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Frequency of Iron Deficiency Anemia in Pre-dialysis Chronic Kidney Disease Patients

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Abstract

Background: Iron deficiency anemia (IDA) is the most common type of anemia. In chronic kidney disease (CKD) patients, it' s a significant burden and becomes more prevalent with decreasing GFR. Though, erythropoietin deficiency remains the major cause of anemia in CKD patients due to decreased renal erythropoietin production, yet the frequency of IDA in pre-dialysis CKD patients has not been well established in Pakistan.

Objective:To determine the frequency of IDA in pre-dialysis CKD patients.

Materials and Methods: 188 pre-dialysis CKD patients of age 18-75 and both genders were included. Patients having obvious causes of anemia were excluded. The percentage of patients with IDA in pre-dialysis CKD was then determined during OPD follow up.

Results: Mean age was 46.03±12.24 years. Out of 188 patients, 102 (54.26%) were males with male-female ratio of 1.2:1. The frequency of IDA in pre-dialysis CKD patients was found in 73 (38.83%) patients.

Conclusion: Study concluded that frequency of IDA in pre-dialysis CKD patients is high and close attention to the causes and its replacement may improve the patient outcome.

Keywords:CKD, Pre-dialysis , IDA, anemia, erythropoietin,

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DOI: 10.53778/pjkd63191
Received: 9 March, 2022 and accepted 12 Sep, 2022 PJKD 2022;6(3):15-22

Introduction

Anemia is a common complication of pre-dialysis chronic kidney disease (CKD) developing early in the course of disease and worsens as CKD progresses. In the world about 1.8 billion people are anemic, mainly due to iron deficiency and common among females and children.[1] Anemia is twice as prevalent among patients with CKD as compared to the general population (15.4% vs 7.6%)[2] with percentage rising from 8.4% in stage-I CKD to 53.4% in stage-V. Iron deficiency is a major contributing factor even in pre-dialysis CKD patients.[3]

Several factors are involved in the causes of iron deficiency in CKD patients, mainly reduced intake and impaired intestinal absorption of dietary iron, blood losses due to uremia induced platelet dysfunction, chronic inflammation associated with CKD.[3] Therefore, in patients with CKD, the ferritin cutoff level for absolute iron deficiency is significantly higher due to chronic inflammation inducing a reactive increase. Therefore, serum ferritin levels ≥ 100 µg/ml are recommended for patients with pre-dialysis CKD and ≥ 200 µg/ml for dialysis patients.[1]

Iron deficiency is an inevitable and frequent complication of pre-dialysis CKD correlating strongly with both CKD progression and patient survival. In one study done in India, the prevalence of IDA among pre-dialysis CKD patients was found to be 39%.[5] In another study, it was shown that hemoglobin level starts to decrease even in early renal deficiencies around 70ml/min eGFR (CKD II) in males and 50 ml/min eGFR (CKD III) in females.[4] In CKD patients increased hepcidin levels inhibit iron absorption from gut and iron recycling from macrophages resulting in iron restricted erythropoiesis and IDA.[6] There is a high burden of IDA among patients with CKD with majority having creatinine clearance < 60ml/min (CKD III) not on dialysis.[7]

There is an ever-growing population of patients with pre-dialysis CKD, exact prevalence is unknown and proper diagnosis remains a challenge in many cases because of the underlying inflammation that influences iron metabolism.[2] Prompt correction of IDA in such population improves the quality of life and at the same time reduces cardiovascular morbidity and mortality.[2,4] Literature search revealed a single study from Pakistan documenting IDA in 53% of pre-dialysis CKD patients and another study just mentioned microcytic anemia in 14%.[8]

The objective of the study was to determine the frequency of IDA in pre-dialysis CKD patients.

Methods:

CKD was defined as "kidney damage or decrease in glomerular filtration rate (GFR) <60ml/min/1.73m^2 for at least 3 months or more , irrespective of the cause and CKD classified as per KDOGI guidelines to identify the stages of CKD, Stage I – Stage V.[9]

Definition of anemia in CKD:

The following threshold values were used to define the diagnosis of anemia.[10]

- Hb <13g/dl in men
- Hb <12g/dl in women

Diagnosis of iron deficiency in CKD based on transferrin saturation:

Absolute Iron deficiency: serum ferritin concentration <100mg/ml TSAT<20%.[3] Functional Iron deficiency: TSAT <20% and normal/high ferritin concentration.Serum Ferritin level ≤ 100ug/L.

Study Design: Descriptive, cross-sectional study.

Setting: Nephrology out patient department of Shifa international Hospital Islamabad, Pakistan.

Duration of study: December 21, 2019 to June 20, 2020.

Sample size: Using a confidence level of 95% margin of error of 10% and hypothesized. Prevalence of IDA in pre-dialysis chronic kidney patients as 39% based on previous study, no local study from Pakistan was available at the time of initiation of study.[5] The sample size is calculated using WHO sample size calculator and taking the following parameters: Confidence interval: 95%, Anticipated population portion: 0.394[1], Absolute precision required: 0.07, Sample size: 188

Inclusion Criteria: All patients of age 18-75 years having CKD and not yet on dialysis. Both males and females were included in this study.

Exclusion Criteria: Individuals having other causes of anemia like sickle cell disease, leukemia, ongoing blood loss, current febrile illness, hemolytic disorders, pregnancy, or those with history of malignancy and taking oral iron supplements were excluded from the study.

Data Collection Procedure

This study protocol has been approved by local hospital ethics committee. Data regarding demographic variables, hemoglobin levels, serum iron, TIBC and ferritin levels were collected as out patient follow up.

The percentage of patients with IDA in pre-dialysis CKD was determined in out patient follow up. All the investigations were done in the hospital laboratory.

Statistical Analysis

Data was entered and analyzed using the statistically package for social sciences (SPSS) version 22 (Maryland, USA). Mean and standard deviation were reported for quantitative variables like age whereas frequencies (%) were reported for qualitative variables like gender, stages of CKD and presence or absence of IDA. Continuous variables were summarized as mean and standard deviation. The effect modifiers like duration of CKD, gender, diabetes and hypertension were controlled by stratification. Chi-square was applied post stratification. P value < 0.05 was taken as significant.

Results

Patient characteristics are shown in Table 1. Mean age was 46.03± 12.24 (18-75) years and majority of patients 102 (54.26%) were between 18 to 45 years of age. Male to female distribution was almost similar, 102 (54.26%) were males with male to female ratio 1.2:1 as shown in figure 1. Distribution of patients according to stage of CKD is shown in figure 2. Mean duration of CKD in our study was 11.36 ± 3.45 months and majority had CKD of less than 12 months duration, table 1.

In our study, frequency of IDA in pre-dialysis CKD patients was found in 73 (38.38%) patients figure 3.

Table 1: General characteristics of 188 chronic kidney disease patients not yet on

dialysis.

Mean Age (years)	46.03± 12.24
Gender	
Male	102(54.26%)
Females	86(45.74%)
Duration of CKD n(%)	
≤12 months	115(61.17%)
>12 months	73(38.83%)
Diabetes Mellitus	
Yes	89(47.34%)
No	99(52.66%)
Hypertension	
Yes	115(61.17%)
No	73(38.3%)
CKD Satge	
III	84(45%)
IV	68(36%)
V (not on dialysis)	36(19%)

Table 2: Frequency of Iron deficiency anemia in 188 predialysis CKD patients.

Frequency of IDA	**N(%)**	**P Value**
Age		
18-45 years	24/102 (24)	0.0001
46-75 years	49/86 (57)	
Gender		
Male	35/102 (34)	0.17
Females	38/86 (44)	
CKD Stage		
III	34/84(40)	
IV	20/68 (29)	0.06
V	19/36 (53)	
Duration of CKD		
≤12 months	49/115 (43)	0.18
>12 months	24/73 (33)	
Diabetes Mellitus		
Yes	35/89 (39)	0.99
No	38/99 (38)	
Hypertension		
Yes	44/116 (38)	0.84
No	29/73 (40)	

Discussion

In the present study, more than one third (38.38%) of our patients with CKD stages 3-5 were found to have IDA. In a recent study from Pakistan, Kanawal S et.al reported 53% of their 300 non dialysis dependent CKD patients had IDA.[8] They however did not mention the CKD stages and may have included early stages, whereas we had patients with pre-dialysis moderate to severe CKD stages 3-5. This reported frequency by Kanwal et. al. is a little higher than the reported worldwide estimated prevelance in 2010 of anemia around 33%, with iron deficiency being the leading cause in half of the cases.[1]
Anemia is more common in women in particular, those in their childbearing years.[11]

It is likely that female patients in their reproductive years will likely to have more prevalence of iron deficiency anemia. In general however anmeia was found to be 36% more common in females compared to male CKD patients. 12

Figure 1: Distribution of patients according to gender among 188 pre-dialysis chronic kidney disease patients.

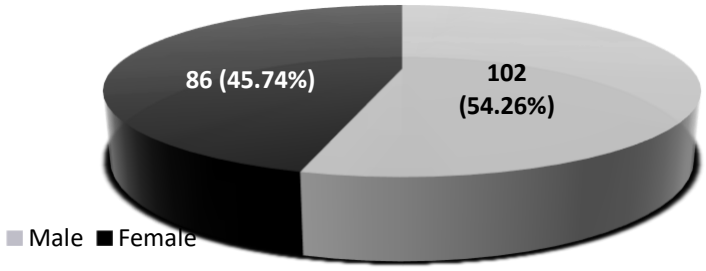
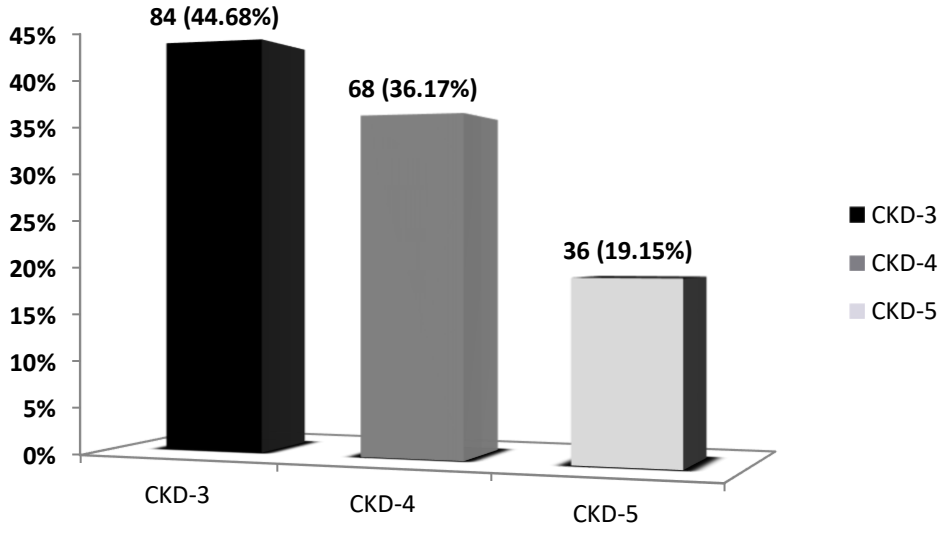


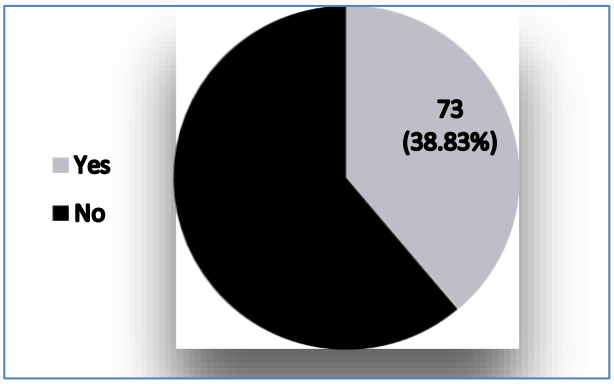
Figure 2: Distribution of patients according to stage of CKD among 188 pre-dialysis chronic kidney disease patients.



In Pakistan mean age of CKD5-HD is <50 years, much younger than the developed nations. [13] In the study by Kanwal et al mean age was <45 years and the female to male ratio was very high (1:2) compared to 1:1 in our study. It is therefore plausible to assume that the presence of high frequency of anemia in their study could be influenced by the presence of higher number of females who are in their reproductive age. The prevalence of concurrent anemia was 5.2% in patients with stage 3 CKD rising to 44% in those with stage IV disease.

In yet another study by Ahmed et al from Pakistan, among 156 patients with CKD (stage of CKD not provided and presence of ESKD not excluded), 13.9% patients were found to have microcytic anemia, however the detailed description of IDA were not reported.[14] In CKD patients, anemia is a clinically significant burden with increasing frequency of declining glomerular filtration rate (GFR). The landmark study by Obrador et al showed that among pre-dialysis patients, 68% of those with advanced CKD requiring renal replacement therapy had a hematocrit of less 30%, and of those, 51% had a hematocrit of less than 28%.[15]

Figure 3: Frequency of IDA in 188 pre-dialysis chronic kidney disease patients.



Anemia is associated with reduced quality of life and increased cardiovascular morbidity and mortality. Erythropoietin (EPO) deficiency remains the major cause of anemia in CKD patients due to the decrease in renal EPO production.[2] However, after the release of the recombinant human EPO (r. HuEPO) in the 1990s and the decline in blood transfusion, iron deficiency started to emerge as an important cause of anemia in CKD patients.[16]

There had always been a concern regarding iron deficiency in hemodialysis patients and intravenous iron is routinely administered during the dialysis session. This repeated iron deficiency has been related to several factors such as blood loss from dialyzer and tubing, regular blood test, impaired dietary iron absorption, gastrointestinal losses, and high levels of hepcidin, nicely explained in a recent review.[3] At the same time, depletion of circulating iron also result from the enhanced erythropoiesis with erythropoiesis stimulating agents, r. HuEPO.

Our study with almost equal gender ratio, showed a higher prevalence of IDA in pre-dialysis CKD truly depicting the burden of this treatable cause. Compared to 38.3% in our patients having IDA the problem is much less in the developed countries. The recent NHANES study from USA reported the prevalence of anemia in 15.4% in CKD patients, almost 8% were in Stage 3-5.[2] Similarly, a recent Chinese report showed that 51.5% of patients with CKD stage I to V had anemia.[17]

Among the developing nations from our subcontinent IDA is similarly high in prevalence. A study conducted in pre-dialysis CKD patient in TU hospital Kathmandu, Nepal showed overall incidence of 47.85% of anemia in overall CKD patients in that set up.[18] Minutolo et al studied CKD patients with eGFR <45ml/min and found out more iron deficiency in women (68.6%) than men (53.8%) but they did not compare the gender difference across different CKD stages.[19]

Anees et al from Pakistan reported anemia to be present in 88% of CKD 5 patients just before initiation of dialysis. [20] It was not mentioned in their study about the percentage of IDA. Still, it does suggest about the poor attention to the management of anemia in CKD pre-dialysis stage in Pakistan consistent with our results.

Conclusion

In our study, high frequency of IDA was observed in pre-dialysis CKD patients where more than one third of patients were diagnosed with IDA. It is therefore recommended that early screening for iron deficiency should be undertaken in pre-dialysis CKD patients.

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