



IRON DEFICIENCY AND CHRONIC KIDNEY DISEASE

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ABSTRACT

Introduction: Iron deficiency is an important cause of anemia in patients with chronic kidney disease (CKD). Anemia develops early during chronic kidney disease (CKD), affects virtually all individuals with stage 5 CKD (GFR <15 ml/min per 1.73 m²), and is associated with increased cardiovascular morbidity and decreased quality of life. Iron deficiency is a common cause of anemia in CKD; the estimated prevalence ranges from 25 to 70%. The causes include decreased intake or absorption of iron; iron sequestration as a result of inflammation; blood loss; and increased iron use for red blood cell production in response to erythropoiesis stimulating agents (ESA). Inadequate production of erythropoietin by the kidney and/or insufficient response to erythropoietin as a result of inflammation contributes to anemia during later stages of CKD. Appropriate management of anemia in CKD often requires both iron and ESA. Thus, assessing

iron status is integral to both iron and anemia management in CKD patients, as iron is essential for Hb formation (as is erythropoietin).

Objective: To determine the frequency of iron deficiency anemia in patients with advanced chronic kidney disease presenting to a tertiary care hospital in Karachi.

Subjects and Methods: Patients with advanced chronic kidney disease attending the nephrology out-patients clinic at Aga Khan University Hospital who fulfilled the inclusion and exclusion criteria were included. Patients were tested for hemoglobin level and transferrin saturation. Those who had both, anemia and iron deficiency were taken as having iron deficiency anemia. Mean and standard deviations were calculated for the quantitative variables and frequencies and percentages were calculated for the qualitative variables. Effect modifiers were controlled through stratification of age and gender to see the effect of these on the outcome variable. Post stratification chi square test was applied. P-value of ≤ 0.05 was taken as significant.

Results: A total of 145 diagnosed advanced chronic kidney disease patients attending the nephrology out-patients clinic at Nephrology Department, Aga Khan University Hospital, Karachi who met the inclusion and exclusion criteria were included in this study. Mean age in our study was 49.06 years with the standard deviation of ± 10.08 . Mean hemoglobin and transferrin saturation in our study was 9.53 ± 2.47 g/dl and 13.99 ± 7.87 % respectively. 89 (61.4%) were male and 56 (38.6%) were female. Out of 145 patients, 118 (81.4%) had iron deficiency anemia and 27 (18.6%) had no iron deficiency anemia in advanced chronic kidney disease patients.

Conclusion: Anemia seen in chronic kidney disease (CKD) patients not on dialysis can be attributed significantly to iron deficiency, and that adequate iron replacement can cause a marked improvement in the anemia even without the use of erythropoietin. Replenishing iron stores in anemic patients with chronic kidney disease significantly increases hemoglobin levels and should be considered as an integral part of the therapy for treating anemia in advanced chronic kidney disease patient population. It is important that regular screening of iron deficiency in renal failure patients should be made part of the treatment and management in order to prevent adverse outcomes.

Keywords: Chronic advanced kidney disease, iron deficiency anemia, hemoglobin and transferrin saturation

INTRODUCTION

Anemia is commonly seen in patients with chronic kidney disease (CKD). It was first related to CKD more than 170 years ago by Bright, and is associated with reduced quality of life, worse cardiovascular outcomes and overall mortality [1, 2]. It is seen in upto 77.5% patients with CKD [3]. Anemia of CKD is a multifactorial process due to relative erythropoietin deficiency, uremic-induced inhibitors of erythropoiesis, shortened erythrocyte survival, and disordered iron homeostasis [1]. Iron deficiency is a major contributor to development of anemia and non responsiveness to erythropoietin in CKD [4, 5].

Iron deficiency has been observed in 60% patients with advanced chronic kidney disease [6]. Iron deficiency in CKD may be due to inadequate dietary intake of iron, poor appetite or advice to consume a low-protein diet, chronic iron loss from repeated intestinal bleeding resulting from CKD-related abnormal platelet function. Induction of hepcidin synthesis occurs due to chronic inflammatory state in CKD. This inhibits uptake of dietary iron by enterocytes and export of iron from enterocytes, macrophages and storage cells. These effects restrict the

availability of iron for hemoglobin synthesis and other functions [7].

Risk factors for iron deficiency include: [1, 8] Inadequate dietary intake of iron or iron rich foods (Poor appetite/Anorexia, Nausea/ vomiting, Vegetarian diet, Doctor's advice to consume a low-protein diet), chronic inflammatory states CKD itself or some other state, repeated bleeding from any site of body due to any cause like (Menstrual abnormalities, Chronic blood loss from repeated intestinal bleeding upper or lower GI, chronic NSAID use leading to gastritis, very high blood urea nitrogen : Uremic Gastritis), use of certain drugs like PPI and phosphate binders and concurrent use of calcium, hemodialysis.

Iron deficiency has been associated with fatigue, reduced exercise capacity, decreased quality of life and cellular functions like generation of cellular energy in skeletal and heart muscle, oxygen storage in myoglobin, T-lymphocyte proliferation and function, neuron myelination, and DNA synthesis [7]. On the other hand, iron overload is associated with oxidative stress and this in turn will also lead to worse cardiovascular outcome [5, 9].

It is therefore very important to assess and ensure adequate iron levels in CKD

patients. The frequency of iron deficiency in CKD has been assessed in some studies at international level [10] but data from Pakistan is lacking in this regard. This study aims to determine the frequency of iron deficiency in CKD patients from our part of the world. It will help us to recognize the magnitude of this problem in our population so that better management protocols catering to the needs of Pakistani population can be implemented. Ultimately this will result in improved patient outcome, improvement in quality of life of the patients and reduced mortality [11].

Objective

To determine the frequency of iron deficiency anemia in patients with advanced chronic kidney disease presenting to a tertiary care hospital in Karachi.

Operational Definition

Advanced Chronic Kidney Disease

Stage III CKD or above (eGFR 30-60 or below) as defined in the K/DOQI (The National Kidney Foundation Kidney Disease Outcomes Quality Initiative) guidelines [11].

Anemia

Hemoglobin level < 12 gm/dL.

Iron Deficiency

Transferrin Saturation <20%.

Iron Deficiency Anemia

Presence of both, anemia and iron deficiency as described above.

METHODS AND MATERIALS

Study Design

Cross-sectional study.

Study Setting

Study will be conducted at Nephrology Department, Aga Khan University Hospital, Karachi.

Duration of Study

Six months after approval of Synopsis.

Sample Size

The required sample size came out to be **145** patients. By taking the prevalence of 60%, [6] margin of error= 8% and confidence level 'C.I'=95%. This sample size was calculated using the WHO software.

Sampling Technique

Non Probability consecutive

Sample Selection

➤ Inclusion criteria:

- Patients with advanced chronic kidney disease, stage III and above attending the nephrology out-patient clinics.
- Age between 20 years and 60 years.
- Either gender.

➤ Exclusion criteria:

- Patients with known hemoglobinopathies.
- Patients with history of chronic liver disease.

- Patients with known malabsorption syndromes.

Data Collection Procedure

This study will be conducted after approval from College of Physicians and Surgeons Pakistan. Patients with advance chronic kidney disease attending the nephrology out-patients clinic at Aga Khan University Hospital who fulfill the inclusion and exclusion criteria will be included in the study after informed consent. Permission from the institutional ethical review committee will be taken prior to conduction of study. Detailed history and physical examination will be done and age and gender will be noted. Patients will be tested for hemoglobin level and transferrin saturation. Presence of anemia and iron deficiency will be noted. Those who have both, anemia and iron deficiency will be taken as having iron deficiency anemia. Data will be collected on a pre prescribed proforma.

Data Analysis Procedure

Data will be analyzed on SPSS Version 16. Mean and standard deviations will be calculated for the quantitative variables like age, hemoglobin level and saturation of transferrin. Frequencies and percentages will be calculated for the qualitative variables gender, presence of iron deficiency anemia. Effect modifiers will be controlled through

stratification of age and gender to see the effect of these on the outcome variable. Post stratification chi square test will be applied. p-value of ≤ 0.05 will be taken as significant.

RESULTS

A total of 145 diagnosed advance chronic kidney disease patients attending the nephrology out-patients clinic at Aga Khan University Hospital who fulfilled the inclusion and exclusion criteria were included in the study.

Out of 145 patients minimum age of the patient was 22 years while maximum age of the patients was 60 years. Mean age in our study was 49.06 years with the standard deviation of ± 10.08 . Mean hemoglobin and transferrin saturation in our study was 9.53 ± 2.47 g/dl and 13.99 ± 7.87 % respectively. As shown in **Table 1**.

Out of 145 patients, 118 (81.4%) had iron deficiency anemia and 27 (18.6%) had no iron deficiency anemia in advance chronic kidney disease patients. As shown in **Figure 1**.

Out of 145 patients, 89 (61.4%) were male and 56 (38.6%) were female. As shown in **Figure 2**.

Frequency distribution of age showed that out of 145 patients, 10 (6.9%), 14 (9.7%), 35 (24.1%) and 86 (59.3%) patients were in age group <30 years, 30-39 years,

40-49 years and >50 years respectively. As presented in **Figure 3**.

Stratification for age with respect to iron deficiency anemia showed that 07 (5.9%), 12 (10.2%), 31 (26.3%) and 68 (57.6%) were in age group age group <30 years, 30-39 years, 40-49 years and >50 years developed iron deficiency anemia respectively. Whereas 03 (11.1%), 02 (7.4%), 04 (14.8%) and 18 (66.7%) were in age group <30 years, 30-39 years, 40-49 years and >50 years did not develop iron

deficiency anemia respectively. P-value was 0.47. As presented in **Table 2**.

Stratification for gender with respect to iron deficiency anemia showed that 73 (61.9%) and 16 (59.3%) developed and did not develop iron deficiency anemia in the male gender respectively. Whereas 45 (38.1%) and 11 (40.7%) developed and did not develop iron deficiency anemia in the female gender respectively. P-value was 0.48. As presented in **Table 3**.

Table 1: Descriptive Statistics (n=145)

Variable	Mean ± SD	Standard Deviation	Min-Max
Age (years)	49.06	±10.08	22-60
Hemoglobin (G/Dl)	9.53	±2.47	4.57-21.90
Transferrin saturation (%)	13.99	±7.87	2.2-40.1

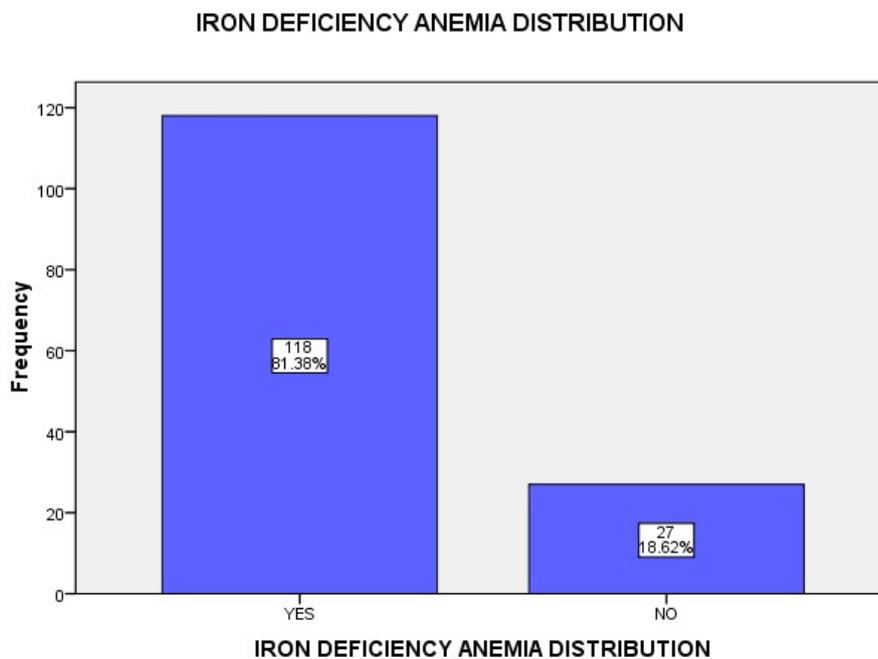


Figure 1: Iron Deficiency Anemia Distribution (n=145)

GENDER DISTRIBUTION

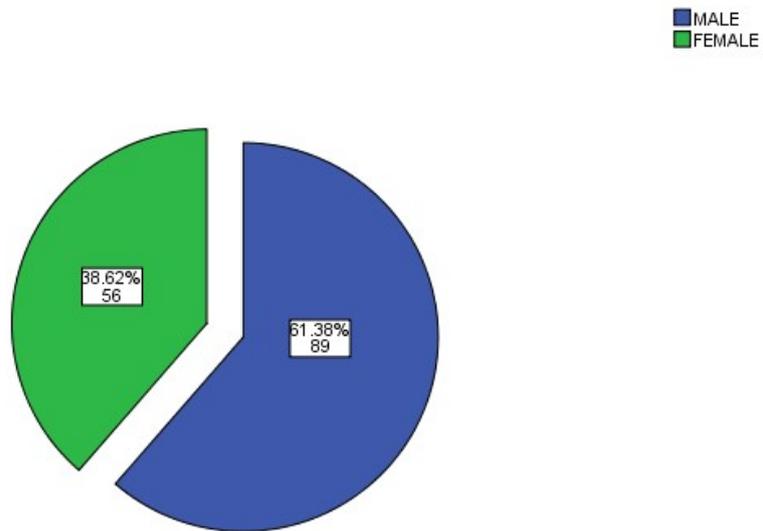


Figure 2: Gender Distribution (n=145)

AGE DISTRIBUTION

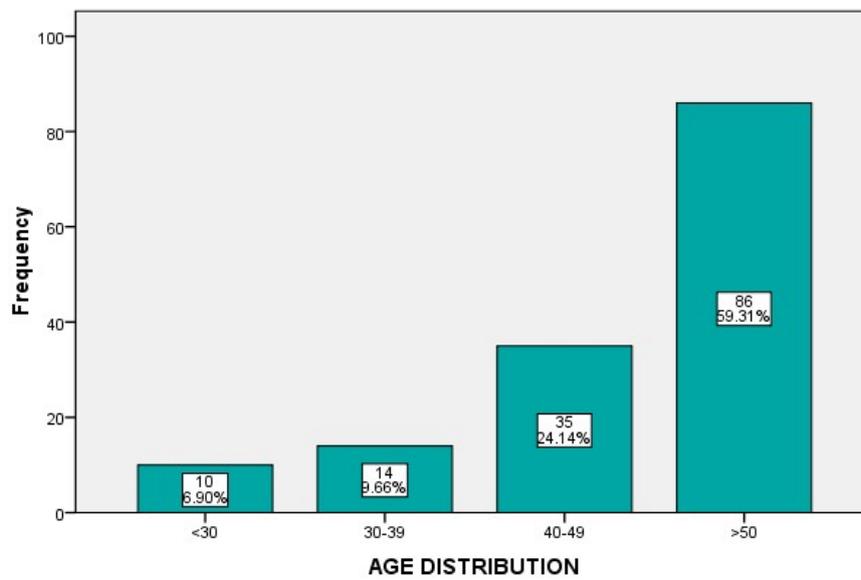


Figure 3: Age Distribution (n=145)

Table 2: Iron Deficiency Anemia According to Age (n=145)

Age (Years)	Iron Deficiency Anemia		Total
	Yes	No	
<30	07 (5.9%)	03 (11.1%)	10 (6.9%)
30-39	12 (10.2%)	02 (7.4%)	14 (9.7%)
40-49	31 (26.3%)	04 (14.8%)	35 (24.1%)
>50	68 (57.6%)	18 (66.7%)	86 (59.3%)
Total	118 (100%)	27 (100%)	145 (100%)
P-Value	0.47		

Table 3: Iron Deficiency Anemia According to Gender (n=145)

Gender	Iron Deficiency Anemia		Total
	Yes	No	
Male	73 (61.9%)	16 (59.3%)	89 (61.4%)
Female	45 (38.1%)	11 (40.7%)	56 (38.6%)
Total	118 (100%)	27 (100%)	145 (100%)
P-Value	0.48		

DISCUSSION

Anaemia is one of common treatable complications of CKD with erythropoietin and iron deficiencies being the major causes. Anemia of CKD may be due to insufficient production of erythropoietin by diseased kidneys, diminished RBC survival, iron or vitamin deficiencies, bleeding diathesis, hyperparathyroidism, chronic inflammation, or comorbidities. Diabetic patients are at increased risk for anemia, and anemia itself is an independent risk factor for CKD.

Our study showed that a total of 145 diagnosed advance chronic kidney disease patients attending the nephrology out-patients clinic at Nephrology Department, Aga Khan University Hospital, Karachi who met the inclusion and exclusion criteria were included in this study. Mean age in our study was 49.06 years with the standard deviation of ± 10.08 . Mean hemoglobin and transferrin

saturation in our study was 9.53 ± 2.47 g/dl and 13.99 ± 7.87 % respectively. 89 (61.4%) were male and 56 (38.6%) were female. Out of 145 patients, 118 (81.4%) had iron deficiency anemia and 27 (18.6%) had no iron deficiency anemia in advance chronic kidney disease patients.

Post *et al.*, 2006, [12] evaluated admission laboratory tests and the Health Care Financing Administration (HCFA) 2728 form were examined to determine the prevalence of erythropoietin use, anemia (Hb<11 g/dl), and iron deficiency (ferritin<100 ng/ml and transferrin saturation %<20%). In a second part of the study, the effect of intravenous iron gluconate replacement in patients with stage III & IV chronic kidney disease was examined. Anemia was present in 68% of all patients starting hemodialysis. Iron deficiency was a common feature occurring in 29% of patients

taking erythropoietin (49% of all patients) and 26% of patients without erythropoietin (51% of all patients).

Gotloib *et al.*, 2006, [13] found that forty-six patients had no evidence of any iron deposits in the bone marrow - consistent with the presence of severe iron deficiency. The mean serum ferritin and % transferrin saturation prior to treatment were 235.9 +/- 54.3 ug/L and 13.5 +/- 4.1%, respectively, and both increased significantly with the iron treatment. Mean Hb increased from 10.16 +/- 1.32 to 11.96 +/- 1.52 g/dL, an increase of 1.80 +/- 1.72 g/dL ($p < 0.01$). Twenty-six patients (55.3%) reached the target Hb of 12 g/dL. Ten patients (21.3%) had an increase of 0.1-0.9 g/dL, nine patients (19.1%) had an increase of 1-1.9 g/dL and 23 patients (48.9%) had an increase of ≥ 2 g/dL.

Anemia was noted early in CRI; 45% of patients with serum creatinine levels of 2 mg/dL or less had an Hct less than 36%, and 8% had an Hct less than 30%. During the course of the study, mean Hct decreased from 35.1% +/- 5.6% to 31.8% +/- 5.6%. Iron studies were obtained in only 19% of patients, and among these, the prevalence of iron deficiency (transferrin saturation $< 20\%$) was 54%. Only 30% and 26% of patients were administered recombinant human

erythropoietin (rHuEPO) and iron, respectively.

Whilst iron supplementation is necessary for CKD patients with IDA, iron metabolism and utilisation can be affected by factors such as infection or inflammation. Iron is essential element for all life, it can be toxic to cells through the process of oxidative stress. It is important that all advanced chronic renal failure management plans should encompass iron deficiency screening and timely treatment [14].

CONCLUSIONS

Anemia seen in chronic kidney disease (CKD) patients not on dialysis can be attributed significantly to iron deficiency, and that adequate iron replacement can cause a marked improvement in the anemia even without the use of erythropoietin. Replenishing iron stores in anemic patients with chronic kidney disease significantly increases hemoglobin levels and should be considered as an integral part of the therapy for treating anemia in advanced chronic renal failure patient population. It is important that regular screening of iron deficiency in renal failure patients should be made part of the treatment and management in order to prevent adverse outcomes.

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