Anemia of Chronic Kidney Disease: Pattern, Prevalence and Clinical Correlates. A Single Center Cross Sectional Study in South Western Nigeria

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ABSTRACT

Introduction: Anemia is a modifiable and very common complication of chronic kidney disease that could be difficult to manage, more so in low income settings due to late recognition, and cost of undergoing required investigations and treatment.

Methods: A cross sectional study in which participants with chronic kidney disease and with glomerular filtration rate (GFR) <60ml/min had urine, blood and radiological investigations to determine albuminuria, GFR with electrolytes concentrations kidney length respectively.

Results: One hundred and forty four (82 males and 62 females) cohorts participated. The mean age of all participants was 48.76 ± 15.87 years. Only cohorts in stage 5 CKD were receiving ESAs, and of the 22, 19 (86.3%) had anemia. The 45-59 years group had the highest blood pressure. A greater proportion of the participants had hypertension as the cause of CKD.

The prevalence of anemia was 39.58%, 37.80% in males and 41.93% in females. The mean hemoglobin concentration for cohorts was 10.96 ± 1.85 g/dL, and was higher in males, P=0.06, and was least with chronic interstitial nephritis. Metabolic acidosis was commoner in females, P=0.04. Calcium Phosphate product was elevated in 10.5% of the participants. The mean serum creatinine was higher in males than females, P=0.001. The mean eGFR and urine ACR were higher in males, P=0.02, P=1.1. The severity of anemia was positively related to stage of CKD, P<0.001.

Conclusion: Anemia complicating CKD is common, with a prevalence of 39.58% in our study. It was commoner in females, aged and elevated urine ACR and was negatively correlated with serum albumin. Determinants of renal anemia were age, and kidney function while predictors were increasing age, stage 5 CKD and urine ACR. Improvement in kidney function, frequent reviews of red cell indices and medications are needed to minimize complications of renal anemia.

Keywords: anemia, chronic kidney disease, erythropoiesis stimulating agents, hemoglobin concentration

INTRODUCTION

Anemia as a complication and a modifiable risk factor in chronic kidney disease (CKD), is highly prevalent and is associated with CKD progression and the occurrence of adverse effects of the disease

particularly cardiovascular disease and events.[1] Renal anemia in addition to several pathophysiologic mechanisms, primarily results from reduced erythropoietin release from renal peritubular interstitium.[2] Anemia correction alleviates the symptoms of disease, as in long term outcome with improvement in cognition and cardiac function, with declining rates of cardiac enlargement and left ventricular hypertrophy, thereby reducing length of hospitalization and, even death. Several factors are implicated in the progression of anemia in CKD including gender differences, infections and the use of inhibitors of the renin angiotensin aldosterone system (RAAS).[3]

A negative relationship exist between the severity of anemia and kidney function, a progressive decline in the hemoglobin concentration (HBC) is commonly seen in CKD from stage 2 disease.[2] While androgens are known to play some stimulating effects on erythropoiesis, females are reported to experience delay in the commencement of this hematocrit decline.[4] The ideal HBC in predialysis CKD is still debatable. While it a known fact that the use of ESAs are associated with improvement in many features associated with CKD, HBC >13.0g/dL they have been reported to increase the risk of thrombotic events and mortality.[5] Recent findings have found no significant adverse effects of using ESAs in person with HBC greater than 9g/dL.[6] Several guidelines have recommended a HBC of <13g/dL as the treatment target in peridialysis CKD.[7]

Though modifiable, anemia correction could be cumbersome due to delayed diagnosis and suboptimal treatment strategies.[7] In low and medium income nations (LMINs), the correction of anemia is even more cumbersome due to the high cost of diagnostic tests, poor availability of ESAs on account of cost, low educational attainment, cultural biases particularly against women, and the poor health financing by governments, private sector, multinational organization and philanthropists.[8-10] Other contributing factors to the prevalence of anemia in CKD are inflammatory state associated with the release of anorexic cytokines coupled with intestinal congestion leading to poor digestion and absorption of nutrients, infections that comes with increased hemolysis, worsening proteinuria and acute depreciation of kidney function. Poor blood pressure control resulting in chronic elevation of intraglomerular, and peritubular capillaries which could alter renal perfusion pressures.[10]

It is reported that the rate of hemoglobin decline in CKD is faster in the early stages of the disease.[4] Considering the adverse effects of anemia on the quality of life (QOL) and mortality in CKD patients, it therefore becomes very imperative that a deeper insight is needed more so in LINs, that will enable nephrologists to offer a better management of anemia from the early stages of CKD. Anemia in CKD is well reported in the advanced nations, and recent studies have revealed an increasing depth of knowledge concerning the epidemiology, correlates and management of anemia.[11] In LMINs where anemia in CKD is expectedly more prevalent, literature is scares concerning anemia and its associates in CKD. We studied anemia in predialysis CKD and assessed its determinants, pattern, prevalence and clinical correlates in Nigeria as way of bridging the knowledge gap.

MATERIALS AND METHODS

This was a single center, cross sectional study conducted between August 2019 and July 2021 at the Nephrology and Hypertension clinic of Babcock University Teaching Hospital in Nigeria where between thirty and forty patients are seen weekly. One hundred and forty four participants (82 males and 62 females), 16 years or older, receiving regular nephrology consultation and had estimated glomerular filtration rate (eGFR) <60 ml/min and were classified as having CKD according to KDOQI 2012 criteria,[12] were studied.

Participants that met study inclusion criteria and gave informed consent were consecutively recruited. Data was taken from history, physical examination, laboratory and radiological findings and from participants' case file, and entered into a standard data form. Variables retrieved included sociodemographics, risk factors and etiology of CKD.

The height in meters (m) and weight in kilogram (kg) were measured using standard protocol and the body mass index (BMI) was calculated as kg/m^2. The blood pressure was taken in the sitting position with arm and back rested on a support, after five minutes of rest. Fresh urine samples were taken for Dip strip analysis with Combi 10 strips, and microalbuminuria testing with micral albustic strips. Blood samples were taken to determine the serum electrolytes, urea creatinine, albumin, full blood count, erythrocyte sedimentation rate. The kidney length from the RUS were also retrieved. The eGFR was estimated using the chronic kidney disease epidemiological collaboration (CKD-EPI) formula.[13]

The micra strip was taken from its container (which was closed immediately) and the end with the strip pad was immersed into the urine in the universal bottle to cover the full length of the strip pads for 50 seconds and remove by rolling it against the edge of the universal bottle to remove excess urine. The strip pad color was now matched against the "strip pad color" inscribed on the strip container and the results were documented.[14] The combi 10 dip strip was taken from the container and the end containing the pad was immersed into the urine to cover the strip pad and remove after 60 seconds by rolling it against the edge of the universal bottle to remove excess urine.

This study was approved by the Babcock University Human Research Ethics Committee (BUHREC) of Babcock University (NHREC/24/01/2018 and BUHREC501/19) and study protocol was in accordance with the tenets Helsinki declaration of 1973 (revised in 2000).[15]

Definitions

The etiological diagnosis of CKD in this study was not biopsy based, therefore,

Hypertension associated CKD was defined as kidney disease cause by long standing hypertension, more prevalent in the elderly and late middle age and,

Chronic glomerulonephritis was defined as kidney disease complicated by hypertension, more prevalent in the young and early middle age with or without antecedent history of pharyngitis or skin sepsis.

Chronic interstitial nephritis was defined as kidney disease resulting from a significant exposure to exogenous nephrotoxins, after ruling out

Hypertension: Blood pressure $\geq140/90$ mmHg.[16]

Diabetes: Confirmed diagnosis, fasting blood sugar (FBS) ≥126 mg/dL, use of antidiabetic drugs.[17]

Anemia: Hemoglobin concentration <13 mg/dL in males, and <12 mg/dL in females [18]

Hypoalbuminemia: serum albumin <35mg/dL[19]

Metabolic acidosis (MA): serum bicarbonate <22mmol/L.[20]

Microalbuminuria: Urine ACR >3.4mg/mmoL[21]

Proteinuria: dip strip protein $\geq1+$[22]

Dyslipidaemia: Total cholesterol ≥6.21 mmol/L[23]

Low-density lipoprotein cholesterol (LDL) >4.14 mmol/L.[23]

High-density lipoprotein cholesterol (HDL) <1.03 mmol/L.[23]

Triglycerides ≥1.69 mmol/L[23]

Shrunken kidneys: Length <9cm.[24]

Data analysis was with SSPS. Continuous variables, presented as mean with standard deviation, were compared using student's t-test while categorical variables, presented as proportions and frequencies, were compared using Chi-square or fisher's exact test. The P-value <0.05 was considered statistically significant. Variables with $p<0.025$ from the univariate model were included as

adjustment variables in multivariate analyses to determine independent predictors of anemia in CKD.[25]

RESULTS

One hundred and forty four cohorts (82 males and 62 females) participated. The mean age of all participants was 48.76 ± 15.87 years. The proportion of the females ≥60 years was higher compared to the males, P=0.003. Thirty three (22.92%) of the CKD cohort had stage 3a disease, 47 (32.63%) in stage 3b, 42 (29.17%) in stage 4, 22 (15.28%) in stage 5 (non-dialytic). Eighty eight (61.1%) of participants were receiving either an angiotensin converting enzyme inhibitors (ACEI) or an angiotensin receptor blocker (ARB), majority of these were middle aged or elderly, and males. Only cohorts in stage 5 CKD were receiving ESAs, and of the 22, 19 (86.3%) had anemia. The mean BMI of all cohorts, males and females were 26.53±4.51 kg/m^2, 26.64 ± 4.26 kg/m^2 and 26.39 ± 4.85 kg/m^2, P=0.8. A greater proportion of the women compared to males had normal SBP (70.97% versus 54.88%) and DBP (80.64% versus 68.29%) respectively. The 16-29 and the 45-59 years age groups had the lowest and the highest systolic and diastolic BP respectively.

Table 1: Sociodemographic and clinical characteristics of participants

Variables	Frequency	Percentage
Sex		
Males	82	56.94
Females	62	43.06
Age, years		
16-29	16	11.11
30-44	40	27.78
45-59	62	43.06
60-74	19	13.20
>75	9	6.25
BMI, kg/m^2		
<25.00	58	40.28
>25.00	86	59.72
SBP, mmHg		
<140	89	61.81
>140	55	38.19
DBP, mmHg		
<90	106	73.61
>90	38	26.39

A greater proportion of the participants had hypertension as the cause of CKD (Figure 1). This was jointly followed by chronic interstitial nephritis (19.4%) and CGN (19.4%). Majority (78.6%) of participants with CIN had NSAIDs associate kidney disease.
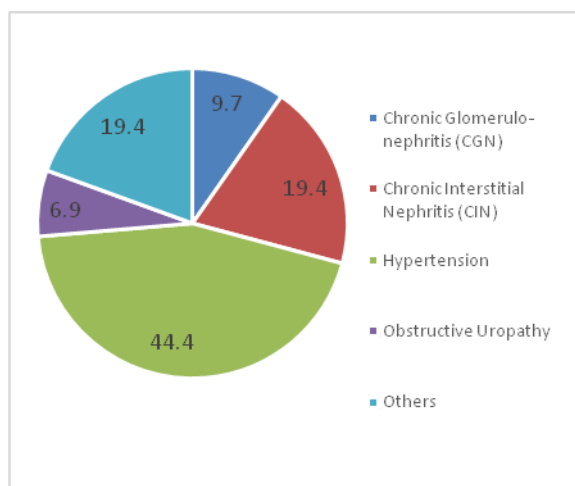

Figure 1: Pie chart showing the etiologies of CKD in the participants

Anemia was found in 39.58% of all participants, 37.80% in males and 41.93% in females. The mean hemoglobin concentration was 10.96 ± 1.85 g/dL, males 11.08 ± 1.85 g/dL and females, 10.78 ± 2.23 g/dL, P=0.06. The mean hemoglobin of the participants with hypertension, CGN, CIN, obstructive uropathy, and others were 13.20 ± 3.86g/dL, 13.59 ± 4.21g/dL, 12.71 ± 3.68 g/dL, 13.29 ±4.40 g/dL and 13.20 ± 4.03 g/dL respectively. The mean serum sodium was less in females, a greater proportion of women than males had hyponatremia (29.03% versus 25.61%). Metabolic acidosis was found in 44.4% of the participants, more so in females, P=0.04. Hypocalcemia was present in 36.80% of participants, and the mean phosphate, and calcium phosphate product ware higher in females than males P=0.03 and P=0.05 respectively. Calcium x Posphate product was elevated in 10.5% of the participants. The mean serum creatinine was higher in males than females, P=0.001. (Table 3) The mean eGFR was higher in males than females, P=0.02.The mean urine ACR was higher in males than females, P=1.1. The mean length of the right kidney was less

than the left (10.03 ± 2.14cm versus 10.53   ± 2.06cm), P=0.06.

Table 2: Laboratory and radiological characteristics of the participants

Variables	Males	Females	P-value
Sodium, mmol/L (mean ± SD)	137.09 ± 4.88	136.18 ± 5.00	0.08
Potassium, mmol/L (mean ± SD)	4.06 ± 0.64	4.05 ± 0.68	0.1
Chloride, mmol/L (mean ± SD)	102.93 ± 5.21	102.48 ± 5.32	0.5
Bicarbonate, mmol/L (mean ± SD)	21.61 ± 3.87	20.57 ± 3.78	0.05
Calcium, mmol/L (mean ± SD)	2.21 ± 0.31	2.18 ± 0.30	0.05
Phosphate, mmol/L (mean ± SD)	1.47 ± 0.39	1.52 ± 0.45	0.04
Calcium x phosphate, $mmol^2/L^2$ (mean ± SD)	3.22 ± 0.85	3.27 ± 0.97	0.05
Urea, mmol/L (mean ± SD)	16.91 ± 1.71	13.96 ± 2.56	0.03
Creatinine, umol/L (mean ± SD)	135.24 ± 11.48	123 ± 2.62	0.001
GFR, ml/min/1.73^2 (mean ± SD)	47.33 ± 22.86	41.28 ± 18.08	0.02
Hemoglobin concentration mg/dL (mean ± SD)	11.08 ± 1.85	10.78 ± 2.23	0.06
Albumin, mg/dL (mean ± SD)	4.59 ± 0.51	4.14 ± 0.47	0.05
Urine ACR, mg/g (mean ± SD)	35.74 ± 8.92	35.63 ± 8.54	1.1
Kidney length, cm (mean ± SD)	10.83 ± 2.13	10.13 ± 1.98	0.06
Kidney cortical thickness, mm (mean ± SD)	9.34 ± 3.15	8.47 ± 3.58	0.03

Table 3: Association between anemia and stages of chronic kidney disease

Variables	HBC, mg/dL M: <13.00 F: <12.00 N=57 (%)	HBC, mg/dL M: >13.00 + F: >12.00 N-87 (%)	P-value
CKD Stage 3a	5 (8.77)	28 (32.18)	0.003
CKD Stage 3b	11 (19.30)	36 (41.38)	
CKD Stage 4	22 (38.60)	20 (22.98)	
CKD Stage 5 (non-dialytic)	19 (33.33)	3 (5.26)	

HBC-hemoglobin concentration

The severity of anemia was positively, though not uniformly related to the stage of CKD (Table 3) as, a higher percentage of participants with Stage 3a disease had normal HBC while a higher percentage of Stage 5 disease had anemia, P<0.001.

Table 4: Association between anemia and participant' characteristics

Variables	Anemia N=57 (%)	No anemia 87 (%)	OR	95% CI	P-value
Sex					
Males	34 (41.46)	48 (58.54)	0.94	0.93-1.86	0.06
Females	23 (37.10)	39 (62.90)			
Age					
<60	37 (31.36)	81 (68.64)	5.22	3.84-873	<0.001
>60	20 (76.92)	6 (23.08)			
BMI					
<25.0	22 (37.93)	36 (62.07)	0.74	0.51-1.05	0.2
>25.0	35 (40.70)	51 (59.30)			
Systolic BP					
<140	19 (21.35)	70 (78.65)	3.38	1.83-4.74	0.003
>140	38 (69.09)	17 (30.91)			
Diastolic BP					
<90	28 (32.18)	59 (67.82)	2.54	2.27-4.38	0.03
>90	29 (50.88)	28 (49.12)			
Bicarbonate, mmol/L					
<22.0	40 (50.00)	40 (50.00)	3.02	1.84-4.15	0.004
>22.0	17 (26.56)	47 (73.44)			
Anion gap, mEq					
<16	19 (21.11)	71 (78.89)	3.11	2.04-4.88	0.003
>16	38 (70.37)	16 (29.63)			
eGFR, ml/min					
<45	48 (43.24)	63 (56.76)	3-32	1.94-4.96	0.001
>45	9 (27.28)	24 (72.72)			
Albumin, mg/dL					
<35.0	8 (88.89)	1 (11.11)	5.85	3.62-7.27	<0.001
>35.0	49 (36.30)	86 (63.70)			
Urine ACR, mg/g					
<30	17 (19.77)	69 (80.23)	5-57	2.89-6.51	<0.001
>30	50 (73.53)	18 (26.47)			
Mean kidney length					
<9	23 (65.71)	12 (34.29)	2.75	2.21-4.55	0.003
>9.0	34 (31.19)	75 (68.81)			

Univariate analysis (Table 4) showed participants age, blood pressure, bicarbonate, anion gap, eGFR, serum albumin, urine albumin creatinine ratio and mean kidney length as independent associates of anemia.

Multiple regression analysis (Table 5) showed age, estimated glomerular filtration rate, serum albumin and urine ACR as independent predictors of anemia.

Table 5: Multivariate regression analysis

Variables	aOR	95% CI	P-value
Age	6.94	2.04-13.86	<0.001
Systolic blood pressure	1.02	0.88-1.06	0.09
Bicarbonate	1.2	1.08-2.97	0.05
Anion gap	1.0	0.85-1.69	0.07
Estimated glomerular filtration rate	2.1	1.33-3.06	0.03
Albumin	6.02	4.82-11.35	<0.001
Urine albumin creatinine ratio	5.92	3.64-9.77	<0.001
Kidney length	0.99	0.37-1.34	0.4

aOR-adjusted odds ratio, CI-95% confidence interval, eGFR-estimated glomerular filtration rate, ACR-albumin creatinine ratio.

DISCUSSION

We found in this cross sectional study a prevalence of 39.6% of anemia, with 37.80% in males and 41.93% in females. A negative relationship was found between the HBC and the stages of CKD. We also found in this study that the predictors of anemia in predialysis CKD were age, glomerular filtration rate, serum albumin and urine albumin creatinine ratio. The prevalence of anemia in this study is similar to the 43.1% reported by Nalado et al[26] in a study involving blacks and white South Africans. It is very much higher than the 20.6% and 18.2% found by Awan et al,[27] and Portoles et al[28] in an Indian/Asian population. Our prevalence is however much lower than the 75-79% found in some low and medium income nations of Africa and Asian.[8-10] Apart from differences in methodological procedure, differences in the diagnostic cut-off values may also play some part.

The relationship between the hemoglobin concentration and the stage of CKD depicted a positive pattern in our study. This is in agreement with Alagoz et al[29] and other authors who reported positive relationship between anemia severity and the stage of CKD.[30] Silverberg et al[31] and Nalado in separate studies, however found alteration in the known "sliding scale like descend" of the HBC as CKD progresses. Anemia is commonly reported from CKD stage 3 disease. The institution of iron supplementation, initially in oral forms, couple with an exaggerated compensatory response from the erythropoiesis stimulating sites and chemical substances can lead to raised HBC even with declining kidney function. It is reported that anemia treatment in CKD results in improvements in both the laboratory and clinical profile in the immediate, short term and long term outcome. However, in LINs, optimal therapy is not commonly achieved, as observed in our cohorts with stage 5 disease who were receiving ESAs.

In our study, males were less likely to be anemic compared to females and this mirrors findings from a previous study. More than a third of females in our study were in their active reproductive years, the monthly blood loss would have been expected to contribute to the higher incidence of anemia in them but the fact that most of these women were not taking an ACEI or an ARB that are known to inhibit erythropoiesis.[32] unlike the men tended to neutralize the contribution of women' monthly flow to anemia. The erythropoiesis enhancing actions of androgens in males could also contribute to the higher HBC in males.[33]

We found a negative relationship between the HBC and age as previously reported.[34] The renal function decline with aging (physiologic or pathologic) coupled with physiologic reductions in androgen, necessitates an accompanying reduction in erythropoiesis. The negative relationship between the HBC and the BMI in our study mirrors findings by Zhao et al.[35] The fact that majority of our cohorts were not in ESRD, could have explain this. as obesity is known to portray a better prognosis in CKD. It would have been expected that higher BMI entails better nutrition and higher serum albumin, which in this study had a

positive relationship with HBC, but the bimodal levels of albumin in inflammation (common in CKD) and in optimal nutrition, makes conclusive assertions difficult without involving other markers of inflammation.[36] The negative association between HBC and blood pressure in CKD is well reported. The incidence of left ventricular hypertrophy (LVH) and anemia that complicate CKD are known to be concurrent events in a cause and effect relationship. Anemia induces cardiac enlargement and LVH in CKD. Progression of LVH could lead to heart failure which worsens the fluid retention, increases plasma volume causing hemodilution and worsening red cell indexes.[16]

The higher incidence of anemia in CIN compared to other etiologic factors agrees with findings from a previous study. The affectation of the fibroblast cells of the peritubular interstitium (site of erythropoiesis) in CIN makes anemia a very common finding in them, often times, anemia becoming out of proportion to the stage of CKD.[37, 38] The rising trend of the use of weight reducing (slimming) substances which could lead to CIN may also contribute to the higher incidence of renal anemia in CIN.[39] The higher prevalence of anemia in stage 5 than stage 4 disease despite the use of ESAs in stage 5 agrees with previous findings.[4] Suboptimal anemia correction in ESRD is commonly attributed to poor access to these drugs on account of the cost and infection and other inflammatory conditions that become more prevalent as kidney function decline.

The higher phosphate in females in this studies mirrors findings by Onufrak et al.[40] But disagrees with previous studies that reported the reverse. In our clime, males commonly take more animal protein, particularly meat, than women and so are expected to have higher serum values. This finding may give credence to the fact that phosphate retention results more from low excretion than increased intake considering the fact that women had lower eGFR than men.

The positive relationship between the severities of anemia and metabolic acidosis agrees with previous findings as Moranne et al[41] had reported the time course of the emergence and progression of features of CKD in relation to the GFR decline. The development of hyperparathyroidism herald metabolic acidosis and anemia in CKD. Though we didn't seek to assess the parathyroid hormone and CKD bone mineral disease (CKD-BMD) in this study, the higher phosphate, and Calcium Phosphate Product in addition to low bicarbonate and elevated anion gap in cohorts further confirms these associations in CKD.[12]

We found a positive relationship between serum albumin and the HBC and this is in agreement with finding from other studies. Hypoalbuminemia induces a stimulatory effect on the anti-diuretic hormone (ADH). The resulting poor salt water retention could lead to plasma dilution and hyponatremia. Although, plasma dilution would have lesser implication on the HBC compared with the hematocrit, the hemodilution it induces could give falsely low red blood cell indices,[42]

Some limitations encountered in this study included our inability to do a complete panel of iron studies. Been a cross sectional study, in design, a reassessment of variables was not done hence possible variation could have been missed. Other indices of nutrition like folate and Vitamin B_{12} were not assayed. We didn't seek to assess participants for CKD-BMD hence the parathyroid was not assessed. The strength of the study is hinged on detailed history concerning the etiology of CKD, use of exogenous nephrotoxins (NSAIDs, slimming drugs and herbal remedies), albuminuria testing and the assessment of drugs with effects on erythropoiesis.

CONCLUSION

Anemia in CKD results primarily from reduced renal erythropoietin production and is very common, with a prevalence of 39.58% in our study. It was

commoner in females, positively associated with age, the BMI and blood pressure, urine ACR and metabolic acidosis. Anemia was negatively correlated with serum albumin. Determinants of renal anemia were age, obesity, kidney function and female gender. Independent predictors of renal anemia were increasing age, stage 5 CKD, hypoalbuminemia and urine ACR. Improvement in kidney function, early and continuous assessment of the red cell indices couple with constant review of prescribed and non-prescribed drugs would be needed in CKD to minimize the various complications associated with renal anemia.

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