of 30 – 59 ml/min/1.73m^2, stage 4 with eGFR of 15 – 29 ml/min/1.73m^2, stage 5 with eGFR of < 15 ml/min/1.73m^2 (31) .

Left ventricular hypertrophy was defined in absolute terms as Left ventricular mass index >115 g/m^2 in men and >95 g/m^2 in women(57).

Left ventricular geometric pattern was classified as follows: Eccentric hypertrophy was defined if the relative wall thickness (RWT) less than or equal to 0.42 in the presence of LVH, while concentric hypertrophy was defined as RWT greater than 0.42 in the presences of LVH, and concentric remodelling was defined as RWT greater than 0.42 in the absences of LVH, and normal left ventricular geometry was defined as RWT less than or equal to 0.42 in the absence of LVH(57).

Left ventricular systolic function was classified as follows: Reference range for males was categorized as; normal was defined as left ventricular ejection fraction (LV EF) ≥ 52%, mildly

abnormal was defined as LV EF between 41 – 51%, moderately abnormal was defined as LV EF between 30 – 40% and severely abnormal was defined as LV EF < 30%(57).

Reference range for females was categorized as; normal was defined as left ventricular ejection fraction (LV EF) ≥ 54%, mildly abnormal was defined as LV EF between 41 – 53%, moderately abnormal was defined as LV EF between 30 – 40% and severely abnormal was defined as LV EF < 30%(57).

Anaemia was defined as haemoglobin (Hb) concentration is less than 13.0 g/dl (<130 g/l) in males and less than 12.0 g/dl (<120 g/l) in females(6). Haemoglobin was converted to packed cell volume by multiplying by a factor of 3 (78).

Impaired quality of life: This was determined using Karnofsky scoring scale. Scores are scaled from 0 – 100, with 0 representing the lowest possible level of functioning / maximum disability and 100 representing the highest possible level of functioning / no disability. Scores less than 80 was defined as impaired quality of life, scores between 80 – 100 was categorized as normal, while scores between 50 – 70 was categorized as limited physical capacity, while scores < 50 was categorized as disabled (74).

Obesity was defined as BMI ≥ 30kg/m^2.(86)

3.9 DATA ANALYSIS

This was computed using statistical package for social science (SPSS) version 20. Continuous variables which includes age, body surface area, body mass index, serum creatinine, eGFR, systolic and diastolic blood pressure, left ventricular mass index, haemoglobin concentration and quality of life assessment score were described by calculating the means and standard deviation, and was compared using unpaired student t test in which normal distribution is assumed.

Categorical variables which includes sex, stage of CKD, left ventricular hypertrophy and left ventricular geometric pattern were analysed using percentages and was compared using Chi squared test appropriately. Analysis of variance (ANOVA) was used to compare means across groups. Pearson's correlation was used to assess the relationship between LVMI and selected variables (age, sex, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), packed cell volume, eGFR, and QoL assessment score), while linear regression was used to control for confounders. Confidence levels was set at $p<0.05$ and taken to be statistically significant and confidence interval was set at 95%. Microsoft Excel was used to produce charts.

3.10 ETHICAL APPROVAL

Ethical approval was obtained from the Health Research Ethics Committee of Lagos State University Teaching Hospital Ikeja, before the commencement of the study. The respondents were assured of strict confidentiality regarding all the information obtained throughout the study period. Written and verbal informed consent was obtained from all respondents before data collection.

CHAPTER 4

RESULTS

4.1 Baseline socio-demographic profile of subjects and controls

A total of one hundred and sixty three subjects were recruited which included one hundred and two anaemic CKD subjects and sixty one CKD subjects without anaemia as controls. However, only ninety three subjects and fifty seven controls completed echocardiography to complete their study session. The mean age of anaemic CKD subjects was 54.04 ± 14.47 years, while those of controls was 54.92 ± 15.67 years, and this was not significantly different ($t = -0.364$, $p = 0.717$). The gender distribution among anaemic CKD subjects, showed male was 53 (52%) and female 49 (48%), while among controls male was 31(50.8%), and female was 30(49.2%), and was not significantly different ($X^2 = 0.20$, and $p = 0.888$), while other socio-demographic parameters are as represented in table 1.

Table 1: Baseline socio-demographic profile of subjects and controls

Parameters	Anaemic CKD n(%)	Control n(%)	X^2	p- value
Age (mean ± SD)	54.04 ± 14.47	54.92 ± 15.67	-0.364[a]	0.717
Gender				
Male	53(52)	31(50.8)	0.020	0.888
Female	49(48)	30(49.2)		
Marital Status				
Single	9(8.9)	5(8.2)	1.701	0.637
Married	83(82.2)	50(82)		
Divorced	0(0)	1(1.6)		
Widow	9(8.9)	5(8.2)		
Occupation				
Unemployed	13(12.9)	10(16.4)	3.695	0.594
Unskilled	25(24.8)	19(31.1)		
Skilled	39(38.6)	18(29.5)		
Professional	8(7.9)	7(11.5)		
Retired	14(13.9)	7(11.5)		
Student	2(2)	0(0)		
Level of Education				
None	6(5.9)	4(6.5)	1.178	0.758
Primary	19(18.8)	14(23)		
Secondary	38(37.6)	18(29.5)		
Tertiary	38(37.6)	25(41)		
Age				
< 40 years	17(16.7)	14(23)	5.773	0.056
40 – 59 years	46(45.1)	16(26.2)		
≥ 60 years	39(38.2)	31(50.8)		

a: Statistics derived with t- test

4.2 Aetiology of chronic kidney disease among subjects and controls

The aetiology of CKD revealed hypertension 68(41.7%), diabetes 34(20.9%), and chronic glomerulonephritis 19(11.7%) as the most common cause of chronic kidney disease, while the least common were congenital abnormality (left renal aplasia), renal artery stenosis and chronic hepatitis B associated nephropathy which were 1(0.6%) each others are as represented in figure 2.

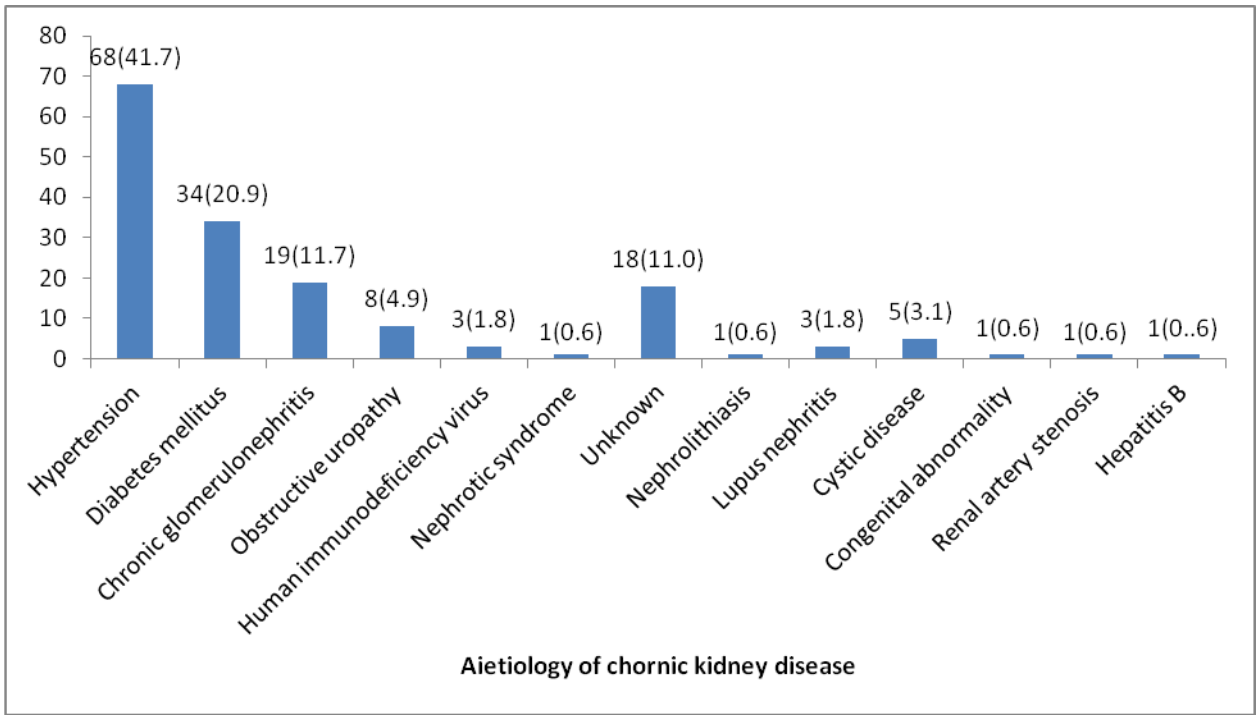

Figure 2: Aetiology of chronic kidney disease among participants

4.3 Baseline clinical profile of subjects and controls

The mean duration of CKD among anaemic CKD subjects was 3.41 ± 5.22 years and controls was 3.09 ± 2.57 years, (t = 0.442 and P = 0.659). While the frequency of hypertension among subjects was not significantly different 87(85.3%) versus 53(86.9%) among controls respectively, with $X^2 = 0.08$, and P = 0.778, other clinical profile are as represented in table 2. The distribution of participants within the stages of CKD is also as shown in table 2.

Table 2: Baseline clinical profile of subjects and controls

Parameter	Anaemic CKD mean ± SD	Control mean ± SD	t	P- value
Duration of hypertension (years)	9.49 ± 9.60	10.53 ± 10.60	-0.596	0.552
Duration of diabetes (years)	9.31 ± 6.39	14.50 ± 11.09	-1.644	0.108
Duration of CKD (years)	3.41 ± 5.22	3.10 ± 2.57	0.442	0.659
Weight (kg)	69.85 ± 15.65	73.26 ± 16.66	-1.314	0.191
Height (m)	1.66 ± 0.09	1.65 ± 0.09	0.534	0.594
Body mass index (kg/m^2)	25.34 ± 5.49	26.98 ± 6.17	-1.766	0.079
Systolic blood pressure (mmHg)	144.13 ± 27.01	147.33 ± 28.87	-0.706	0.481
Diastolic blood pressure (mmHg)	83.40 ± 15.36	86.75 ± 15.78	-1.318	0.189
Body surface area (m^2)	1.77 ± 0.20	1.80 ± 0.21	-0.530	0.958
Stages of chronic kidney disease				
Stage 3 n(%)	30(29.4)	41(67.2)	29.699[a]	<0.001
Stage 4 n(%)	32(31.4)	17(27.9)		
Stage 5 n(%)	40(39.2)	3(4.9)		
Dialysis				
Yes n(%)	17(16.8)	1(1.6)	8.888[a]	0.003
No n(%)	84(83.2)	60(98.4)		
Blood pressure control				
Controlled n(%)	55(55.6)	25(41.7)	2.88[a]	0.90
Uncontrolled n(%)	44(44.4)	35(58.3)		
Body mass index (kg/m^2)				
< 18	6(5.9)	2(3.3)	1.592[a]	0.661
18 – 24.9	48(47.5)	25(41.0)		
25 – 29.9	28(27.7)	21(34.4)		
>30	19(18.8)	13(21.3)		

BMI; Body mass index, SBP; Systolic blood pressure, DBP; Diastolic blood pressure, BP; Blood pressure, BSA; Body surface area, a: statistics result derived with chi square test.

4.4 Clinical characteristics and drug profile of subjects and controls

The overall prevalence of hypertension was 140 (85.9%) with 95% C.I = 80.53 – 91.25, while the overall prevalence of diabetes was 43(26.4%) with 95% C.I = 13.60 – 25.90. The overall prevalence of obesity among participants was 32(19.8%) with 95% C.I = 13.52 – 25.75. The prevalence of hypertension among anaemic CKD subjects was 78(85.3%) while among control was 53(86.9%), with no significant difference $X^2 = 0.08$ and $p = 0.778$. The frequency of antihypertensive use was similar among both study groups, which was 80(78.4%) and 47(77%) among both anaemic CKD subjects and controls respectively with $X^2 = 0.042$ and $p = 0.837$. Other medication usage, are shown in table 3.

Table 3: Clinical characteristics and drug profile of subjects and controls

Parameter	Anaemic CKD n(%)	Control n(%)	X^2	p- value
Hypertension				
Yes	87(85.3)	53(86.9)	0.080	0.778
No	15(14.7)	8(13.1)		
Antihypertensive Use				
Yes	80(78.4)	47(77)	0.042	0.837
No	22(21.6)	14(23)		
Diabetes				
Yes	37(36.3)	6(9.8)	13.739	<0.001
No	65(63.7)	55(90.2)		
Anti-diabetic Use				
Yes	28(27.5)	5(8.2)	8.764	0.003
No	74(72.5)	56(91.8)		
Anti-platelet Use				
Yes	41(40.2)	11(18)	9.406	0.002
No	61(59.8)	50(82)		
Anti-lipid use				
Yes	45(44.1)	19(31.1)	3.036	0.081
No	57(55.9)	42(68.9)		
Erythropoietin Use				
Yes	18(17.4)	3(5)	5.653	0.017
No	84(82.4)	58(95)		

4.5 Antihypertensive and anti-diabetic medication profile of subjects and controls

However, among both study group most frequently used anti-hypertensive medication was calcium channel blocker (CCB), which was 70(30.4%) among CKD subjects with anaemia, and 22(15.2%) among CKD subjects without anaemia, but was not statistically significant (X^2 = 3.043, p = 0.693). The most frequently used anti-diabetic agent among CKD subjects with anaemia was sulfonylurea which was 13(32.5%), while among CKD subjects without anaemia the most frequently used anti-diabetic agent was biguanides which was 4(66.6%), and there was no significant difference (X^2 = 5.223, p = 0.389) this are as represent in table 4.

Table 4: Antihypertensive and anti-diabetic medication profile of subjects and controls

Parameters	Anaemic CKD n(%)	CKD without anaemia n(%)	X^2	p – value
Antihypertensive				
Diuretics	46(20.0)	34(23.4)	3.043	0.693
ACE-inhibitor	39(17.0)	22(15.2)		
Calcium channel blocker	70(30.4)	43(29.7)		
Beta blocker	14(6.1)	13(9.0)		
Centrally acting	29(12.6)	19(13.1)		
Angiotensin receptor blocker	32(13.9)	14(9.7)		
Anti-diabetic				
Biguanide	12(30.0)	4(66.7)	5.223	0.389
Sulfonylurea	13(32.5)	1(16.7)		
Glitiazone	3(7.5)	-		
DPP-4-inhibitor	7(17.5)	-		
Alpha glucosidase inhibitors	1(2.5)	-		
Insulin	4(10)	-		

DPP-4-inhibitor: Di-peptidyl peptidase 4 inhibitor

4.6 Biochemical and haematological parameters of subjects and controls

The mean sodium for anaemic CKD subjects was 140 ± 6.51mmol/l, and control was 141.34 ± 7.32mmol/l, without significant difference (t = 1.176, p = 0.241), the mean potassium for anaemic CKD subjects was 4.99 ± 0.81mmol/l, and control was 3.97 ± 0.66mmol/l, with a significant difference (t = -6.590, p < 0.001). The mean packed cell volume(PCV) for anaemic CKD subjects was 28.48 ± 5.37%, and control was 40.51 ± 3.29%, with a significant difference (t = -4.105, p <0.001), while the mean eGFR for anaemic CKD subjects was 22.67 ± 15.21ml/min/1.73m^2 and control was 38.73 ± 14.79ml/min/1.73m^2, with a significant difference (t = -6.590, p <0.001), other biochemical parameters are as represented in table 5.

Table 5: Biochemical and haematological parameters of subjects and controls

Parameters	**Anaemic CKD** **mean ± SD**	**Control** **mean ± SD**	**t**	**p – value**
Sodium (mmol/l)	140 ± 6.51	141.33 ± 7.32	-1.176	0.241
Potassium (mmol/l)	4.99 ± 0.81	3.97 ± 0.66	4.105	< 0.001
Bicarbonate (mmol/l)	19.86 ± 4.58	22.39 ± 3.60	-3.509	0.001
Chloride (mmol/l)	102.41 ± 10.26	101.82 ± 4.83	0.407	0.685
Urea (mg/dl)	103.08 ± 66.13	51.90 ± 26.71	5.720	<0.001
Creatinine (mg/dl)	4.91 ± 4.03	2.37 ± 1.56	4.696	<0.001
Total Cholesterol (mg/dl)	191.16 ± 48.15	206.64 ± 59.63	-1.708	0.090
High density lipoprotein (mg/dl)	53.34 ± 18.69	58.73 ± 20.89	-1.616	0.108
Low density lipoprotein (mg/dl)	117.90 ± 37.32	128.09 ± 48.09	-1.428	0.155
Triglyceride (mg/dl)	112.84 ± 55.05	111.96 ± 52.28	0.095	0.924
Very low density lipoprotein (mg/dl)	21.83 ± 10.32	25.99 ± 15.81	-1.824	0.070
Packed cell volume (%)	28.48 ± 5.37	40.51 ± 3.29	-15.78	<0.001
Fasting blood sugar (mg/dl)	107.36 ± 36.71	103.37 ± 23.91	0.747	0.456
Estimated glomerular filtration rate ($ml/min/1.73m^2$)	22.67 ± 15.21	38.73 ± 14.79	-6.590	<0.001

4.7 Distribution of packed cell volume across stages of chronic kidney disease among subjects and controls

The mean PCV for stage 3, 4 and 5 were 31.54 ± 4.00%, 28.16 ± 5.79% and 26.45 ± 4.98% among subjects respectively, which was significantly different across the group (F = 8.987, p < 0.001), while among controls was 40.64 ± 3.30%, 40.65 ± 3.48% and 38 ± 1.00% respectively, which was not significantly different across the group (F = 0.914, p = 0.406). The 25th, 50th and 75th percentile distribution of PCV among both groups, are as shown in figure 3 and 4.

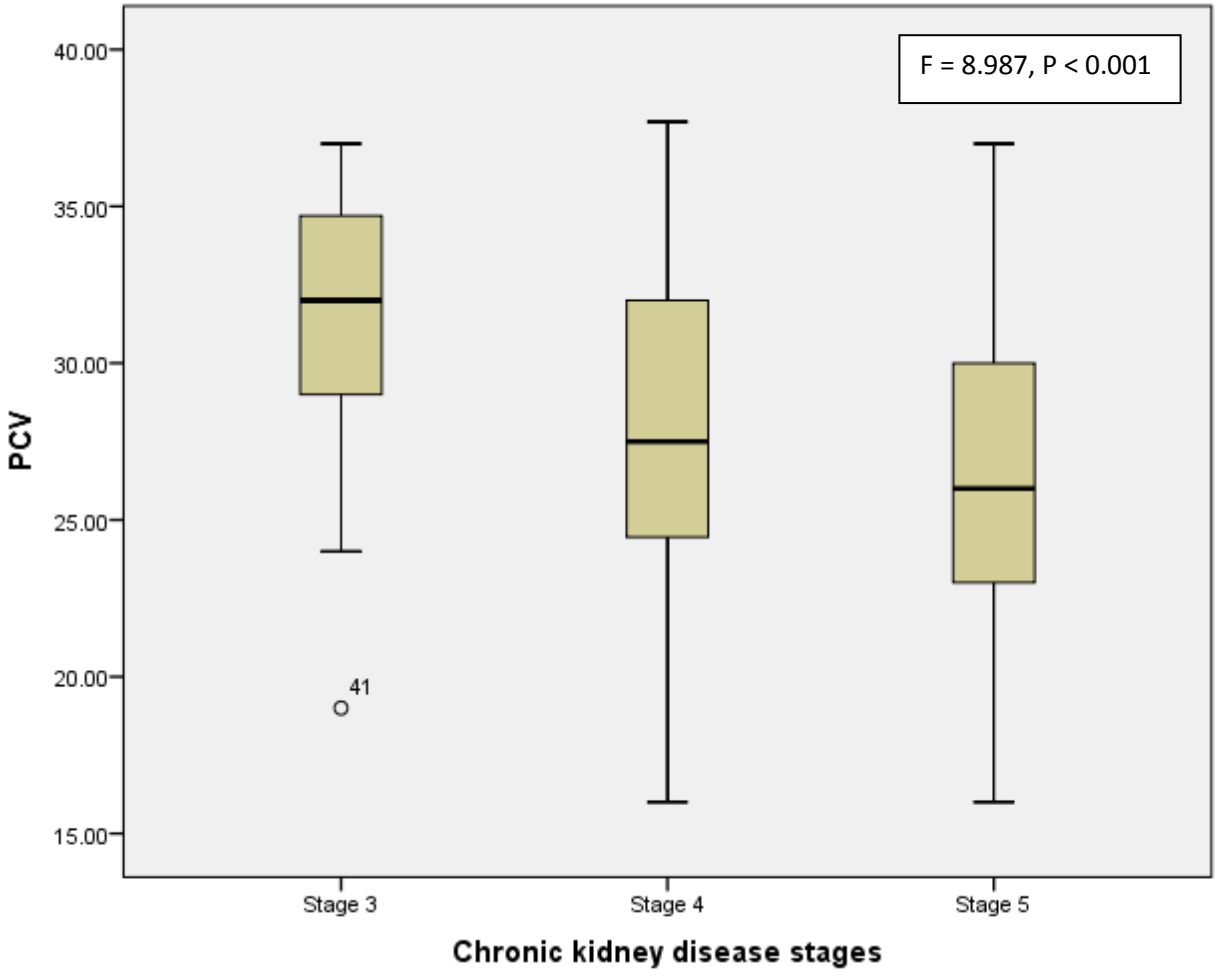

Figure 3: Box and whisker chart plots of the distribution of packed cell volume across stages of chronic kidney disease among subjects.

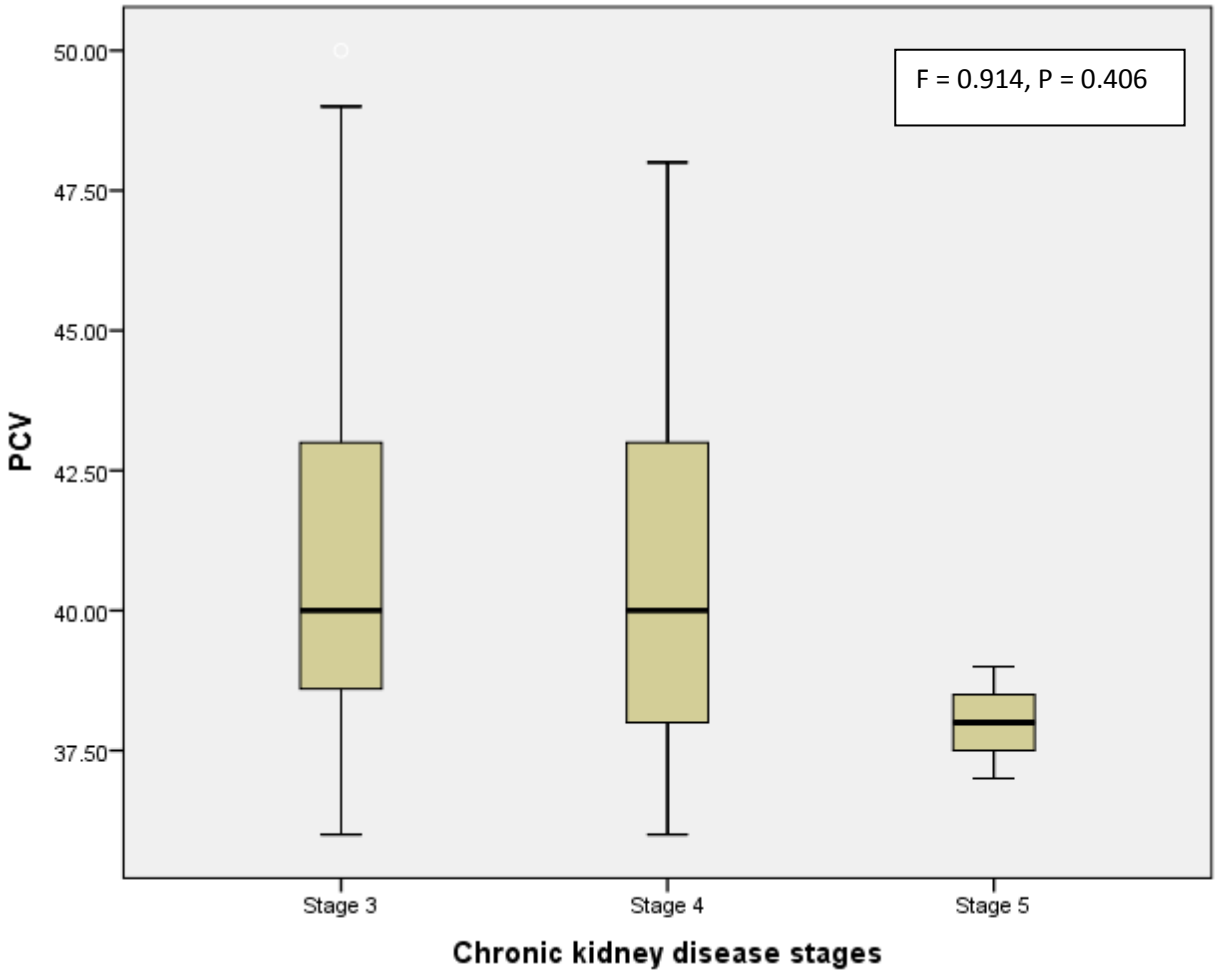

Figure 4: Box and whisker chart plots of the distribution of packed cell volume across stages of chronic kidney disease among controls.

4.8 Frequency of hypertension and anaemia across the stages of chronic kidney disease among subjects and controls

The frequency of hypertension among stage 3 CKD subjects was 59(83.1%), while among stage 5 CKD subjects was 39(90.7%), which was not significantly different ($x^2 = 1.278$ and $p = 0.528$). The frequency of anaemia among stage 3 CKD subjects was 30(42.3%) and among stage 5 CKD subjects was 40(93%), with $x^2 = 29.69$ and $p < 0.001$, this is as represented in table 6.

Table 6: Frequency of hypertension and anaemia across the stages of chronic kidney disease among subjects and controls

Stages of CKD	**Subjects with hypertension**		**Controls with hypertension**		**Subjects**	**Controls**
	Yes n(%)	**No n(%)**	**Yes n(%)**	**No n(%)**	**Anaemia n(%)**	**No anaemia n(%)**
Stage 3 CKD	23(76.7)	7(23.3)	36(87.8)	5(12.2)	30(42.3)	41(57.7)
Stage 4 CKD	27(84.4)	5(15.6)	15(88.2)	2(11.8)	32(65.3)	17(34.7)
Stage 5 CKD	37(92.5)	3(7.5)	2(66.7)	1(33.3)	40(93.0)	3(7.0)
Total	87(85.3)	15(14.7)	53(86.9)	8(13.1)	102(62.6)	61(37.4)
X^2	3.458		1.134		26.69	
P - value	0.177		0.567		< 0.001	

4.9 Quality of Life among subjects and controls

The overall prevalence of impaired QoL was 68(43%), and 95% C.I was 34.35 – 49.60%. The prevalence of impaired QoL was significantly higher among anaemic CKD subjects 57(55.9%) than controls 11(18.3%), with $X^2 = 21.869$, $p < 0.001$, O.R = 5.64, and 95% C.I = 2.65 – 12.02, this is as shown in figure 5.

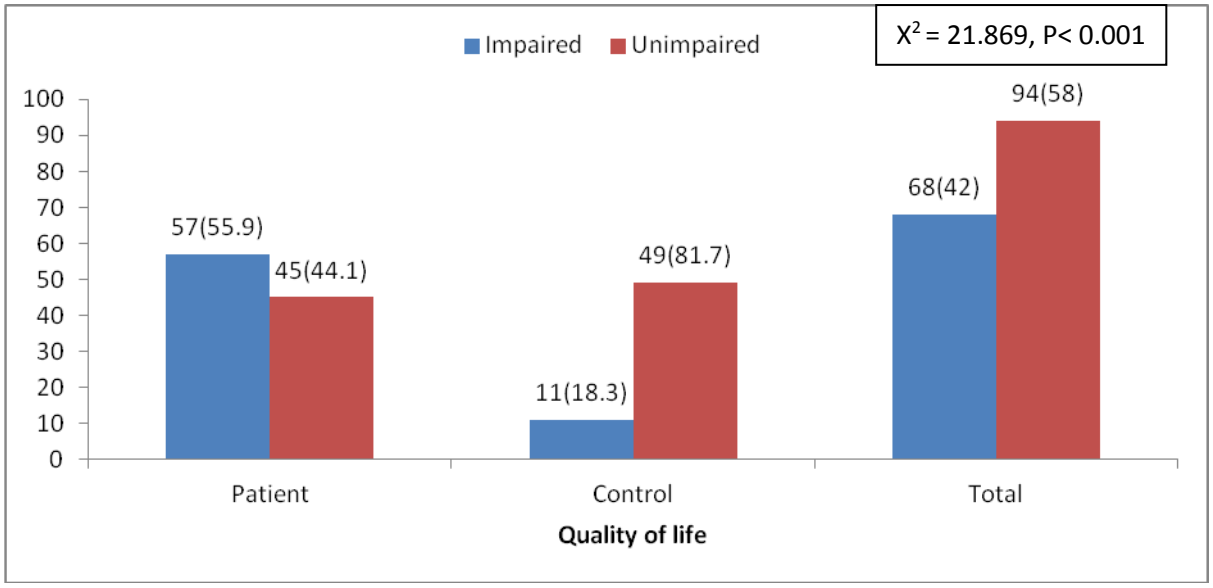

Figure 5: Prevalence of impaired quality of life (physical performance) among subjects and controls

4.10 Comparison of physical performance across stages of CKD among subjects and controls

Furthermore, the mean Karnofsky score decreases with advancing stages of CKD among both groups, but it was statistically significant among subjects (F = 4.104, P = 0.019) as compared to controls (F = 1.967, P = 0.149), which is as shown in Table 7.

Table 7: Comparison of physical performance across stages of CKD among subjects and controls

Stages of CKD	Anaemic CKD mean ± SD	F	p – value	Control mean ± SD	F	p – value
Stage 3	76.33 ± 9.28	4.104	0.019*	85.85 ± 10.94	1.967	0.149
Stage 4	75.81 ± 12.85			83.53 ± 11.15		
Stage 5	68.75 ± 14.36			73.33 ± 5.77		

* p value < 0.05

4.11 Comparison of physical function between each stage of CKD among subjects and controls

The mean physical performance score was significantly lower among anaemic CKD subjects than controls, which was 73.17 ± 12.95 and 84.59 ± 11.04 respectively, with t = -5.739 and p < 0.001. Comparison of mean physical performance between each stages of CKD among both anaemic group and controls shows significantly lower mean score among anaemic group than control at each stages of CKD. Although, physical function was not significantly lower among stage 5 anaemic CKD subjects than controls, because of the small sample size in stage 5 CKD subjects in the control group, this is as represented in table 8.

Table 8: Comparison of physical function between each stage of CKD among subjects and controls

Stages of CKD	Anaemic CKD mean ± SD	Control mean ± SD	t	p – value	95% C.I
Stage 3	76.33 ± 9.28	85.85 ± 10.94	-3.86	<0.001	-14.44 - -4.59
Stage 4	75.81 ± 12.85	83.53 ± 11.15	-2.09	0.042	-15.14 - -0.29
Stage 5	68.75 ± 14.36	73.33 ± 5.77	-0.54	0.589	-21.58 - 12.42
Total	73.17 ± 12.96	84.59 ± 11.04	-5.739[a]	<0.001[*]	-15.34 - -7.49

4.12 Grading of physical limitation among subjects and controls

The degree of physical limitation as categorized by Karnofsky score revealed anaemic CKD subjects have significantly limited physical function than controls ($x^2 = 22.346$, and $p < 0.001$), which is as represented in figure 6, while the relationship between Karnofsky score and clinical and socio-demographic profile are shown in Table 10.

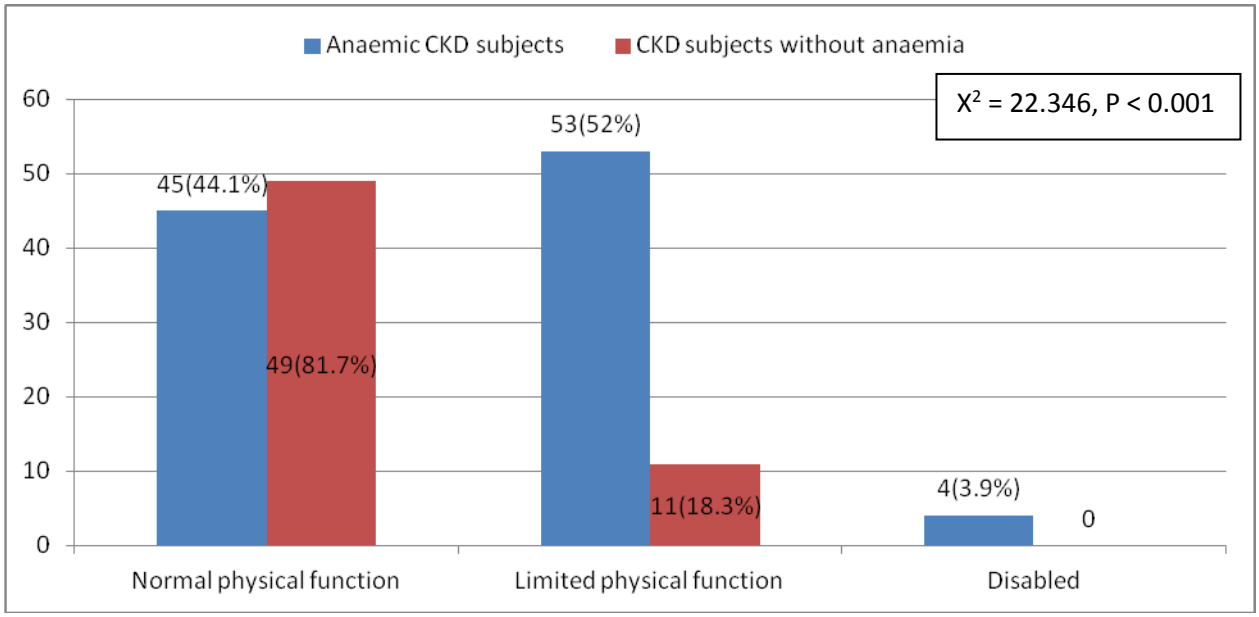

Figure 6: Grading of physical limitation among subjects and controls

4.13 Distribution of physical performance score within the socio-demographic and clinical profiles of subjects and controls

The mean physical performance score was not significantly different between both genders among both study groups. The relationship between Karnofsky performance score and other clinical profile are as represented in table 9.

Table 9: Distribution of physical performance score within the socio-demographic and clinical profiles of subjects and controls

Parameters	Anaemic CKD mean ± SD	t	p – value	Control mean ± SD	t	p - value
Gender						
Male	75.38 ± 11.28	1.79	0.076	86.13 ± 9.55	1.109	0.272
Female	70.82 ± 14.26			83.00 ± 12.36		
Age range						
<40 years	74.12 ± 16.22	0.078[a]	0.925	87.86 ± 10.51	3.006[a]	0.057
40 – 59 years	73.26 ± 11.93			88.13 ± 9.11		
≥60 years	72.63 ± 12.88			81.29 ± 11.47		
Marital status						
Single	68.89 ± 18.33	1.464[a]	0.236	90.00 ± 7.07	0.542[a]	0.656
Married	74.02 ± 11.95			84.40 ± 11.63		
Widow	67.78 ± 14.81			82.00 ± 8.37		
Divorced	-			80.00 ± 0		
Educational status						
None	70.00 ± 20.00	0.651	0.584	72.50 ± 17.08	2.088[a]	0.112
Primary	71.58 ± 14.24			83.57 ± 8.42		
Secondary	71.84 ± 11.59			85.00 ± 7.86		
Tertiary	75.26 ± 12.68			86.80 ± 12.49		
Obese	71.67 ± 16.54	-0.632	0.529	82.31 ± 10.13	-0.838	0.405
Not Obese	73.78 ± 11.93			85.21 ± 11.30		
Controlled Blood pressure	74.07 ± 11.08	0.851	0.397	84.00 ± 10.41	-0.292	0.771

Uncontrolled Blood pressure	71.82 ± 15.14			84.86 ± 11.72		
Diabetes	74.05 ± 10.13	0.520	0.604	80.00 ± 12.65	-1.74	0.287
No Diabetes	72.66 ± 14.39			85.09 ± 10.86		
Antihypertensive						
Yes	73.29 ± 13.37	0.180	0.858	85.11 ± 10.60	0.666	0.508
No	72.73 ± 11.62			82.86 ± 12.66		

a: Statistics derived using Analysis of variance

4.14 Quality of life (physical performance) among stage 5 chronic kidney disease subjects and controls

CKD subjects with anaemia with stage 5 CKD who are on dialysis have significantly higher frequency of impaired quality of life, as compared to stage 5 CKD subjects with anaemia not on dialysis, which was 14(82.4%) and 11(50%) respectively, O.R = 4.14, 95% C.I = 1.09 – 15.73, $X^2 = 4.356$ and p = 0.037. However, because of few subjects with stage 5 CKD without anaemia, effect of dialysis could not be analyzed, this is as shown in figure 7.

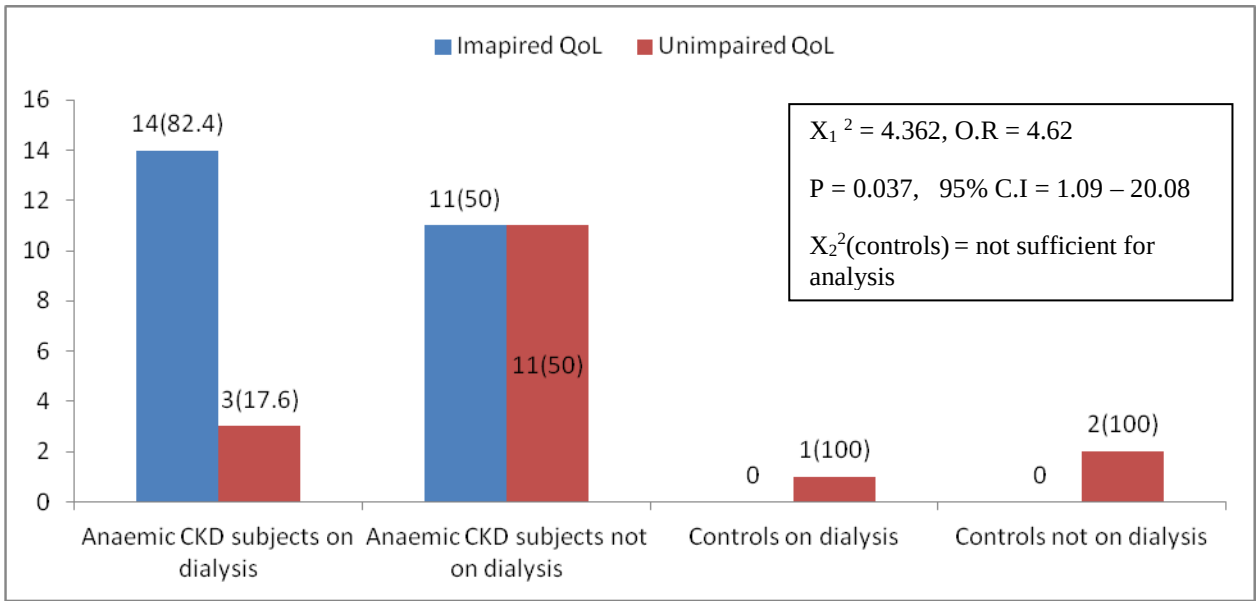

Figure 7: Quality of life (physical performance) among stage 5 chronic kidney disease subjects and controls

QoL; Quality of life, X_1^2; Chi square test for anaemic CKD subject group, X_2^2; Chi square test for control group.

4.15 Relationship between quality of life scores (physical performance) and selected variables among subjects and controls

There was a significantly strong positive correlation between packed cell volume and quality of life (physical performance) score among CKD subjects with anaemia, with correlation coefficient (r = 0.297), and p = 0.003, but a weak positive correlation among controls (r = 0.128 and p = 0.324). There was also a significant strong positive correlation between eGFR and QoL score (r = 0.357 and p = 0.001) among CKD subjects with anaemia, unlike among controls (r = 0.246 and p = 0.056), these is as represented in Table 10.

Table 10: Relationship between quality of life scores (physical performance) and selected variables among subjects and controls

	Anaemic CKD		Controls	
Parameters	**R**	**p – value**	**r**	**p - value**
Packed cell volume	0.297	0.003	0.128	0.324
eGFR	0.357	0.001	0.246	0.056
Ejection fraction	0.524	<0.001	0.442	0.001

Fractional shortening	0.357	0.001	0.353	0.010
Left ventricular mass index	-0.158	0.133	-0.260	0.051
Systolic blood pressure	0.028	0.787	-0.015	0.911
Diastolic blood pressure	0.108	0.291	0.075	0.568
Age	-0.060	0.550	-0.297	0.020
Body mass index	-0.053	0.599	-0.090	0.489

eGFR; estimated glomerular filtration rate

4.16 Echocardiographic findings among subjects and controls

Echocardiographic parameter among participants revealed similar interventricular wall thickness among both studied group 12.34 ± 2.36mm and 12.45 ± 2.87mm, among anaemic CKD patients and controls respectively which was not significantly different (t = -0.274 and p = 0.784). However, there was a significantly higher ejection fraction among controls than anaemic CKD subjects 60.42 ± 12.89%, versus 50.52 ± 10.16% respectively, t = -5.234 and p < 0.001, others are represented in table 11.

Table 11: Echocardiographic findings among subjects and controls

Parameters	**Anaemic CKD mean ± SD**	**Control mean ± SD**	**t**	**p – value**
Interventricular septum thickness in diastole (mm)	12.34 ± 2.37	12.45 ± 2.87	-0.274	0.784
Left ventricular internal diameter in diastole (mm)	47.82 ± 7.53	47.04 ± 8.80	0.583	0.561
Left ventricular internal diameter in systole (mm)	33.40 ± 8.54	33.68 ± 10.91	-0.172	0.864
Left ventricular posterior wall thickness in diastole (mm)	12.33 ± 3.11	12.08 ± 2.91	0.487	0.627
Fractional shortening (%)	26.20 ± 7.56	32.54 ± 10.03	-4.175	<0.001*

Ejection fraction (%)	50.52 ± 10.16	60.42 ± 12.89	-5.234	<0.001*
Mitral peak E wave velocity (m/s)	0.64 ± 0.24	0.59 ± 0.24	1.243	0.216
Mitral peak A wave velocity (m/s)	0.68 ± 0.22	0.59 ± 0.17	2.623	0.010*
E velocity deceleration time (ms)	182.91 ± 55.66	191.40 ± 46.16	-0.871	0.386
Relative wall thickness	0.53 ± 0.16	0.53 ± 0.17	-0.053	0.958
Left ventricular mass (g)	232.54 ± 79.05	226.65 ± 89.63	0.422	0.673
Left ventricular mass index	130.35 ± 41.70	126.49 ± 49.38	0.513	0.609

* $P < 0.05$

E; early transmitral filling, A; late transmitral filling, AV Vmax; aortic valve maximal velocity, PG; pressure, PV Vmax; pulmonary valve maximal velocity, TRV Vmax; tricuspid valve maximal velocity.

4.17 Prevalence and pattern of left ventricular hypertrophy and left ventricular function among subjects and controls

The overall prevalence of left ventricular hypertrophy among CKD subjects was 97(64.7%) with 95% C.I = 56.99 – 72.34. The prevalence of LVH among anaemic CKD subjects was 64(68.8%), while among CKD subjects without anaemia was 33(57.9%), and was not statistically different ($X^2 = 1.845$, $p = 0.174$, O.R = 1.61, and 95% C.I was 0.81 – 3.17).

The most frequent pattern of LVH seen among both groups was concentric LVH which was 50 (53.8%), and 25(43.9%) among both anaemic CKD subjects and controls respectively, with no statistical difference ($X^2 = 2.385$, and $p = 0.497$), others as shown in table 13.

The overall prevalence of left ventricular systolic dysfunction among subjects was 68(45%), with significantly higher frequency among anaemic CKD subjects 58(61.7%), than controls 10(17.5%), with $X^2 = 27.952$ and $p < 0.001$, O.R = 7.57, and 95% C.I = 3.43 – 16.73, these are as shown in table 12.

Table 12: Prevalence and pattern of left ventricular hypertrophy and left ventricular function among subjects and controls

Parameters	Anaemic CKD n(%) N = 93	Control n(%) N = 57	X^2	O.R	p – value	95% C.I
Left ventricular hypertrophy						
Present	64(68.8)	33(57.9)	1.845	1.61	0.174	0.81 – 3.17
Absent	29(31.2)	24(42.1)				
Left ventricular geometry						
Normal	11(11.8)	7(12.3)	2.385		0.497	
Concentric remodelling	18(19.4)	17(29.8)				
Eccentric hypertrophy	14(15.1)	8(14.0)				
Concentric hypertrophy	50(53.8)	25(43.9)				
Systolic function						

Abnormal	58(61.7)	10(17.5)	27.952	7.57	<0.001*	3.43 – 16.73
Normal	36(38.3)	47(82.5)				
Systolic dysfunction severity						
Normal	36(38.3)	47(82.5)	29.726		<0.001*	
Mildly abnormal	41(43.6)	7(12.3)				
Moderately abnormal	14(14.9)	1(1.8)				
Severely abnormal	3(3.2)	2(3.5)				

* $P < 0.05$

4.18 Left ventricular geometric pattern among hypertensive subgroup among subjects and controls

Subgroup analysis of left ventricular geometric pattern among hypertensive subjects in both CKD subjects with anaemia and control groups, shows that concentric left ventricular hypertrophy has the highest frequency among both study group, this is as shown in Table 13.

Table 13: Left ventricular geometric pattern among hypertensive subgroup among subjects and controls

	Anaemic CKD N = 93				**Controls N = 57**			
Left ventricular Geometry	**Hypertensive n(%)**	**No hypertension n(%)**	**X^2**	**p value**	**Hypertensive n(%)**	**No hypertension n(%)**	**X^2**	**p value**
Normal	9(9.7)	2(2.2)	4.23	0.23	6(10.5)	1(1.8)	10.73	0.013
Concentric remodelling	15(16.1)	3(3.2)			15(26.3)	2(3.5)		
Eccentric hypertrophy	10(10.8)	4(4.3)			4(7)	4(7)		

Concentric hypertrophy	46(49.5)	4(4.3)		24(42.1)	1(1.8)

4.19 Prevalence of left ventricular hypertrophy across stages of chronic kidney disease among subjects and controls

The distribution of LVH across the stages CKD showed increasing frequency with advancing CKD stages among both study groups, which is as shown in figure 8 and 9, while relationship between LVH and other clinical parameters are as shown in table 14.

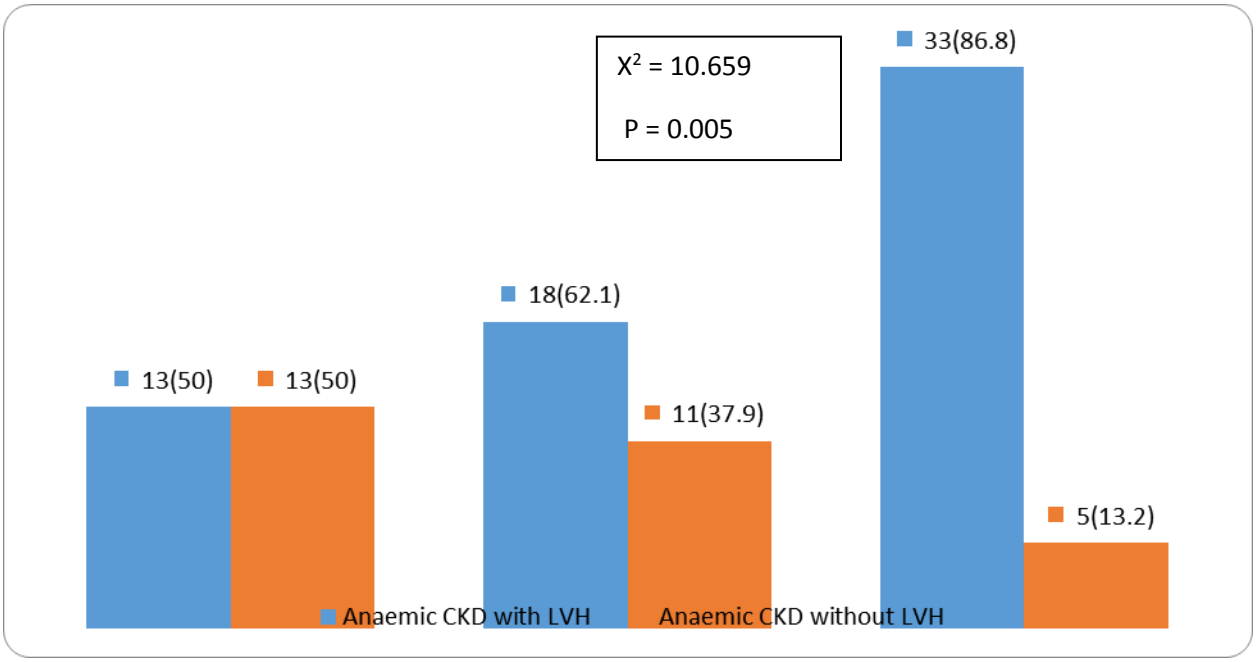

Figure 8: Prevalence of left ventricular hypertrophy across stages of chronic kidney disease among subjects

LVH; left ventricular hypertrophy.

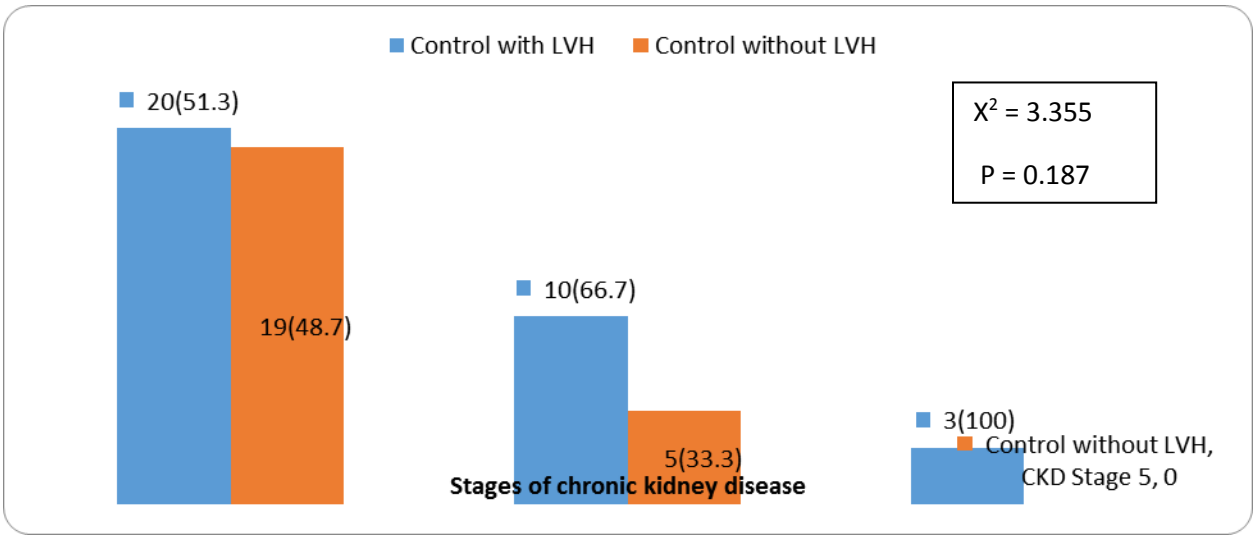

Figure 9: Prevalence of left ventricular hypertrophy across stages of chronic kidney disease among controls

LVH; left ventricular hypertrophy.

4.20 Relationship between left ventricular hypertrophy and clinical variables among subjects and controls

There was a statistically significantly high frequency of LVH among middle age group within the group of subjects with anaemia, which was 30(32.3%) with $X^2 = 6.793$, $p = 0.033$, but there was no significant difference across age group among controls. The relationship between LVH and other clinical variables are as represented in table 14.

Table 14: Relationship between left ventricular hypertrophy and clinical variables among subjects and controls

	Anaemic CKD N = 93				Controls N =57			
Parameter	**LVH**	**No LVH**	**X^2**	**p value**	**LVH**	**No LVH**	**X^2**	**p value**
Age range								
< 40 years	15(16.1)	2(2.2)	6.793	0.033	10(17.5)	4(7)	1.83	0.40
40 – 59 years	30(32.3)	11(11.8)			7(12.3)	8(14)		
≥60 years	19(20.4)	16(17.2)			16(28.1)	12(21.1)		
Gender								
Male	31(33.3)	20(21.5)	3.396	0.065	14(24.6)	16(28.1)	3.27	0.07
Female	33(35.5)	9(9.7)			19(33.3)	8(14)		
Hypertension								
Yes	56(60.2)	24(25.8)	0.373	0.541	28(49.1)	21(36.8)	0.081	0.77
No	8(8.6)	5(5.4)			5(8.8)	3(5.3)		
Diabetes								
Yes	20(21.5)	12(12.9)	0.907	0.341	3(5.3)	1(1.8)	0.516	0.472
No	44(47.3)	17(18.3)			30(52.6)	23(40.4)		
Blood pressure control								
Controlled	32(34.1)	18(19.8)	1.77	0.183	15(26.8)	10(17.9)	0.151	0.698
Uncontrolled	33(35.1))	10(11)			14(25)	17(30.3)		
Dialysis								
Yes	14(15.2)	3(3.3)	1.86	0.173	1(1.8)	0(0)	0.740	0.390
No	49(53.3)	27(28.2)			32(56.1)	24(42.1)		
Quality of life								
Impaired	37(39.8)	15(16.1)	0.30	0.584	8(14.3)	2(3.6)	2.233	0.135
Unimpaired	27(29)	14(15.1)			25(44.6)	22(37.5)		
Antihypertensive								
Yes	49(52.7)	23(24.7)	0.08	0.76	28(49.1)	15(26.3)	3.745	0.053
No	15(16.1)	6(6.5)			5(8.8)	9(15.8)		

4.21 Relationship between left ventricular mass index and selected variables among subjects and controls

There was a significantly strong negative correlation between packed cell volume and left ventricular mass index among CKD subjects with anaemia ($r = -0.345$, $p = 0.001$), while in the control group there was a weak positive correlation ($r = 0.001$, $p = 0.993$). There was also a negative correlation between eGFR and left ventricular mass index among both CKD subjects with anaemia ($r = -0.436$ and $p < 0.001$) and controls ($r = -0.363$, $p = 0.006$), these is as shown in Table 15.

Table 15: Relationship between left ventricular mass index and selected variables among subjects and controls

	Anaemic CKD		Controls	
Parameters	**r**	**p – value**	**r**	**p – value**
Packed cell volume	-0.345	0.001	0.001	0.993
eGFR	-0.436	<0.001	-0.363	0.006
Systolic blood pressure	0.112	0.292	0.098	0.472
Diastolic blood pressure	0.212	0.043	0.078	0.567
Body mass index	-0.084	0.423	0.016	0.909
Age	-0.372	<0.001	-0.008	0.951

4.22 Linear regression for the predictors of left ventricular mass index among participants

Furthermore, linear regression analysis revealed anaemia as a significant predictor of increased left ventricular mass index when compared to other selected variables; this is as represented in Table 16.

Table 16: Linear regression for the predictors of left ventricular mass index among participants

Parameters	Unstandardized Coefficient (β)	Std error	Standardized Coefficient	t	p - value	95% C.I
Constant	152.793	35.897		4.256	< 0.001	81.813 – 223.773
SBP	-0.012	0.177	-0.008	-0.068	0.946	-0.361 – 0.337
DBP	0.452	0.316	0.159	1.433	0.154	-0.172 – 1.077
FBS	-0.139	0.120	-0.096	-1.158	0.249	-0.377 – 0.099
PCV	-1.170	0.495	-0.198	-2.362	0.020	-2.149 – -0.191
Hypertension	-6.495	11.296	-0.049	-0.575	0.566	-28.831 – 15.841

SBP; Systolic blood pressure, DBP; Diastolic blood pressure, FBS; Fasting blood sugar, PCV; Packed cell volume.

4.23 Distribution of ejection fraction distribution across stages of chronic kidney disease among anaemic CKD subjects and controls

However, mean ejection fraction reduces as CKD stages advances among both anaemic CKD subjects and controls. The mean ejection fraction for stage 3, 4 and 5 among anaemic CKD subjects are 54.76 ± 7.79%, 52.02 ± 11.67%, and 46.45 ± 8.97% respectively (F = 6.281 and P =

0.003); while among controls was 63.19 ± 9.87%, 55.25 ± 17.07%, and 50.27 ± 16.08% respectively (F = 3.286 and P = 0.045). The 25th, 50th, and 75th percentile is as shown in figure 10.

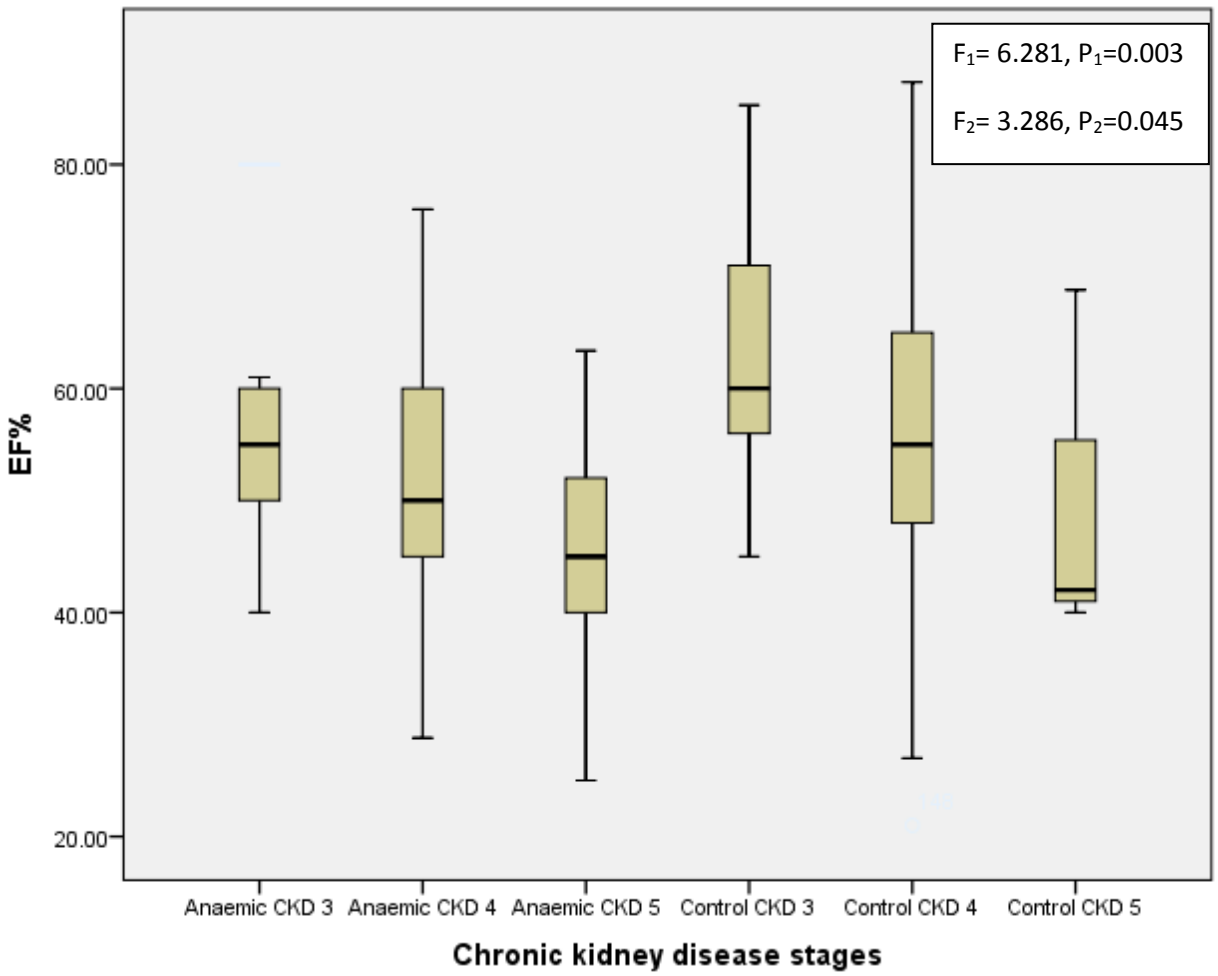

Figure 10: Box and whisker representing distribution of ejection fraction distribution across stages of chronic kidney disease among anaemic CKD subjects and controls.
F_1; Analysis of variances for anaemic CKD subjects group,
P_1; P value for anaemic CKD subjects group,
F_2; Analysis of variances for CKD subjects without anaemia group
P_2; P value for CKD subjects without anaemia group.

Chapter 5

DISCUSSION

Anaemia is a common complication of chronic kidney disease, which has been shown to impair their quality of life(6), and has been identified as a risk factor for the development of left ventricular hypertrophy(44). However, most studies focus on anaemia and its complications, but few studies have focused on the impact of anaemia on quality of life and cardiovascular status of CKD patients.

The aetiologies of CKD in this study revealed hypertension (41.7%), diabetes (20.9) and chronic glomerulonephritis (11.7%) as the leading cause of CKD in this environment, which is similar to other reported studies in this locality(24,25,87-92).

Prevalence and pattern of left ventricular hypertrophy among anaemic CKD patients

The overall prevalence of LVH was 64.7% (95% C.I = 56.99 – 72.34%). The prevalence of LVH was slightly higher among anaemic CKD subjects (68.8%) than CKD subjects without anaemia (57.9%), although not significantly different (P = 0.174). Anaemia may contribute to the development of LVH in CKD patients. This is slightly lower to reports by Adejumo et al(89) and Jesurobo et al(25) who reported a prevalence of 76 and 77.6% respectively, and much lower to reports by Ulasi et al(24) with a prevalence of 95.5%. The explanation for this variance could be attributed to subject selection, in that those studies where primarily focused on hypertensive patients with CKD; furthermore, patients on antihypertensive with good blood pressure control were excluded from their study. However, it was significantly higher than reports by Chijioke et al(93), reporting a prevalence of 27.6%, but used electrocardiogram, which has a lower sensitivity for the detection of LVH, and the subjects were dialysis naive patients.

The overall prevalence of hypertension in this study was 85.9%, but no significant difference in both study groups, with a prevalence of 85.3% versus 86.9%, (P = 0.778) among anaemic CKD subjects and CKD subjects without anaemia respectively. However, LVH analysis of the subgroup of subjects with hypertension revealed a high prevalence of LVH (60.2% and 49.1%) in both anaemic CKD subjects and CKD subjects without anaemia. This pose as a strong confounding variable, in determining the impact of anaemia, therefore, hypertension is also a strong determinant for the development of LVH. However, this was statistically controlled for with a linear regression.

LVH has been shown to be an independent risk factor for cardiovascular mortality, especially among CKD patients(94,95). According to Weiner et al(20), the mortality rate for CKD patients with LVH and anaemia was 80%, as compared to LVH without anaemia (50%), anaemia without LVH was 54%, and those without anaemia and CKD was 31.2%. Other studies(49,94,96) have confirmed the high mortality rate of LVH in CKD patients with relative risk of 1.61 over CKD patients without LVH. Therefore, aggressive and sustained management of factors known to cause LVH may reduce the risk of development of LVH, with resultant improvement in mortality outcome of CKD patients.

Prevalence of LVH increases as CKD stage advance among both groups of studied participants, with a negative correlation between eGFR and LVMI among both anaemic CKD subjects ($r = -0.436$, $p < 0.001$) and CKD subjects without anaemia ($r = -0.363$, $p = 0.006$). This is similar to reports by Adejumo et al(89) and Levine et al(96), that both reported increasing prevalence of LVH as CKD stages advanced. These observations could be attributed to the increasing prevalence of anaemia and hypertension as CKD progresses. For instance in the index study, 42.3% of CKD stage 3 patients in this study were anaemic, and 83.1% were hypertensive,

compared to 93% and 90.7% prevalence of anaemia and hypertension stage 5 CKD respectively. Therefore, a great majority of stage 5 CKD patients are at higher risk of developing LVH, thus underscoring the importance of assessment for LVH especially in patients with advanced CKD(89,96,97).

The most frequent left ventricular geometric pattern seen among both anaemic CKD group and those without anaemia were concentric hypertrophy (53.8% versus 43.9%) and concentric remodelling (19.4% versus 29.8%). These findings are comparable to reports from Foley et al(49), who reported higher frequency of concentric LVH (39.4%) among CKD patients with anaemia. But, this contrary to Ulasi et al(24), who reported higher frequency of eccentric hypertrophy among CKD patients (54.6%). The explanation for the variance in L.V geometric pattern seen in both studies could be attributed to the criterion used for the classification of left ventricular geometry, although their study was focused on hypertensive patient, which should have shown a higher prevalence of concentric LV geometric pattern. The high frequency of eccentric hypertrophy may be explained by the diagnostic criteria used and method of measurement of left ventricular dimensions. Their study used Penn convention(48), but this method has been abolished because of inaccuracy, while the American Society of Echocardiography and the European Association of Cardiovascular Imaging convention(57) is the most recent recommendation, in which LVMI assessment has good correlation with cardiac MRI which is the gold standard. Furthermore, the expected pathophysiology of LVH among CKD patients is usually multifactorial, which includes both traditional (hypertension, diabetes etc) and non-traditional risk factors (uraemic milieu such as anaemia, mineral bone disease, volume overload, aterio-venous fistula and others); although, anaemia usually present with left

ventricular dilatation(44), but the expected outcome of left ventricular geometric pattern may not be attributable to a single risk factor such as anaemia alone(44,49,96).

However, in this present study, 14.6%, of participants were on erythropoietin therapy, the explanation for this low prevalence especially in the control group is not well understood. But, the cost of erythropoietin can account of the low prevlence of its use, and we would expect symptomatic patients to go any length in securing the medication as compared to less symptomatic patients. Erythropoietin use can contribute significantly to the change in their left ventricular geometric pattern. This can be supported by studies from Eckwardt et al(19), which revealed a change in geometric pattern from baseline (irrespective of the geometry) after commencement of erythropoietin therapy (irrespective of haemoglobin target) in a 2 year period. Abnormal left ventricular geometric pattern has been associated with adverse cardiovascular outcomes as compared with normal geometry among CKD patients(19).

Impact of anaemia on quality of life

The prevalence of anaemia among CKD studied participants was 62.6%, and the prevalence increased significantly as CKD advanced from 42.3% in stage 3 to 93% in stage 5 ($X^2 = 29.69$, $p < 0.001$). This was similar to reports by Ijoma et al(97), who reported an overall prevalence of 77.5% among CKD patients, and prevalence was noticed to increase as CKD advances with highest prevalence in stage 5 CKD having a prevalence of 98%. Similar pattern was reported by Akinsola et al.(98) and Levin et al.(96).

The overall prevalence of impaired quality of life score was 42% (95% C.I was 34.35 – 49.6%). However, there was significantly higher prevalence of impaired quality of life (QoL) among anaemic CKD subjects 55.9%, than CKD subjects without anaemia 18.3%, (O.R = 5.64, p <

0.001). Furthermore, mean physical performance score was significantly lower among anaemic CKD subjects (73.17 ± 12.95), than those without anaemia (84.59 ± 11.04) with $p < 0.001$. Also, there was a strong negative impact of anaemia on QoL, with correlation coefficient ($r = 0.297$, $p = 0.003$) among anaemic CKD subjects compared to those without anaemia ($r = 0.128$, $p = 0.324$). Studies in this environment have also reported lower scores of QoL among CKD patients, in which anaemia was identified as an important risk factor for impaired QoL(99,100). The negative impact of impact of anaemia on QoL has also been reported in other studies(26,66,68,69,101–103).

However, CKD patients with higher haemoglobin level have been shown to have better QoL outcomes than those with lower haemoglobin(62). Therefore, management of anaemia cannot be overemphasized, with supporting evidence from studies showing improvement of quality of life among CKD patients treated with erythropoietin(26,31,68,69,104,105). Furthermore, achieving optimal haemoglobin target of 11 – 12g/dl has been shown by guidelines to favour better QoL outcomes among anaemic CKD patients(31,67–69,104). However, higher targets has been shown to worsen cardiovascular outcome(104,105).

Among anaemic CKD subjects, QoL score was shown to worsen with advancing CKD with a significantly lower mean score in stage 5 CKD (68.75 ± 14.35), as compare to stage 3 CKD (76.33 ± 9.27), $F = 4.104$ and $p < 0.019$, and a significantly post Hoc difference ($p = 0.028$). Although, there was lower mean score of QoL CKD stage 3 (85.85 ± 10.94) and stage 5 (73.33 ± 5.77) among control group, but not significantly different ($p = 0.149$). This further emphasize that aside from advanced CKD worsening patients quality of life, the presence of anaemia further worsen their quality of life. Also, the presences of disability only among anaemic CKD study group also buttress the negative impact of anaemia on QoL.

Ayanda et al(99), also identified the negative impact of the severity of CKD on the quality of life of CKD patients, and this was also supported by larger studies by Mujas et al(106) Other studies have reported similar findings(29,107). Therefore, retarding the progression of CKD will impact positively on the quality of life outcome of CKD patients(107).

Further observation noticed among the subgroup analysis of stage 5 CKD subjects revealed that, stage 5 CKD subjects with anaemia on dialysis had a significantly higher frequency of impaired quality of life than those not on dialysis which was 14(82.4%) versus 11(50%) respectively (X^2 = 4.362, O.R = 4.62 and p = 0.037). However, because of few subjects in stage 5 CKD subjects without anaemia, sub-group analysis of subjects on dialysis was insufficient for statistical analysis.

This high prevalence of impaired quality of life among dialysis patients have been supported by other studies(107,108). This could arise as a result of inadequate and infrequent dialysis, high cost of dialysis and complications of haemodialysis such as anaemia, catheter site infection and others(108).

However, there was no significant difference in QoL scores among subjects with controlled and uncontrolled blood pressure, subjects with and without diabetes and obesity, among both study groups. Other studies have reported inconsistent conclusion of the effect of these risk factors on QoL(109 - 111).

Impact of anaemia on left ventricular mass index and systolic function

There was a strong negative correlation between packed cell volume and left ventricular mass index among anaemic CKD patients (r = -0.345, p = 0.001), compared to those without anaemia (r = 0.001, p = 0.993). Furthermore, linear regression analysis to control for confounders such as hypertension revealed anaemia as the only predictor that significantly increased the risk of

increased left ventricular mass index (β coefficient = -1.170, p = 0.002, and 95% C.I = -3.879 - -0.866). Therefore, there is a strong evidence that anaemia is associated with a 1.170g/m^2 increase in left ventricular mass per 1% decrease in packed cell volume (0.33g/dl of haemoglobin) after controlling for other confounders such as hypertension, thus anaemia may contribute to the development of LVH.

This has also been supported from larger studies by Foley et al(49), which revealed 50% increase in the risk of developing LVH and systolic dysfunction with each decrease of 1g/dl of haemoglobin. While, Levine et al(96) further quantified a 10g/m^2 increase in left ventricular mass index with every 0.5g/dl decrease in haemoglobin. Similar impact has been reported in other studies in this environment by Ulasi et al(24) and Jesurobo et al(25).

The overall prevalence of left ventricular systolic dysfunction was 45% among studied participants, with significantly higher prevalence among anaemic CKD group (61.7%), than CKD subjects without anaemia (17.5%) with $p < 0.001$. This was significantly higher than the prevalence of 22% for systolic dysfunction reported by Foley et al(49), and other studies(112–115). This difference could be explained by the diagnostic method used for defining systolic dysfunction, in which fractional shortening was employed by these studies for assessing ejection fraction, and this has been shown to be unreliable in the presences of asymmetric left ventricular geometry and regional wall motion abnormality from coronary artery disease or conduction abnormality, which are common in CKD patients, and it's not the currently recommended standard(57).

The presences of high prevalence of left ventricular systolic dysfunction in the setting of anaemia and LVH categorizes CKD patients as high risk population, and these has been shown to worsen

their cardiovascular outcome, with a hazard ratio of 4.15 over the general population(14), and also increase their risk of hospitalization(96,116).

There was a positive correlation between left ventricular ejection fraction and physical performance score ($r = 0.524$, $p < 0.001$ and $r = 0.442$, $p = 0.001$) in both CKD subjects with anaemia and those without anaemia. Thus, poor left ventricular function may possibly impact negatively on quality of life of CKD patients. Other studies have shown that poor ejection fraction impairs quality of life, which worsens their New York Heart Association (NYHA) functional class, and increases their rate of hospitalization and morbidity(117,118).

5.2 Limitations

1. Limitation in subject selection into control group affects achieving sufficient subjects into stages 5 CKD group without anaemia, and also the high confounding prevalence of hypertension among the subjects.

5.3 Conclusion

This study showed that CKD patients with anaemia had significant impairment in their physical ability than CKD patients without anaemia, and this patients have high prevalence of LVH and poor left ventricular systolic function. Furthermore, poor left ventricular systolic function impacted negatively on their physical ability. Therefore, early assessment and management of anaemia and other cardiovascular risk factors may improve their quality of life and cardiovascular outcomes.

5.4 Recommendation

1. There should be increased awareness among physicians and health care providers on the high prevalence of anaemia and its complication among CKD patients.
2. There should be advocacy for regular and prompt assessment of the quality of life of CKD patients, with special emphasis on those who have developed anaemia as a complication.
3. There should be early assessment and prompt management of cardiovascular risk factors (such as anaemia and hypertension) and its complications (such as LVH and poor left ventricular systolic function), in order to prevent adverse cardiovascular outcomes.

REFERENCE

1. Locatelli F, Pozzoni P, Vecchio LD, Tentori F. Effect of anaemia on left ventricular hypertrophy in end-stage renal disease. European Journal of Heart Failure. 2003; 1;2(2):207-212.
2. Locatelli F, Marcelli D, Conte F, Del Vecchio L, Limido A, Malberti F, et al. Patient selection affects end-stage renal disease outcome comparisons. Kidney Int. 2000;57(74):94–99.
3. Donne RL, Foley RN. Anaemia management and cardiomyopathy in renal failure. Nephrology Dialysis Transplantation. 200217(1):37-40.
4. Ayus JC, Go AS, Valderrabano F, Verde E, De Vinuesa SG, Achinger SG, et al. Effects of erythropoietin on left ventricular hypertrophy in adults with severe chronic renal failure and hemoglobin <10 g/dL. Kidney Int. 2005;68(2):788–795.
5. Parfrey PS, Lauve M, Latremouille-Viau D, Lefebvre P. Erythropoietin therapy and left ventricular mass index in CKD and ESRD patients: a meta-analysis. Clin J Am Soc Nephrol [Internet]. 2009;4(4):755–762.
6. Kidney Disease Improving Global Outcome (KDIGO). Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Int Supplements. 2012; 2(4): 279 - 334
7. Finkelstein FO, Mujais SK, Story K, Brouillette J, Takano T, et al. Health-Related Quality of life in CKD patients: correlates and evolution over time. CJASN 2009 Aug; 4 (8):1293-1301.
8. Pagels AA, Söderkvist BK, Medin C, Hylander B, Heiwe S. Health-related quality of life in different stages of chronic kidney disease and at initiation of dialysis treatment. Health and quality of life outcomes. 2012;10(1):71.

9. Collins AJ, Foley RN, Gilbertson DT, and Chen SC. United States Renal Data System public health surveillance of chronic kidney disease and end stage renal disease. Kidney International Supplements 2015; 5(1): 2 - 7.

10. Allan J. Collins, Robert N. Foley, Blanche Chavers, David Gilbertson, Charles Herzog, Areef Ishani, Kirsten Johansen, Bertram L. Kasiske, Nancy Kutner, Jiannong Liu, Wendy St. Peter, Haifeng Guo, Yan Hu, Allyson Kats, Shuling Li, Suying Li, Julia Maloney, JS. 2013 USRDS Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. AJKD. 2014;63(1):e1–478.

11. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney international. 1995;47(1):186-192.

12. Ma JZ, Ebben J, Xia H, Collins AJ. Hematocrit level and associated mortality in hemodialysis patients. Journal of the American Society of Nephrology. 1999;10(3):610-619.

13. Xia H, Ebben J, Ma JZ, Collins AJ. Hematocrit levels and hospitalization risks in hemodialysis patients. Journal of the American Society of Nephrology. 1999;10(6):1309-1316.

14. Weiner DE, Tighiouart H, Vlagopoulos PT, Griffith JL, Salem DN, Levey AS, et al. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. J Am Soc Nephrol. 2005;16(6):1803–1810.

15. Collins AJ, Li S, PETER WS, Ebben J, Roberts T, Ma JZ, Manning W. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. Journal of the American Society of Nephrology.

2001;12(11):2465-2473.

16. Locatelli F, Conte F, Marcelli D. The impact of haematocrit levels and erythropoietin treatment on overall and cardiovascular mortality and morbidity-the experience of the Lombardy Dialysis Registry. Nephrology Dialysis Transplantation. 1998;13(7):1642-1644.

17. Levin, A, Thompson CR, Ethier J et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. Am J Kidney Dis. 1999;34:125–134.

18. Holland DC, Lam M. Predictors of hospitalization and death among pre-dialysis patients: a retrospective cohort study. Nephrology Dialysis Transplantation. 2000;15(5):650-658.

19. Eckardt KU, Scherhag A, Macdougall IC, Tsakiris D, Clyne N, Locatelli F, Zaug MF, Burger HU, Drueke TB. Left ventricular geometry predicts cardiovascular outcomes associated with anemia correction in CKD. Journal of the American Society of Nephrology. 2009;20(12):2651-2660.

20. Weiner DE, Tighiouart H, Vlagopoulos PT, Griffith JL, Salem DN, Levey AS, et al. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. J Am Soc Nephrol. 2005;16(6):1803–1810.

21. Portolés J, Torralbo A, Martin P, Rodrigo J, Herrero JA, Barrientos A. Cardiovascular effects of recombinant human erythropoietin in predialysis patients. American Journal of Kidney Diseases. 1997;29(4):541-548.

22. Hayashi T, Suzuki A, Shoji T, Togawa M, Okada N, Tsubakihara Y, Imai E, Hori M. Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. American Journal of Kidney Diseases. 2000 Feb 29;35(2):250-256.

23. Parfrey PS, Lauve M, Latremouille-Viau D, Lefebvre P. Erythropoietin therapy and left ventricular mass index in CKD and ESRD patients: a meta-analysis. Clin J Am Soc Nephrol. 2009;4(4):755–762.

24. Ulasi II, Arodiwe EB, Ijoma CK. Left ventricular hypertrophy in African Black patients with chronic renal failure at first evaluation. Ethnicity and Disease. 2006;16(4):859.

25. Jesuorobo DE, Odia JO, Uchenna DI. Left Ventricular Hypertrophy and Its Correlates in Chronic Kidney Disease Patients in a Nigerian Tertiary Hospital. International Journal of Internal Medicine. 2012;1(3):11-16.

26. Alexander M, Kewalramani R, Agodoa I, Globe D. Association of anaemia correction with health related quality of life in patients not on dialysis. Curr Med Res Opin. 2007; 23(12):2997-3008.

27. Farag Y, Keithi-Reddy S, Miltal B, Surana S, Addabbo F et al. Anaemia, inflammation and health-related quality of life in chronic kidney disease patients. Clin Nephrol 2011; 75(6):524-533.

28. Salim K, Ken S, John B, Tomoko T, Steven S et al. Health-related Quality of life in Chronic Kidney Disease patients: Correlates and evolution over time. Clin J Am Soc Nephrol 2009; 4:1293-1301.

29. Cruz M, Andrade C, Urrutia M, Draibe S, Nogueira-martins L et al. Quality of life in patients with Chronic Kidney Disease (Sao Paulo). CLINICS 2011;66 (6):991-995.

30. Arogundade F.A, Zayed B, Daba M, and Barsoum R.S. Correlation Between Karnofsky Performance Status Scale and Short-Form Health Survey in Patients on Maintenance Hemodialysis. JOURNAL OF THE NATIONAL MEDICAL ASSOCIATION 2004; 96,(12):1661-1667.

31. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 2013; 3: 1-163.

32. de L.S, Chan T, Stevens P, O'Donoghue D, Hague N, Dzregah B, et al. Identifying patients with chronic kidney disease from general practice computer records. Fam Pract.2005;22(3):234–241.

33. Foster M, Rawlings A.M, Marrett E, Neff D, Willis K, Inker L.A et al. Cardiovascular risk factor burden, treatment, and control among adults with chronic kidney disease in United States. Am Heart J. 2013 July ; 166(1): 150–156.

34. Nangaku M, Eckardt KU. Pathogenesis of renal anemia. InSeminars in nephrology 2006; 26(4): 261-268).

35. Eschbach JW: The anemia of chronic renal failure: Pathophysiology and the effects of recombinant erythropoietin. Kidney Int 1989; 35:134-148.

36. Adamson JW: The erythropoietinlhematocrit relationship in normal and polycythemic man: Implications for marrow regulation. Blood 1968; 32:597—609.

37. Nissenson AR, Strobos J: Iron deficiency in patients with renal failure. Kidney Int 1999; 55:S18-S21.

38. Akmal M, Sawelson S, Karubian F, et al: The prevalence and significance of occult blood loss in patients with predialysis advanced chronic renal failure, or receiving dialytic therapy. Clin Nephrol 1994; 42:198-202.

39. Macdougall IC, Cooper AC: Hyporesponsiveness to erythropoietic therapy due to chronic inflammation. Eur J Clin Invest 2005; 35:32-35 (suppl 3).

40. Barany P, Divino Filho JC, Bergstrom J: High C-reactive protein is a strong predictor of

resistance to erythropoietin in hemodialysis patients. Am J Kidney Dis 1997; 29:565-568.

41. Schooley JC, Kullgren B, Allison AC: Inhibition by interleukin-1 of the action of erythropoietin on erythroid precursors and its possible role in the pathogenesis of hypoplastic anemias. Br J Haematol 1987; 67:11-17.

42. Tomosugi N, Kawabata H, Wakatabe R, et al: Detection of serum hepcidin in renal failure and inflammation by using ProteinChip System(R). Blood e-Pub 2006; 36: 12 - 45.

43. Deicher R, Horl WH: New insights into the regulation of iron homeostasis. Eur J Clin Invest 2006; 36:301-309.

44. London GM. Left ventricular hypertrophy: why does it happen? Nephrol Dial Transplant. 2003;18 Suppl 8:viii2-i6.

45. Middleton RJ, Parfrey PS, Foley RN. Left ventricular hypertrophy in the renal patient. J Am Soc Nephrol. 2001;12(5):1079–84.

46. Arodiwe EB. Left ventricular hypertrophy in renal failure a review. Niger J Clin Pract. 2007;10(1):83–90.

47. Hunter J.J and Chien K.R. Signalling Pathways for Cardiac Hypertrophy and Failure. NEJM 1999; 341(17): 1276 – 1283.

48. Foppa M, Duncan BB, Rohde LE. Echocardiography-based left ventricular mass estimation. How should we define hypertrophy?. Cardiovascular ultrasound. 2005;3(1):17.

49. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. American journal of kidney diseases. 1996;28(1):53-61.

50. London GM, Fabiani F, Marchais SJ, De Vernejoul MC, Guerin AP, Safar ME, Metivier

F, Llach F. Uremic cardiomyopathy: An inadequate left ventricular hypertrophy. Kidney international. 1987;31(4):973-980.

51. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giacone G, Stancanelli B, Cataliotti A, Malatino LS: Left ventricular mass monitoring in the follow-up of dialysis patients: Prognostic value of left ventricular hypertrophy progression. Kidney Int 65: 1492.

52. London GM, Pannier B, Guerin AP, Blacher J, Marchais SJ, Darne B, Metivier F, Adda H, Safar ME: Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. J Am Soc Nephrol. 2012, 12: 27 - 59.

53. Silberberg JS, Barre PE, Prichard SS, Sniderman AD. Impact of left ventricular hypertrophy on survival in end-stage renal disease. Kidney Int. 1989;36(2):286–290.

54. Ritz E, Wanner C: The challenge of sudden death in dialysis patients. Clin J Am Soc Nephrol 3: 920–929, 2008.

55. Krane V, Winkler K, Drechsler C, Lilienthal J, Marz W, Wanner C: Effect of atorvastatin on inflammation and outcome in patients with type 2 diabetes mellitus on hemodialysis. Kidney Int 74: 1461–1467, 2008.

56. Unit R, Infirmary W, Kingdom U. Echocardiography overestimates left ventricular mass in hemodialysis patients relative to magnetic resonance imaging. Kidney international. 1999;56:2248–2253.

57. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography. J Am Soc Echocardiogr. 2015;28(1):1–39.

58. Pascual J, Teruel JL, Moya JL, Liano F, Jimenez-Mena M, Ortuno J. Regression of left ventricular hypertrophy after partial correction of anemia with erythropoietin in patients on hemodialysis: a prospective study. Clinical nephrology. 1991 Jun;35(6):280-287.

59. Zehnder C, Zuber M, Sulzer M, Meyer B, Straumann E, Jenzer HR, Blumberg A. Influence of long-term amelioration of anemia and blood pressure control on left ventricular hypertrophy in hemodialyzed patients. Nephron. 1992 Jul 1;61(1):21-25.

60. Wizemann V, Schäfer R, Kramer W. Follow-up of cardiac changes induced by anemia compensation in normotensive hemodialysis patients with left-ventricular hypertrophy. Nephron. 1993 Jul 1;64(2):202-206.

61. Foley RN, Parfrey PS, Morgan J, Barré PE, Campbell P, Cartier P, Coyle D, Fine A, Handa P, Kingma I, Lau CY. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. Kidney international. 2000 Sep 30;58(3):1325-1335.

62. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. New England Journal of Medicine. 2006 Nov 16;355(20):2071-2084.

63. Churchill D, Keown P, Laupacis A, Muirhead N, Sim D, Slaughter D. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. BMJ. 1990;300(6724):573-578.

64. World Health Organization. Quality of life assessment: an annotated bibliography. In Quality of life assessment: an annotated bibliography 1994. World Health Organization.

65. Dowling TC. Prevalence, aetiology and consequences of naemia and clinical and economic benefits of anaemia correction in patients with Chronic kidney disease. An overview. Am J Health Syst Pharm. 2007; 64(13 Suppl 8): S3-7.

66. Finkelstein FO, Story K, Firanek C, Mendelssohn D, Barre P et al. Health related quality of life and Haemoglobin levels in Chronic Kidney Disease patient. Clin J Am Soc Nephrol. 2009; 4:33-38.

67. Lefebvre P, Vekeman F, Sarokhan B, Enny C, Provenzano R et al. Relationship between haemoglobin level and quality of life in anaemic patients with chronic kidney disease receiving epoetin alfa. Curr Med Res Opin 2006 Oct; 22(10): 1929-1937.

68. National Kidney Foundation. KDOQI. Clinical Practice Guideline and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease: 2007 Update of Hemoglobin Target. Am J Kidney Dis 2007;50:471-530.

69. Kimel M, Leidy NK, Mannix S, Dixon J. Does epoetin alfa improve health-related quality of life in chronically ill patients with anemia? Summary of trials of cancer, HIV/AIDS, and chronic kidney disease. Value in Health. 2008 Jan 1;11(1):57-75.

70. Ware JE, Kosinski M, Dewey JE, Gandek B. SF-36 health survey: manual and interpretation guide. Quality Metric Inc.; 2000.

71. Evans RW, Manninen DL, Garrison Jr LP, Hart LG, Blagg CR, Gutman RA, Hull AR, Lowrie EG. The quality of life of patients with end-stage renal disease. New England journal of medicine. 1985 Feb 28;312(9):553-9.

72. Kurtin PS, Davies AR, Meyer KB, DeGiacomo JM, Kantz ME. Patient-based health status measures in outpatient dialysis: Early experiences in developing an outcomes assessment program. Medical care. 1992 May 1:MS136-149.

73. Brazier JE, Harper R, Jones NM, O'cathain A, Thomas KJ, Usherwood T, Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. Bmj. 1992; 18;305(6846):160 - 164.

74. Karnofsky DA, Barchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Evaluation of chemotherapeutic agents, edited by Macleod CM. New York, NY: Columbia University Press, 1949; l91-205.

75. Rebollo P, Bobes J, Gonzalez MP, et al. Factors associated with health related quality of life in patients undergoing renal replacement therapy. Nefrologia 2000; 20: 171 - 181.

76. Daniel WW. Biostatistics: a foundation for analysis in the health sciences, 7th edition. New York: John Wiley and Sons 1999.

77. Thrusfield M. Veterinary epidemiology, 2nd edition. Blackwell Science, Oxford, UK 2005.

78. WHO nutritional anaemia: Report of a WHO Scientific Group. Geneva, World Health Organization; 1968.

79. Kouno T, Katsumata N, Mukai H, Ando M, Watanabe T. Standardization of the body surface area (BSA) formula to calculate the dose of anticancer agents in Japan. Jpn J Clin Oncol. 2003;33(6):309–313.

80. Hoste L, Deiteren K, Pottel H, Callewaert N, Martens F. Routine serum creatinine measurements : how well do we perform ? BMC. 2015;16(1):1–9.

81. Iyauchi TM, Iyachi YM, Akahashi MT, Shikawa NI. Determination of Urea in Serum Based on the Combination of an Enzymatic Reaction with Immobilized Urease and Ion Chromatographic Analysis. 2010;26(August):847–851.

82. Zelmat M. Direct and indirect ion selective electrodes methods: the differences specified through a case of Waldenstrom's macroglobulinemia. Ann Biol Clin. 2015;73(3):345–

352.

83. Heider J., Boyett R. The picomole determination of free and total cholesterol in cells in culture. J Lipid Res. 1978;19:514–518.

84. Kalia V, Pundir C. Determination of serum triglycerides using lipase, glycerol kinase, glycerol-3-phosphate oxidase and peroxidase co-immobilized onto alkylamine glass beads. Indian J Biochem Biophys. 2004;41(6):326–328.

85. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. Jama. 2003; 289(19):2560-2571.

86. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults – The evidence report. National Institutes of Health. Obes Res. 1998;6(Suppl 2):51S–209S.

87. Ulasi I.I, Ijoma C.K, Onodugo O.D, Arodiwe E.B, Ifebunandu N.A and Okoye J.U. Towards prevention of chronic kidney disease in Nigeria: a community-based study in Southeast Nigeria. Kidney International Supplements (2013) 3, 195–200.

88. Ulasi II, Ijoma CK. The enormity of chronic kidney disease in Nigeria: the situation in a Teaching Hospital in South-east Nigeria. J Trop Med 2010;1 - 7.

89. Adejumo O.A, Okaka E.I, Madumezia G, Okwuonu C.G, and Ojogwu L.I. Assessment of some cardiovascular risk factors in predialysis chronic kidney disease patients in Southern Nigeria. Niger Med J. 2015; 56(6): 394–399.

90. Akinsola W, Odesanmi WO, Ogunniyi JO LG. Diseases causing chronic renal failure in Nigerians- a prospective study of 100 cases. Afr J Med Med Sci 1989 Jun; 18(2) 131-137.

91. Alebiosu C.O, Ayodele O.O, Abbass A, Olutoyin A.I. Chronic renal failure at the Olabisi Onabanjo university teaching hospital, Sagamu, Nigeria. Afr Health Sci. Sep 2006; 6(3):132-138.

92. Wachukwu C.M, Emem-Chioma P.C WF. and O-JRI. Prevalence of risk factors for chronic kidney disease among adults in a university community in southern Nigeria. Pan African Med Journal. 2015;21:120–125.

93. Chijioke A, Makusidi AM, Kolo PM. Electrocardiographic abnormalities among dialysis naïve chronic kidney disease patients in Ilorin Nigeria. Ann Afr Med. 2012;11(1): 21 - 26.

94. Port FK, Ashby V.B, Dhingra R.K, Roys EC WR. Dialysis dose and body mass index are strongly associated with survival in haemodialysis patients. JASN. 2002;13(4):1061–1066.

95. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. AJKD. 2002;392:1–266.

96. Levin A, Thompson C, Either J, Carlisle E.J.F, Tobe S, Mendelssohn D, Burgess E, et al. Left ventricular mass inex increase in early renal disease: Impact of decline in haemoglobin. AJKD. 1999;13(1):125–134.

97. Ijioma C and Ulasi I. High prevalence of anaemia in predialysis patients in Enugu, Nigeria. Nephrology review 2010; 2: 61 -65.

98. Akinsola A, Durosinmi MO, Akinola NO. The haematological profile of Nigerians with chronic renal failure. Afr J Med Med Sci. 2000;29:13–16.

99. Ayanda KA, Abiodun OA, Ajiboye PO. Quality of life of chronic kidney disease patients in a Nigerian teaching hospital. J Biol Agric Healthc. 2014;4(5):17–28.

100. Ojeh-Oziegbe O.E, Okaka E.I, Okwuonu C.G, Oviasu E, Ojogwu L.I. Quality of life of

Nigerian Chronic Kidney Disease patients: experience from Benin City, Nigeria. Pioneer Med J. 2015;8:1–17.

101. Soni RK, Weisbord SD, Unruh ML. Health-related quality of life outcomes in chronic kidney disease. Curr Opin Nephrol Hypertens. 2010;19:153–159.

102. Hansen RA, Chin H, Blalock S, et al. Predialysis chronic kidney disease: evaluation of quality of life in clinic patients receiving comprehensive anemia care. Res Soc Adm Pharm. 2009;5(2):143–153.

103. Leaf DE, Goldfarb DS. Interpretation and review of health-related quality of life data in CKD patients receiving treatment for anemia. Kidney Int. 2009;75(1):15–24.

104. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D. Correction of anemia with epoetin alfa in chronic kidney disease. New England Journal of Medicine. 2006 Nov 16;355(20):2085-2098.

105. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. New England Journal of Medicine. 2009;361(21):2019 - 2032.

106. Mujais SK, Story K, Brouillette J, Takano T, Soroka S, Franek C, Mendelssohn D, Finkelstein FO. Health-related quality of life in CKD patients: correlates and evolution over time. Clinical Journal of the American Society of Nephrology. 2009 Aug 1;4(8):129.

107. Porter AC, Lash JP, Xie D, Pan Q, DeLuca J, Kanthety R, Kusek JW, Lora CM, Nessel L, Ricardo AC, Nunes JW. Predictors and Outcomes of Health–Related Quality of Life in Adults with CKD. Clinical Journal of the American Society of Nephrology. 2016; 11(7): 1154 - 1162.

108. Kalender B, Ozdemir AC, Dervisoglu E, Ozdemir O. Quality of life in chronic kidney disease: effects of treatment modality, depression, malnutrition and inflammation. International journal of clinical practice. 2007 Apr 1;61(4):569-576.

109. Lash JP, Wang X, Greene T, Gadegbeku CA, Hall Y, Jones K, Kusek JW, Sika M, Unruh M. Quality of life in the African American Study of Kidney Disease and Hypertension: effects of blood pressure management. American Journal of Kidney Diseases. 2006; 47(6): 956 - 964.

110. Adedapo AD, Akume OO, and Adedokun BO. Comparative assessment of determinants of health related quality of life in hypertensive patients and normal population in South West Nigeria. Int J Clin Pharmacol Ther. 2015;53(3):265-271.

111. Ogunlana M.O, Adedokun B, Dairo M.D and Odunaiya N.S. Profile and predictors of health related quality of life among hypertensive patients in South Western Nigeria. BMC Cardiovascular Disorders 2009; 9(25): 1 – 8.

112. Arodiwe EB1, Ulasi IL, Ijoma CK, Ike SO. Left ventricular systolic function in a Nigerian pre-dialysis patient population with chronic kidney disease. Niger Postgrad Med J. 2010 Dec;17(4):301-317.

113. Mpembe BC, Lepira FB, Mbutiwi FI, Makulo JR, Kintoki EV, Bayauli MP, M'Buyamba-Kabangu JR. Left Ventricular Structure, Geometry and Systolic Function among Hypertensive Black Patients with Reduced Kidney Function. World Journal of Cardiovascular Diseases. 2015;5(10):278.

114. Agarwal S, Dangri P, Kalra OP, Rajpal S. Echocardiographic Assessment of Cardiac Dysfunction in Patients of Chronic Renal Failure. Journal, Indian Acad Clin Med. 2003;4(4):296–303.

115. Debnath A, Chaudhury SR, Nath A, Sarkar S, Mandal S, Saha TK. Echocardiographic Assessment of Left Ventricular Systolic Dysfunction in Chronic Kidney Disease Patients of a Rural Tertiary Medical Care Centre in West Bengal. 2014;13(1):69–73.

116. Levin A, Djurdjev O, Barrett B, Burgess E, Carlisle E, Ethier J, Jindal K, Mendelssohn D, Tobe S, Singer J, Thompson C. Cardiovascular disease in patients with chronic kidney disease: getting to the heart of the matter. American Journal of kidney diseases. 2001; 38(6): 1398 – 1407.

117. Juenger J, Schellberg D, Kraemer S, Haunstetter A, Zugck C, Herzog W, Haass M. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. Heart. 2002 Mar 1;87(3):2.

118. Hoekstra T, Lesman-Leegte I, Veldhuisen DJ, Sanderman R, Jaarsma T. Quality of life is impaired similarly in heart failure patients with preserved and reduced ejection fraction. European journal of heart failure. 2011 Sep 1;13(9):1013-1018.

Anaemia in chronic kidney disease in LASUTH: impact on quality of life

and left ventricular mass index

QUESTIONNAIRE

SECTION A

SOCIO DEMOGRAPHIC DATA

1) Serial No: DATE:

2) NAME:

4) AGE IN YEARS: 5) GENDER: M [ ] F [ ]

6) HOSPITAL NO: 7) TELEPHONE NO:

8) OCCUPATION: UNEMPLOYED [ ] UNSKILLED [ ] SKILLED [ ] PROFESSIONAL [ ]

9) RELIGION: CHRISTIAN [ ] ISLAM [ ] OTHERS [ ]

10) MARITAL STATUS: SINGLE [ ] MARRIED [ ] DIVORCED [ ] WIDOW [ ]

11) EDUCATION: NONE [ ] PRIMARY [ ] SECONDARY [ ] TERTIARY [ ]

12) TRIBE: IGBO [ ] HAUSA [ ] YORUBA [ ] OTHERS [ ]

SECTION B

13) HISTORY OF KIDNEY DISEASE AND AETIOLOGY

A) DURATION OF CHRONIC KIDNEY DISEASE:

B) AIETIOLOGY OF CHRONIC KIDNEY DISEASE: HYPERTENSION [ ]

DIABETES [ ] CHRONIC GLOMERULONEPHRITIS [ ] CYSTIC KIDNEY [ ]

OBSTRUCTIVE UROPATHY [ ] HIV [ ] UNKNOWN [ ]

OTHERS SPECIFY:

C) HISTORY OF KIDNEY TRANSPLANT: YES [ ] NO [ ]

D) Are you on Dialysis: YES [ ] NO [ ]

E) HISTORY OF HYPERTENSION: YES [ ] NO [ ]

F) DURATION OF HYPERTENSION:

G) MEDICATIONS USED FOR HYPERTENSION:

Diuretics[ ] ACE I [ ] ARB [ ] CCB [ ] BB [ ] Centrally acting [ ]

H) HISTORY OF DIABETES: YES [ ] NO [ ]

I) DURATION OF DIABETES:

J) MEDICATIONS USED FOR DIABETES:

Oral hypoglycaemic drugs [ ] Insulin [ ]

Combination of Oral hypoglycaemic drugs and Insulin [ ] None [ ]

K) USE OF ERYTHROPOIETIN STIMULATING AGENT: YES [ ] NO [ ]

L) Frequency of erythropoietin use:

L) Duration on erythropoietin use:

M) Number of blood transfusion:

N) Most recent blood transfusion

O) Use of Vitamin D: YES [ ] NO [ ]

P) Use of Calcium supplement: YES [ ] NO [ ]

14) **EVALUATION OF CARDIOVASCULAR DISEASE**

A) Any Breathlessness : YES [ ] NO [ ]

B) Breathlessness on mild activity or at rest: YES [ ] NO [ ]

C) Orthopnea : YES [ ] NO [ ]

D) Number of pillows used for sleeping:

E) Paroxysmal nocturnal dyspnoea: YES [ ] NO [ ]

F) Palpitations: YES [ ] NO [ ]

G) Cough: YES [ ] NO [ ]

H) Easy fatigue: YES [ ] NO [ ]

I) Light headedness or dizziness: YES [ ] NO [ ]

J) Syncope or Fainting spells: YES [ ] NO [ ]

K) Leg swelling: YES [ ] NO [ ]

L) Previous history of myocardial infarction: YES [ ] NO [ ]

M) Previous history of heart failure: YES [ ] NO [ ]

N) Family history of cardiovascular disease: YES [ ] NO [ ]

15) **Drug History**

A) Use of antiplatelet (Aspirin or Clopidrogel): YES [ ] NO [ ]

B) Use of lipid lowering agents (e.g statins): YES [ ] NO [ ]

C) Use of vitamin D supplement: YES [ ] NO [ ]

D) Use of calcium and phosphate binders: YES [ ] NO [ ]

E) Herbal ingestion: YES [ ] NO [ ]

16) History of cigarette smoking: YES [ ] NO [ ]

A) Duration of smoking: .....

B) Pack Years: .....

16) History of Alcohol ingestion: YES [ ] NO [ ]

A) Duration: ..... B) Volume consumed (units): .....

SECTION C

PHYSICAL FINDINGS

1) Weight (kg): .....

2) Height (m): .....

3) Body Mass Index (kg/m^2): .....

4) Blood Pressure (mmHg): .....

5) Body Surface Area: .....

7) CVS Findings: Pulse Locomotor Brachialis

JVP Precordium

8) Chest Findings:

10) Abdominal Findings:

11) Neurologic Findings:

SECTION D

INVESTIGATIONS

1) Serum Creatinine : ..... 2) eGFR:.....

3) Random Blood Sugar:

4) Other evidence of CKD

5) Fasting Lipid Profile:

a) Total Cholesterol: b) HDL:

c) LDL: d) TG:

e) VLDL f) PCV

7) ECHO findings:

Left Atrial Size:

Aortic Diameter:

Left Ventricular Wall Thickness:

Interventricular Wall Thickness:

Posterior Wall Thickness:

Left Ventricular Diameter in Diastole:

Left Ventricular Diameter in Systole:

LVH pattern:

E.F: E/A ratio:

Regional Wall abnormality:

Left Ventricular Mass (grams):

Left Ventricular Mass Index:

Conclusions:

Consent Form

Name of Principal Investigator: Dr OLADIMEJI OLUWASEYE MICHAEL

Department: Internal Medicine

E-mail: seye.oladimeji@yahoo.com

Phone number: 08174486689

Title of the research: Anaemia in chronic kidney disease: Impact on left ventricular mass index and quality of life.

Name and affiliation of researcher of applicant: This study is being conducted by Dr Oladimeji Oluwaseye Michael of Lagos State University Teaching Hospital, Ikeja, Lagos State.

Sponsor of research: This study is self sponsored by the principal investigator.

Purpose of research: The aim of this study is to assess correlation between the level of anaemia and left ventricular mass among chronic kidney disease patients.

Procedure of the research, what is required of each participant and approximate total number of participants that would be involved in the research: Subjects who are eligible and give their consent to participate in this study will be required to fill a questionnaire. A full physical examination will be conducted including your height and weight measurement. Blood sample will be taken from you for investigation purposes. Echocardiography will be performed on you. In total I expect to recruit 110 participants.

Expected duration of research and of participants involvement: This study is expected to run for 12 months, and it is estimated that you should not spend more than 2 hours at each clinic visit.

Risk: Your participation in this research does not constitute any health risk to you in anyway. However, you might experience some discomfort when your blood sample is being taken.

Cost to the participant: Your participation in this study is at no cost to you.

Benefits: The purpose of this is study is to identify left ventricular hypertrophy among anaemic chronic kidney disease patients. This will help inform you concerning any damage to your heart and help give proper counsel on available treatment options, in order to reduce further organ damage.

Confidentiality: All information collected in this will be held in the strictest confidence. Your personal details will be coded such that the information you provide cannot be linked to you in anyway. Your name or any other detail that identifies you will not be used in any publication from this study. As part of our responsibility to conduct this research properly officials from NHREC may have access to these records.

Voluntariness: Your participation in this research is entirely voluntary.

Alternatives to participation: If you choose not to participate, this will not affect your treatment in this hospital in anyway.

Due Inducement: You will not be paid any fee for participating in this research.

Consequences of participants' decision to withdraw from research and procedures for order termination of participation: You can choose to withdraw from the research at anytime. Please note some of the information that has been obtained about you before you choose to withdraw may have been modified or used in reports and publications. These unfortunately cannot be

removed anymore. However, the researcher promises to make good faiths effort to comply with your wishes as much as is practicable.

Modality of providing treatments and actions to be taken in case of injury or adverse events: Though it is unlikely you may suffer any untoward effect from participating in this study, in the unlikely event you suffer injury as a result of your participating in this study you will be treated in Lagos State University Hospital and the researcher will bear the cost of this treatment.

What happens to research participants and communities when the research is over: At the end of the research you should be interested in the study outcome; this will be forwarded to your contact details provided. During the course of the research you will be informed about any information that may affect your continued participation or your health.

Statement about sharing benefits among researchers and whether this includes or excludes research participants: Any commercial product that may be produced during this study is owned by Lagos State University teaching Hospital, Ikeja, Lagos State. No participant owns any right to any commercial product that may be produced by this study.

Any apparent or potential conflict of interest: I have no conflict of interest.

Statement of person obtaining informed consent: I have fully explained this research to and have given sufficient information, including about risks and benefits, to make informed decision.

Date: **Signature:**

Name:

Statement of person giving consent:

I have read the description of the research or have had it translated into language I understand. I have also talked it over with the doctor to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, method, risk and benefits of the research study to judge that I want to take part in it. I understand that I may freely stop being part of this study at any time. I have received a copy of this consent form and additional information sheet to keep for myself.

DATE: **SIGNATURE:**

NAME:

WITNESS NAME: **WITNESS' SIGNATURE:**

Detailed contact information including contact address, telephone, fax, email and any other contact information of researcher, institution HREC and head of the institution:

Name: Dr Oladimeji Oluwaseye Michael

Contact address: Nephrology unit, Department of Internal Medicine, Lagos State University Teaching Hospital, Ikeja, Lagos

Telephone: 08174486689

Email: seye.oladimeji@yahoo.com

Consent Patient Information

Chronic kidney disease is any disease of the kidney lasting more than 3 months, which can result in anaemia and enlargement of the heart. Anaemia (reduced blood level) and enlarged heart (left ventricular hypertrophy) can both lead to heart failure, reduced quality of life and result in death. However, early identification of anaemia and enlarged heart with prompt treatment of these conditions will improve the quality of life and reduce the rate of death from these conditions. This study is designed to evaluate the presence of anaemia and left ventricular hypertrophy among chronic kidney disease patients. It will entail asking some questions from you about symptoms of heart disease, and complete examination of your body system with proper investigation to identify heart disease.

All information in this study will be confidential and you retain the right to withdraw at any point during the study. This will not affect your statutory rights.

Please feel free to ask about anything you may need clarification on.

Thank you very much for your time.

I ..... have read and understood the above written information and I consent to partake in this study.

Date: Signature: Phone no:

Witness Name:

Address:

Date: Signature: