

Iron Status in Patients with Pre-dialysis Chronic Kidney Disease in a Tertiary Hospital in North-central Nigeria

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ABSTRACT

Anaemia in CKD is associated with poor quality of life and cardiovascular disease. Iron deficiency anaemia contributes to the anaemia burden in patient with CKD but studies on iron status in patients with non-dialysis dependent CKD in Nigeria are sparse. The aim of the study therefore is to determine iron status of patients with CKD in a tertiary hospital in North-central Nigeria. We conducted a cross-sectional study on 130 patients with pre-dialysis CKD. We obtained data on the socio-demography, and etiology of CKD. We assessed the complete blood count, serum ferritin, transferrin, iron, total iron binding capacity (TIBC), transferrin saturation (TSAT), and serum creatinine. CKD epidemiology collaboration (CKD-EPI) was used to estimate glomerular filtration rate (eGFR). The mean age of the study participants was 55 ± 15 years with a male to female ratio of 2.3: 1. The mean haemoglobin was 9.8 ± 2.2g/dl and was worse as eGFR declined. Iron deficiency anaemia was present in 27.7% of the patients (17.7% had functional iron deficiency while 10% had absolute iron deficiency). The median serum ferritin was 257.50 (102.75 – 465.00) ng/ml, serum transferrin 298.00 (216.00 – 343.25) mg/dl, serum iron was 21.85 (11.80 – 29.63) umol/l, TIBC 74.00 (54.00 – 84.65) umol/l, and TSAT of 32.55 (19.06 – 43.00) %. There was no significant association between Iron deficiency anaemia and age, or gender. Functional iron deficiency is the major contributor to iron deficiency anaemia in our patients with pre-dialysis CKD. Initial assessment of iron status is recommended for patients with CKD, to inform early treatment.

Keywords: Anaemia, chronic kidney disease, iron deficiency, pre-dialysis.

INTRODUCTION

Anaemia, is a common manifestation and complication of CKD, and its occurrence is proportional to the severity of CKD¹. The burden of anaemia in CKD is huge globally, but higher in developing countries especially in Africa. The prevalence of anaemia in patients with pre-dialysis CKD in the United States was 47.7%². In Nigeria,

there is no national study on the burden of anaemia in CKD, but earlier studies in South-West and South-East reported prevalence of 69%, and 77.5% respectively^{3,4}. Anaemia in patients with CKD leads to poor quality of life, increased morbidity and mortality, and it is a major cardiovascular risk factor in CKD⁵. Furthermore, it is associated with a rapid

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decline in kidney function and increases the risk of progression to end-stage renal disease (ESRD)^{5,6}.

The etiology of anaemia in CKD is multifactorial, but it is mainly due to a decreased production of erythropoietin. In addition, iron deficiency which diminishes the efficacy of erythropoietin accounts for a significant proportion of anaemia in CKD. The third National Health and Nutrition Examination Survey (NHANES) of 1999-2004 found high rates of iron deficiency in adult men (57.8%-58.8%) and women (69.9% -72.8%) with CKD stage 3-5⁷. In North-West Nigeria, a study of 120 pre-dialysis patients with CKD reported the prevalence of iron deficiency of 78% when ferritin was used as an index for assessing iron deficiency⁸.

Iron deficiency in CKD usually results from impaired dietary intake, reduced gastrointestinal absorption, increased blood loss, infection and chronic inflammation⁹. Erythropoietin use often results in iron deficiency from insufficient iron stores for accelerated erythropoiesis and iron deficiency is the most common cause of poor response to erythropoietin administration^{10, 11}. Serum ferritin is a strong predictor of hospitalization and mortality in patients undergoing dialysis¹². Iron studies in CKD can be used to diagnose iron deficiency anaemia, guide decision on iron therapy and also monitor response of patients to erythropoietin-stimulating agents¹³. In Nigeria, iron deficiency anaemia has not been fully investigated, and poorly characterized, making it a challenge for therapeutic intervention¹⁴.

In this study, we investigated iron status in pre-dialysis CKD patients in the university of Ilorin teaching hospital located in North-central Nigeria. The outcome of the study was expected to improve the understanding of iron status in patients with CKD that may inform treatment modalities.

MATERIALS AND METHODS

Study setting: This was a hospital-based cross-sectional study carried out in the University of Ilorin Teaching Hospital (UIITH) over a period of 6 months. Ethical approval was obtained from the University of Ilorin Teaching Hospital Ethical Research

Committee, with the approved protocol number UHREC/02/05/2010. The study involved 130 consecutive pre-dialysis patients with CKD, who were recruited from the nephrology clinic, medical out-patient clinic, the renal ward and general medical ward. A non-probability convenience sampling technique was used to recruit adult patients with CKD. The inclusion criteria were pre-dialysis patients with CKD aged ≥ 18 years with eGFR < 60 ml/min/1.73m² (using the CKD-EPI formula) for ≥ 3 months. Patients excluded from the study were those on renal replacement therapy, those who had recent blood transfusion, patients with sickle cell disease, Human Immunodeficiency Virus infection, multiple myeloma, acute kidney injury (AKI), and active infections.

Clinical and laboratory assessment

Under aseptic condition, 10ml of venous blood was collected from the participants. The blood sample was evaluated for full blood count, serum iron, ferritin, transferrin, electrolytes, urea and creatinine. Full blood count was assayed using the Hematology analyzer (Sysmex XP-300™ (USA)), serum creatinine by Modified Jaffe's method, and serum iron by the Ferrozine method. Serum transferrin levels were analysed using enzyme linked immunosorbent assay (ELISA) kit (AssayMax Human transferrin ELISA kit (USA)). Serum ferritin levels were measured using ELISA (Monobind Inc. Lake Forest, USA). Total iron binding capacity (TIBC) in $\mu\text{mol/l}$ was calculated by multiplying serum transferrin in g/l by 25. Transferrin saturation (TSAT) in percentage was calculated as the ratio of serum iron and TIBC; Serum iron/TIBC was multiplied by 100.

Operational definition

Chronic kidney disease was defined as eGFR < 60 ml/min/1.73 m² using the CKD-EPI formula for 3 months or more with or without other signs of kidney damage. Anaemia was defined as Hb concentration < 13.0 g/dL in men and post-menopausal women, and < 12.0 g/dL in other women.

Normal Iron status was defined as serum ferritin > 100 ng/ml and TSAT > 20 %¹⁵. Functional iron deficiency was defined as serum ferritin > 100 ng/ml

and TSAT <20% while absolute iron deficiency was defined as serum ferritin <100 ng/ml and TSAT <20%¹⁵. Iron deficiency was defined as the presence of either absolute or functional iron deficiency. Iron overload was defined as serum ferritin > 800ng/ml¹⁵.

Data analysis

We analyzed the data using statistical package for social science, IBM SPSS statistics® 2012 version 21.0 for windows by IBM USA, Armonk, NY 10504. Sociodemographic and clinical characteristics of the study participant were presented using frequency table and expressed as proportions. Distribution of iron status in the study participants was expressed using bar chart. The mean hemoglobin (Hb) and packed cell volume (PCV) were expressed as mean \pm standard deviation while variables that were not normally distributed were described as median and inter-quartile range, such as serum ferritin, serum transferrin, serum iron, serum total iron binding capacity (TIBC) transferrin saturation (TSAT), serum creatinine, and estimated glomerular filtration rate (eGFR). Analysis of variance (ANOVA) was used to compare the mean hemoglobin concentration and packed cell volume (PCV) across stages of CKD, while Kruskal Wallis test was used to compare serum ferritin, transferrin and iron, TIBC, TSAT, serum creatinine and eGFR between the stages of CKD. Chi square test were used to determine the prevalence of anaemia according to iron status, prevalence of iron deficiency according to age, sex and stages of CKD and for proportion of patients on Iron supplements and erythropoietin stimulating agents (ESA). Yates corrected chi square was used to determine the prevalence of anaemia in those with absolute iron deficiency and for routes of administration of iron supplements. Statistical significance was set at p value < 0.05, at confidence interval of 95%.

RESULTS

Table 1 shows the socio-demographic and clinical characteristics of the study participants. One hundred and thirty pre-dialysis patients with CKD consisting of 91 (70.0%) males, and 39 (30%) females were recruited into the study with a mean age of 55.9 ± 15 years. Majority of the patients (59.2%, $n=77$) were

between the ages of 40-65 years. Most of the participants had secondary school education or more (65.4%, $n=85$). Thirty-eight (29.2%) of the patients were in stage 3, and 46 (35.4%) were in each of stage 4 and 5 respectively. Hypertension (40%, $n=52$) was the leading cause of CKD among the patients, followed by diabetes mellitus (29.2%, $n=38$), chronic glomerulonephritis (22.3%, $n=29$) and obstructive nephropathy (8.5%, $n=11$).

The laboratory characteristics of the study participants are shown in Table 2. The mean Hb concentration was 9.79 ± 2.20 g/dl. The median serum levels of the iron status parameters were within the interquater ranges, such as ferritin, 257.50 (102.75 – 465.00) ng/ml; serum transferrin, 298.00 (216.00 – 343.25) mg/dl; serum iron, 21.85 (11.80 – 29.63) μ mol/l; TIBC, 74.00 (54.00 – 84.65) μ mol/l; and TSAT, 32.55 (19.06 – 43.00) %. The median eGFR was 19.50 (11.00 – 34.00) ml/min/1.73m². As shown in table 3, the Hb concentration and PCV were reduced with advancing stage of CKD ($p=0.017$ and $p=0.001$ respectively). Serum ferritin and transferrin concentrations were observed to increase as CKD advanced ($p=0.011$ and $p=0.042$ respectively). There was no significant difference in the serum level of iron, the TIBC, and TSAT across the stages of CKD. Figure 1 shows that eighty-nine (68.6%) of the patients had normal iron status based on TSAT >20% and ferritin >100ng/ml. Thirteen patients (10%) had absolute iron deficiency based on same criteria, while 23 (17.7%) had functional iron deficiency. Five patients (3.8%) had iron overload based on serum ferritin > 800ng/ml. Table 4 describes the prevalence of anaemia according to iron status. Anaemia was seen in all the patients with functional iron deficiency and in majority of the patients in other classes of iron status. Table 5 shows the prevalence of iron deficiency in the study participants according to age, sex and stages of CKD. There was no significant difference in prevalence of iron deficiency among age group ($p=0.379$), gender ($p=0.650$), and stages of CKD ($p=0.334$). Table 6 shows that more men were using iron supplement and Erythropoiesis stimulating agents (ESA) than women.

Table 1: Socio-demographic and clinical characteristics of the study participants

Variable	Frequency	Proportion (%)
Age (Years)		
<40	19	14.6
40 -65	77	59.2
>65	34	26.2
Sex		
Male	91	70.0
Female	39	30.0
Level of education		
Non-formal	21	16.2
Primary	24	18.5
Secondary	35	26.9
Tertiary	50	38.5
Stage of CKD		
3	38	29.2
4	46	35.4
5	46	35.4
Aetiology of CKD		
Hypertension	52	40
Diabetes mellitus	38	29.2
Chronic glomerulonephritis	29	22.3
Obstructive nephropathy	11	8.5

SD= Standard deviation, CKD- Chronic Kidney Disease

Table 2: Laboratory characteristics of the study Participants

Hematologic parameters		
Variable	Mean ± SD	Normal range
Hb (g/dl)	9.79 ± 2.20	Men=14 -17.5 Women=12.3-15
PCV (%)	29.31 ± 6.09	Men= 40-52 Women=36-46
MCV (fl)	80.63 ± 6.55	76 -96
MCH (pg)	27.85 ± 2.51	27 -32
MCHC (g/dl)	33.36 ± 2.81	32 -36
WBC (cells/mm ³)	6.33 ± 1.70	2.5 -10.000
Median (IQR)		
Platelet (cells/mm ³)	245.50 (185.00 – 308.25)	100,000-300,000
Serum Ferritin (ng/ml)	257.50 (102.75 - 465.00)	18 -304
Serum Transferrin (mg/dl)	298.00 (216.00 – 343.25)	132 -452
Serum Iron (umol/l)	21.85 (11.80 – 29.63)	6.8 -40
Serum TIBC (umol/l)	74.00 (54.00 – 84.65)	33 -113
TSAT (%)	32.55 (19.06 – 43.00)	20 -50
Serum creatinine (umol/l)	320.00 (193.25 – 507.25)	53 -106
eGFR (ml/min/1.73m ²)	19.50 (11.00 – 34.00)	

SD= Standard deviation, Hb= Haemoglobin Concentration, PCV= Packed Cell Volume, MCV= Mean Cell Volume, MCH= Mean Corpuscular Haemoglobin, MCHC= Mean Corpuscular Haemoglobin Concentration, WBC= White Blood Cell Count, TIBC= Total Iron Binding Capacity, TSAT= Transferrin Saturation, CRP= C-Reactive Protein, eGFR=Estimated Glomerular Filtration Rate.

Table 3: Laboratory characteristics of the study population according to stages of CKD

Variable	CKD stages			F	p value
	Stage 3	Stage 4	Stage 5		
	Mean ± SD	Mean ± SD	Mean ± SD		
Hb (g/dl)	10.59±2.29	9.69±1.86	9.24±2.30	4.182	0.017*
PCV (%)	32.06±6.29	29.12±4.99	27.24±6.18	7.157	0.001*
Ferritin (ng/ml)	182.50 (82.50-360.00)	232.50 (73.75-403.75)	412.50 (183.75-538.50)	9.101 ^K	0.011*
Transferrin (mg/dl)	261.50 (183.50-329.75)	279.00 (206.50-344.75)	317.00 (235.25-380.38)	6.322 ^K	0.042*
Iron (umol/l)	20.50 (9.75-33.00)	21.85 (13.30-30.75)	22.00 (12.75-29.50)	0.177 ^K	0.915
TIBC (umol/l)	66.55 (46.53-83.00)	67.25 (46.20-84.08)	79.00 (58.78-94.13)	4.478 ^K	0.107
TSAT (%)	37.40 (17.08-50.55)	33.15 (23.25-42.03)	30.35 (17.25-38.50)	2.609 ^K	0.271
Creatinine (umol/l)	147.00 (129.75-185.00)	305.00 (263.50-338.75)	608.50 (492.00-769.75)	105.077 ^K	<0.001*
eGFR (ml/min/1.73m ²)	46.50 (35.75-53.25)	21.00 (17.75-24.00)	9.00 (6.00-12.00)	111.529 ^K	<0.001*

F= Analysis of variance (ANOVA), K= Kruskal Wallis test; * = p value <0.05, CKD= Chronic Kidney Disease, SD= Standard deviation, Hb= Haemoglobin Concentration, PCV= Packed Cell Volume, TIBC= Total Iron Binding Capacity, TSAT= Transferrin Saturation, eGFR= Estimated Glomerular Filtration Rate.

Table 4: Incidence of anaemia according to iron status.

Variable	Anaemia			χ ²	p value
	Yes	No	Total		
	n (%)	n (%)	N (%)		
Incidence	114 (87.7%)	16 (12.3%)	130		
Iron status					
Absolute iron deficiency	10 (76.9)	3 (23.1)	13	2.821	0.420
Functional iron deficiency	23 (100.0)	0 (0.0)	23		
Normal iron status	77 (86.5)	12 (13.5)	89		
Iron overload	4 (80.0)	1 (20.0)	5		

χ²=Chi square, Y= Yates corrected Chi square

Anaemia was defined as Hb concentration <13.0g/dL in men and post-menopausal women, and <12.0 g/dL in others.

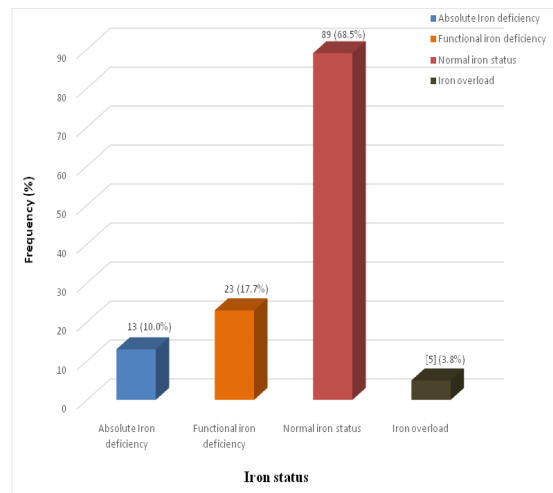


Fig. 1: Distribution of iron status in the study participants

Table 5: Estimation of rate of iron deficiency in the study participants according to age, sex and stages of CKD

Variable	Iron deficiency n (%)	Normal iron status n (%)	N	χ ²	p value
Age (years)					
< 40	8 (42.1)	11 (57.9)	19	1.942	0.379
40 -65	20 (26.7)	55 (73.3)	75		
> 65	8 (25.8)	23 (74.2)	31		
Sex					
Male	24 (27.6)	63 (72.4)	87	0.206	0.650
Female	12 (31.6)	26 (68.4)	38		
Stage					
Stage 3	10 (27.8)	26 (72.2)	36	2.195	0.334
Stage 4	10 (22.2)	35 (77.8)	45		
Stage 5	16 (36.4)	28 (63.6)	44		

χ²=Chi square

NB: Patients with iron overload not included in the table

Table 6: Proportion of patient on Iron supplement and Erythropoiesis stimulating agents (ESA)

Variable	Sex		Total N (%)	χ^2	p value
	Male n (%)	Female n (%)			
ESA					
Yes	19 (20.9)	5 (12.8)	24 (18.5)	1.178	0.278
No	72 (79.1)	34 (87.2)	106 (81.5)		
Iron supplement					
Yes	43 (47.3)	10 (25.6)	53 (40.8)	5.280	0.022*
No	48 (52.7)	29 (74.4)	77 (59.2)		
Route of administration of iron supplement					
Oral	31 (72.1)	7 (70.0)	38 (71.7)	0.066 ^Y	0.797
Parenteral	12 (27.9)	3 (30.0)	15 (28.3)		

χ^2 : Chi square; Y: Yates corrected Chi square; *: p value <0.05 (i.e., statistically significant)

DISCUSSION

Iron status of the participant

The prevalence of iron deficiency anaemia (IDA) in this was 27.7%, 10% of the patients had absolute iron deficiency and 17.7% had functional iron deficiency. This was based on serum ferritin <100ng/ml and TSAT <20% for absolute iron deficiency and serum ferritin >100ng/ml and TSAT<20% for functional iron deficiency. The level of iron deficiency in this study is similar to the studies by Deoriet *al*¹⁶ and Mohammed A¹⁷ that reported prevalence of 26% and 31.2% respectively. However, our figure is much lower than the value reported by Arogundadeet *al*¹⁸ of 56.1% and Raji *et al*¹⁹ of 42.7% in other parts of the country. The study by Arogundadeet *al*¹⁸ used a higher cut-off of serum ferritin of <300ng/ml and TSAT of <25% for definition of inadequate iron stores.

The study by Raji *et al* had one third of their patients on maintenance haemodialysis. This explained why absolute iron deficiency was the predominant form compared to our study where functional iron deficiency was more prevalent. Łukaszyk *et al*²⁰ reported a predominance of absolute form of iron deficiency anaemia; their study involved Caucasian patients with a larger proportion (61%) being in early stages of CKD. The lower level of inflammation in the Caucasian population when compared to blacks may account for the predominance of absolute iron deficiency in their study²⁰. Functional iron deficiency occurs because chronic inflammation in CKD induces cytokine release with consequent increase in hepcidin level which prevents the release of iron from the reticuloendothelial system and gastrointestinal absorption of iron. This results in increase ferritin

level, accompanied by a decrease in TSAT, suggesting inflammation-mediated reticuloendothelial blockade. The use of ESAs and iron therapy might have contributed to the predominance of functional iron deficiency in our study. Functional iron deficiency was also the predominant form of Iron deficiency in other similar studies^{17,21}.

The National Kidney Foundation (NKF-K/DOQI)¹³ practice guidelines recommend serum ferritin >100ng/ml and transferrin saturation TSAT >20% to ensure adequate iron supply for erythropoiesis in patients with CKD. In our study, only 68.5% met NKF-K/DOQI guidelines.

Iron deficiency prevalence of 27.7% in our study also corroborates the fact that iron deficiency is not the major cause of anaemia of CKD, more so that majority of the patients were on iron supplements.

Markers of Iron status of the participants

In our study, the median value of the serum ferritin agrees with the report of Gangadhar *et al*¹¹ in India on the predictive value of iron store markers in anaemia of CKD. The findings in this study are in contrast with the report by Aoun *et al*²² in Lebanon on iron deficiency across chronic kidney disease stages and Rubab *et al*²³ in Pakistan. The study by Aoun *et al* was done in pre-dialysis patients on erythropoiesis-stimulating agents without concomitant iron therapy and this could have worsened iron deficiency status of the patients because stimulation of new RBC production exhausts existing iron stores. The study by Rubab *et al* was done in patients with end-stage renal disease who are likely to have higher levels of serum ferritin due to chronic inflammation in CKD that is more prevalent in them and chronic blood transfusion. The median value of serum ferritin level in this study was found to increase with worsening of renal function, in agreement with previous studies^{8,17}. The increasing level of ferritin with worsening renal function can be due to the increased non-specific hepatic protein synthesis from protein loss in advanced stage of CKD²⁴.

The median serum transferrin in this study was higher than the mean transferrin level reported by Brantenet *al*²⁴. This difference could be due to the fact that the

s. Iron deficiency had no significant association with age, gender, or stage of CKD. There is significant association between serum ferritin and transferrin with decline in renal function.

We recommend routine measurement of iron indices in the initial evaluation of patients with CKD in order to effectively diagnose, treat and follow up patients with functional and absolute forms of iron deficiency according to KDOQI recommendations.

Conflict of interest

The authors declare no conflict of interest.

First authorship Contribution

The Authors; Oyedepo D.S: and Olanrewaju T O are co-first authors and contribute equally to this manuscript.

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