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TITLE: Assessment of iron status in pre-dialysis chronic kidney disease in a Nigerian tertiary Hospital.

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ABSTRACT

BACKGROUND: Anemia in chronic kidney disease (CKD) is associated with poor overall outcome if not promptly managed with erythropoietin when indicated. Iron deficiency (ID) accounts for about 40% of erythropoietin hypo-responsiveness; however information on iron status in pre-dialysis CKD patients in Nigeria is limited. This study assessed iron status and associated factors in pre-dialysis CKD patients in Southern Nigeria

METHODS: A cross-sectional study that assessed and compared iron status in 100 pre-dialysis CKD subjects and 90 healthy controls.

RESULTS: Mean age of the CKD subjects was 49.39 ± 14.84 years. ID was present in 14% of CKD subjects compared to 3% of the controls ($p=0.036$). Amongst CKD patients with ID, 11(85.7%) had functional ID while 3(14.3%) had absolute ID. Serum ferritin was significantly higher in the pre-dialysis subjects ($p=0.001$). There was no significant gender difference in iron indices among the CKD subjects.

Functional ID was present in 11(11%) of the CKD subjects compared to none among the control subjects ($p=0.005$). There was no significant association between ID and age, gender, aetiology and stage of CKD.

CONCLUSION: Functional ID was the predominant form of ID in our pre-dialysis CKD patients and there was no significant association with age, gender, stage or aetiology or CKD.

Keywords: Iron status, pre-dialysis CKD, functional iron deficiency, absolute iron deficiency

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in chronic kidney disease (CKD).¹⁻³ Factors that have been found contributory to CVD in CKD patients are highly prevalent cardiovascular risk factors and lack of appropriate intervention aimed at mitigation or modification of these factors.⁴ These cardiovascular risk factors include diabetes mellitus, hypertension, smoking, dyslipidaemia, left ventricular hypertrophy (LVH), anaemia, albuminuria, homocysteinaemia, inflammation, uremia, abnormalities of calcium and phosphate metabolism and reduced vascular compliance.^{4,5} Early treatment of these risk factors is important in retarding progression of CKD and preventing attendant cardiovascular morbidity and mortality.^{2,4}

Anemia is one of the non-traditional cardiovascular risk factors that commonly occurs in CKD patients.⁵⁻⁸ Causes of anemia in CKD are multifactorial including relative deficiency of erythropoietin, malnutrition, inflammation, uremic toxins, bone marrow fibrosis, chronic blood loss, reduced red cell life span and abnormal platelet function.

Anemia contributes significantly to development of CVD in CKD patients by causing left ventricular dilatation and hypertrophy.⁹ Anemia is also associated with rapid progression to end stage renal disease, prolonged hospitalization, exercise intolerance, impaired cognitive and sexual function and reduced quality of life in CKD patients, hence there is need for early treatment.¹⁰⁻¹³ Left ventricular hypertrophy may be reversed and other secondary effects of anemia in CKD may be improved if correction of anemia is instituted early with erythropoietin.¹⁴⁻¹⁶ However patients may become unresponsive to EPO treatment in the presence of iron deficiency which may be functional or absolute.¹⁷ Approximately 40% of patients with EPO resistance have iron deficiency. Deficiency of iron which is an integral

element in hemoglobin leads to impaired hemoglobin production.^{17,18} The common causes of iron deficiency in CKD include anorexia, vomiting, reduced intestinal absorption, inflammation, infection, acute and or chronic blood loss. CKD patients are also at risk of iron overload if iron therapy is instituted without close monitoring of iron status with possible attendant complications such as hospitalization, cardiovascular disease and mortality.¹⁹⁻²¹

Serum iron, ferritin, transferrin saturation, total binding iron capacity, percentage hypochromic red cells, reticulocyte hemoglobin content, zinc protoporphyrin and soluble transferrin receptors are useful in iron status assessment. However, two most widely available and used tests for assessing iron status are the transferrin saturation (TSAT) and serum ferritin even though they have limitations in terms of specificity and sensitivity in patients with CKD.²²

There is still limited information on iron status and associated factors in pre-dialysis CKD patients in Nigeria. This study assessed iron status and associated factors in predialysis CKD patients. The findings of this study, add to the body of knowledge and also provide information that may be helpful in reviewing and improving local guidelines for anaemia management in CKD.

METHODS

This was a hospital-based cross sectional analytical study carried out in the University of Benin Teaching Hospital (UBTH) over a period of one year from the time of ethical approval (October 2013- November 2014). Consecutive pre-dialysis CKD patients who met the inclusion criteria were recruited over one year period from the nephrology clinic, medical wards and the emergency unit of the hospital. Controls were recruited from among healthy staff of the hospital and patients relatives who did not have CKD. The consent of all participants was gotten before recruitment into the study by filling and signing a consent form.

Ethical clearance for this study was gotten from the Ethics and Research Committee of University of Benin Teaching Hospital on the 2nd of October 2013 with protocol number ADM/E 22/A/VOL.VII/956.

SAMPLE SIZE

This was calculated using 94% as the prevalence of anemia in CKD patients using the Leslie Kish formula for sample size determination in a finite population as shown below.²³

$$N = \frac{Z^2 P(1-P)}{E^2}$$

Where

N = Sample size

Z = Value of 95% confidence interval = 1.96

P = Prevalence 94% (0.94)

E = Sampling error = 0.05

$$N = \frac{1.96^2 \times 0.94 (1 - 0.94)}{0.05^2}$$

$$N = 1.96^2 \times 0.94 \times 0.06 / 0.05^2$$

$$N = 86.66$$

N is approximately 87

The minimum sample size in this study was 96 after including 10% attrition rate.

A total of 100 predialysis CKD subjects and 90 age and sex matched apparently healthy adults without CKD were involved in the study.

Inclusion criteria were newly-diagnosed CKD patients or those on conservative management who were ≥ 18 years of age and gave informed consent to participate in the study while exclusion criteria were CKD patients on renal replacement therapy (RRT), those with HIV infection, hemoglobinopathies, chronic infections, malignancy, history of cigarette smoking, use of erythropoiesis stimulating agents and iron products for a period of 4 weeks to the time of evaluation or history of blood transfusion in the previous 4 weeks.

Ten mls of blood were collected from participants of this study for serum creatinine, erythrocyte sedimentation rate (ESR), serum iron, total iron binding capacity (TIBC), ferritin levels and transferrin saturation. Estimated glomerular filtration rate (eGFR) was calculated using Modification of Diet in Renal Disease that has been previously validated in Nigerians. ²⁴

Definition of Terms

Absolute iron deficiency was defined as TSAT < 20%; serum ferritin < 100ng/ml while functional iron deficiency was defined as TSAT < 20%; serum ferritin >100ng/ml.²²

Transferrin saturation was calculated using the formula (TSAT) = SI/TIBC X 100;²²

Where TIBC ($\mu\text{g/dl}$) = Iron level + UIBC and Serum Iron.

CKD was defined as presence of markers of kidney damage and or estimated GFR of less than 60 ml/min/1.73 m² for at least three months²⁴. Predialysis CKD patients were those patients who fulfilled the criteria for the definition of CKD and had not been dialysed.

CKD stages were defined according KDIGO as follows: stage 1, eGFR greater than 90 ml/min/1.73 m² and/or persistent proteinuria; stage 2, eGFR of 60 to 89 ml/min/1.73 m² and/or persistent proteinuria; stage 3, eGFR of 30 to 59 ml/min/1.73 m²; stage 4, eGFR of 15 to 29 ml/min/1.73 m²; and stage 5, eGFR less than 15 ml/min/1.73m².²⁵

Data Analysis

Data entry and analysis was performed using International Business Machines Statistical Product and Service Solution (IBM-SPSS) Version 21. Data was presented as frequencies, percentages and means (standard deviation). Frequencies were compared using chi-square test. Continuous variables were presented as means and standard deviation for unskewed data and median, interquartile range for skewed data. Student t-test was used to compare mean values of the sub-groups for those with unskewed data while Mann Whitney U was used to compare skewed data.

Pearson's correlation test was used to find association between continuous variables. A p-value ≤ 0.05 was considered as statistically significant for all test conducted.

RESULTS

One hundred pre-dialysis CKD patients and ninety aged matched controls participated in the study with a mean age of 49.39 ± 14.84 years and 52.66 ± 13.90 years respectively. There were 56 (58.9%) male pre-dialysis subjects and 39 (41.1%) male controls while there were 44 (46.3%) female pre-dialysis subjects and 51 (53.7%) female controls. The difference was not statistically significant ($p=0.081$). (Table 1)

Sixty-two (62%) of the CKD subjects were young or middle aged. Fifty-one (61.9%) of the control subjects had tertiary level of education compared to 32 (38.6%) of the CKD subjects. This was statistically significant ($p=0.001$). Fourteen (14%) of the CKD subjects were in stage 1, 8 (8%) in stage 2, 29 (29%) in stage 3, 14 (14%) in stage 4 and the remaining 16 (16%) were in stage . (Table 1) The etiology of CKD in the study subjects were hypertension (32%), diabetes mellitus (31%), CGN (25%) and obstructive uropathy (12%). (Figure 1)

There were 14 (14%) predialysis CKD patients found to have iron deficiency which was significantly higher than 3 (3%) present in the control group ($p=0.036$). Amongst CKD patients with iron deficiency, 85.7% had functional iron deficiency, while 14.3% had absolute iron deficiency. (Figure 2)

There was significant difference between haemoglobin concentration (8.71 ± 2.70 versus 12.93 ± 8.7 , $p < 0.001$) and packed cell volume (26.64 ± 12.17 versus 38.05 ± 6.11 , $p < 0.001$) between the pre-dialysis CKD and control group. The ESR and serum ferritin levels were significantly higher in the predialysis subjects than the controls ($p \text{ value} < 0.001$). There was no statistical difference in the mean values of the serum iron, transferrin saturation, TIBC between the CKD and control groups. (Table 3)

The mean serum creatinine was significantly higher in the CKD group compared to the control group. (3.28 ± 2.75 mg/dl versus 0.90 ± 0.78 mg/dl; $p < 0.001$) while the mean eGFR in the CKD subjects was significantly lower compared to the control group (35.74 ± 26.26 ml/min/1.73m² versus 114.19 ± 41.24 ml/min/1.73m²; $p < 0.001$) (Table 2) There was no significant difference in median values of iron indices between male and female pre-dialysis CKD subjects. (Table 4)

Fourteen (14%) of the pre-dialysis CKD group had low TSAT compared to 3(3%) in the control group. ($p = 0.036$). There was no significant difference in proportion of subjects who had low ferritin and absolute iron deficiency between the control and CKD subjects. However, functional iron deficiency was present in 11(11%) of the CKD subjects compared to none among the control subjects. This was significant with a p value of 0.005 (Table 5). There was no significant association between age, gender, aetiology of CKD, CKD stage and functional iron deficiency. (Table 6)

There was significant negative correlation between estimated glomerular filtration rate and TIBC ($r = -0.226$, $p = 0.024$). (Table 7) There was also significant positive correlation between serum ferritin and ESR ($r = 0.312$, $p = 0.002$) (Table 8)

DISCUSSION

This study showed that 14% of the CKD subjects were iron deficient, which was higher than 3% found in healthy control subjects using a cut off value of greater than 20% and 100ng/ml for TSAT and serum ferritin respectively in the definition of iron deficiency. Functional iron deficiency was the predominant form of iron deficiency in the CKD subjects accounting for 85.7% of the CKD subjects with iron deficiency.

The prevalence of iron deficiency in our study is lower than 31.2% and 56.1% reported in previous studies by Mohammed and Arogundade et al.^{26,27} However, the variation in the prevalence may be accounted for by differences in methodology used in the various studies. Arogundade et al used a higher cut off of serum ferritin of >300ng/ml and TSAT of >25% for definition of normal iron store.²⁷ Iron status was assessed in all our CKD subjects irrespective of hemoglobin concentration unlike in the study of Arogundade et al²⁶ where iron status was assessed in those with anemia using a cut off of hemoglobin concentration of <11g/dl. Mohammed found iron deficiency in 31.2% of their study population in a similar study done in Northern Nigeria using the similar cut off values for defining iron deficiency as done in our study.²⁶ The higher prevalence of iron deficiency in the study compared to this present study may be related to the fact that the study involved both pre-dialysis CKD and those on maintenance HD.

The predominant form of iron deficiency in this study is functional iron deficiency which is similar to report of some previous studies.^{26,27} However, Lukaszka et al reported that absolute iron deficiency was more common than functional iron deficiency in their study population.²⁸ This latter study was done in white subjects with a higher proportion (61%) in early CKD stages

2 and 3. The relatively lower level of inflammation in the white population compared to the black^{29,30} and the fact the study involved more patients who were in early CKD stage compared to our study may be partly responsible for difference in pattern of iron deficiency.

Level of inflammation assessed by ESR, a non-specific inflammatory marker was significantly higher in the CKD subjects compared to the controls. This may explain why functional iron deficiency whose underlying aetiological factor is inflammation was higher. Ferritin which is an acute phase reactant was the only parameter among the iron indices assessed that showed significant correlation with ESR. Functional iron deficiency is characterized by presence of adequate body iron store in the reticuloendothelial system but there is impaired iron release to meet the demand for erythropoiesis.

The mean value of serum ferritin was significantly higher in CKD subjects than non-CKD control which is similar to findings from previous studies involving either predialysis CKD patients or those already on renal replacement therapy.^{31,32} The mean value of serum ferritin is similar to that reported by Ifudu et al,³³ but lower to that reported by Jairam.³² The higher mean value of ferritin in the latter study may be related to the fact that they studied end stage renal disease patients who were more likely to have higher degree of inflammation that may raise the level of serum ferritin. This is also corroborated by the positive association observed between ESR and ferritin in this study even though it is a non-specific inflammatory marker.

There was no significant difference in the mean values of serum iron and TIBC between the control and CKD subjects which is similar to previous report by Mohammed.²⁶ There was also no significant difference between TSAT values in the CKD and control subjects in our study which is similar to reports by Oluboyode et al and Deori et al^{33,34} however Mohammed and Jairam et al

^{26,32}reported a significantly lower value in the CKD patients compared to controls in their studies. This may be because our study only included pre-dialysis patient unlike the latter studies that involved end stage renal disease patients on RRT who were more likely to be iron depleted compared to pre-dialysis subjects.

There was no significant difference in iron indices between male and female pre-dialysis CKD subjects in this study. Mohammed also reported similar pattern except ferritin that was significantly higher in male CKD patients.²⁶ There was no significant association between serum iron indices and estimated GFR except TIBC which showed a positive association. Total iron binding capacity (TIBC) is the maximum amount of iron needed to saturate plasma transferrin which is the primary iron-transport protein and increased in state of iron deficiency. This may therefore imply that with worsening renal function, there is tendency towards iron deficiency.

There was no significant association between etiology and stage of CKD, age, gender and iron deficiency. A slightly higher proportion of the female CKD patients had iron deficiency than the male CKD patients. This may be related to additional blood loss that occurs in the females during menstruation for those with mild to moderate renal insufficiency who are not amenorrhoeic. Therefore, iron status should be evaluated in CKD patient before commencing on iron supplementation irrespective of their age, CKD stage, gender or aetiology of CKD.

Limitation of this study was that it was difficult to get equal representation of all stages of CKD because it was carried out in a tertiary hospital setting where most of the patients were likely to present late. Also, underlying inflammation could not be completely ruled out in these patients which could have affected the serum ferritin level.

In conclusion, this study showed that functional iron deficiency is the predominant form of iron deficiency in our patients and there was no significant association with age, gender, aetiology or stage of CKD.

Recommendations:

1. All CKD patients should be evaluated for iron deficiency.
2. Initiation of iron therapy and follow-up should be guided by iron status of the patient, hence iron status should be checked regularly as not all CKD patients may require iron therapy
3. Multi-centre studies to be conducted across Africa to further characterized iron status in our CKD patients.

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Table 1: Characteristics of the Study Population

	Pre-dialysis subject n=100 n(%) / mean(sd)	Control n=90 n(%) / mean(sd)	p-value
Age (years)			
Mean age	49.39(14.8)	52.66(13.90)	0.120
≤45	42(60.0)	30(40.0)	0.350
46-65	20(47.6)	22(52.4)	
>65	38(50)	38(50.0)	
Gender			
Male	56(58.9)	39(41.1)	0.080
Female	44(46.3)	51(53.7)	
Level of Education			
Primary	30(57.7)	22(42.3)	0.001
Secondary	38(69.1)	17(30.9)	
Tertiary	32(38.6)	51(61.9)	
Stage of CKD			
1	14(14)		
2	8(8)		
3	29(29)		
4	33(33)		
5	16(16)		

Table 2: Hematological Indices of Pre-dialysis CKD and Control subjects (N=190)

	Subject n=100 mean(SD)	Control n=90 mean(SD)	p-value
Hb concentration (g/dl)	8.71(2.70)	12.93(8.7)	<0.001
Packed cell volume (%)	26.64(12.17)	38.05(6.11)	<0.001
ESR (mm/hr)	51.99(32.74)	17.50(8.59)	<0.001
Serum Iron (µg/dl)	101.67(57.16)	99.47(34.77)	0.752
Serum Ferritin (ng/ml)	223.23(121.90)	158.82(68.06)	<0.001
TIBC (µg/dl)	281.05 (238.01)	259.91(78.20)	0.422
Transferrin saturation (%)	45.94(45.83)	46.95(48.17)	0.882
Creatinine (mg/dl)	3.28(2.75)	0.90(0.78)	<0.001
eGFR(ml/min/1.73m ²)	35.74(26.26)	114.19(41.24)	<0.001

TABLE 3: COMPARISONS OF IRON INDICES BETWEEN MALE AND FEMALE PRE-DIALYSIS CKD SUBJECTS.

IRON INDICES	MALE Median(IQR)	FEMALE Median(IQR)	P value
SERUM IRON ($\mu\text{g}/\text{dl}$)	83.44(79)	107.05(87)	0.84
TSAT (%)	38.6(27.5)	35.2(37.2)	0.55
SERUM FERRITIN (ng/ml)	215.8(149)	218.6(165)	0.84
TIBC ($\mu\text{g}/\text{dl}$)	239.7(143)	286.5(108)	0.07

TABLE 4: Comparison of TSAT, serum ferritin and Iron deficiency between CKD and Control subjects

	CKD GROUP	CONTROL GROUP	P value
Transferrin Saturation			
< 20%	14(14%)	3(3.3%)	0.036
≥ 20%	86(86%)	87(96.7%)	
Serum Ferritin			
<100	15(15%)	13(14.4%)	0.839
≥100	85(85%)	77(85.6%)	
Functional Iron Deficiency			
Present	11(11%)	0(0%)	0.005
Absent	89(89%)	90(90%)	
Absolute Iron Deficiency			
Present	3(3%)	3(3.3%)	0.955
Absent	97(97%)	87(96.7%)	

TABLE 5: Association between age, gender aetiology and stage of CKD and Iron deficiency amongst CKD subjects

	Present	Absent	P value
AGE			
≤ 45 years	6(14.3%)	36(85.7%)	0.58
Above 45 years	8(13.8%)	50(86.2%)	
GENDER			
Male	6(10.7%)	50(89.3)	0.22
Female	8(18.2%)	36(81.8%)	
AETIOLOGY			
Diabetes Mellitus	3(9.7%)	28(90.3%)	0.69
Hypertension	6(18.8%)	26(81.3%)	
Obstructive Nephropathy	1(8.3%)	11(91.7%)	
Chronic Glomerulonephritis	4(16.0%)	21(84.0%)	
CKD STAGE			
1	3(21.4%)	11(78.6%)	0.85
2	1(12.5%)	7(87.5%)	
3	3(10.3%)	26(89.7%)	
4	4(12.1%)	29(87.9%)	
5	3(18.8%)	13(81.3%)	

Table 6: Association between GFR and Iron Indices in CKD subjects

IRON INDICES	R	P value
Serum Iron	-0.129	0.202
Serum Ferritin	-0.141	0.162
Total Iron Binding Capacity	-0.226	0.024
Serum Transferrin Saturation	-0.026	0.796

Table 7: Association between ESR and Iron Indices in CKD subjects

IRON INDICES	R	P value
Serum Iron	0.061	0.547
Serum Ferritin	0.312	0.002
Total Iron Binding Capacity	0.131	0.194
Serum Transferrin Saturation	-0.029	0.775