www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v6i11.54

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Marrow Iron Status and its Correlation with Serum Ferritin in Anaemia of Chronic Kidney Disease

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Abstract
Anemia, a common entity in Chronic Kidney Disease can increase the morbidity and mortality. This study was done to determine the haematological profile and bone marrow stores in patients with anemia of CKD and also to study the usefulness of serum ferritin as a single screening tool for assessing the status of body iron stores. 35 patients with chronic Kidney disease and a hemoglobin level less than l0g/dl were assessed in this study. Their sociodemographic details and aetiology of the disease was noted. Reports of Hemogram, Peripheral smear and other investigations like Blood urea, Serum creatinine, Serum calcium, Uric acid, Serum albumin, Serum Ferritin etc were also noted. Glomerular filtration rate was estimated using the Cockcroft Gault Formula. Bone marrow aspiration was done and the aspirate was semi quantitatively graded for its iron content. Data collected was entered in Microsoft excel 2010 and analysed. It was found that 60 % were males and common causes were diabetes mellitus and hypertension. 45.7% had hypochromic microcytic anemia. Mean creatinine and blood urea were 9.8 mg/dl and 163 mg/dl respectively. A Normocellular marrow was seen in majority of cases. A significant correlation was seen between serum ferritin level and bone marrow iron status. It was concluded that serum ferritin estimation can be used as a screening test to detect the iron status in patients with anemia of Chronic Kidney Disease
Keywords: *Anemia, Chronic kidney Disease, Serum Ferritin, Haemoglobin, Bone marrow iron stores.*

Introduction

Chronic Kidney Disease, a common problem in India affecting 35 lakh people[1], is often associated with anemia, which causes increased morbidity and mortality. In the Indian population, iron deficiency in anemia of Chronic Kidney Disease is seen in 50-60%[2,3]. This study was done to determine the haematological profile and bone marrow stores in patients with anemia of CKD and also to study the usefulness of serum ferritin as a single screening tool for assessing the status of body iron stores.

Methods

This cross sectional descriptive study was done on 35 chronic Kidney Disease (CKD) patients with

serum creatinine level more than 3 mg/dl and a haemoglobin level less than l0g/dl who had documented serum creatinine of >2mg% or bilateral contracted kidney at least one month prior to the study, who never underwent haemodialysis, blood transfusion, Intravenous Iron therapy or erythropoietin therapy and no evidence of Acute kidney injury.

The sociodemographic details of the patients and aetiology of chronic renal failure were recorded in a predesigned proforma. Hemogram was done using an automated analyser and the following parameters were noted:

- Haemoglobin (Hb), Haematocrit or Packed cell volume (PCV), WBC count, Platelet count.
- Mean red cell volume(MCV): (Haematocrit x 10 / Red cell count x 10^6)
- Mean red cell haemoglobin (MCH): (Haemoglobin x 10 / Red cell count x 10^6)
- Mean cell Hemoglobin concentration (MCHC): (Hemoglobin x 10 / Haematocrit)
- Red cell distribution width (RDW), Reticulocyte count.
- Reticulocyte Production Index (RPI): (Reticulocyte count x haemoglobin correction / Maturation time correction).
- Hemoglobin correction: (Actual Hb / Expected Hb).

If haematocrit is around 25%, maturation correction factor is taken as 2 and if haematocrit is 15, then latter is taken as 2.5.

Peripheral smears of patients were taken and examined after Giemsa staining. The RBCs were examined and the anemia categorized into normochromic-normocytic, hypochromic-microcytic and macrocytic. The WBCs were examined for any abnormalities including toxic granules, shift to left and differential counts were confirmed.

Reports of biochemical investigations like Blood urea, Serum creatinine, Serum calcium, Uric acid, Serum albumin, Serum Ferritin were also noted. Glomerular filtration rate was estimated using the Cockcroft Gault Formula77ie GFR = (l42-Age) X $\frac{\text{Weight (kg)}}{\text{72-Creatinine}}$

Bone marrow aspiration was done and the aspirate was subjected to iron staining. The smear was semi quantitatively graded using Prussian blue reaction for its iron content.

Results

Out of the 35 patients enrolled in this study, 60 % were males and 40 % were females. Figure 1 shows the age wise distribution of patients. Mean age was 57 years. Maximum number of cases were within the 50 to 60 year age group (Figure 1).

Figure 1: Age wise distribution of patients

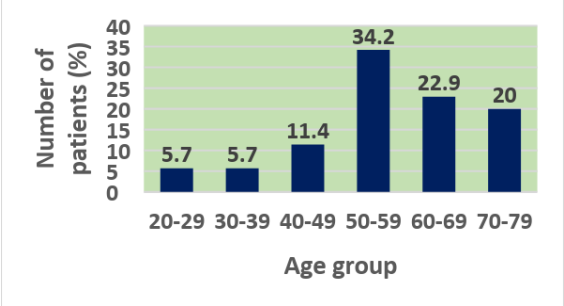
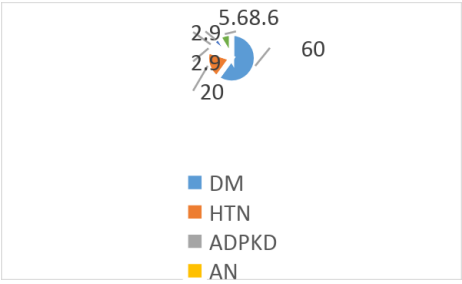


Figure 2 shows the aetiology of CKD in the study population. 60% patients developed CKD due to diabetic nephropathy and in 20%, it was due to hypertension.

Figure 2: Aetiology of CKD in study population



(DM: Diabetes Mellitus, HTN: Hypertension, ADPKD: Cystic kidney disease, AN: Analgesic nephropathy, CGN: Chronic glomerulonephritis (CGN), I: Idiopathic)

Hb levels of the patients ranged from 3.69 gm/dl to 9.2 gm/dl. The mean Hb was 6.9 gm/dl. 3 patients had Hb less than 5 gm, /dl. Mean values for PCV, MCV, MCH and MCHC were 22%, 83 fl, 25.8 pg/cell and 31g/dl respectively as shown in Table 1.

Table 1: Haemoglobin and RBC indices in the patients

Hb (g/dl)	**n (%)**	**Mean**
3 -5 g/dl	3 (8.6)	6.9 g/dl
> 5 - 7 g/dl	15 (42.9)	
>7 - 10 g/dl	17 (48.5)	
PCV (%)	**n (%)**	
<20	10 (28.6)	22 %
20-30	24 (68.6)	
>30	1 (2.8)	
MCV (fl)	**n (%)**	
<80	13 (37.1)	83 fl
80-85	8 (22.9)	
>85	14 (40)	
MCH (pg/cell)	**n (%)**	
<30	12 (34.3)	25.8 pg/cell
30-32	7 (20)	
>32	16 (45.7)	
MCHC (g/dl)	**n (%)**	
<28	21 (60)	31 g/dl
28-33	14 (40)	

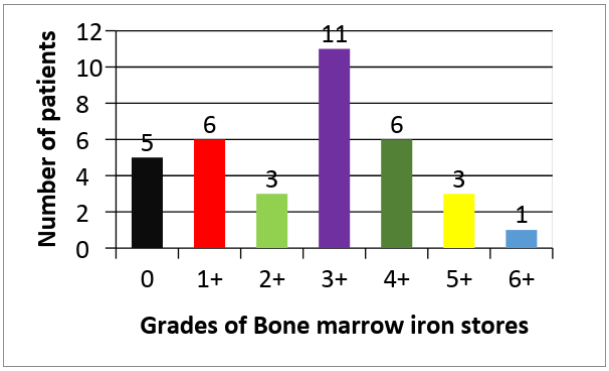
Microcytic hypochromic anaemia was seen in 45.7 % patients. Platelet count of the patients ranged from 0.95 lakh/mm^3 to 4.27 lakhs/mm^3 with a mean of 2.8 lakhs/mm^3. Only 2 cases had a platelet count less than 1.3 lakh/mm^3. None of the patients had significant thrombocytosis. 68% patients had an erythrocyte sedimentation rate (ESR) greater than 70 mm/ 1st hour.13 patients had an ESR more than 100 mm / 1st hour. The lowest ESR was 20 mm/ 1st hour.

Red cell distribution width (RDW) was more than 15% in 54% patients. The highest RDW was 17.8% and the mean RDW was 15.1%. Reticulocyte count was between 2 to 4% in 26% patients and less than 2% in rest of the patients. The Reticulocyte production index (RPI) was less than 1 in all the patients, the highest value being 0.74. Mean reticulocyte count was 2.

The values of serum Creatinine ranged between 3.1 to 18 mg/dl. The mean creatinine was 9.79 ± 6:94mg/dl. Blood urea level varied from 78 to 243 mg/dl and mean level was 163.1. The Glomerular Filtration rate ranged from 3.3 ml/min to 17.4ml/min. and the mean GFR was 8.13 mL/min ± 3.09.Calcium level ranged between 6.5 mg/dl to 10.5 mg/dl. The mean level was 8.8mg/dl. In 20 patients, it was less than 9 mg/dl. Significant correlation was seen between calcium level and creatinine but not between calcium level and hemoglobin level (p = 0.14). Mean uric acid was 5.25 mg/dl. 3 patients had an elevated serum uric acid. Albumin levels ranged from a minimum of 1.2 g/dl to 4.3 g/dl and average level was 2.7g/dl. 20 patients had albumin levels less than 3 g/dl. Only 3 patients had albumin more than or equal to 3.5g/dl. Significant correlation was seen between serum Albumin levels and severity of anemia.

Serum Ferritin ranged from 20 microgram/L to 800 micro gram/L. Ferritin level < 100 micro gram/L was seen in 14 cases, of whom, 5 had levels less than 50 micro gram/L. Those with levels of ferritin less than 50pg/L had absent bone marrow iron stores. Bone Marrow Cellularity was normal in 62.9% patients. 10 cases had grades more than 3+ as shown in figure 3. Bivariate analysis using Kendall Correlation Coefficient revealed a positive correlation coefficient of 0.731 with a p value of 0.01 between serum ferritin and bone marrow iron.

Figure 3: Frequency Distribution of Grades of Marrow Iron



40% of cases (14 cases) had ferritin level less than 100 pg/L. Of these cases, 78.5% (11 cases) had hypochromic microcytic anemia. Marrow iron was absent in only 31% of these patients. All the 5 patients with absent bone marrow iron had hypochromic microcytic anemia. Among patients with hypochromic microcytic anemia, 68% had ferritin levels less than 100 pg/L. The highest ferritin level among those with hypochromic microcytic anemia was 408 pg/L. This patient also had a high level of iron stores in the bone marrow. 5 patients had iron stores more than 2+ and ferritin more than 100 pg/L with the blood picture showing hypochromic microcytic anemia.

Discussion

60 % of the study population were males. The mean age was 57 years. The most common cause of chronic Kidney Disease was Diabetes Mellitus, followed by Hypertension. This correlates well with other western and Indian studies[7, 15]

Mean Hb level in the present study was 6.9gm/dl. There was a significant correlation between the severity of anemia and severity of renal failure as was seen in several studies[3,5]. In our study, mean MCV was 83 and 60% had low MCV, mean MCHC was 31 and mean MCH was 25.8. Red cell indices were consistent with the findings in a study by Talwar et al[15] where mean MCV was 83 with 61% having a low MCV, mean MCHC was 32.3 and mean MCH was 27.14 with 61% having low values of MCH. In the present study, 54% had RDW more than 15%. Docci et al reported that RDW tends to be higher in those with uremia compared to healthy individuals [8] A study by Talwar et al[15] reported a mean RDW of 15.35 with 67% of patients with RDW more than 14%. Talwar et al also reported a mean reticulocyte count of 1.92% with 45% cases having high reticulocyte count. In the present study mean reticulocyte count was 2%. Only 26% had high reticulocyte count, but in all cases the reticulocyte production index was less than 1, which is expected; given the fact that there is a defect in erythrocyte production and maturation in any patient with anemia of chronic renal failure. In the present study 45.7% cases had hypochromic microcytic anemia. This is in variance from a study by Callen et al[5] who found that 81% of patients with chronic renal failure had normocytic normochromic anemia, 4% had microcytic hypochromic anemia and 15% had macrocytic anemia[3]. Talwar et al[15] reported 60%. Arun et al reported combined microcytic anemia and normochromic anemia[2] the prevalence of hypochromic microcytic anemia in the present study was higher than the data from western studies and lower than other Indian studies. Variance from this study can be explained by better diet, lower rates of chronic illness such as tuberculosis and possibly due to lower parasitic infection rate. Moreover in the study by Talwar et al[15], there was a significant number of cases with absolute eosinophilia which the authors had attributed to the high rate of parasitic infection. This observation was not seen in the present study.

Mean creatinine value in the present study was 9.8 mg/dl and mean blood urea was 163. In the study by Talwar et al[15]done on 28 patients with CRF (with /without anemia, the mean creatinine was 7.3mg/dl and mean blood urea was 107 mg/dl respectively. ESR was elevated in majority of cases. 54% of cases had ESR more than 100 mm/1st hour, most of whom were diabetic.

Bone marrow examination showed Normocellular marrow in the majority of cases similar to studies done elsewhere[5,15]. Bone marrow iron stores were absent in 5 cases in the present study and it was increased (grade 5+ and 6+) in 4 patients. Blumberg A.B. et al studied 20 patients on Continuous Ambulatory peritoneal Dialysis and found absent marrow iron in 8 cases[4]. Prevalence of iron deficiency was 50% in the study conducted by Gupta et al on marrow iron estimation based on the combined use of serum ferritin and serum transferrin receptor.[11] Thalib S.H et al studied 190 CKD patients and reported an incidence of 42.63%[16]. There is a lack of correlation with other Indian studies which could be attributed to the dietary characteristics and better health awareness of the patient population of Kerala. Analysis of the present series show significant correlation between serum ferritin level and bone marrow iron status, with a p value < 0.05. Many groups have shown that serum ferritin concentration correlate well with iron stores.[15,4 12,3]

Considering 100 ug/L as the threshold of normal range of serum ferritin in patients with CKD, then the sensitivity of the test in detecting an absence of iron store is 100% and the specificity is 70%. The negative predictive value of a ferritin level of > l00ug/L is 100%. According to this study the chance that a patient with ferritin > l00ug/L has absent bone marrow iron is nil. Thus ferritin

estimation can be considered as a good screening test in CKD patients being evaluated for possible iron deficiency. Mirahmadi KS et al reported that Ferritin level less than 105 ug/L suggest decreased iron stores[13.] Milman N et al[12] in his study in 50 non dialysis patients and 50 controls, Serum Ferritin less than 60 ug/L was associated with absent or reduced marrow iron and concentrations greater than 80 microgram/L was associated with normal marrow iron. Fernandez-Rodriguez et al in his series of 63 patients on dialysis reported serum ferritin cut off point at 121 microgram /L[9.] All these 3 series correlate well with the present study with regard to the utility of Serum ferritin in the diagnosis of deficient iron stores in patients with anemia of chronic renal failure. In the present series, 45.7% cases had hypochromic anemia and 31.6% of them had absent marrow iron. 5 cases had normal ferritin ranging from 124 to 408. A significant proportion of patients with hypochromic anemia had good iron stores. This can be attributed to functional iron deficiency[6]. 11.5% of cases had increased bone marrow iron, one patient had bone marrow iron grading of 6+ and serum ferritin of 800. Hussein et al reported a high prevalence of iron overload but further trials have not substantiated the finding[10]. The corresponding prevalence reported by Milman et al[12] was 6.6% and that by Talwar et al[15] was 18.5%. Thus the present study highlights the possibility of iron overload in the setting of anemia of CKD. Simon P et al reported body iron overload in patients receiving blood transfusion and iron while on maintenance dialysis[14].

Conclusion

Serum ferritin estimation is a good screening test in estimating the iron status of patients with anemia of Chronic Kidney Disease. It was seen to have a significant correlation with bone marrow iron stores. A serum ferritin of less than l00ug/L has a sensitivity of 100% and a specificity of 70% in detecting absence of marrow iron. The prevalence of hypochromic microcytic anemia was 45.7% and normochromic normocytic anemia was 54.3% .A significant number of cases with hypochromic microcytic anemia bone marrow iron had normal marrow iron.

Conflict of Interest: Nil

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