*Proceeding S.Z.P.G.M.I. Vol: 29(2): pp. 83-87, 2015.*

# Iron Markers in Patients with Advance Chronic Kidney Disease on First Dialysis at Shaikh Zayed Hospital, Lahore

**Waqar Ahmad, Muhammad Rizwan Ul Haque, Abad Ur Rehman and Sammiullah Khan**
*Department of Nephrology, Shaikh Zayed Hospital, Lahore*

## ABSTRACT

Anemia in chronic kidney disease (CKD) is associated with mortality and morbidity. Iron stores may be low in CKD patients and the major cause of erythropoietin (EPO) hyporesponsiveness. This study was conducted in the advance chronic kidney disease patients approaching end stage renal disease (ESRD) who requiring dialysis for the first time. **Objective:** To know the iron status and anemia in advance chronic kidney disease patients (newly diagnosed end stage renal disease patients), presented in the emergency department of Shaikh Zayed Hospital Lahore. **Methods**: This was a single centre, open label, prospective study, carried out at Shaikh Zayed Hospital Lahore. Serum samples for iron(Fe), total iron binding capacity (TIBC), ferritin, haemoglobin( Hb), mean corpuscle volume(MCV), mean corpuscle hemoglobin concentration( MCHC) were taken of every chronic kidney disease patient requiring dialysis for the first time. Transferin saturation was counted by the formula (S. Iron /TIBC) ×100. Then mean values of these markers were calculated. **Results**: In this study, 100 out of total 101 patients were anemia and there mean hemoglobin was 8.47 g/dl ±2.60. Mean iron was 68.71±34.49 mcg/dl, TIBC 337.89±102.05 mcg/dl, ferritin level 595.47±434.17ng/ml, MCV 75.36±14.55fl and MCHC 33.34±2.65 gm/dl and mean hypochromic cell percentage was 5.3±4.6. **Conclusion:** Conventional iron markers in newly diagnosed ESRD patients were found to be within normal limits, so erythropoietin deficiency seems to be the major cause of anemia in these patients.

## INTRODUCTION

Anemia is one of the major complication of chronic kidney disease (CKD). Anemia causes fatigability, decreased quality of life and worsening of congestive cardiac failure. Major causes being erythropoietin deficiency, iron deficiency and decreased RBC life span.[1] There are many causes of iron deficiency in CKD patients. Major causes of iron deficiency in CKD patients are poor absorption of oral iron from gastrointestinal tract, frequent blood sampling, and gastrointestinal blood loss, where as in dialysis patients, blood loss in dialysis filters and lines also contribute to iron deficiency.[2] Iron deficiency is evaluated with iron indices like serum iron, serum ferritin and total iron binding capacity (TIBC). However Iron deficiency is confirmed with bone marrow iron examination.[3] KDOQI recommend that TSAT should be more than 25% and ferritin more than 200 ng/ml in CKD patients.[4] Absolute iron deficiency is known when there is TSAT<20% and ferritin <100ng/ml and absence of stainable iron in the bone marrow. Iron deficiency is usually present in CKD patients who are not on dialysis. Prevalence of low iron indices like TSAT <20% and ferritin <100ng/ml is about 20-70[5]. Functional iron deficiency is characterized by adequate iron stores (ferritin >200ng/ml) with low transferring saturation (TSAT<20% ) is present in 23% of patient on hemodialysis patient.[6]

For monitoring the iron status in CKD patients biochemical marker such as serum iron, total iron binding capacity (TIBC), transferin saturation (TSAT) and serum ferritin levels are measured.[3] It is shown in literature that serum ferritin and transferrin saturation (TSAT) have the

sensitivity of 48% and 81% and specificity of 75% and 63% respectively for evaluation of iron status in CKD patients.(7) The diagnosis of iron deficiency is important before the start of erythropoietin treatment because iron deficiency is the major cause of erythropoietin hypo responsiveness.[8,9] As a CKD patient approaches to end stage renal disease patient requiring dialysis, development of anemia becomes universal. As anemia increases the morbidity and mortality in CKD patients, therefore, treatment of anemia became the essential step in the management of such CKD patients. It is reported in literature that iron replacement has important role for anemia treatment in 40 to 70% of patients without use of erythropoietin in CKD patients.[10] As there is no local practice guidelines and no national data is available regarding iron status of CKD patients, we conducted this study to know about the status of iron indices in chronic kidney disease patients approaching end stage renal disease (ESRD) requiring dialysis for the first time and to evaluate whether erythropoietin (EPO) or iron deficiency is the major cause of anemia in these patients.

## MATERIALS AND METHODS

It was a cross sectional, single centre, and prospective study carried at Shaikh Zayed Hospital Lahore. All the patients of age >18 years were included in the study. They were not on any iron supplements and erythropoietin before the start of study. World Health Organization (WHO) definition for anemia like Hb <130g/L in male and <120g/L in females was used. Cohort consists of 101 patients, CKD stage V, both males and females. All the patients provided written informed consent. Patients were excluded from study if they were getting iron preparations, EPO, active gastrointestinal bleed, non renal cause of anemia, active malignant disease, chronic uncontrolled inflammatory disease, chronic congestive heart failure and history of blood transfusion in the previous 8 weeks. Study was conducted in accordance with declaration of Helsinki and was approved by local ethical committee.

### Laboratory data

Serum sample for iron, TIBC, ferritin, Hb, MCV, MCHC and hypochromic cell percentage were taken. Transferrin saturation was calculated by iron/TIBC×100. Iron deficiency was considered if TSAT <25% and serum ferritin level <200ug/l.

### Statistical Analysis

Data collected for above mentioned parameters .Data like sex and cause of renal failure was presented by frequency and percentages. Data like age, Hb, MCV, MCHC, iron, ferritin level, TIBC, TSAT and percentage of hypochromic RBCs was presented by mean ± standard deviation (SD).

## RESULTS

Our cohort consists of 101 CKD-V patients, 63 male and 38 female. Their mean age was 47.9±15.23 years. Out of these 101 ESRD patients, 44(43.6%) were due to Diabetic Nephropathy, 36 (35.5%) because of chronic glomerulonephritis, 10(10%) due to hypertensive nephropathy, 6 (6%) due to stone disease and 5 patients (5%) due to unknown reasons. The mean values for hemoglobin, serum iron, ferritin, TIBC, transferrin saturation, MCHC, MCV ,are shown in Table 1.

**Table 1: Mean values of iron parameters**

| Parameters | Mean value | Normal value |
|---|---|---|
| Hb | 8.47±2.60 g/dl | 11.5- 17 g/dl |
| MCV | 75.36±17.98 fL | 76-96 fL |
| MCHC | 33.34±2.65 g/dl | 32-36 g/dl |
| Iron | 68.71±39.49 µg/dl | Male:65-176 µg/dl<br>Female: 50- 170 µg/dl |
| Ferritin | 595.47±434.17 ng/l | 18-270 ng/ml |
| TIBC | 337.89±102.05 µg/dl | 240-450 µg/dl |
| TSAT | 25.97±22.11%. | 20-45% |

It was found that all patients were anemic with their mean hemoglobin values were less than 8.47±2.6gm/dl, but mean values for iron indices were within normal limits, although ferritin levels were on the higher side.

## DISCUSSION

Anemia is the defined by the World Health Organization (WHO) as a hemoglobin (Hb) concentration of less than 13.0g/L in adult men and

non-menstruating women, and less than 12.0g/dl in menstruating women.[11] The incidence of anemia in patients with chronic kidney disease (CKD) increases as the glomerular filtration rate (GFR) declines. Population studies such as the National Health and Nutrition Examination Survey (NHANES) by the national Institutes of Health suggests that the incidence of anemia is 10% in CKD stages 1 and 2, 20% to 40% in CKD stages 3, 50% to 60% in CKD stage 4, and more than 70% in CKD stage 5.[3,12] The major clinical manifestations of anemia in patients with or without CKD are fatigue (both with exercise and at rest), decreased cognitive function, loss of libido, and decreased sense of well-being. These symptoms occur when the Hb is less than 10g/dl, and they are more severe at lower Hb levels. Furthermore, cardiac complications of anemia like left ventricular hypertrophy (LVH) contribute to the adverse cardiovascular morbidity and mortality among patients with CKD.[13] A decrease in Hb of 0.5g/dl below normal correlates with a 32% increase in LVH risk, whereas a 5 mm Hg increase in systolic blood pressure correlates with only an 11% increase in LVH risk.[14]

Prevalence of anemia among patients with CKD stages 1 and 2 is as high as 10% and consequences of anemia are severe, therefore, National Kidney Foundation (NKF) Kidney Disease Out-comes Quality Initiative (K/DOQI) clinical practice guidelines recommend screening for anemia in all patients with CKD (regardless of stage). If anemia is present, then further evaluation is required to determine the cause of the anemia.[(4)] This evaluation should include a complete blood count including RBC indices, reticulocyte count, percentage of hypochromic RBCs, serum iron, serum ferritin concentration, total iron binding capacity (TIBC), transferring saturation (TSAT) and reticulocyte Hb content.[(1,2,4)] The anemia of EPO deficiency is normocytic and normochromic that means normal mean corpuscular volume (MCV) and normal mean corpuscular Hb concentration (MCHC) respectively. A low MCV (microcytosis) is suggestive of iron deficiency.[15]

The serum ferritin level correlates with iron bound to tissue ferritin in the reticuloendothelial system. Serum ferritin is also an acute phase reactant and it increases in the setting of acute or chronic inflammation, independent of tissue iron stores.[16,17] The TSAT is a measure of circulating iron available for delivery to the erythroid marrow and is calculated by dividing the serum iron concentration by the total iron binding capacity (TIBC). The TIBC correlates with the serum level of transferrin, which is the major iron carrying protein in the blood. A TSAT of less than 20% and ferritin <100 ng/ml in an anemic patient with CKD is consistent with absolute iron deficiency.[5] When patient has low transferrin saturation (TSAT) <20% along with adequate iron stores (ferritin level) >200ng/ml this is consistent with functional iron deficiency.[6]

Easy availability of iron indices make these parameters favorable for assessment of iron status in CKD patients. Peoples have great interest regarding iron status in dialysis patients but little is known about iron status of CKD patients. Clinician decide to give iron to CKD patients if they have TSAT <20% and ferritin <100ng/ml as recommended by KDOQI.[(4,18)] Deteriorating renal function may enhance the overall inflammatory response due to decreased renal clearance of the factors that are directly or indirectly involved in inflammation.[19] So inflammation is major cause of misleading results and also causes EPO resistance in CKD patients. Bone marrow biopsy remains the gold standard for iron deficiency anemia, and shows that 48% of patients were iron depleted. But bone marrow examination is a complicated, costly, and invasive method of determining iron stores.[20,21]

International studies having diverse results regarding iron deficiency as one of the major factor in CKD patients. Majority of studies are not in favour of iron deficiency as a major cause, while few are in favour of iron deficiency as contributing factor in anemia in CKD patients.[8,15,22,23] This may be due to difference in dietary habits, social set up and patient selection in different study population. In our study mean age of patients was 47 years with 63 males and 38 females. Mean values of Hb, MCV, MCHC, and Iron were in accordance with other studies reportedly in literature and suggest that iron deficiency is not a major contributing factor for anemia in CKD patients.[8,21-23] As our patients were not yet on hemodialysis, so the factor such as blood

loss during hemodialysis may not be the contributing factor for iron deficiency in our study population. Higher level of serum ferritin in our study may be due to inflammatory response that usually present in these chronic kidney disease patients.[21,23] Cause and status of inflammation in these patients were not evaluated in our study.

There are certain limitations to our study. This was single centre study; results regarding iron indices are different than other internationally done studies. Investigation of choice like bone marrow biopsy and liver iron concentration by using magnetic resonance imaging (MRI) was not performed. Duration of study was short and numbers of patient included in this study were also limited. Status of inflammation was not evaluated in this study that may affect results especially of serum ferritin level.

## CONCLUSION

Iron deficiency is not the major cause of anemia in CKD patients but erythropoietin deficiency along with other conditions like inflammation, malnourishment, and drugs may be the cause of anemia in our settings.

## REFERENCES


1. Tareshcenko SN, Uskach TM, Kocheta AG; Analysis of causes of development of anemia in patients with chronic heart failure. Kardioloqia 2011;51: 20-6.
2. Fishbane S, Kowalski EA, Imbriano LJ, Maesaka JK; The evaluation of iron status in hemodialysis patients. *J Am Soc Nephrol* 1996; **7**:2654–57.
3. Steven Fishbane, Simcha Pollack, Harold I. Feldman and Marshall M; Iron Indices in Chronic Kidney Disease in the National Health and Nutritional Examination Survey 1988–2004. Clin J Am Soc Nephrol 2009; 4: 57–61.
4. National Kidney Foundation: K/DOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target, Am J Kidney Dis 2007; 50:471-530.
5. Jolanta Małyszko, Ewa KocŻórawska, Nomy Levin, Jacek Małyszko; New parameters in iron metabolism and functional iron deficiency in patients on maintenance hemodialysis. Polskie Archiwum Medycyny Wewnętrznej 2012; **122(1).**
6. Kopelman RC, Smith L, Peoples L, Biesecker R, Rizkala AR; Functional iron deficiency in hemodialysis patients with high ferritin. Hemodial Int 2007; **11**:238-246.
7. Fishbane S, Nissenson AR; Anemia management in chronic kidney disease; Kidney Int 2010; 78 (Suppl 117): S3-S9.
8. Fishbane S; Iron supplementation in renal anemia. Semi Nephrol; 2006,26:319-324
9. Tessitore N, Solero GP, Lippi G, et al. Poor predication of ESA response by iron markers. Nephrol Dial Transplant 2001; 16: 1416-23
10. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group; KDIGO Clinical Practice Guidelines for Anemia in CKD, Kidney Int, 2012.
11. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.1)
12. McClellan W, Aronoff SL, Bolton WK, et al; The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin. 2004; 20: 501-10.
13. Besarab A, Bolton WK, Browne JK, et al: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and erythropoietin, N Engl J Med 1998; 339: 584-90.
14. Macdougall IC, Lewis NP, Saunders MJ, et al. Long term cardiorespiratory effects of amelioration of renal anaemia by erythropoietin. Lancet. 1990;335: 489-93.
15. Pfeffer M, Burdmann E, Chen C, et al: Arial of darbepoetin alfa in type 2 diabetes and chronic kidney disease, N Engl J Med 2009; 361:2019-32.
16. Takeshi Nakanishi, Takahiro Kuragano,

Masayoshi Nanami, Yoshinaga Otaki: Importance of Ferritin for Optimizing Anemia Therapy in Chronic Kidney Disease. Am J Nephrol 2010; 32:439–46.

17. Kalanter – Zadeh K, Rodriguez RA, Humphreys MH; Association between serum ferritin and measure of inflammation, nutrition and iron in hemodialysis patient. Nephrol Dial Transplant 2004; 19: 141-49.
18. K/DOQI. Anemia guidelines in CKD patients. Am J Kidney Dis. 2006; 47(Suppl 3): S1-S146.
19. Balla J, Jeney V, Varga Z, Komodi E, Nagy E, Balla G; Iron homeostasis in chronic inflammation. Acta Physiol Hung 2007; 94: 95-106.
20. Jay B. Wish. Assessing Iron Status: Beyond Serum Ferritin and Transferrin Saturation. Clin J Am Soc Nephrol 2006; 1: 8.
21. Gangadhar T, Srikanth P, Sunneatha Y: Predictive value of iron stores marker in aneamia in chronic kidney diseases. J. Chem. Pharma Res; 2010: 2: 400-10.
22. Simona Stancu, Liliana Baˆrsan, Ana Stanciu, and Gabriel Mircescu; Can the response to iron therapy be predicted in anemic nondialysis patients with chronic kidney disease? Clin J Am Soc Nephrol 2010; 5:416.
23. Mehdi Rambad, Csaba P. Kavosdy, Kalavta Kalanter Zadeh K; Combination of high serum ferritin and low iron saturation in hemodialysis patients- Clin J Am Soc Nephrol 2008; 3: 1691–1701.

**The Authors:**

Waqar Ahmad,
Professor
Department of Nephrology,
Shaikh Zayed Hospital,
Lahore

Muhammad Rizwan Ul Haque,
Department of Nephrology,
Shaikh Zayed Hospital,
Lahore

Abad Ur Rehman
Department of Nephrology,
Shaikh Zayed Hospital,
Lahore

Sammiullah Khan
Department of Nephrology,
Shaikh Zayed Hospital,
Lahore

**Corresponding Author:**

Waqar Ahmad,
Professor
Department of Nephrology,
Shaikh Zayed Hospital,
Lahore
E-mail: waqar3013@gmail.com