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Influence of Age and Gender on the Prevalence of Anaemia in Dialysis Naïve Patients with Chronic Kidney Disease (CKD) in Zaria, Nigeria

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ABSTRACT

Background: Decrease in Glomerular Filtration Rate occurs with advancing age. Average age of diagnosis of CKD in Nigeria is below 45 years of age and male gender has been shown to be a risk factor for worsening CKD. The influence of age and gender on prevalence of anaemia in CKD differs across the world, thus this study aims to determine the prevalence of anaemia and to evaluate associations between age, gender and anaemia in patients with CKD.

Method: This was a cross-sectional descriptive study of patients with CKD. Age, gender, primary renal disease, stage of CKD and associated clinical conditions as well as blood samples of study subjects were analyzed for complete blood counts, creatinine, and Ferritin levels.

Results: Mean age of the participants was 45.8±14.6 years with 59.3% diagnosed at or greater than 45 years of age, male-to-female ratio 1:1.2. Mean haemoglobin concentration (Hb) was 11.0±2.8g/dl, red cell indices were normal. Prevalence of anaemia was 61.5%, and it was very common among both genders; 80.49 % of males and 62.0% of females. Mean serum ferritin and RDW-CV were 70.57±46.43ng/ml and 16.29±3.70 % respectively. Chi Square for trend for age at diagnosis and worsening stage of CKD was statistically significant ($\div^2 = 4.387$, df=4, p=0.036). Similarly, a statistically significant trend was observed between the degree of anaemia and stage of CKD ($\div^2 = 11.888$, df=4, p=0.001).

Conclusion: There is a high prevalence of anaemia among CKD patients and the burden is relatively higher in the male gender at and or above 45 years of age.

Keywords: *Age, Anaemia, CKD, Dialysis, Age, Gender, Nigeria*

INTRODUCTION

Chronic kidney disease (CKD) and anaemia are common conditions in the outpatient population and often present concurrently.[1] The symptom profiles of both conditions are similar with some overlap with aging and other common disease conditions, such as heart failure and malnutrition.[1] The World Health Organization (WHO) defines anaemia as haemoglobin concentration <12 g/dL in women and <13 g/dL in men.[2-4]Chronic kidney disease (CKD) is defined as kidney damage for e" 3 months and or glomerular filtration rate (GFR) < 60ml/min per 1.73m^2 e" 3 months with or without kidney damage.[2, 4]

Epidemiologic studies have shown that the incidence of kidney diseases is higher in developing countries than in the industrialized world.[5] Previously the number of patients with end-stage renal disease is increasing in both developed and developing countries,[6] but there is a shift in the more affluent society where there is noticed stability in the number.[7-9]The incidence of end-stage renal failure is increasing worldwide at an annual growth rate of 8%.

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[10, 11]Data from most parts of the world have been criticized for being non-representative, inadequate and sometimes unreliable especially in the developing world.[5, 12, 13]

In industrialized countries, the incidence of CKD increases with age.[6, 10, 14, 15]The incidence is 6–10 times higher in patients between 70 and 90 years of age compared with those between 30 and 50 years, a finding that may be as a result of the rising prevalence of diseases causing chronic kidney damage such as hypertension and diabetes among other modifiable and non modifiable risks.[14] In the U.S and Italy the prevalence of End stage renal disease (ESRD) is seen more with aging.[16] The epidemiologic characteristic of ESRD is strikingly different in sub-Saharan Africa (SSA) compared with developed economies. While it predominantly affects the middle-aged and elderly populations in developed countries, CKD however affects young adults in their prime of life and the most economically productive years in SSA.[13] Average age of diagnosis of CKD in Nigeria is below 45 years of age and male gender has been shown to be a risk factor for worsening CKD.[17, 18]

Estimating the burden of ESRD in low and middle income Countries (LMIC) is difficult.[19] In all African countries there are no reliable statistics describing CKD.[12] In North Africa, the incidence of kidney diseases is much higher than that in West Africa,[20] while available hospital-based studies in Nigeria showed a prevalence of CKD among patients on admission to be 8-10%,[18, 21] though prevalence data from Nigeria is still emerging.[5]

Anaemia is an independent risk factor associated with a variety of adverse outcomes in older adults, including hospitalization, disability, and mortality.[3, 22] Its causes are often multi-factorial and its prevalence increases with advancing age becoming more prominent after 50 years where a third have evidence of renal insufficiency. Anaemia is a complication of declining renal function. In the National health and nutrition survey III (NHANES III) study, 8% of older participants with anaemia had renal insufficiency; others had anaemia that was unexplained.[3]

This study determines the prevalence of anaemia among CKD patients and the associations between age and anaemia in CKD patients attending the nephrology clinic of Ahmadu Bello University Teaching Hospital (ABUTH), Zaria.

MATERIALS AND METHODS

This was a cross-sectional descriptive study using questionnaires and laboratory tests where 91 participants were enrolled consecutively; those who were e”18 years old with chronic kidney disease (CKD) as defined by NKF-KDOQI clinical practice guidelines. The study was from July 2014 to September 2014. Patients with recent haemorrhagic episodes (2 weeks), malignancy, haematological disorder, dialysis, recent blood transfusion (4 weeks), and erythropoietin or Iron replacement therapy were excluded from the study. Kidney function was determined by assessing albuminuria, and creatinine clearance calculated according to the Cockcroft-Gault formula. Complete blood count was determined by automated haematology analyzer BioMaxima BM HEM 3 haematology analyser.

All participants were recruited from the nephrology clinic of ABUTH, and those participating provided written informed consent. The protocol was approved by the hospitals’ Health Research Ethics Committee (HREC).

Measurements

Predictors

Primary:

· CKD was defined and stratified according to the documented calculated creatinine clearance which staged the participants into five different groups: Stage I CKD, e”90mL/min/1.73m and with the documented persistent albuminuria in the patient’s case files; Stage II, kidney damage with normal or elevated GFR: 60-89 mL/min/1.73m; Stage III, mild renal insufficiency; 30-59mL/min/1.73m; Stage IV, moderately decreased GFR (moderate to severe renal insufficiency); Stage V, 15-29 mL/min/1.73m, severely decreased GFR (severe renal insufficiency); d”15 mL/min/1.73m, kidney failure (End-stage renal disease, ESRD)[2, 4]

· Anaemia: The haemoglobin level used for definition of anaemia and calculation of overall prevalence of anaemia in the population in both sexes was as proposed by the European Best practice for management of CKD and NKF/KDOQI guidelines for management of CKD.[23] Severity of anaemia was stratified according to WHO recommendations as follows: where severe anaemia -Hb<8.0g/dl, Moderate anaemia -Hb 8.0-10.9g/dl and mild anaemia -Hb 12.0-12.9 g/dl.[24] The Hb used for determining

overall prevalence of anaemia in the population in both sexes is Hb <12.0g/dl (European Best practice for management of CKD), while when gender was considered for calculating prevalence, Hb of <12.0g/dl was used as cut off for females and Hb <13.0g/dl for males (NKF/KDOQI guidelines for management of CKD)[4].

Secondary:

- Age at diagnosis, gender

Outcomes

Primary:

- Prevalence of anaemia in CKD amongst the study population

Secondary:

- Influence of gender and age on the prevalence of anaemia in CKD amongst the study population
- Age and gender at presentation of CKD
- Type and level of anaemia

Statistical Analyses

Data obtained were analyzed using Epi Info version 3.5.3. Continuous variables were summarized as means and standard deviations. Categorical variables were presented as percentages. Associations between categorical variables were evaluated using chi-square for trends tests. Odds ratios were also calculated. The level of statistical significance was set at p d" 0.05

Ethical Considerations

Ethical clearance was obtained from the Ethical and Scientific Committee of Ahmadu Bello University Teaching Hospital. Before any participant was recruited to the study, its nature and objectives were explained and a signed written informed consent obtained. Assurance of confidentiality was given, anonymity was ensured as no name was required from the respondents. Any participant who did not consent to participate in the study was exempted. Finally, the cost of the investigations was borne by the study and benefit as it relates to improving management of the participant extended to the participant in question.

RESULTS

The mean age of the participants was 45.8±14.6 years with most diagnosed at e"45 years 54(59.3%) compared to <45 years 37(40.7%). Females constituted 54.9% (Table 1) of the participants. The overall mean weight of the study participants was 66.47±16.51Kg, with male and female participants having mean weights of 69.51±17.73 Kg and 63.92±15.13 Kg (p= 0.11) respectively. Red cell indices are shown in table 2. The mean Haemoglobin (Hb) concentration, Mean corpuscular volume (MCV), Mean corpuscular haemoglobin (MCH) and Mean corpuscular haemoglobin concentration (MCHC) were 11.0±2.8g/dl, 83.31±8.74fl, 28.34±3.12pg and 34.11±4.93g/dl respectively. The overall prevalence of anaemia was 56/91(61.5%) – where 33/41(80.49) and 31/50(62.0%) of males and females respectively had anaemia.

Age influence was stratified into two groups (Table 1) and the distribution of CKD among different age groups and its effect on development of anaemia is depicted in table 5. The mean serum ferritin and Red cell distribution width coefficient of variation (RDW-CV) were 70.57±46.43ng/ml and 16.29±3.70 % respectively.

Chi Square for trend (table 4) was conducted to evaluate any trend in age at diagnosis (Age <45 versus e" 45 years) and worsening stage of CKD of participants. This revealed the presence of a statistically significant trend ($\div^2$ = 4.387, df=4, p=0.036) signifying waning kidney function with age. A statistically significant trend between degree of anaemia and stage of CKD ($\div^2$ = 11.888, df=4, p=0.001) was also revealed, meaning that the odds for developing anaemia increased with worsening kidney function. When gender influence on stage of CKD and age at diagnosis was assessed, it revealed no statistical significance even though crude rate shows male sex predominance (Table 6).

DISCUSSION

Majority of the participants (59.3%) in this study were diagnosed above 45 years of age consistent with the age reported among African-Americans,[25] which contrasted with the findings among Africans in Africa where incidence of CKD tend to occur 20 years younger than the more affluent countries of the West.[18, 26, 27] We found higher odds for developing CKD and anaemia with increasing age with a

Table 1: Age at diagnosis by gender of participants

Age (Years)	Male (%)	Female (%)	Total (%)
< 45	15 (36.59%)	22 (44%)	37 (40.66%)
e" 45	26 (63.42%)	28 (56%)	54 (59.34%)
Total	41 (45.06%)	50 (54.95%)	91 (100%)

Table 2: Prevalence of Anaemia by gender of participants

Gender	Hb level (g/dl)	N	n	%
Male	<13.5	41	33	80.49
Female	<12.0	50	31	62.00
Total		91	64	100

Key: *N, Total of at risk participants. n, number of anaemic based on approved Hb*

Table 3: Haemoglobin and red cell indices

Haematological parameter	Overall meanN (88)	MaleN (40)	FemaleN (48)	P value
Hb (g/dl)	11.0±2.80	11.10±3.00	10.90±2.70	0.49
MCV (fl)	83.31±8.74	82.84±8.61	83.72±8.91	0.83
MCH (pg)	28.34±3.12	28.35±3.03	28.34±3.22	0.70
MCHC (g/dl)	34.11±2.22	34.29±1.95	33.97±2.43	0.16
RDW-CV (%)	16.29±3.70	15.70±2.71	16.80±4.31	0.004

Table 4: Trend of age at diagnosis in CKD of participants

CKD Stage	Age at diagnosis < 45 Yrs	Age at diagnosis eH 45 Yrs	Odds Ratio
1	15	7	1.00
2	10	20	4.29
3	7	12	3.67
4	3	4	2.86
5	3	9	6.43

Chi Square for trend 4.387, P-Value 0.036

Table 5: Level of anaemia by gender and age group

	Level of Anaemia						
Age group	Mild (Hb 11.0-12.0g/dl)		Moderate (Hb 8.0-10.9g/dl)		Severe (Hb<8.0g/dl)		Total
(Years)	M	F	M	F	M	F	
18-24	4	1	0	0	2	1	8 (8.82%)
25-54	5	15	5	7	3	7	42 (61.77%)
>55	4	4	6	4	0	0	18 (26.47%
Total	13	20	11	11	5	8	68 (100%)

Table 6: Influence of gender on stages of CKD and age at diagnosis

	Age at diagnosis (yrs)		
	M	F	p-value
CKD Stage			
1	40.80 (±17.34)	35.60 (±10.88)	0.1474
2	53.10 (±16.88)	44.90 (±16.47)	0.9227
3	48.40 (±9.29)	41.40 (±8.92)	0.9195
4	42.80 (±21.05)	46.00 (±26.87)	0.5833
5	55.90 (±9.8)	43.30 (±7.77)	0.8720

significant association existing between age at diagnosis of CKD. This is consistent with the age-related decrease in estimated Glomerular Filtration Rate (eGFR) as one advances in age.[28] Other additional non-modifiable risk factors for CKD documented in the literature include race/ethnicity.[29]

When gender is considered as a risk factor for the development of CKD and anaemia, male gender appear to have a higher risk as shown in tables 1 & 2, where, there were more females (44%) than males (36.59) diagnosed at less than 45 years while a reversal of the pattern seen at age 45 years and above (Males 63.42%, Females 56%). This shows that as one advances in age more males will come down with CKD than females. Female sex has been noted to be protective from developing CKD and ESRD especially during reproductive years.[25,] Though the deterioration of kidney function is the same in both genders, females develop CKD later than the males,[25] most likely due to nitric oxide, a vasodilator which is higher in women.[28] The higher risk of developing CKD in the male gender may be due to risk factors for CKD such as hypertension, diabetes mellitus, smoking and large volume of alcohol consumption that is higher in men than women.[25]

The prevalence of anaemia was found to be 61.5%, using an Hb of 12.0g/dl which is the cut off for assessment of anaemia in CKD for both sexes.[30] This prevalence is low compared with the report of Ijoma *et al* (77.5%) in Enugu South East Nigeria, Shittu *et al* (94%) in Ilorin North Central Nigeria and Amoako *et al* (86.7%) in Ghana,[17, 26, 31] but higher than that reported by McCellan *et al* (47.7%) in Atlanta U.S.A.[32]. The differences are likely due to differences in population studied. Race and ethnicity are shown to be predictors of development of anaemia in CKD.[29, 32]

Our findings of gender-specific prevalence of anaemia in CKD in this study is consistent with the reports of the "kidney early evaluation program" (KEEP), and national health and nutrition examination survey (NHANES) of 1999-2004, where anaemia was commoner in males than females with CKD.[3,] [32]However higher prevalence rates of 70% in females

and lower rates of 50% was reported in males in a Saudi Arabian study.[30] Regional variations and normal physiologic adaptation to anaemia[33] in women where they tend to have reduced oxygen affinity could explain the differences and the reason why males will present to the hospital earlier than females. McCellan *et al* have demonstrated that female gender is a predictor of anaemia in CKD.[29] This is similar to the reports of Ijoma *et al* in their 2010 review where they noted a high prevalence of anemia among females in predialysis patients in Enugu, Nigeria.[17]

The levels of anaemia in this study, revealed a predominance of mild anaemia (48.5%) which was predominant in females within the age group of 25-54 years. This is not an uncommon finding and is consistent with what Guralnik *et al* and Minutolo et al noticed.[34, 35] Where though anaemia prevalence rises rapidly with age, females present with the milder form of anaemia, consistent with what we are reporting in patients with CKD in Zaria. There is an age-related decline in kidney function which can explain the development of anaemia in CKD but as to why the younger and middle age group of 25-54 had higher prevalence, more studies are needed to define that especially in sub Saharan Africa.

The pattern of anaemia in CKD is predominantly that of a normocytic, normochromic picture. The red cell indices were all within normal range (table 3), consistent with most studies.[31, 36, 37]The reason for this is that in 'renal anaemia' there is erythropoietin resistance and or deficiency, leading to a blighted response,[36-38] which leads to functional iron deficiency,[39] hence a predominant picture of normocytic and normochromic red blood cells, "the anaemia of erythropoietin reduction or resistance".

The mean haemoglobin concentration in this study was 10.97±2.81 g/dl; this is however below the cut-off level of females and males. It has been shown that in CKD, there is an overall reduction in iron,[39] and iron deficiency is established when the mean serum Ferritin level fall below 100ng/ml[16, 39] and Red cell distribution width is above 14.50%[40] respectively. Relating the result of this study where the mean serum ferritin and RDW-CV are 70.57±46.43ng/ml and 16.29±3.70 % respectively, with the established cut off, suggests an existing iron deficient state. Red cell distribution width (RDW) percentage has been noted to be an early marker of iron deficiency.

CONCLUSION

There is a high prevalence of anaemia among patients with CKD in Zaria. Anaemia in CKD is higher among the male gender and predominantly at or above the age of 45 years with the greatest burden in the 25-54 years age group. Iron deficiency is present in almost all patients in our centre.

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