PATTERN OF HAEMATOLOGIC ABNORMALITIES IN INCIDENT DIALYSIS PATIENTS AND THE EFFECT OF USING LOCALLY DERIVED HAEMATOLOGIC REFERENCE RANGES.

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ABSTRACT

BACKGROUND
The aim of the study was to compare the prevalence of haematologic abnormalities seen in incident haemodialysis patients using standard laboratory reference ranges with reference ranges derived locally.

STUDY DESIGNAND METHODS
This was a retrospective study of 97 patients with renal failure who received haemodialysis at a single dialysis unit in Lagos, Nigeria. All patients were 18 years of age or older, had renal failure requiring dialysis, and had not previously dialyzed. Patients with a history of haemoglobinoapthy or other red cell disorders, recent history of overt blood loss or blood transfusion and pregnancy were excluded.

RESULTS
Fifty six (57.7%) of the patients were males; and 55 (56.7%) had chronic kidney disease. There were no significant differences in baseline characteristics between males and females, however, patients with CKD had significantly higher mean systolic and diastolic blood pressures, mean serum creatinines and lower mean haemoglobin concentrations.
Overall, anaemia was the most common haematologic abnormality (97.9%), followed by leukocytosis (34.0%). Leukopenia, thrombocytosis and thrombocytopenia were less common (3.1%, 7.2% and 10.3% respectively). The use of locally derived reference ranges was associated with significantly higher frequencies of occurrence of majority of the haematologic abnormalities studied.

CONCLUSION
Haematological abnormalities occurred frequently in the study population. Use locally derived haematologic reference ranges was associated with significant differences in the frequency and pattern of some of the haematologic abnormalities. Further studies are needed to determine the clinical implications of these findings.

KEYWORDS: Haematologic abnormalities; chronic kidney disease; acute kidney injury; dialysis.

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INTRODUCTION

Haematologic parameters are frequently deranged in patients with renal failure. Abnormalities of red cells are the commonest haematologic derangements seen in these patients, though abnormalities of white cells and platelets have been reported in the literature. The frequency and pattern of haematologic abnormalities may vary significantly based on the aetiology, type and severity of kidney disease as well as the presence of co-morbidities.

Anaemia is the most prominent abnormality seen in patients with renal failure. The pathogenesis of anaemia is multifactorial including reduced erythropoietin production from the diseased kidneys, deficiencies of iron, vitamin B12 and folate,[1,2,3] shortened red blood cells survival,[4] chronic

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inflammation, and hyperparathyroidism.[5,6,7] The anaemia in patients with renal failure has been described as moderate to severe with a normocytic normochromic blood picture in most cases.[8,9,10] In patients with chronic kidney disease (CKD), the severity of the anaemia parallels the degree of renal impairment.

Although white cell count may be decreased in uraemic patients as a result of uraemic suppression of the marrow; they may also be elevated especially in the presence of sepsis. Unlike its effects on red and white cell, uraemia is more likely affect platelet function rather than number. Bleeding tendency from platelet dysfunction occurs as a result of abnormal platelet aggregation and adhesiveness.[11,12] However, most authors have reported total white cell and platelet counts in patients with renal failure to be normal.

Interpretation of laboratory test results with diagnostic accuracy, and by extension, identification of abnormalities in the test results, require appropriate reference or cutoff values. Many haematological variables are influenced by factors such as ethnic origin, gender, and geographical and dietary peculiarities.[13] As early as 1941, hematology reference ranges were found to differ by race.[14] A study among four ethnic groups in the United Kingdom reported that black women had significantly lower white cell and neutrophil counts compared to Indian, Northern European and Oriental women.[15] Reference ranges used in majority of the laboratories in Nigeria were developed largely from studies in western populations. Studies involving apparently healthy adult Nigerians have consistently shown that these reference ranges may not be representative of the Nigerian population.[13,16,17]

Virtually all available data relating to haematologic abnormalities in renal failure patients from developing countries, Nigeria included, have employed standard laboratory reference ranges without taking into account locally derived values. We set out to determine the pattern of haematologic abnormalities seen in incident haemodialysis patients at our dialysis unit and compared the prevalence of these abnormalities using standard laboratory reference ranges with reference ranges established from studies that recruited apparently healthy adult Nigerians.

Study design and methods

This was a retrospective study of patients with renal failure requiring dialysis who presented for haemodialysis at a privately-run, stand-alone dialysis unit located in Lagos, southwest Nigeria between 1st January and 31st December 2014. The study protocol was approved by the Health-Research and Ethics Committee (HREC) of the Lagos University Teaching Hospital prior to commencement of the study. The hospital records of all patients who presented for dialysis at the unit during the study period were be retrieved and reviewed for eligibility to be included in the study.

Patients were included in the study if they were 18 years of age or older, had renal failure with either a clinical or biochemical indication for dialysis, and had not previously received haemodialysis or peritoneal dialysis. Patients were excluded from the study if they; had a known disorder of red blood cells e.g sickle cell anaemia, or thalassaemia; had a recent history of overt blood loss or had received blood transfusion in the preceding four weeks; or were pregnant. Information retrieved included; biodata, blood pressure at presentation, type and aetiology of kidney disease, co-morbid conditions, serum urea and creatinine and complete blood count.

For the purpose of this study 11 haematologic abnormalities were identified and included; anaemia, microcytosis, macrocytosis, reduced mean corpuscular haemoglobin (MCH), elevated MCH, reduced mean corpuscular haemoglobin concentration (MCHC), elevated MCHC, leukopenia, leukocytosis, thrombocytopenia, and thrombocytosis. Each individual abnormality was determined using two sets of reference ranges. The first set of reference ranges were those currently being employed at the haematology laboratory of our teaching hospital (Table 1), while the second set of reference ranges were those derived by Miri-Dashe et al[13] from a cohort of apparently healthy adult Nigerians.

Statistical analysis

Data obtained was analysed using Epi Info™ statistical software package version 7.0 (United States Centers for Disease Control and Prevention, Clifton Rd. Atlanta, Georgia, USA). Continuous variables are presented as means and standard deviation while categorical variables are presented as percentages. Patients were stratified into two groups based on whether renal failure is as a result of acute kidney injury or chronic kidney disease. The proportion of patients with each haematologic abnormality determined using both standard laboratory reference ranges and the reference ranges established by Miri-Dashe et al[13] were compared. Comparison between means was carried out using the student's t-test while comparison between percentages was done using chi-square test. The level of statistical significance was set at a p-value less than 0.05.

RESULTS

A total of 97 patients met the study inclusion criteria and were included in the review. Of these, 56 (57.7%) were males; 55 (56.7%) had CKD and 42 (43.3%) had acute kidney injury (AKI). Table 2 shows the baseline clinical and laboratory characteristics of the study population stratified according to gender. There were no significant differences in baseline characteristics between males and females in the study population. Table 3 show the baseline clinical and laboratory characteristics of the study population stratified according the type of kidney disease. Compared to patients with AKI, patients with CKD had significantly higher mean systolic and diastolic blood pressures as well as mean serum creatinines. They also had lower mean haemoglobin concentrations.

Table 4 shows the frequency of occurrence of the identified haematologic abnormalities based on standard laboratory reference ranges as well as a comparison of this frequency of occurrence between patients with AKI and CKD. There were no significant differences in the frequency of occurrence of the haematologic abnormalities between patients with AKI and CKD. Table 5 shows a comparison of the frequency of occurrence of the identified haematologic abnormalities based on the two reference ranges used in the study. With the exception of anaemia, reduced MCH, reduced MCHC and leukocytosis, the use of locally derived reference ranges was associated with significantly higher frequencies of occurrence when compared to using standard laboratory references.

DISCUSSION

This study reviewed the haematologic parameters at initial presentation of 97 subjects with either AKI or CKD who were dialyzed at a single, stand-alone haemodialysis unit in Lagos, Nigeria. At baseline, although there was a trend towards lower haemoglobin concentration in female patients, there was no statistically significant difference in the clinical and laboratory parameters between the male and female patients in the study. However, when subjects were stratified according to whether they had AKI or CKD, there were significant differences in baseline clinical and haematologic parameters between the two sets of patients. Specifically, patients with CKD had significantly higher mean systolic and diastolic blood pressures as well as higher mean serum creatinine. They also had a lower mean haemoglobin concentration.

Overall, anaemia was by far the most common haematologic abnormality in the study population being almost universally present. This high frequency of anaemia is similar to that previously reported by Abdu et al.[18] The pattern of anaemia found in this study however differs dramatically from those reported in earlier studies of haematologic indices in Nigerian patients. The anaemia in this study was mainly microcytic hypochromic as against the normocytic normochromic reported in previous studies.[8,9,18] This suggests that iron deficiency may be a major factor in the aetiology of the anaemia in our study population and as was the hypothesized by Talwar et al[19] who reported similar findings from an Indian population of CKD patients, intestinal blood loss as a result of parasitic infestation needs to be considered. This view is further strengthened by the fact that the frequency of microcytosis did not differ significantly between patients with CKD and AKI.

Abnormalities of white blood cells were not uncommon in the study with just over a third of the patients having either leukocytosis or leukopenia. Leukocytosis was particularly more frequent in the study population than leukopenia. Shittu et al[9] had previously reported similar findings among patients with advanced CKD. In their study, patients with advanced CKD had significantly higher mean white cell counts than not only patients with milder degrees of renal impairment, but also the control arm. It is difficult to say whether the white cell abnormalities seen here are as a result of uraemia though. More likely, multiple factors may have influenced the pattern of white cell abnormalities, including presence of infections, a possible reaction to the stress of severe illness as well as a possible role for uraemia Abnormalities of platelets were the least frequent in the study population with thrombocytosis being slightly more common than thrombocytopenia. This finding is consistent with what is known about the effects of uraemia on platelets as well as the results of previous studies. It has been suggested over time that the effects of uraemia is on platelet function rather than number.[11] How both Shittu et al[9] and Islam et al[20] have reported low platelet counts in patients with advanced CKD. In fact, in the study by Shittu et al, platelet count reduced progressively as CKD became more advanced.

Overall, we observed no significant differences between patients with AKI and those with CKD in the frequency of any of the haematologic abnormalities studied. When locally derived reference ranges were employed in determining the frequency of haematologic abnormalities, the prevalence anaemia in the study population did not differ significantly from those from those obtained using standard laboratory references. However, there was a significant change in the pattern of the anaemia, with the proportion of patients with microcytic anaemia as well as macrocytic anaemia increasing significantly. In terms of abnormalities of white cell, although the prevalence of leukocytosis increased when locally derived reference

ranges were employed; the increase fell short of reaching statistical significance. The frequency of leukopenia however increased significantly when locally derived reference ranges were employed compared to standard laboratory references. The effect of using locally derived reference ranges was most prominent on the frequency of abnormalities of platelet as there was a significant and marked increase in the frequencies of both thrombocytosis and thrombocytopenia. Further studies are needed to determine the clinical implications of these differences in pattern of haematologic abnormalities that were noticed following the use of locally derived haematologic reference ranges.

Table 1. Standard haematology laboratory references used in the study.

S/N	Haematologic Parameter	Reference Range
1	Haemoglobin Concentration	Males: 13.5 – 16.5g/dL Females: 11 – 15g/dL
2	Mean Corpuscular Volume	76 – 96fL
3	Mean Corpuscular Haemoglobin	27 – 32pg
4	Mean Corpuscular Haemoglobin Concentration	32 – 36g/dL
5	White Cell Count	2.5 – 10 X 10^9/L
6	Platelet Count	100 – 400 X 10^9/L

Table 2. Baseline clinical and haematologic parameters of the study population stratified according to gender.

S/N	Characteristics	All Patients	Females	Males	P-Value
		97	41(42.3%)	56(57.7%)	
1	Mean Age (years)	56.6 ± 17.0	48.3 ± 15.8	52.2 ± 17.8	0.27
2	Mean SBP (mmHg)	154.1 ± 36.5	160.2 ± 38.4	149.6 ± 34.6	0.15
3	Mean DBP (mmHg)	94.7 ± 24.1	97.6 ± 25.4	92.6 ± 25.4	0.31
4	Mean S/Urea (mg/dl)	239.2 ± 150.0	239.0 ± 136.7	239.3 ± 160.2	0.99
5	Mean S/Creatinine (mg/dl)	11.1 ± 7.6	12.4 ± 8.0	10.2 ± 7.2	0.16
6	Mean Hb (g/dl)	8.5 ± 1.9	8.1 ± 1.7	8.7 ± 2.0	0.08
7	Mean MCV (fl)	70.7 ± 11.5	71.1 ± 10.3	70.4 + 10.3	0.74
8	Mean MCH (pg)	24.6 ± 4.2	25.1 ± 4.1	24.2 ± 4.3	0.29
9	Mean MCHC g/dl)	33.7 ± 4.9	33.5 ± 4.3	33.9 ± 5.3	0.67
10	Mean WBC Count (x10^9)	11.5 ± 9.1	11.9 ± 11.3	11.2 ± 7.1	0.73
11	Mean Plt Count (x10^9)	246.9 ± 120.5	246.4 ± 128.8	247.3 ± 115.9	0.97

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; S/Urea = Serum Urea; S/Creatinine = Serum Creatinine; Hb = Haemoglobin concentration; MCV = Mean Corpuscular Volume, MCH = Mean Corpuscular Haemoglobin; MCHC = Mean Corpuscular Haemoglobin Concentration; WBC = White Blood Cell; Plt = Platelet.

Table 3. Baseline clinical and laboratory parameters of the study population stratified according to type of kidney disease.

S/N	Characteristics	All Patients	AKI	CKD	P-Value
		97	42 (43.3%)	55 (56.7%)	
1	Mean Age (years)	56.6 ± 17.0	53.2 ± 17.3	48.5 ± 16.6	0.17
2	Mean SBP (mmHg)	154.1 ± 36.5	124.8 ± 20.0	176.5 ± 29.7	<0.001
3	Mean DBP (mmHg)	94.7 ± 24.1	77.4 ± 12.1	107.9 ± 22.7	<0.001
4	Mean Serum Urea	239.2 ± 150.0	216.0 ± 161.6	256.9 ± 139.4	0.18
5	Mean Serum Creatinine	11.1 ± 7.6	8.1 ± 6.6	13.5 ± 7.5	<0.001
6	Mean Hb (g/dl)	8.5 ± 1.9	9.0 ± 2.2	8.1 ± 1.7	0.03
7	Mean MCV (fl)	70.7 ± 11.5	77.1 ± 10.3	70.4 ± 10.3	0.74
8	Mean MCH (pg)	24.6 ± 4.2	25.1 ± 4.1	24.2 ± 4.3	0.29
9	Mean MCHC g/dl)	33.7 ± 4.9	33.5 ± 4.3	33.9 ± 5.3	0.67
10	Mean WBC ($x10^9$)	11.5 ± 9.1	11.9 ± 11.3	11.2 ± 7.1	0.73
11	Mean Plts ($x10^9$)	246.9 ± 120.5	246.4 ± 128.8	247.3 ± 115.9	0.97

AKI = Acute Kidney Injury; CKD = Chronic Kidney Disease; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; S/Urea = Serum Urea; S/Creatinine = Serum Creatinine; Hb = Haemoglobin concentration; MCV = Mean Corpuscular Volume, MCH = Mean Corpuscular Haemoglobin; MCHC = Mean Corpuscular Haemoglobin Concentration; WBC = White Blood Cell; Plt = Platelet.

Table 4. Frequency of occurrence of the identified haematologic abnormalities.

S/N	Haematologic Abnormality	All Patients	AKI	CKD	P-Value
		97	42	55	
1	Anaemia	95 (97.9%)	40 (95.2%)	55 (100%)	0.18
2	Microcytosis	71 (73.2%)	31 (73.8%)	40 (72.7%)	0.91
3	Macrocytosis	2 (2.1%)	2 (4.8%)	0 (0%)	0.18
4	Reduced MCH	73 (75.3%)	31 (73.8%)	42 (76.4%)	0.77
5	Elevated MCH	7 (7.2%)	2 (4.8%)	5 (9.1%)	0.41
6	Reduced MCHC	43 (44.3%)	16 (38.1%)	27 (49.1%)	0.28
7	Elevated MCHC	25 (25.8%)	13 (30.95%)	12 (21.8%)	0.31
8	Leukopenia	3 (3.1%)	1 (2.3%)	2 (3.6%)	0.60
9	Leukocytosis	33 (34.0%)	15 (35.7%)	18 (32.7%)	0.76
10	Thrombocytopenia	7 (7.2%)	4 (9.5%)	3 (5.5%)	0.35
11	Thrombocytosis	10 (10.3%)	3 (7.1%)	7 (12.7%)	0.29

AKI = Acute Kidney Disease; CKD = Chronic Kidney Disease. MCH = Mean Corpuscular Haemoglobin; MCHC = Mean Corpuscular Haemoglobin Concentration

Table 5. Comparison of the frequency of occurrence of the identified haematologic abnormalities based on the two reference ranges used in the study.

S/N	Haematologic Abnormality	?Frequency 1	?Frequency 2	P-Value
		97	97	
1	Anaemia	95 (97.9%)	97 (100%)	1
2	Microcytosis	71 (73.2%)	81 (83.5%)	< 0.001
3	Macrocytosis	2 (2.1%)	14 (14.6%)	< 0.001
4	Reduced MCH	73 (75.3%)	73 (75.3%)	1
5	Elevated MCH	7 (7.2%)	18 (18.5%)	< 0.001
6	Reduced MCHC	43 (44.3%)	43 (44.3%)	1
7	Elevated MCHC	25 (25.8%)	47 (48.5%)	< 0.001
8	Leukopenia	3 (3.1%)	7 (7.2%)	< 0.001
9	Leukocytosis	33 (34.0%)	90 (92.8%)	0.05
10	Thrombocytopenia	7 (7.2%)	47 (48.5%)	0.004
11	Thrombocytosis	10 (10.3%)	42 (43.3%)	< 0.001

?Frequency 1 = Frequency of the haematologic abnormalities using standard laboratory reference ranges. ?Frequency 2 = Frequency of the haematologic abnormalities using reference ranges established from studies in healthy adult Nigerians. MCH = Mean Corpuscular Haemoglobin; MCHC = Mean Corpuscular Haemoglobin Concentration;

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