International Journal of Medical Science and Education
pISSN- 2348 4438 | eISSN-2349- 3208
Published by Association for Scientific and Medical Education (ASME)
Int.J.Med.Sci.Educ. Oct-December. 2019; 6(4):120-126
Available Online atwww.ijmse.com
Original Research Article

ANALYSIS OF IRON INDICES IN PRE-DIALYSIS CHRONIC RENAL INSUFFICIENCY PATIENTS

Uday Vachhani[1],Chandrakant Kamariya[2],Deepak N Parchwani[3]

1.Associate Professor, Department of Biochemistry, GMERS Medical College, Himmatnagar, Gujarat 2.Associate Professor, Department of Biochemistry, PDU Medical College, Rajkot Gujarat,3 Professor Department of Biochemistry, GMERS Medical College, Himmatnagar, Gujarat
*Corresponding author – **ChandrakantKamariya**
Email id – drkamariya@gmail.com

Received:12/09/2019 ***Revised:28/10/2019*** ***Accepted:08/11/2019***

ABSTRACT

Background: Anemia is a common and debilitating condition in patients with chronic renal insufficiency (CRI), where its related complications can be avoided if patients receive optimal and quality care of anemia. Aims: To ascertain the prevalence of anemia in pre-dialysis chronic renal insufficiency patients and to examine the iron indices in the patient group so as to establish any putative relationship. **Materials and Methods:** This cross-sectional analytical study included 124 CRI patients and 157 control participants. Blood samples were analyzed for serum iron, serum ferritin, serum Total Iron Binding Capacity (TIBC) and other hematological/hemodynamic parameters by standard methods. Suitable descriptive statistics was used for different variables. **Results:** In CRI patient group, mean serum ferritin was 546.6 $\pm$ 103.5 ng/ml, which was significantly greater than healthy control population (81.2 $\pm$ 13.4 ng/ml; $p<0.0001$). On the contrary mean estimated levels of serum iron in healthy controls and CRI patients were 108.0 ± 21.0 µg/dl and 46.4 ± 11.6 µg/dl respectively and exhibited a significant difference ($p<0.0001$). TIBC in healthy controls and CRI patients were 332.4 ± 39.8 µg/dl and 304.6 ± 43.7 µg/dl respectively which is in accepted reference range. Of the enrolled patients, in CKD stages 1, 2, 3 and 4, there were 18, 42, 50, and 14 patients, respectively. Anemia was observed in 81.45% of the enrolled patients. Prevalence of anemia and alterations in iron indices were significantly increased (ANOVA; $p<0.05$) with advancing stages of disease. **Conclusions:** Anemia prevalence was very high in studied CRI cohort, characterized by low iron and elevated serum ferritin levels. Additional studies are warranted to guide an ideal biomarker which should provide optimization of iron status; correlate with degree of anemia along with predict response to iron repletion.

Keywords: Chronic renal insufficiency, Ferritin, Iron, TIBC

INTRODUCTION

Chronic Renal Insufficiency (CRI), a worldwide public health problem, is a slowly progressive loss of renal function over a period of months or years and defined as abnormally low glomerular filtration rate or kidney damage, distinctive as any pathological abnormalities or markers of damage in blood, urine or imaging investigations.**(1-2)** Its prevalence is estimated to be 8-16% worldwide.**(3)** Complications include increased cardiovascular disease, kidney disease progression, cognitive decline, anemia, mineral and bone disorders.**(4)** All stages of chronic kidney disease (CKD) **(1)** are associated with increased risk of aforementioned complications, premature mortality and decreased quality of life.**(1-2)**

Among the allied complications, anemia is exceedingly prevalent and one of the most common co-morbidities of chronic kidney disease.**(4)** It is an

early complication, develops from transitional stages of CKD and severity increases with succession of the disease.**(4)** Moreover, anemia in CRI patients is linked with cognitive/sexual dysfunction, left ventricular dilatation and hypertrophy, exercise intolerance, hurried progression to end-stage renal disease, lengthened hospitalization,**(4-5)** i.e. it is associated with increased morbidity with poor overall outcome. Hence, there is a need for early identification and treatment, so as to reverse the secondary effects of anemia in chronic renal insufficiency. However, patients with chronic renal insufficiency are also at risk of iron toxicity, if instituted iron therapy is not stringently monitored for systemic iron status.**(6)** Thus, proper quantification of the iron indices in CRI patients is crucial. Incorrect assessment may result in improper management of patients.

In 1836 Richard Bright for the first time described the association of CKD and anemia, when he observed pallor in the development of Bright's disease.**(7)** Subsequently, much has been written on anemia among chronic kidney disease patients on hemodialysis, but there is a dearth of direct evidence about the iron status among pre-dialysis CRI patients, more so specifically in Gujarati population. Thus, in this study an attempt has been made to examine the prevalence of anemia and to evaluate the iron indices in pre-dialysis chronic renal insufficiency patients.

MATERIALS AND METHODS

This was a cross-sectional study conducted on newly and previously diagnosed patients of CRI, reporting to the nephrology clinic/Medicine OPD or wards, and the emergency unit of the Hospital over a period of twenty four months. Inclusion criteria were, patients who were ≥18 years of age; have not been started on hematinics, dialysis, or erythropoietin stimulating agents. Exclusion criteria included patients of acute kidney injury, concomitant hemolytic anemia, hematological neoplasm, and those with chronic infections, malignancy, on any hemopoetic drug, thrombosis, immunosuppressive therapy, current or history of tobacco or alcohol intake, or history of blood transfusion in preceding one month, pregnant and lactating females and refusal to sign the consent form. CRI were categorized into five different stages namely 1, 2, 3, 4 and 5 as per the guidelines laid down by National kidney foundation; NKF-K/DOQI.**(1-2)**

A total of 281 participants (124 patients and 157 healthy controls) were recruited in the present study after explaining the study protocol and obtaining written informed consent form. Healthy controls were selected at random from patients' relatives and participants on routine health checkup who did not have CRI or any significant medical illness. The study was approved by the Institutional Ethical Committee. Information on demographics (such as gender, age, education, economic status, residency), occupation and history suggestive of any systemic illness were collected through a self-administered questionnaire. Blood pressure was measured in the seated position after 10 min of rest with a standard manual mercury sphygmomanometer and stethoscope by auscultatory method[8]. Age was defined as the age at the time of interview (though no documentary proof had been entertained). A sample of venous blood was drawn with an aseptic technique and subjected to estimation of serum ferritin **(9)**, serum iron **(10)**, serum Total Iron Binding Capacity (TIBC) **(11)**, serum creatinine **(12)**, serum urea **(13)**, plasma glucose **(14)** and hemoglobin.

The statistical analyses were performed using Med Cal statistical software and MS Excel. Data were expressed as mean ± SD (continuous variables), or as percentages of total (categorical variables). Two-group comparisons were made using chi-square (x^2) for categorical variables and Student's t tests or one-way ANOVA for continuous variables. For all analyses, the nominal level of statistical significance was <0.05.

RESULTS

Table 1 shows the mean values of age, gender distribution and other hemodynamic profiles in CRI patient group and in control participants. The average age of healthy controls was 48.8 $\pm$ 8.6 years and 56.05 % were men while in patient group

61.29% were males and 50.2 ± 7.8 years as a mean age. There was no statistically significant difference (p: 0.1593) in mean age between the studied groups. Among the study participants there was a dominance of male individuals as compared with females (Table 1) but male to female ratio ($p<0.05$) as well as mean age of case participants and controls were statistically similar, indicating that the two studied group were well-matched.

Table 1: Characteristics of cases and controls participants.

Parameters	Controls (n:157)	Cases(n: 124)	t	p	95% CI
	Mean ± SD	Mean ± SD			
Age (years)	48.8 ± 8.6	50.2 ± 7.8	1.41	0.1593	-0.55 – 3.35
Sex, males; n (%)	88 (56.05%)	76 (61.29%)	0.58 (x^2)	0.4455	-6.85% - 17.08
PCV %	39.4 ± 6.1	23.8 ± 7.2	-19.65	<0.0001	-17.16 - -14.04
Systolic blood pressure (mmHg)	124.8 ± 6.2	138.8 ± 18.4*	8.91	<0.0001	10.91 – 17.09
Diastolic blood pressure (mmHg)	80.2 ± 2.8	86.2 ± 3.6*	15.71	<0.0001	5.25 – 6.75
Fasting plasma glucose (mg/dl)	80.7 ± 6.6	102.0 ± 17.2*	14.25	<0.0001	18.36 – 24.24
Hb (g/dl)	13.8 ± 2.8	7.9 ± 2.1	-19.52	<0.0001	-6.49 - -5.31
Vegetarian/Non-Vegetarian	120/37(23.56%)	93/31(25.00%)	0.0195 (x^2)	0.889	-8.99% - 12.13

PCV: Packed Cell Volume; $x^{2:}$ Chi-square; CI: Confidence Interval; SD: Standard Deviation

The mean PCV %, in controls and CRI patients were 39.4 ± 6.1and 23.8 ± 7.2 respectively while hemoglobin status in respective group were 13.8 ± 2.8 g/dl and 7.9 ± 2.1 g/dl. Taken together, data indicate an anemic status in CRI patient group. There was no statistical significant difference noticed among healthy controls and CRI patients with reference to dietary habits, physical activity and any other lifestyle variation. However, patients had higher plasma glucose ($p<0.0001$), systolic blood pressure readings ($p<0.0001$) and diastolic pressure ($p<0.0001$) as compared with healthy counterparts.

The results of iron status markers are summarized in Table 2. In patient cohort, mean serum ferritin was 546.6 ± 103.5ng/ml, which was significantly greater than healthy control population (81.2 ± 13.4ng/ml). Mean estimated levels of serum iron in healthy controls and CRI patients were 108.0 ± 21.0 µg/dl and 46.4 ± 11.6 µg/dl respectively, i.e. the decrease in serum iron levels in patients is statistically significant ($p<0.0001$). TIBC in healthy controls and CRI patients were 332.4 ± 39.8 µg/dl and 314.6 ± 43.7 µg/dl respectively which is in accepted reference range.Table 3 revels the number/percentage of patients in stratified stages of CRI. Maximum number of patients were in stages 2 and 3; collectively amounting to 74.19% (n: 92; stage 3 – n: 50, stage 4 – n: 42) of total reported patients. We did not found any patient in stage 5 and only 11.2% patient in stage 4 of CRI, probably because of inclusion criteria laid down for the study protocol. Various biochemical variables reflecting iron indices in stratified stages of CRI are presented in Table 4. The prevalence of anemia was higher in patients with more advanced stage of CKD. Result also suggests that alterations in iron balance (indicated by serum iron, serum ferritin and serum TIBC) increases with advancing CKD stage (ANOVA; $p<0.05$).

Table 2: Clinico-biochemical indices of CRI patients and control groups.

Parameters	Controls (n:157)	Cases (n: 124)	t	p	95% CI
	Mean ± SD	Mean ± SD			
Creatinine (mg/dl)	0.81 ± 0.09	7.8 ± 2.4	36.47	<0.0001	6.61 – 7.36
Urea (mg/dl)	23.8 ± 7.2	138.4±35.8*	39.13	<0.0001	108.84 – 120.36
Anemia; n (%)	7 (4.4%)	101 (81.45%)	228.9 (x^2)	<0.0001	84% - 95%
Serum Iron (µg/dl)	108.0 ± 21.0	46.4 ± 11.6	29.31	<0.0001	-65.74 - -57.46
TIBC (µg/dl)	332.4 ± 39.8	314.6 ± 43.7	3.56	0.0004	-27.63 - - 7.97
Serum Ferritin (ng/ml)	81.2 ± 13.4	546.6 ± 103.5	55.78	<0.0001	448.98-481.82
Hypertension; n (%)		63 (50.8%)			
Diabetes Mellitus; n (%)		78 (62.9%)			
Polycystic kidney Disease; n (%)		09 (7.2%)			
Chronic glomerulonephritis; n (%)		23 (18.5%)			
Obstructive uropathy; n (%)		07 (5.6%)			

CRI: Chronic Renal Insufficiency; TIBC: Total Iron Binding Capacity; CI: Confidence Interval; SD: Standard Deviation

Table 3: Proportion of patients in stratified stages of CRI.

Stages of CRI	n(%)
1	18(14.5)
2	42(33.87)
3	50(40.32)
4	14(11.2)
5	00(00)

CRI: Chronic Renal Insufficiency

Table 4: Iron indices and renal sufficiency biochemical variables of patients in stratified stages of CRI.

Parameters	Stage 1	Stage 2	Stage 3	Stage 4	ANOVA
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	p
Creatinine (mg/dl)	3.3 ± 1.1	6.8 ± 3.1	8.6 ± 2.9	9.1 ± 1.8	<0.001
Urea (mg/dl)	78.5± 27.1	127.3± 33.6	145.8± 57.2	157.1±66.5	<0.001
Anemia; n (%)	10 (55.55%)	34 (80.9%)	44 (88.0%)	13 (92.85%)	<0.001
Serum Iron (µg/dl)	67.4 ± 8.7	48.4 ± 12.4	39.8 ± 14.1	35.8 ± 6.6	<0.01
TIBC (µg/dl)	321.6 ± 60.6	316.6 ± 33.4	298.8 ± 59.7	285.3 ± 35.3	<0.05
Serum Ferritin (ng/ml)	446.3 ± 98.1	501.6 ± 143.6	606.5 ± 93.8	667.6 ± 123.1	<0.001

CRI: Chronic Renal Insufficiency; TIBC: Total Iron Binding Capacity; ANOVA: Analysis of Variance

DISCUSSION

Of the total body iron, only about 0.1% circulates in the plasma as an exchangeable poo l**(15)** and it plays a vital role in many physio-biochemical reactions including cellular respiration and oxygen transport. However, excess iron generates free radicals and renders it toxic.**(6,15)** Thus, systemic iron level must be tightly monitored, even more so in CRI, in whom anemia is widely prevalent. Therefore in this study, it is considered important to unravel the prevalence of anemia and level of iron indices with respect to CRI and found that the majority of pre-dialysis CRI patients {101 (81.45%)} were anemic, reflected by; lower hemoglobin than the target values;**(16)** low iron levels in the presence of elevated serum ferritin.

The etiology of anemia in CRI is not clear-cut; it engages a complex interaction of nutritional deficiency, decreased red cell survival, inflammation, uremic inhibitors or compromised marrow function.**(4,17)** Nevertheless, the leading cause is deficient in erythropoietin synthesis.**(4)** Kidney is a foremost situate for erythropoietin production contributing 80-90%, as compared to the liver which contributes 10-15% of erythropoietin in circulation.**(4,7,18)** As the disease progresses, specialized peritubular cells that produce erythropoietin are partially or completely depleted/injured resulting inappropriately low erythropoietin comparative to the degree of anemia.**(4,18)**

Of the CRI patients, 78 patients (62.9%) were diabetic, 63 patients (50.8%) were hypertensive, 23(18.5%), 09 (7.2%) and 07 (5.6%) patients had history of chronic glomerulonephritis, polycystic kidney disease and obstructive uropathy respectively (Table 02). 52 patients were suffering from hypertension and Diabetes mellitus both and 04 patients were suffering from three or more mentioned conditions. Thus, Diabetes Mellitus and Hypertension were found to contribute maximally to the cases and constitute the high risk population.

It is very much evident from the data (Table 01 and Table 02) that various parameters among the healthy controls were within accepted reference range. A comparison of characteristics between CRI patients and control individuals revealed that patients had more altered hematological/hemodynamic profiles compared with healthy participants. Serum ferritin levels in patient group were significantly greater than in healthy controls ($p<0.0001$; Table 02). On the contrary serum iron was significantly decreased in CRI patients when compared to control participants ($p<0.0001$; Table 02). These finding with regards to serum iron status are in accordance with previous studies.**(19-21)** The increase in ferritin in our study is in agreement with other studies.**(20-22)** Progressive loss of kidney function (indicative by stratified stages of chronic kidney disease) leads to marked alterations in iron homeostasis with the advancing stages of CKD (Table 4). Moreover, disturbances of iron indices (serum iron, serum ferritin and serum TIBC) at each stage was significantly higher from its preceding stage (Table 4; ANOVA: $p<0.05$). Likewise, prevalence of anemia kept on increasing with advancing stages of disease (Table 4; ANOVA: $p<0.05$).

Though serum ferritin concentration is a surrogate marker for iron stores, but it also behaves as an acute phase reactant and the consequences of CRI associated inflammation is reflected as an increase in ferritin values and thus its levels comes in reference range or even elevated for CRI patients, in whom actually iron is deficient.**(23)** This imbalance in the iron availability leads to iron deficiency in most of the patients. The inverse correlation of ferritin level and anemia in CRI patients could also be explained by hepcidin. Hepcidin lowers the available serum iron levels by limiting iron efflux from the body's iron stores i.e. by inhibiting the iron transporter ferroportin.**(24)** This may cause bone marrow iron deficiency despite sufficient ferritin levels.**(25)** Researchers also have reported an elevated level of hepcidin in CRI patients.**(26)**

Additionally, in CRI as earlier pointed, iron stores keeps on depleting as a result of decreased intake due to malnutrition, decreased appetite associated with uremia and increased loss through chronic GIT bleeding due to blood vessel fragility associated with uremia, platelet dysfunctional related to uremia.

(4,17) The difference between estimated levels of TIBC in healthy controls and CKD patients were not statistically significant and were within accepted reference range. This finding was similar to as reported by Locatelli et al.**(22)**

CONCLUSION

Our findings suggest that, anemia characterized by low iron levels in the presence of elevated serum ferritin was a characteristic attribute to the studied CRI cohort. Thus, there is need for clinicians for early evaluation and treatment of anemia, as soon as diagnosis is made of CRI. Iron supplementation is necessary for a satisfactory response to erythrooietin therapy in CRI patients because the demands for iron by the erythroid marrow commonly surpass the quantity of iron that is instantly accessible for erythropoiesis. However, advocating extensive use of iron supplementation (oral or IV) may causes iron toxicity and leads to oxidative stress and infection. Thus, it is suggested that in CRI population, iron indices must be stringently monitored to avoid under/over load.

Nonetheless, this study has a few limitations. Firstly, sampling may not be representative of all of the CRI population as participants were enrolled from one Hospital, having more or less same socio-economic status and cultural environment, which may reduce the generalizability of our findings. Secondly, the study was cross-sectional and thus, we are not able to infer causality. Another limitation is that serum iron, TIBC, and serum ferritin had a limited sensitivity and specificity in predicting bone marrow iron stores. Still, taken together, these results provide important information for clinical practice as these laboratory indices are routinely done for assessment of anemia/iron status. However Additional studies are warranted in this regard to guide an ideal biomarker which should provide optimization of iron status; correlate with degree of anemia along with predict response to iron repletion.

REFERENCES

1. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 2002;39:S1-S266.
2. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease KDOQI; National Kidney Foundation. Am J Kidney Dis 2006;47:S11-145.
3. Coresh J. Update on the Burden of CKD. JASN 2017;28(4):1020-22.
4. Bello AK, Alrukhaimi M, Ashuntantang GE, Basnet S, Rotter RC, DouthatWG, et al. Complications of chronic kidney disease: current state, knowledge gaps, and strategy for action. Kidney IntSuppl 2017;7(2):122-9.
5. Hegarty J, Foley RN. Anaemia, renal insufficiency and cardiovascular outcome. Nephrol Dial Transplant 2001;16:102-4.
6. Bailie GR, Larkina M, Goodkin DA, Li Y, PisoniRL, Bieber B, et al. Data from the dialysis outcomes and practice patterns study validate an association between high intravenous iron doses and mortality. Kidney Int 2015;87:162-8.
7. ParchwaniDN, Upadhyah AA. Diabetic nephropathy: Progression and pathophysiology. Int J Med Sci Public Health. 2012;1(2): 59-70.
8. Rose GA, Blackburn H. Cardiovascular survey methods. WHO Monogr Series. 1968;56:90–5.
9. Wick M, Pinggera W, Lehmann P. Diagnosis of Anemias. In: Ferritin in Iron Metabolism. Springer, Vienna; 1995;second edition 89-98
10. Persijn JP, W van der Slik, Riethorst A. Determination of Serum Iron and Latent Iron-Binding Capacity (LIBC). ClinChimActa 1971;35(1):91-8.
11. Goodwin JF, Murphy B, Guillemett M. Direct Measurement of Serum Iron and Binding Capacity. ClinChem 1966;12(2):47-57.
12. Chasson AL, Grady HJ, Stanley MA. Determination of creatinine by means of automatic chemical analysis. Tech Bull Regist Med Technol 1960;30:207-12.

13. Chaney AL, Marbach EP Modified Reagents for Determination of Urea and Ammonia ClinChem 1962;8:130-2.
14. Trinder P. Determination of blood glucose using an oxidase-peroxidase system with a non-carcinogenic chromogen. J ClinPathol 1969;22:158-61.
15. Saito H. Metabolism of iron stores. Nagoya J Med Sci 2014;76:235-54.
16. Volkova N, Arab L. Evidence-based systematic literature review of hemoglobin/hematocrit and all-cause mortality in dialysis patients. Am J Kidney Dis 2006;47:24-36.
17. PinevichAJ, Petersen J. Erythropoietin therapy in patients with chronic renal failure. Western J Med 1992;157:154-7.
18. McGonigle RJ, Wallin JD, ShadduckRK, Fisher JW. Erythropoietin Deficiency and Inhibition of Erythropoiesis in Renal Insufficiency. Kidney Int 1984;25(2):437-44.
19. AnatGafter-Gvili, Schechter A, Rozen-Zvi B. Iron Deficiency Anemia in Chronic Kidney Disease. ActaHaematol 2019;142(1):44-50.
20. Fishbane S, MaesakaJK. Iron Management in End-Stage Renal Disease Am J Kidney Dis 1997;29(3):319-33.
21. Dabla PK. Renal Function in Diabetic Nephropathy. World J Diabetes 2010;1(2):48-56.
22. Locatelli F, Bárány P, Covic A, Francisco A, Del Vecchio L, Goldsmith D, Horl W, London G, Vanholder R, Biesen WV. Kidney Disease: Improving Global Outcomes Guidelines on Anaemia Management in Chronic Kidney Disease: A European Renal Best Practice Position Statement. Nephrol Dial Transplant 2013;28(6):1346-59.
23. Ueda N, Takasawa K. Impact of Inflammation on Ferritin, Hepcidin and the Management of Iron Deficiency Anemia in Chronic Kidney Disease Nutrients 2018;10(9):1173.
24. Donovan A, Lima CA, PinkusJL, PinkusGS, Zon LI, Robine S, Andrews NC. The iron exporter ferroportin/Slc40a1 is essential for iron homeostasis. Cell Metab 2005;1:191-200.
25. Ali M, Rigolosi R, Fayemi AO, Braun EV, Frascino J, Singer R. Failure of serum ferritin levels to predict bone-marrow iron content after intravenous iron-dextran therapy. Lancet 1982;1:652-5.
26. Ganz T. Hepcidin and iron regulation, 10 years later. Blood 2011;117:4425-33.

How to cite this article: Vachhani U, Kamariya C, Parchwani D.N., Analysis of iron indices in pre-dialysis chronic renal insufficiency patients. Int.J.Med.Sci.Educ 2019;6(4):120-126