Hypoferritinemia in anemic patients attending a tertiary hospital in Maiduguri, Nigeria

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ABSTRACT

It has been reported that over one-quarter of the world population is anemic and half of these were due to iron deficiency anemia. Since serum ferritin is widely used to assess iron load, this study sought to determine the serum ferritin concentrations of anemic patients attending the University of Maiduguri Teaching Hospital (UMTH), Nigeria. This was a prospective study carried out from March to September 2015. Blood samples of ninety-one anemic patients were analyzed for their individual packed cell volume (PCV) and serum ferritin concentrations using microhematocrit centrifuge and enzyme linked immunosorbent assay (using Bio-Quant™, San Diego, CA, USA) respectively. Findings from these analyses were correlated in respect to their age, gender and prior clinical diagnosis. Fifty-nine (64.8%) patients out of 91 had normal and 28 (30.8%) had high ferritin concentration, however, 4 (4.4%) had hypoferritinemia. The overall mean±standard deviation of PCV (L/L) was 0.21±0.46. There was statistical association between serum ferritin concentration and gender of adults but not with gender of children (≤12 years) (P=0.013 and P=0.555 respectively). There was no significant statistical association between serum ferritin concentration with age of subjects (P=0.250) and prior clinical diagnosis of subjects (P=0.125) Serum ferritin has been proven to be a logical measure of iron deficiency anemia; however, hypoferritinemia may also be affected by inflammation especially in subjects with chronic diseases. In order to gain better insight into iron metabolic activities, it is recommended to conduct serum transferrin and total iron binding capacity assays in these patients.

Introduction

Iron is the fourth most abundant element in the earth's crust; but it is only a trace element in biological systems, making up to only 0.004% of the body's mass. Yet it is an essential component or cofactor of numerous metabolic reactions[1] and fundamentally required by the body to form adequate normal red blood cells.[2]

Most body iron is present in circulating red blood cells. The macrophages of the reticuloendothelial system store iron released from hemoglobin as ferritin and hemosiderin.[3] They also release iron to plasma, where it attaches to transferrin, which takes it to tissues with transferrin receptors especially the bone marrow where the iron is incorporated by erythroid cells into hemoglobin. There is a small loss of iron each day in urine, feces, skin and nails, and in menstruating females as blood. This loss (1-2 mg daily) is usually replenished by iron absorbed from the diet.[3] Pathogenesis of iron deficiency anemia is heralded by *negative iron balance* which causes decreased iron supply to the bone marrow and hence iron deficiency anemia. The factor responsible for iron deficiency anemia is mainly insufficient dietary iron intake and absorption, or iron loss from bleeding.[4]

Iron deficiency is the most prevalent nutritional disorder in the world. An estimate of 2 billion people, suffer from anemia.[5] Iron deficiency is the most frequent cause of anemia, affecting nearly 1 billion people.[6] In 2011, anemia due to iron deficiency resulted in about 183,000 deaths, down from 213,000 deaths in 1990.[7] Iron deficiency anemia has adverse effects on infants, school children, and pregnant women. It is

also known to be a major nutritional deficiency in developing countries.[8]

Iron deficiency anemia (IDA), caused as a result of blood loss (*e.g.*, from menstrual cycle), insufficient dietary intake and absorption of iron. These are associated with deleterious effects, such as growth and developmental retardation, gastrointestinal alterations, impaired immune responses, reduced cognitive functions, behavioral changes and intolerance to exercise.[7,8]

Iron stores in the body exist primarily in the form of ferritin. The ferritin molecule is an intracellular hollow protein shell composed of 24 subunits surrounding an iron core that may contain as many as 4000-4500 iron atoms. In the body, small amounts of ferritin are secreted into the plasma. The concentration of this plasma (or serum) ferritin is positively correlated with the size of the total body iron stores in the absence of inflammation.[7,8]

When the serum ferritin is less than 15 ng/mL, iron deficiency is virtually certain.[9] Iron deficiency is unlikely if the serum ferritin level is greater than 100 ng/mL. Although ferritin levels between 15 ng/mL and 100 ng/mL are moderately predictive of iron deficiency anemia, patients with levels in this range may have iron deficiency anemia, anemia of chronic disease, or both. If it is important to determine which is present or if the patient does not respond to iron therapy, a bone marrow biopsy might be necessary to directly measure iron stores. The concentration of ferritin in plasma/serum could be a suitable index of stored iron in the human body.[9] Concentrations of ferritin are one of the best indices of stored iron and the effect of complementary iron in compensating for iron deficiency in the body.[10] Previous studies investigated the prevalence of anemia in diverse clinical entities in the several African communities however, the exact causes of the anemia are inadequately reported.

Since IDA is a major nutritional disorder in sub-Saharan Africa, this study aimed to determine the serum ferritin concentrations in relation to available clinical entities such pregnancy, chronic kidney diseases (CKD), human immunodeficiency virus (HIV) infection and leukemia (LK) among anemic patients attending the University of Maiduguri Teaching Hospital, Nigeria thereby promoting awareness of IDA and encouraging the need for treatment where and when necessary.

Materials and Methods

Study area

This prospective study was carried out from March to September 2015 in the Hematology Department, University of Maiduguri Teaching Hospital (UMTH), Maiduguri, Nigeria. UMTH is the major referral medical center in the North-eastern Nigeria, with 500 bed size and sub-specialities in medicine and training of other health care professionals.

Maiduguri is the capital of Borno state, which lies on latitude 115° N and longitude 135° E, and occupies an area of 50,778 square kilometers. Borno State is bordered by the Republic of Niger to the North, Chad to the North-East and Cameroon to the East. The climate of Maiduguri has a mean annual maximum temperature of 35°C. The estimated population of Borno State according to 2006 population census report is 4,098,391. Maiduguri which is a cosmopolitan town is inhabited majorly by the Kanuri amongst other ethnical groups.

Study participants

A total number of 91 subjects were recruited for the study, which included both pediatric and adult population. Criteria of inclusion in the study were patients with low packed cell volume <0.30 L/L for adults and <0.35 L/L for children, those who are not malnourished and those not on known drugs that cause hemolysis.

Sample collection

Five mL of venous blood were collected from individual patients with a sterile syringe; 3 mL of venous blood were dispensed into ethylenediaminetetraacetic acid container, mixed gently and thoroughly for 10 s, labelled and kept for analysis. The remaining 2 mL were dispensed into plain blood container, allowed to clot and retract at room temperature.

Analytical procedures

Packed cell volume (PCV) and serum ferritin concentrations were done using microhematocrit centrifuge and enzyme linked immunosorbent assay (using Bio-Quant™, San Diego, CA, USA) respectively. Finding from these analyses were statistically analyzed with the age, gender and prior clinical diagnosis of anemic patients.

Statistical analysis

Frequency distribution and incidences of the various serum ferritin status parameters were determined. Differences in proportions were determined by Chi-square tests using the SPSS software (IBM Corp., Armonk, NY, USA). A two-sided P<0.05 at 95% confidence interval was considered statistically significant for the variables.

Ethics and informed consent

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethical Research Committee of the Uni-

versity of Maiduguri Teaching Hospital, Nigeria. All adult participants gave their written informed consent for inclusion before they voluntarily participated in the study. However, the purpose of this work was explained to parents/guardians of the children before they voluntarily consented to allow their children to participate in the research. All data were analyzed anonymously throughout the study.

Results

Out of 91 patients with low packed cell volume (*i.e.*, ≤0.30 l/L), 4 patients (4.4%) had PCV of ≤0.10 l/L, 36 (39.6%) had PCV ≤0.20l/l and 51 (56%) had PCV≤0.30 (Table 1). The overall mean ± standard deviation of PCV of subjects was 0.21±0.46. The gender distribution of the patients recruited in this study included 36 (39.6%) adult males and 40 (44%) adult females. The ferritin status of 15 (16.4) children (7 females and 8 males) was determined. 8 had normal ferritin concentration, 1 had low ferritin while the remaining 6 had high ferritin level (Table 2). A total of 20 adult females had normal ferritin status, and 18 adult females had high ferritin status while 2 had low ferritin status. On the other hand, out of the 36 adult males, 31 had normal ferritin status, 1 with hypoferritinemia and 4 with hyperferritinemia. In summary, out of 91 subjects, 59 (64.8%) had normal, 28 (30.8%) had high serum ferritin concentration, while 4 (4.4%) had hypoferritinemia. There was no statistical significant association between serum ferritin concentration with age of subjects (P=0.25) (Table 3). There was statistical association between serum ferritin concentration and gender of adults

Table 1. Relationship between clinical diagnosis and ferritin status.

Clinical status	Low (<6 ng/mL)	Ferritin status Normal (6-189 ng/mL)	High (≥190 ng/mL)	Mean±SD (L/L)	Total
CKD	0	2	2	0.18	4
SCA	1	9	2	0.18	12
LK	0	4	1	0.21	5
HIV	0	1	1	0.24	2
ANC	1	39	3	0.24	8
Not available	2	4	19	0.22	60
Total	4	59	28	0.21±0.46	91
P-value	0.125	0.333	0.275	0.075	

SD, standard deviation; CKD, chronic kidney disease; SCA, sickle cell anemia; LK, leukemia; HIV, human immunodeficiency virus; ANC, antenatal care.

Table 2. Distribution of serum ferritin status across gender.

Gender	Low	Ferritin status Normal	High	Total	P value
Adults					
Female	2	20	18		
Male	1	31	4		
Total	3	51	22	76	0.013*
Children					
Female	1	4	2		
Male	0	4	4	15	
Total	1	8	6	91	0.555

*Statistical association as determined by Chi-square test.

Table 3. Relationships between age of participants and serum ferritin status.

Age group	Low	Ferritin status Normal	High	Total	P-value
<12	1	8	6	15	
12-24	1	12	6	19	
25-37	1	16	6	23	
38-50	0	15	9	24	
>50	1	8	1	10	
Total	4	59	28	91	0.355

but not with gender of children (≤12 years) (P=0.013 and P=0.56 respectively).

Discussion

Since IDA is an important nutritional and public health issue in underdeveloped and developing countries, it is crucial to evaluate the serum ferritin level of anemic patients attending our healthcare facility in order to ascertain those with IDA so that appropriate clinical modalities can be instituted.

The low serum ferritin status of the subjects could be, as a result of greater iron demand, due to their monthly menstrual cycle (in females) as they tend to lose blood and deplete iron stores in the process or due to increased demand of iron during pregnancy and during removal of atypical cells by the RE system in case of sickle cell anemia, inadequate iron containing food products like meat and vegetables (non-veterans and poverty). The low frequency of hypoferritinemia in these patients was not in consistence with the previous studies which reported higher frequencies of low ferritin levels.[11-13] The differences could be due to differences in study location/race, exclusion of undernourished subjects from our study and subject dietary preferences. Most of our patients were not vegetarians coupled with adequate nutritional advice given to them by health professionals in our healthcare center, they were expected to exhibit less cases of IDA.

Fifty-nine (56%) patients had normal ferritin status, which included 39 women for antenatal care (ANC). These findings were not consistent with that of Patel *et al.*[14] and Bhale *et al.*,[15] who reported that the majority of subjects and pregnant women respectively had low ferritin levels. The disparity with this finding could be due to the fact that majority of their subjects were severely anemic and also vegetarian. These show that severity of anemia and vegetarian feeding style drastically predispose chronically ill patients to hypoferritinemia.

Twenty-eight (30.7%) patients had high ferritin status, 19 (67.9) which had no clinical diagnosis but 2 were sickle cell anemia (SCA) patients, 1 LK patient, 4 women for ANC, 1 HIV and 2 CKD patients. This condition is known as hemochromatosis/iron overload and could be due to various factors like genetic inheritance, hepatitis, alcoholism, massive blood transfusions, increased intake of iron through increased rate of consumption iron rich meals *e.g.* meat, vegetables, which is common among the northern Nigeria. On the other hand, transfusion is usually indispensable in management of sickle cell disease. Iron overload is a major factor associated with morbidity in these patients when they benefit from repeated blood transfusions.[16] This could be a reason why more SCA subjects had hyperferritinemia than hypoferritinemia.

There was statistical association between serum ferritin concentration and gender of adults but not with gender of children. This finding is in conformity with the study of Kolahi *et al.*[11] Hypoferritinemia was relatively higher in adult females than the males. This difference could be due to monthly menstrual blood loss women undergo, which invariably causes more hemolysis than erythropoiesis and eventually predispose them to low serum iron store. However, we cannot categorically relate hypoferritinemia with gender due to very few subjects with low serum ferritin concentration. Hence there is need for a large-scale study in order to ascertain sociodemographic risk factors and etiologies of anemia responsible for hypoferritinemia.

Conclusions

Serum ferritin has been proven to be a logical measure of iron deficiency anemia; however, the result may also be affected by inflammation especially in those with chronic infections or diseases. In order to gain better insight into iron metabolic activities, it is recommended to conduct serum transferrin and total iron binding capacity assays in these patients.

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