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ORIGINAL ARTICLE

Serum Iron Profile in Chronic Renal Failure Patients

Md. Helal Miah[1], Md. Zakir Hossain[2], Bidhu Bhusun Das[3], Md. Mokhlesur Rahman Sarker[4], Sumanta Kumar Saha[5], Md. Ashraful Haque[6], Md. Ghulam Yusuf[7]

ABSTRACT

Background & objective: Chronic Renal Failure (CRF) is a serious condition with a worldwide impact. Anemia is a common complication of CRF leading to significant morbidity. Iron deficiency may be a contributing factor for developing anemia in CRF patients. It may be particularly problematic during erythropoietin therapy. This study was intended to find the serum iron status in CRF patients.

Method: This cross sectional study was conducted on 100 consecutive patients of CRF in the Department of Medicine, Rangpur Medical College & Hospital, Rangpur and Hypertension & Research Centre, Rangpur between July 2010 to June 2012.

Result: 40% of the patients were 40-59 years old, 28% were 20 - 39 years and 32% >60 years old. Males were predominant (64%) than the females (36%). None of the biochemical variables (serum creatinine, haemoglobin and serum iron profile), except total iron binding capacity (TIBC) differ by sex. TIBC was significantly higher in females than that males (p = 0.029). Of the 100 patients 40% were iron deficient; of them 12(30%) had absolute iron deficiency and 28(70%) relative iron deficiency. Iron deficiency was not influenced by sex (p = 0.519). It was not even affected by the degree of renal insufficiency (p = 0.524). However, the incidence of severe anemia increases significantly with the degree of renal insufficiency (p = 0.037).

Conclusion: Serum iron profile remains normal in most of the cases of CRF patients. It should be investigated in every CRF patients before deciding for iron therapy.

Key words: *Serum iron and chronic renal failure (CRF) .*

INTRODUCTION

The term Chronic Renal failure (CRF) applies to the process of continuing significant irreversible reduction in nephron number, and typically corresponds to Chronic Kidney Disease (CKD) stages 3-5.[1] It has worldwide distribution including India, Bangladesh, Pakistan. Anemia affects 60-80% of the patients with renal impairment with absolute or functional iron deficiency being present in 25-38% cases. Anemia of CRF is one of the first signs of kidney dysfunction and is of multi-factorial etiology. Anemia develops gradually as kidney function declines. Epidemiologic data indicate that 2/3rd of patients in the early stages of kidney failure are anaemic as well.[2] Serum ferritin, total iron binding capacity (TIBC), serum iron, and transferrin saturation (T_{SAT}) percentage are the most commonly used indicators for assessing iron status and for diagnosing iron deficiency

Authors' Information:

1. ***Dr. Md. Helal Miah,*** *Junior Consultant (Medicine), Kurigram Sadar Hospital, Kurigram.*
2. ***Prof. Dr. Md. Zakir Hossain,*** *MBBS, FCPS (Medicine), MD (Internal Medicine), FACP (USA), FRCP (Edinburg), Head, Department of Medicine, Rangpur Medical College, Rangpur.*
3. ***Dr. Bidhu Bhusun Das,*** *MBBS, MD (Internal Medicine), Associate Professor, Department of Medicine, Rangpur Medical College, Rangpur.*
4. ***Dr. Md. Mokhlesur Rahman Sarker,*** *Junior Consultant (Medicine), Sadar Hospital, Lalmonirhat.*
5. ***Dr. Sumanta Kumar Saha,*** *MBBS, MD (Cardilology, Ukraine), MRCP (UK), Senior Consultant, Medicine. Brahmanbaria Medical College Hospital Ltd., Brahmanbaria.*
6. ***Dr. Md. Ashraful Haque****, Asst. Prof. Medicine, Rangpur Medical College, Rangpur.*
7. ***Dr. Md. Ghulam Yusuf****, Registrar Medicine, Prime Medical College Hospital, Rangpur.*

Address of Correspondance: ***Dr. Md. Helal Miah****, Junior Consultant (Medicine), Kurigram Sadar Hospital, Kurigram, Cell: 01126-863689*

anemia.[3] CRF is a pro-inflammatory state that results in limited ability to use iron stores. For this reason, patients with CRF require higher levels of iron. The T_{SAT} represents the percentile of iron bound to transferrin and is a good indicator of the body's functional capacity to use stored iron.[4]

Individuals with a T_{SAT} level <20% and a ferritin concentration <100 ng/ml are considered as having absolute iron deficiency anemia, while individuals with a T_{SAT} <20% and a ferritin level of 100-700 ng/ml are termed as functional iron deficient. These individuals have adequate iron stores but due to insufficient release of iron they cannot meet the demands of erythropoiesis. It is commonly seen among CRF patients under treatment of erythropoiesis stimulating agents (ESA).[5] Iron deficiency whether absolute or relative is an important cause of anemia in CRF.[6] Improvement of hemoglobin (Hb) level in CRF patients improves performance status, reduces disease progression and decrease the rate of mortality and morbidity.[7] On the other hand, increased tissue iron can aggravate the disease progression by precipitation of infection and generation of hyper-reactive free radical leading to tissue injury.[8]

Current treatment guidelines recommend giving recombinant human erythropoietin (rHuEPO) in CRF patients as soon as their Hb concentration falls below 11 gm/dl provided alternative causes of anemia have been ruled out. However, despite adequate use of erythropoietin, over 50% of the patients do not attain targeted Hb level (11-12 gm/dl) and the most common reason for poor response to erythropoietin is iron deficiency[9-10] which should be treated either by oral or parenteral iron therapy or by blood transfusion.

Therefore, it is important to know the exact body iron status in CRF patients to rule out iron deficiency anemia as well to justify giving iron in CRF patients. So, the present study intended to find the serum iron profile of CRF patients might be helpful for their better management, rationalizing the use of iron thereby reducing the side effects of over doses of iron.

MATERIALS AND METHODS

Having obtained permission from the Ethical Committee of Rangpur Medical College & Hospital, Rangpur (RMCH), Bangladesh, this cross sectional study was carried out on 100 consecutive patients (age 18 years onwards) of CRF in the Department of Medicine, RMCH, Rangpur and Hypertension & Research Centre, Rangpur between July 2010 to June 2012. Patients with known co-morbid conditions that may cause anemia, or patients with previous iron or erythropoiesis stimulating agent therapy or patients with a history of blood transfusion or CRF patients under renal replacement therapy or pregnant women were excluded from the study. A patient to be a candidate of CRF, he/she must have raised serum creatinine on two consecutive tests at least three months apart. So before selecting patients, their serum creatinine was measured and then estimated glomerular filtration rate (eGFR) was estimated using Cockcroft and Gault formula [eGFR = (140 - age in years) × bodyweight in kg / serum creatinine (mg/dl) × 72 × 0.85 if female].[11] Previous investigation records of the patients were searched to find any evidence of raised serum creatinine for at least three months back to come to a diagnosis of CRF. If serum creatinine was not tested before or previous document was unavailable, serum creatinine levels of those patients were measured three months after the present one to confirm CRF. Anemia was defined as hemoglobin < 12 g/dl for men and postmenopausal women and < 11 g/dl for premenopausal women.[12] Then iron profile were estimated by - Immulite 2000 (DPC)/Vitros Eci System (J & J)/About AxSym System Random Access Multibatch Immunoassay Analyzer. Serum creatinine was measured by Photometric Colorimetric Test for Kinetic Measurements (Jaffe-Reaction). Serum iron profile meant for serum iron, serum ferritin, TIBC and T_{SAT}[13] the normal values of which are as follows:

- serum iron = 56-178µg/dl
- serum ferritin = 20-300ng/ml
- serum TIBC = 41-141µg/dl, and
- T_{SAT} = male 25-56% and female 14-51%.[14]

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Absolute iron deficiency - meant for serum ferritin < 100 ng/ml and T_{SAT} <20%. Relative iron deficiency - meant for serum ferritin >100 ng/ml and a T_{SAT} < 20% and normal iron status = ferritin >100 ng/ml and $T_{SAT} \geq 20\%$.[12,15]

Data were processed and analyzed using software SPSS (Statistical Package for Social Science) version 16. The tests statistics used to analyze the data were Chi-square (χ^2) Test and Independent sample t-Test. Levels of significance were set at 0.05 and p <0.05 was considered significant.

RESULTS

Age distribution of the study patients showed that 40% were 40-59 years old, 28% were 20–39 years and 32% > 60 years old. Males were predominant (64%) than the females (36%) (Table I). Sex distribution and biochemical variables (serum creatinine, haemoglobin and serum iron profile) were presented in Table II. TIBC which was found significantly higher in None of these variables differ by sex, except females than that in their male counterparts (p = 0.029). Of the 100 patients 40% were iron deficient; of them 12(30%) had absolute iron deficiency and 28(70%) relative iron deficiency. Iron deficiency was not influenced by sex (p = 0.519) (Table III). It was not even affected degree of renal insufficiency (p = 0.524) (Table IV). However, the incidence of severe anemia increases significantly with the degree of renal insufficiency (0% in CKD stage-III, 29.4% in stage-IV and 49.2% in stage-V, p = 0.037) (Table V).

TABLE I: Distribution of study subjects by demographic characteristics (n =100).

Age group (yrs)	Frequency	Percentage
20-39	28	28.0
40-59	40	40.0
> 60	32	32.0
Sex		
Male	64	64.0
Female	36	36.0

TABLE II: Distribution of serum creatinine, hemoglobin and iron profile by sex.

Biochemical variables	Sex		p-value
	Male (n=64)	Female (n=36)	
Serum creatinine (mg/dl)	6.0±2.9	6.1±4.9	0.301
Hemoglobin (gm/dl)	7.6±2.1	7.42±1.8	0.340
Serum iron (µg/dl)	81.5±15.9	75.9±16.7	0.062
TIBC (µg/dl)	417.2±65.2	522.3±78.3	0.029
Serum ferritin (ng/ml)	223.0±45.1	212.0±38.4	0.112
T_{SAT} (%)	30.9±7.1	32.8±6.3	0.402

Data were analysed using unpaired t-Test and were presented as mean ± SD.

TABLE III: Distribution of iron status according to sex.

Iron status	Sex		p-value
	Male (n=64)	Female (n=36)	
Deficient	26(40.7)	14(38.9)	
Normal	38(59.3)	22(6.1)	0.519

Figures in the parentheses denote corresponding percentage. Chi-Square (χ^2) Test was employed to analyze the data.

TABLE IV: Association between the degree of renal failure and iron status.

Stages of CKD	Iron status		p-value
	Deficient (n=40)	Normal (n=60)	
Stage 3 (n=7)	3(42.9)	4(57.1)	
Stage 4 (n=34)	11(32.4)	23(67.6)	0.524
Stage 5 (n=59)	26(44.1)	33(55.9)	

Figures in the parentheses denote corresponding percentage. Chi-Square (χ^2) Test was employed to analyse the data.

TABLE V. Association between CKD staging and severity of anemia.

Stages of CKD	Anemia severity			p-value
	Mild (Hb>10gm/dl)	Moderate (Hb 7-10gm/dl)	Severe (Hb<7gm/dl)	
Stage 3 (n=7)	5(71.4)	2(28.6)	0(0.0)	
Stage 4 (n=34)	6(17.6)	18(52.9)	10(29.4)	0.037
Stage 5 (n=59)	8(13.6)	22(37.3)	29(49.2)	

Figures in the parentheses denote corresponding percentage. Chi-Square (χ^2) Test was employed to analyse the data.

DISCUSSION

This study demonstrated that young and early middle aged (20 – 39 years) CRF patients comprised more than one-quarter (28%) middle-aged (40 – 59 years) 40% and elderly population (>60 years) 32% with mean age of the patients being 48.0 ± 15.1 years (range 22-88 years). This compares well with the findings of Rhaman *et al.*[2] (mean age 46.8 ± 12.6 years, range 23 – 75 years). Samy *et al.*[16] in Kidney Early Evaluation Programme (KEEP) found that 8% of the patients were in the age group 18 – 30 years, 35.1% in 4–60 years and 34.4% in > 60 years, while the same investigators, in National Health and Nutrition Examination Survey (NHANES) demonstrated that 25.1% patients were 46– 60 years, 23.9% patients 18 – 30 years and 20.1% > 60 years old. As the age group of the present study and those of Samy *et al.* are different, it is difficult to make a head-to-head comparison between studies. But compared to KEEP study, the present study had a higher proportion young and early middle aged population, while the NHANES study bears consistency with present one. In the present study males were predominant (64%) which is quite opposite to KEEP study where females outnumbered (68.3%) the males (31.7%), while NHANES study did not find any sex differential in CRF population (52% female and 48% male). However, Rhaman *et al.*[2], in a study conducted in Bangladeshi found a similar sex distribution (65.4% male and 34.6% female) as of ours.

The most frequent morphological features of RBC in peripheral blood film were microcytic-hypochromic (60%) which correspond well with iron deficiency status of the patients (40%). Contrary to these findings, Afsar *et al.*[17] reported in their study microcytic-hypoochromic, macrocytic and normocytic-normochromic to be 15%, 5% and 80% respectively. In our study mean Hb concentration was 7.55 ± 1.97 gm/dl which goes in favour of the findings of Rhaman *et al.*[2] 9.36 ± 2.13 gm/dl. However, NHANES III study reported a higher mean Hb concentration (12.1 ± 1.9 gm/dl) in CRF patients. In our study all the patients were anemic to some extent and the severity of anemia was found to increase with the degree of renal insufficiency. This might be due to inadequate management of CRF patients on the part of the physicians concerned or due to poor compliance of the patients to treatment regimen prescribed by the physicians.

Iron availability is essential for optimal erythropoiesis. Much has been written on the important contribution of iron deficiency toward anemia and erythropoetin resistance among end-stage renal disease (ESRD) patients. The very high cost of erythropoetin therapy renders optimizing iron status particularly significant. Hemodialysis patients are at particular risk for iron deficiency because of blood loss associated with the dialysis procedure. In contrast to the abundant ESRD literature, there are few studies of iron status among CRF subjects, defined as subjects with decreased GFR but not requiring dialysis or transplantation (CKD stage I-IV).[18]

Bone marrow iron is rarely used for clinical decision in day to day practice, and decisions are instead based only on peripheral iron indices. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Practice Guidelines recommend maintaining ferritin ≥ 100 ng/ml and T_{SAT} ≥ 20% to ensure adequate iron supply for erythropoiesis.[19] Although these targets are recommended for both dialysis-dependent ESRD patients and nondialysis CRF patients, the data supporting these targets are derived from studies of ESRD patients.[19] Now question arises what proportion of anemic CRF subjects have ferritin ≥ 100 ng/ml and T_{SAT} ≥ 20% and whether these targets are in fact appropriate for the CRF population.[20, 21] The answer to these questions have substantial public health and policy implications, given the large number of anemic CRF subjects and the enormous cost that would result from widespread and aggressive use of erythropoetin (or darbepoetin) in this population.

In this study the proportion of patients who had both of these values below cut-off level were 12% and who had only T_{SAT} <20% but serum ferritin >100 ng/ml was 28% and the rest 60% had both the parameters above recommended level (ferritin ≥ 100 ng/ml and T_{SAT} ≥ 20%).

It means 60% of anemic, CRF patients (CKD stage III-V) are not iron deficient according to the current NKF-K/DOQI targets, as they have hemoglobin <11 g/dl and ferritin ≥ 100 ng/ml. These results bring into question whether the current K/DOQI ferritin and T_{SAT} targets, derived from studies of ESRD patients, are applicable to CRF subjects. In this context, the ESRD population differs from the CRF population in several important ways. First, for those on hemodialysis, there is obligatory blood loss several times a week. Second, it is generally agreed that ESRD patients suffer from generalized inflammation, which has been ascribed to clinically apparent infection, occult vascular access infection, less than-sterile dialysate, dialysate back leak, and nonbiocompatible membranes.[22] Inflammation leads to blockage in iron utilization and "anemia of chronic disease." Ferritin levels are elevated and TIBC levels are depressed in the presence of inflammation; therefore, the diagnostic properties of these parameters may be altered in ESRD.[22] If ferritin and T_{SAT} targets developed for the ESRD population might not be applicable to evaluating iron status in CRF subjects, what parameters should clinicians use? Do the conventional cutoffs of ferritin 100 ng/ml and T_{SAT} 20% apply to them? Answers to these questions and development of treatment guidelines to optimize iron status and Hb level in this population can only come from studies conducted specifically among CRF patients. So far, there have been few of these. In our study we found that 88% of the CRF patients with Hb <11 g/dl had serum ferritin ≥ 100 ng/ml meaning that majority of the anemic CRF subjects had ferritin sufficient for adequate erythreopoiesis, but because of renal impairment erythropoietin is not being released in sufficient quantity to stimulate erythropoiesis. So despite being serum ferritin ≥ 100 ng/ml, erythropoetin therapy should be augmented or an even higher target of serum ferritin should be set for iron or erythropoetin therapy in order to ensure adequate erythropoiesis in patients with CRF not requiring dialysis yet.[21] Proposed a much higher alternative ferritin and T_{SAT} targets (500 ng/ml and 40%, respectively), but it is still premature to accept without further study.

Furthermore, Chi-Yuan *et al.*[13] in their cross sectional study there was no threshold effect at the NKF-K/DOQI target of T_{SAT} of 20% as the reference, the increase in hemoglobin associated with T_{SAT} ≥ 40% was similar in magnitude to the decrease in hemoglobin associated with T_{SAT} < 20% (as an indicator of absolute iron deficiency).

However, like any other scientific study the present study is not without limitation. Before going to conclude those limitations are to be mentioned. As the study was hospital-based cross sectional study and the sample size was small, it is difficult to generalize the findings to the whole population. Besides, bone marrow iron stain and soluble transferrin receptor (sTfR) are two good markers of iron storage in CRF patients, but they were not feasible to be investigated in the present study.

From above discussion it may be concluded that serum iron profile remains normal in most of the cases of CRF patients as long as the present NKF-K/DOQI guideline is followed to classify anemia. It may also be concluded that severity of anemia increases with degree of renal failure but iron deficiency is not influenced by degree of renal failure. Therefore, the physicians should be aware about anemia in CRF patients and before giving iron to them rational decision should be taken whether iron therapy will be beneficial or harmful to them.

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