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Research Article

Iron status in chronic kidney disease patients

Rumi Deori[1]*, Bedanta Bhuyan[2]

[1]Department of Biochemistry, Assam Medical College and Hospital, Dibrugarh, Assam, India
[2]Department of Pathology, Bharat Laboratory, Dibrugarh, Assam, India

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***Correspondence:**
Dr. Rumi Deori,
E-mail: rumideori@rediffmail.com

ABSTRACT

Background: In developing countries, chronic kidney disease (CKD) associated with anaemia is one of the major public health problems. With the progression of the disease, development of haematological abnormalities including iron deficiency increases. Renal anaemia may further increase the morbidity in these patients. Therefore, earlier detection and correction of anaemia may be helpful in preventing the progression of the diseases and its other adverse outcomes.
Methods: The present study was designed to observe the iron status in diagnosed CKD patients (pre-dialysis). For this purpose, 50 adult diagnosed CKD subjects who were not on any haematinics were randomly selected from the Departments of Medicine and Nephrology in a tertiary care hospital in Assam, India. 50 age and sex matched healthy controls were also included. Haemoglobin concentration, serum iron, TIBC, transferrin saturation (TSAT) and serum creatinine were estimated by standard laboratory techniques. Statistical data were analyzed by using SPSS 21.
Results: All the CKD subjects were anaemic with haemoglobin concentration below 11g/dl and 48% of them showed moderate degree of anaemia. Their serum creatinine level were >3mg/dl. The primary aetiologies of CKD were diabetes (44%) and hypertension (36%). Serum creatinine and total iron binding capacity (TIBC) were significantly ($P < 0.05$) raised in CKD patients while serum iron was significantly lower in CKD subjects than in the control group. 26% of them had iron deficiency anaemia (TSAT <20%).
Conclusions: Anaemia is one of the commonest and earliest manifestations in CKD patients. With serum creatinine >3 mg/dl, iron deficiency anaemia may be present.

Keywords: Anaemia, Chronic kidney disease, Iron deficiency, Transferrin saturation

INTRODUCTION

Chronic kidney disease (CKD) is a permanent and significant reduction in glomerular filtration rate, or chronic irreversible destruction of kidney tissue.[1] CKD is a worldwide public health problem with an increasing incidence and prevalence, poor outcomes, and high cost.[2] CKD prevalence is estimated to be 8-16% worldwide.[3] The current burden of CKD may be due to a change of the underlying pathogenicity of the disease. Few decades ago glomerulonephritis was the leading cause of kidney disease, though nowadays, infections have become a less important cause for kidney disease, at least in the western world.[4] Current evidence suggest diabetes and hypertension to be the major causes of kidney disease worldwide.[5,6]

In India too, there is a significant burden of CKD although the exact figures vary.[7] About 20-30 patients have some degree of renal dysfunction for each patient who needs renal replacement treatment. But less than 10% of end stage renal disease patients have access to any kind of renal replacement therapy.[8,9]

Iron deficiency anaemia is also common in patients with chronic kidney disease. Iron deficiency may be absolute, often due to poor dietary intake or sometimes occult bleeding, or functional, when there is an imbalance between the iron requirements of the erythroid marrow and the actual iron supply. Iron deficiency leads to a reduction in formation of red cell haemoglobin, causing hypochromic microcytic anaemia. Other causes for anaemia in CKD include the presence of uremic inhibitors (e.g., parathyroid hormone, inflammatory cytokines), reduced half-life of circulating blood cells and deficiencies of folate or vitamin B12.[10] As CKD patients commonly presents with anorexia, nausea and vomiting, less dietary intake of nutrients needed for erythropoiesis might also be a factor for anaemia in this group of patients. Moreover, CKD patients are on protein restricted diet which might also have some role for occurrence of anaemia in this series of patients.[11]

Iron deficiency is also accompanied by reductions in serum iron and transferrin saturation (TSAT) and by elevations in red cell distribution width, free erythrocyte protoporphyrin concentration, total serum iron-binding capacity (TIBC), and soluble transferrin receptor (sTfR).[12] TSAT (the ratio of serum iron to total serum iron-binding capacity) is a measure of circulating iron and is <20% in patients with iron deficiency. TSAT fluctuates widely as a result of diurnal variation in serum iron, and transferrin is affected by the nutritional status.[13]

Anaemia is common in North-Eastern region of India.[14,15] The present study was done to evaluate the iron status in the CKD patients as iron deficiency is common in this region and this kind of study has not been done previously in this part of India.

METHODS

A hospital based case control study was conducted for a period of one year in Assam Medical College and Hospital, Dibrugarh, Assam, India. The study included diagnosed patients of CKD who were attending the department of medicine and nephrology in the study setting.

Inclusion and exclusion criteria

50 (fifty) adults above 17 years age, of either sex, diagnosed with CKD (pre-dialysis) were randomly selected as cases and 50 (fifty) healthy persons as controls. Patients providing informed consent and patients with documented chronic kidney disease were included. Patients on dialysis, haematinics, recombinant human erythropoietin (rHuEPO) and blood transfusion in the last three months were excluded from the study. Patients with malignancy or known haematological disorder or with recent severe hemorrhagic episode were excluded. Patients with burns, trauma or on drugs that were likely to cause haematological disturbances were also excluded. A detailed clinical history and thorough physical examination was done in all the subjects. Institutional ethical clearance was taken prior to the study. Informed written consent was obtained from all the participants after explaining the objectives of the study, risks and benefits involved. The personal details of the participants were kept confidential throughout the study.

Sample collection

Under aseptic and antiseptic precaution, 5 ml of blood was collected from each subject from a suitable vein (preferably from antecubital vein) with a sterilized syringe. The blood samples were collected between 8-10 AM to avoid creeping in of errors owing to the diurnal variation of serum iron and TIBC levels. The serum was separated and used for test in the same day and hemolysed samples were discarded.

Laboratory analysis

Each participant was evaluated for haemoglobin concentration, serum iron, TIBC, transferrin saturation and serum creatinine. The haemoglobin level was measured using cyanmethaemoglobin method; serum creatinine by Mod. Jaffe's Kinetic method; serum iron by the Ferrozine method; total iron binding capacity (TIBC) by the Ferrozine method and transferrin saturation (TSAT) was calculated as the ratio of serum iron and TIBC [(Serum iron÷TIBC) x 100] and expressed as a percentage. (Normal value: 20%-55%).[16-19]

Statistical analysis was done by using SPSS version 21. Data were analyzed by student t-test and Pearson correlation coefficient test. P value <0.05 was considered significant.

RESULTS

50 diagnosed cases of pre-dialyzed chronic kidney disease patients were included in the study. Majority (46%) of the participants belonged to 41 to 60 year age group (mean age 47.6 years) and males constituted 72% of the study subjects (Table 1).

Table 1: Age and sex distribution in CKD patients (n=50).

Category	Frequency	Percentage
Age group (years)		
≤ 20	1	2
21-40	19	38
41-60	23	46
61 and above	7	14
Sex		
Male	36	72
Female	14	28

Diabetes mellitus and hypertension were the most common aetiological cause, seen in 44% and 36% of the CKD subjects respectively (Figure 1). All the cases were anaemic with haemoglobin concentration (Hb) below 11g/dl and the mean haemoglobin concentration was (8.1±2.2) g/dl. The mean Hb level in males was 7.1±2.0 g/dl and in females was 6.7±1.9 g/dl. The proportions with mild, moderate and severe anaemia among CKD subjects were 18%, 48% and 34% respectively (Figure 2).

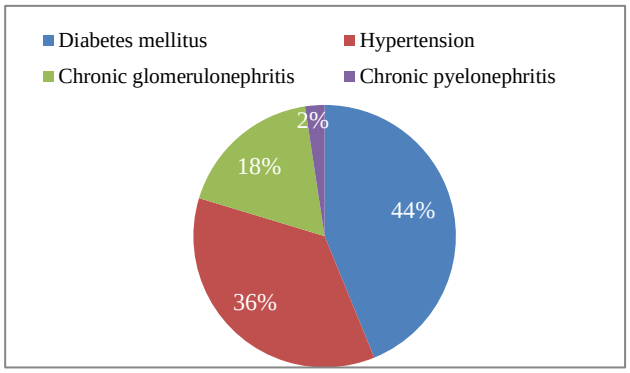

Figure 1: Aetiological diagnosis in CKD patients (n=50).

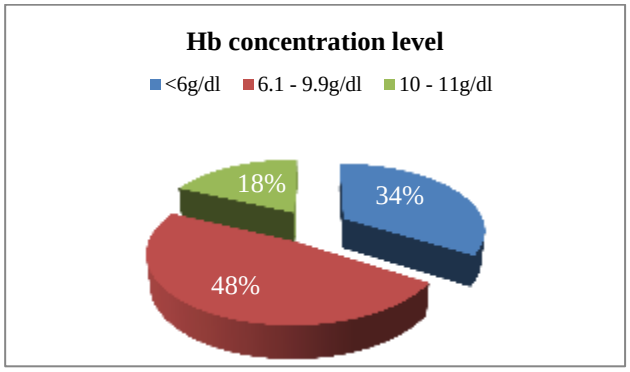

Figure 2: Severity of anaemia in CKD patients (n=50). Mild anaemia (10-11g/dl), moderate anaemia (6.1-9.9g/dl) and severe anaemia (<6g/dl).

The mean (±SD) of serum iron, TIBC, transferrin saturation (TSAT) and serum creatinine in CKD patients and control groups were shown in Table 2. Serum iron was significantly lower in CKD group as compared to the control group, whereas TIBC and serum creatinine were significantly higher in CKD patients than in the control group (Table 2). All the CKD patients had serum creatinine level above 2.96 mg/dl.

Following national kidney foundation/kidney disease outcomes quality initiative guidelines, either serum ferritin <100 ng/ml or TSAT <20% means iron depletion.[20] 74% of CKD patients showed transferrin saturation (TSAT) level >20%, 24% patients were in level <16% and 2% patients showed transferrin saturation level between 16-20% (Figure 3). Among males 13.8% had iron deficiency and among females 57.1% had iron deficiency (TSAT <20%).

Table 2: Revealed the biochemical parameters among control and CKD patients.

Estimated parameters	Cases (n=50)	Control (n_1=50)	p-value
Serum iron (µg/dl) Mean±SD	98.0±37.08	111.28±29.32	<0.05*
TIBC (µg/dl) Mean±SD	345.22±75.43	321.84±46.71	<0.05*
Transferrin saturation (%) Mean±SD	30.78±14.45	34.30±6.06	> 0.05
Serum creatinine (mg/dl) Mean±SD	7.77±3.24	1.14±0.20	<0.001*

Control= healthy subjects, Cases = Chronic Kidney Disease patients, TIBC=Total iron binding capacity, results are expressed as Mean±SD, n=no of subjects in cases, n_1=number of subjects in control group, *p value is significant.

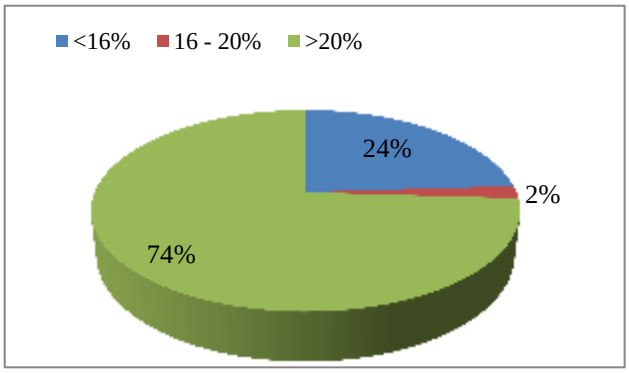

Figure 3: Transferrin saturation levels in CKD patients.

The TSAT value showed a wide variation in study subjects and the mean was lower as compared to the control group, but was not significant. Absolute iron deficiency was present in 26% of the CKD subjects. Anaemia in the remaining 74% may not be due to iron deficiency but might be due to other causes, which could not be evaluated in this study due to the lack of funds and cost related issues.

Correlation between haematological parameters and serum creatinine were done by pearson correlation coefficient in CKD patients. Serum iron (p=0.01) and TSAT (p=0.03) were found to be significantly correlated with serum creatinine whereas Haemoglobin concentration (p=0.39) and TIBC (p=0.39) were not significant.

DISCUSSION

Anaemia is a cardinal feature of chronic kidney disease, which is usually due to impaired erythropoietin production. But iron deficiency also plays a major role in causation of anaemia. Iron deficiency affects more than 2 billion people worldwide and iron deficiency anaemia remains the top cause of anaemia, the prevalence now highest in central and West Africa and South Asia.[21] In patients with CKD, dietary deficiency, low intestinal absorption, and gastrointestinal bleeding may result in absolute iron-deficiency anaemia. The national health and nutrition examination survey IV suggest that up to 50% of patients with CKD stages 2-5 have absolute or relative (functional) iron deficiency.[22] Absolute iron deficiency is defined as a depletion of tissue stores evidenced by a serum ferritin level <100 ng/ml or a TSAT <20%. Functional iron deficiency anaemia is adequate tissue iron defined as a serum ferritin ≥100 ng/ml and a reduction in iron saturation.[23] In the present study, 26% CKD patients had absolute iron deficiency, which is similar to the findings of Lukaszyk E et al where 17% had absolute iron deficiency, (Table 3) but unlike by Talwar et al where 65% had mirocytic hypochomic anaemia because of iron deficiency and 33% had parasitic infestation.[24,25]

Table 3: Comparison of the study.

Study	Aetiological factor	Severity of anaemia	Hb (g/dl) (Mean±SD)	Iron deficiency anaemia
Present study	Diabetes mellitus 44%, hypertension 36%, CGN 18%, CPN 2%	34% severe , 48% moderate and 18% mild	8.1±2.2	26%
Ashfar R et al[26]	Diabetes 49.1%, hypertension 28.3%, glomerular disease 17.1% and polycystic kidney disease 5.6%	55% moderate and 45% mild	11.11±2.26	-
William Mcclellan et al[30]	Diabetes 49.5%, hypertension 33.0%	-	-	-
Seuga K et al[27]	-	50% moderate and 50% mild	-	-
Lukaszyk K et al[24]	-		-	17%

This study, like others revealed presence of moderate degree of anaemia in 34% of CKD patients (Table 3).[26,27] The higher prevalence of anaemia in present study was within the range of figures reported in similar groups of patient's elsewhere.[26,28]

The mean age of CKD in the present study was 47.6±14.4 years and the females showed higher prevalence of iron deficiency anaemia as compared to males which was also observed in other studies. The early correction of anaemia was associated with improved renal and patient survival compared with delayed treatment of anaemia.[25,29-31]

The primary aetiology of CKD was diabetes followed by hypertension which is comparable to some other studies.[26,30] (Table 3). In general, kidney disease with diabetes is progressive, and it has been hypothesized that anaemia may contribute to progression of kidney disease.[32-35] Possible mechanisms include renal ischemia caused by reduced oxygen delivery due to low haemoglobin and underlying heart failure. For example, anaemia may worsen renal medullary hypoxia, leading to renal interstitial injury and fibrosis.[36,37]

Anaemia in CKD is usually evident when a patient's creatinine clearance is <30 ml/min/1.73 m^3, glomerular filtration rate (GFR) is below 40-50 ml/min, or serum creatinine (S Creat) is more than 3 mg/dl. If the GFR is less than 20 ml/min or S. Creatinine of more than 5 mg/dl, anaemia is invariably present, and the haemoglobin level is found below 10 g/dl.[38-40] In this study all the CKD patients had haemoglobin level below 11 g/dl and S. Creatinine level more than 3mg/dl.

Present study found a significant correlation between serum iron and TSAT with serum creatinine of CKD patients. Ashfar R et al found a positive correlation between creatinine clearance and haemoglobin concentration.[26] However, among CKD patients, the correlation of hematocrit with GFR or serum creatinine is imprecise and some studies did not find such correlation.[27]

The study had certain limitations. These include the relatively small number of sample size and inability to investigate the full spectrum of aetiologies of anaemia in observed population owing to the high cost of investigations and the absence of study funding. Study could have learned more by investigating serum ferritin, soluble transferring receptor, reticulocyte counts, vitamin B12, folate, and faecal test for occult blood or parasites.

Therefore to conclude, anaemia is a hallmark of CKD patients. High prevalence of moderate degree of anaemia is seen with serum creatinine levels >3.0 mg/dl and the most common cause is iron deficiency. All CKD subjects

must therefore be screened for iron deficiency anaemia for its early treatment and to improve the quality of life.

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