ANAEMIA AND ITS PREDISPOSING FACTORS IN PRE-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS IN JOS, NIGERIA

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is a rising global health problem. The association of CKD with anaemia, which causes are multifactorial, portends a poorer prognosis. When diagnosed and treated, CKD patients with anaemia experience improved cognitive function and quality of life. We determined the prevalence of anaemia and associated factors among pre‒dialysis CKD patients in Jos.

Methods: A cross‒sectional study was carried out in the Jos University Teaching Hospital (JUTH) from September 2016 to May 2017 involving 55 CKD patients enrolled consecutively. History, physical examination and laboratory investigations (full blood count by automated haemato‒analyser, reticulocyte count by manual supravital stain, serum creatinine by Jaffe reaction) were performed on all patients. The obtained data was analyzed using Epi Info verison 3.5.4 and p values <0.05 were considered statistically significant.

Results: The mean age of the CKD study population was 47±13years. The mean values for haemoglobin (Hb) concentration, mean cell volume (MCV) and mean cell haemoglobin (MCH) were 11.89±3.01g/dl, 86.6±51.2fl and 27.87±8.89pg respectively. The mean white blood cell (WBC) and platelet counts were 6.22±2.42 $X10^9$/L and 283±137 $X10^9$/L respectively. The mean reticulocyte production index was 1.2±1.5%. The prevalence of anaemia among CKD patients was 54.5%. Factors associated with anaemia were aging, female gender, history of diabetes mellitus and declining eGFR.

Conclusion: The prevalence of anaemia in pre‒dialysis CKD patients in JUTH is high. It is recommended that CKD patients be evaluated routinely for the possible factors that may predispose or predict anaemia.

Conflict of interest: Nil

Key words: Chronic kidney disease, anaemia

Introduction

Chronic kidney disease (CKD) is a rising global health problem. Approximately 500 million individuals globally have CKD, a number that translates to about 1 in every 10 adults been affected.[1] The prevalence of CKD is reportedly 10.4% in Ilesha, South–Western Nigeria.[2] The rise in CKD prevalence can be linked to other non–communicable diseases such as chronic hypertension and diabetes mellitus which are also on the increase in recent times.[3] In Nigeria and other developing countries, this burden is even higher due to the high cost of care required by CKD patients. Majority of these patients cannot afford renal replacement therapy which is the present long term treatment for CKD.[4] They therefore come down with complications of the disease earlier than their counterparts in the developed world. These complications may be cardiovascular, haematological, gastro–intestinal or endocrine.[5] Various haematological complications have been associated with CKD, foremost being anaemia. The incidence of anaemia was found to increase with progression of the disease.[6] Other predisposing factors previously identified include increasing age, female gender and certain drugs. A prior history of diabetes mellitus also increases risk of developing anaemia in CKD patients. Anaemia is a contributing factor to many of the symptoms associated with reduced kidney function.[7] It also has direct adverse cardiovascular disease consequences.[7] Patients with anaemia due to CKD are at increased risk of hospitalization and lengthy hospital stay, reduced quality of life and increased mortality.[8] Treating anaemia in CKD patients reportedly has benefits such as improved physical performance, immune function, thermoregulation and cognitive function.[9,10] These make it important to prevent, identify and treat CKD patients with anaemia.

Materials and methods

Patients were consecutively enrolled from the Nephrology clinic in JUTH after ethical approval was granted and informed consent to participate in the research was obtained. These patients were already diagnosed and staged following estimated glomerular filtration rate (eGFR) calculation using the CKD Epidemiology Collaboration (CKD–EPI) equation. Earlier evidences of kidney damage were also documented from urine, blood and or by imaging studies. For the purpose of the study, a repeat serum creatinine was however done to confirm present CKD stage. Exclusion criteria included prior history of dialysis and recent blood transfusion (<3months). Relevant history and physical examination findings were documented in a case record form. Venous blood was obtained into ethylene di–amine tetra–acetic acid (EDTA) anticoagulated bottle aseptically for immediate automated full blood count (Sysmex KT 2000–i1 Haematology auto–analyzer) while peripheral blood film was also made for quality control. A manual reticulocyte count (supravital stain technique) was done and reticulocyte index was calculated as:

$$= \frac{\text{Observed reticulocyte \% x Measured Hb (g/dL)}}{\text{Expected normal Hb for patient (g/dL) x Correction factor for premature release}}$$

All blood films were reported by trained haematologist at the hospital□s haematology laboratory. Anaemia was defined using World Health Organization (WHO) criteria, <13.0g/dl for men and <12.0g/dl in non–pregnant women {mild anaemia at Hb concentration 10.0–12.9g/dl for men and 10.0–11.9g/dl for non–pregnant women; moderate anaemia at Hb concentration 7.0–9.9g/dl and severe anaemia at Hb concentration <7g/dl for both genders}. The obtained data was analyzed using Epi Info verison 3.5.4 and p values <0.05 were considered statistically significant.

Results

We evaluated a total of 55 pre-dialysis CKD patients, comprising 20 males and 35 females, between September, 2016 and May, 2017. Their clinical and laboratory data are presented in Table 1. The mean (± SD) age of the study population was 47±13 years with M: F ratio of 1:2. Identified aetiologies for CKD were hypertension (38.2%), diabetes mellitus (32.7%), chronic glomerulonephritis (18.2%) and others (10.8%). Common physical examination findings included pallor (41.8%), pedal swelling (25.5%) and facial swelling (14.5%). Some drug classes used by the patients were angiotensin converting enzyme inhibitors [ACEIs] (67.3%), calcium channel blockers [CCBs] (63.6%), Diuretics (67.3%), beta blockers (23.6%) and angiotensin receptor blockers [ARBs] (18.2%). The aetiology of CKD and distribution of patients among CKD stages are shown in Figure 1 and 2 respectively. The mean values for Hb concentration, MCV and MCH were 11.89±3.01 g/dl, 86.6±51.2 fl and 27.87±8.89 pg respectively. The mean WBC and platelet counts were 6.22±2.42 $X10^9$/L and 283±137 $X10^9$/L respectively. The mean reticulocyte production index was 1.2±1.5%. The prevalence of anaemia among CKD patients was 54.5%. This comprised mild anaemia (27.3%), moderate (20%) and severe anaemia (7.2%). Peripheral blood film findings were predominantly a normocytic normochromic red cell picture, with microcytic hypochromic and macrocytic red cells seen in 10.9% and 7.3% of patients respectively. Other findings were burr cells, schistocytes and target cells. There was a negative correlation between age and haemoglobin concentration (r= –0.17; p= 0.20) though not statistically significant. There was a statistically significant difference in haemoglobin concentration between males and females (X^2= 10.48; p= 0.02). The prevalence (but not the severity) of anaemia was worse in females than males. Among the CKD patients, there was a statistically significant, negative association between haemoglobin concentration and diabetes mellitus as the aetiology of CKD when compared to other CKD aetiologies (X^2= 11.02; p= 0.01). The frequency of anaemia among CKD patients with diabetes mellitus (61.1%) was higher than in others without diabetes mellitus (43.2%). There was no statistically significant difference in the haemoglobin concentration of CKD patients who used ACEIs compared to those who did not (X^2= 43.65; p= 0.49). The prevalence of anaemia in CKD patients on ACEIs was 54.1% while it was 55.5% in those not on ACEIs. There was also no statistically significant difference in the haemoglobin concentration of those who used ARBs and those who did not (X^2= 48.28; p= 0.30). The prevalence of anaemia among CKD patients on ARBs was 50% as opposed to 55.6% in those who were not on ARBs. There was a positive correlation between haemoglobin concentration and eGFR which was statistically significant (r= 0.51; p< 0.01). This is represented in Figure 3.
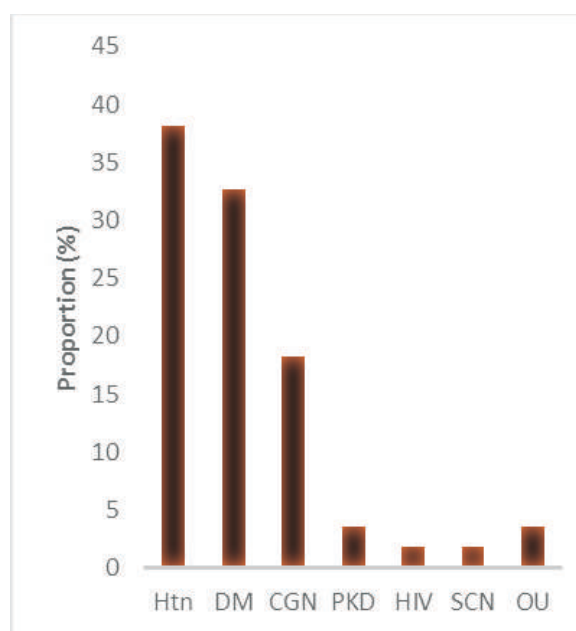
Table 1: CLINICAL AND LABORATORY DATA OF PATIENTS

Variable (mean±SD)	Males (n=20)	Females (n=35)	p
Age (years)	48±15	47±12	0.73
Blood pressure (mmHg)			
Systolic	126±21	140±29	0.06
diastolic	82±13	86±16	0.34
BMI (kg/m^2)	24.7±5.8	26.6±6.3	0.27
eGFR (ml/min/1.73m^2)	41.4±25.5	31.5±18.1	0.09
Hb concentration (g/dl)	12.7±4.1	11.4±2.1	<0.01
WBC (x10^9/L)	7.0±3.0	5.7±1.9	0.05
Plt (x10^9/L)	302±172	290±109	0.75
RDW (%)	15.6±3.6	15.5±2.5	0.93
MCV (fL)	81.3±4.8	78.9±8.0	0.23
MCH (pg)	26.8±3.1	26.8±2.5	0.97
RPI (%)	1.5±2.1	1.1±1.1	0.31
Anaemia*	9(45)	21(60)	
Mild	4(20)	11(31.4)	
Moderate	2(10)	9(25.7)	
Severe	3(15)	1(2.9)	

*= (n,%)

All CKD patients in CKD class two had a normal haemoglobin concentration. Mild anaemia was observed in CKD class three, four and five at 40%, 42.9% and 7.7% respectively. Moderate anaemia was seen in CKD class three, four and five at 20%, 14.3% and 38.5% respectively. Severe anaemia was noted in only CKD class three (5%) and class five (23.1%) CKD patients.

FIGURE 1: AETIOLOGY OF CKD AMONG THE STUDY POPULATION

KEY
Htn: Hypertension
DM: Diabetic nephropathy
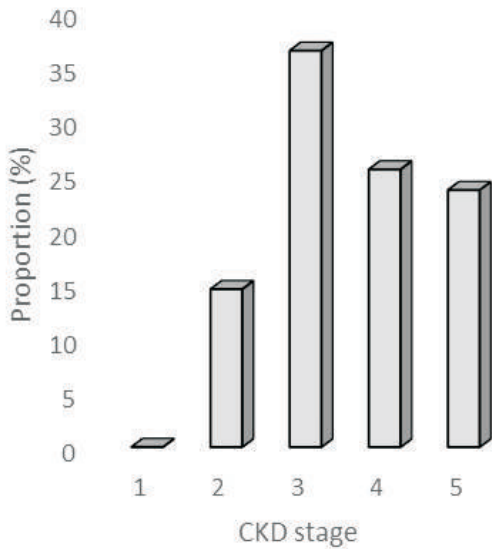**CGN:** Chronic glomerulonephritis
PKD: Polycystic kidney disease
SCN: Sickle cell nephropathy
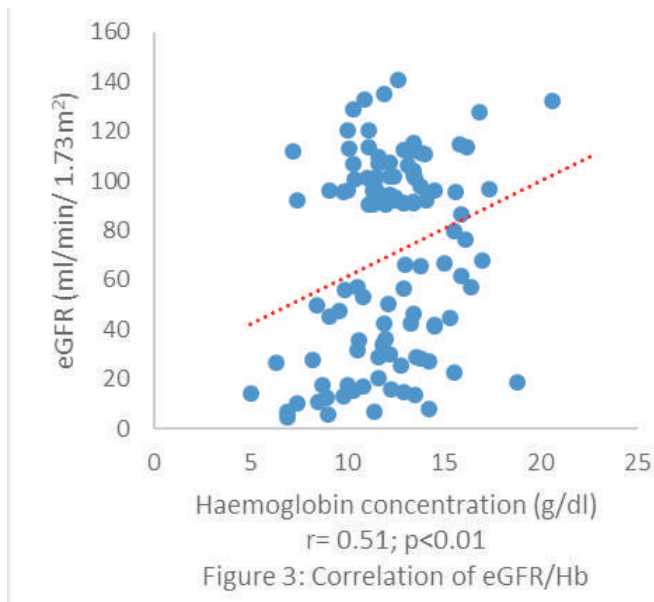**HIV/AIDS:** Human immunodeficiency virus infection/Acquired immune deficiency syndrome
OU: Obstructive uropathy

FIGURE 2: EGFR CLASS DISTRIBUTION OF STUDY POPULATION

KEY:
1= GFR >90ml/min/1.73m^2
2= GFR between 60–89ml/min/1.73m^2
3= GFR between 30–59ml/min/1.73m^2
4= GFR between 15–29ml/min/1.73m^2
5= GFR <15ml/min/1.73m^2

r= 0.51; p<0.01
Figure 3: Correlation of eGFR/Hb

Discussion

The prevalence of anaemia among CKD patients in this study was as high as 54.5%. There were similar reports from developed countries such as Catalonia, Spain (58.5%), North Korea (44.9%) and China (51.5%).[11–13] However, lower values were noted in the National Health and Nutritional Examination Survey (NHANES) in USA (15.4%) and in a cohort study in Japan (32.3%).[14, 15] Higher values were observed in Africa and Nigeria previously. Amoako *et al* found out that 86.7% of CKD patients in Ghana had anaemia at presentation.[16] In Enugu–Nigeria,

Ijoma *et al* reported that 77.5% of CKD patients were anaemic and 94.3% of end stage renal disease patients in Port Harcourt had anaemia as stated by Wokoma *et al*.[6, 17] These studies included patients who were already on dialysis as well as a high number of patients with advanced renal disease. These may explain the higher values as compared to this study which focused on pre–dialysis CKD patients. However, Akinsola *et al* in Ile–Ife, southwest Nigeria, who studied 37 pre–dialysis CKD patients found comparable results to that of this study.[18]

A predominantly normocytic normochromic red cell picture in this study is as expected in most chronic disorders and similar to the finding of Akinsola *et al.*[18] Also, 29.1% of patients had a microcytic hypochromic picture which may depict on-going iron deficient erythropoiesis Those patients (7.3%) who had a macrocytic blood picture may require further investigations to confirm Vitamin B12 and folate deficiency. Possible causes of these include malabsorption, uraemia-induced inhibition of erythropoiesis as well as disordered iron homeostasis.[19]

A negative correlation between age and haemoglobin concentration (r= −0.17; p= 0.20) was noted in this study. Though not statistically significant, this is expected physiologically, as the bone marrow haemopoietic capacity reduces with age due to marrow replacement by adipocytes.[20] Among CKD patients, Chen *et al* equally found an increase in anaemia with age when they compared younger and older adults in China.[21]

In this study, there were more females with mild and moderate anaemia, while severe anaemia was more in males. This is not in total agreement with most reports. Ijoma *et al* found that the frequency of anaemia was higher in females than males and this was uniform across all forms of anaemia and CKD classes.[6] The finding of this study was a statistically significant difference in haemoglobin concentration between males and females (X^2= 10.48; p= 0.02). Due to menstrual blood loss as well as events accompanying parturition and lactation, adult females may also be more anaemic than adult males.[22, 23] These influences in women may be heightened by comorbidities such as CKD making them more affected by anaemia than their male counterparts.

There was no statistically significant difference in the haemoglobin concentration of CKD patients who used ACEIs compared to those who did not (X^2= 43.65; p= 0.49). The prevalence of anaemia in CKD patients on ACEIs was 54.1% while it was 55.5% in those not on ACEIs. There was also no statistically significant difference in the haemoglobin concentration of those who used ARBs and those who did not (X^2= 48.28; p= 0.30). The prevalence of anaemia among CKD patients on ARBs was 50% as opposed to 55.6% in those who were not on ARBs. These drugs (ACEIs and ARBs) are known to induce anaemia by sparing a circulating natural inhibitor of the bone marrow, which is usually metabolized by angiotensin converting enzyme (ACE) which they inhibit.[8] In a meta-analysis by Cheungpasitporn *et al*, an association between anaemia and the use of ACEIs and ARBs was documented.[24] They concluded with a recommendation of routine monitoring of haematological parameters in the concerned patients.[24] In a study on diabetic CKD patients, Inoue *et al* found that only ARB use (but not ACEIs) was associated with modest decrease in haemoglobin concentration.[25] Also, in a study on the effect of ACEIs and ARBs on haemoglobin level, Ajmal *et al* opined that these drugs be used with consideration especially in patients already at risk of developing anaemia.[26] This includes patients with diabetes mellitus and hypertension who formed majority of CKD patients enrolled in this study. The smaller sample size of this study compared to that in the above reports may account for the difference in these findings. There was also no local data for comparison. However, this study revealed that the prevalence of anaemia in CKD patients on ACEIs was higher than in those on ARBs, a finding in keeping with that of Ajmal and his colleagues.[26]

Wokoma *et al* and other researchers reported a positive correlation between eGFR and haematocrit.[6, 8, 17] This was at par with the finding of this study which showed a positive correlation

between haemoglobin concentration and eGFR among CKD patients (r= 0.5, p<0.01). Due to worsening renal function, it is expected that the incidence and severity of anaemia should rise because of the declining kidney☐s role in erythropoietin synthesis.[27] It is therefore not surprising that the enrolled CKD patients in class five had a higher burden of moderate and severe anaemia than those in classes three and four. Worthy of note is the finding of a normal haemoglobin concentration among all those in eGFR class two. Adejumo et al had a similar experience and reported the prevalence of anaemia increased across the CKD classes of their study participants.[28] Ijoma et al had in an additiona lwork reported that the severity of anaemia worsened with decline in eGFR just as observed in this study.[6]

Barbieri et al stated that CKD patients with diabetes mellitus had the highest risk of developing anaemia.[29] Poor glycemic control and increased risk of cardiovascular disease have been implicated for this additional risk in diabetics.[30] The prevalence of anaemia in diabetic patients with CKD in this study was 61.1% while 43.2% was the case in others without diabetes mellitus. A statistically significant difference in the haemoglobin concentration when comparing those CKD patients with and without diabetes mellitus was found (X^2= 11.02; p= 0.01). This was similar to what Adejumo et al found when they compared diabetics with renal insufficiency and non−diabetic controls.[30] Several reports of studies outside Nigeria concurred with this finding.[31,32]

Conclusion
The prevalence of anaemia in pre−dialysis CKD patients in JUTH is high. Predisposing factors include aging, female gender, history of diabetes mellitus and a declining eGFR. It is recommended that anaemic CKD patients be screened routinely for the possible aetiology.

Acknowledgement

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