

A STUDY OF HAEMATOLOGICAL PROFILE AND SERUM IRON INDICES IN NONDIALYSIS CHRONIC KIDNEY DISEASE PATIENTS

Dr. Selvarajan Chettiar KP¹ , Dr. Yokesh M²

1.Professor, Department of General Medicine, Sree Mookambika Institute of Medical Sciences Kanyakumari, Tamil Nadu, India.

2.Junior Resident, Department of General Medicine Sree Mookambika Institute of Medical Sciences College Kanyakumari, Tamil Nadu, India.

Corresponding Author: Dr.Yokesh M,Junior Resident, Department of General Medicine Sree Mookambika Institute of Medical Sciences College Kanyakumari, Tamil Nadu, India.

ABSTRACT :

Background: Chronic kidney disease (CKD) encompasses a spectrum of various pathophysiologic processes leading to abnormal kidney function, and a progressive decline in glomerular filtration rate may postpone the onset of ESRD and improve survival. The identification, evaluation and optimal treatment of anemia in CKD essentially involve complete blood count, determination of serum ferritin and transferrin saturation to assess iron stores and adequacy of iron for erythropoiesis

Methods: Data was collected from patients attending the Department of General Medicine of Sree Mookambika Institute of Medical sciences, kanyakumari, tamil nadu, from march 2023 to may 2024. A total of 54 patients were included in our study who satisfied the diagnostic criteria of CKD and patients underwent clinical and renal parameters, haematological profile and iron status. For comparison of the results with the general population adequate number of controls were taken.

Results: Our study results showed low level of Haemoglobin, and packed cell volume with increase in severity of chronic kidney disease. Bleeding time was increased in 5.6% patients and elevated ESR was present in more than half of patients. Anemia was universal in our population. Normocytic normochromic anemia was found in 70.4 % of the patients and microcytic hypochromic anemia in another 20.4%, and 9.2% had both type of peripheral smear picture. Applying the NKF-K/DOQI guidelines for nondialysis chronic kidney disease to our population it was found that nearly 38.9% of the study population did not have target serum ferritin of 100 ng/ml and 44.4% of study population did not have target TSAT of >20%.

Conclusion: So it is vital to address this issue of iron deficiency in patients with chronic kidney disease so that necessary investigations can be undertaken to find the cause of iron deficiency if any. So every effort should be done to identify the cause of anemia in CKD patients and treat the

coexistent iron deficiency anemia in chronic kidney disease patients. And other haematological parameters should be monitored to find out coexisting abnormality.

Keywords: Chronic kidney disease, Total iron saturation.

INTRODUCTION:

Chronic kidney disease (CKD) encompasses a spectrum of various pathophysiologic processes leading to abnormal kidney function, and a progressive decline in glomerular filtration rate (GFR). The burden of chronic kidney disease cannot be assessed accurately. The approximate prevalence of CKD is 800 per million population, and the incidence of end stage renal disease (ESRD) is 150- 200 per million population.

CKD is a worldwide epidemic associated with a number of co- morbidities and hence a disease with high mortality.^{1, 2} Anemia of chronic disease is a complex disorder determined by variety of factors. Although the primary defect is decreased erythropoietin production from the kidney, a number of other factors may play contributory roles. For example iron, folate, vitamin B12 deficiency due to nutritional insufficiency or increased blood loss, shortened RBC survival, hyperparathyroidism, mild chronic inflammation and aluminium toxicity. Anemia in CKD worsens co-morbidities of diabetes and hypertension, contributing to poor outcome and high mortality.

Untreated chronic anemia leads to a number of physiologic disorders including cardiovascular complications and increased mortality and morbidity. According to GFR and 2006 NKF-K/DOQI guidelines, CKD has been divided into 5 stages^{3, 4}. Anemia usually appears at GFR below 60ml/min or at stage 3.

Renal insufficiency is also associated with bleeding tendency attributed to platelet dysfunction due to abnormal platelet aggregation and adhesiveness^{5, 6}. White blood cell count may be decreased in uremic patients and anemia correction is followed by an increase in natural killer cells and improvement in leukocyte phagocytic function. Early identification and treatment of anemia in CKD may improve cardiovascular morbidity and mortality.⁷ Early treatment of anemia in CKD may postpone the onset of ESRD and improve survival.

The identification, evaluation and optimal treatment of anemia in CKD essentially involve complete blood count, determination of serum ferritin and transferrin saturation to assess iron stores and adequacy of iron for erythropoiesis.

The National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI) anemia guidelines recommend that during erythropoiesis-stimulating agent (ESA) treatment in nondialysis CKD that serum ferritin and transferrin saturation (TSAT) be maintained >100 ng/ml and 20%, respectively⁸. Treatment of anemia in CKD when indicated may involve iron therapy, use of erythropoietin, and correction of anemia to a target hemoglobin of 11- 12 gm /dl.⁸

Renal replacement therapy poses a huge economic burden to the family and health care delivery

system. This study was conducted to determine the haematological profile and serum iron indices of non dialysis CKD patients.

AIM AND OBJECTIVES OF THE STUDY:

AIM :

To assess haematological profile and serum iron indices in nondialysis chronic kidney disease patient

OBJECTIVES :

- To study the haematological profile and serum iron indices in non dialysis chronic kidney disease patients.
- To detect the types of anemia in patients with chronic kidney disease
- To study the prevalence of iron deficiency in non dialysis chronic kidney disease patients according to National Kidney Foundation's Kidney Disease Quality Initiative (NKF-K/DOQI) Guidelines.

MATERIALS AND METHODS:

Data was collected from patients attending the Department of General Medicine of Sree Mookambika Institute of Medical sciences, kanyakumari, tamil nadu, from march 2023 to may 2024. The study subjects were newly diagnosed chronic kidney disease patients of either sex. Healthy adult individuals were recruited as controls. To ensure homogeneity between the control and CKD population, healthy individuals were selected from the friends and relatives accompanying the CKD patients.

General physical examination, urinalysis and blood sugar, and creatinine estimation were done to establish the healthy nature of controls. A total of 54 patients and 20 controls were studied.

Haemoglobin, Red blood cell count, White blood cell count, Haematocrit, Differential count, MCV, MCH, MCHC, Platelet count, RDW, Peripheral smear, Bleeding time Clotting time, ESR, Serum ferritin, Total iron binding capacity, Serum iron were done.

Blood sugar, renal parameters (blood urea, serum creatinine), serum electrolytes, Urine spot protein creatinine ratio.

Serum ferritin: The serum ferritin was determined by enzyme linked immunosorbent assay. Iron level was determined by Ferrozine method.

Statistical analysis was done using the statistical package for social sciences (SPSS). Different statistical methods were used as appropriate. Mean \pm SD was determined for quantitative data and

frequency for categorical variables. The independent t- test was performed on all continuous variables. The normal distribution data was checked before any t-test. The Chi-Square test was used to analyze group difference for categorical variables. In logistic regression models, age was adjusted for estimation of each or all the independent effects of hypertension, ischemic heart disease and diabetes mellitus . A p- value < 0.05 was considered significant.

RESULTS:**ASSOCIATION BETWEEN CKD STAGES AND OTHER QUANTITATIVE HAEMATOLOGICAL PARAMETERS**

Parameter	Values (Mean \pm SD) in cases with			'p'
	CKD 3	CKD4	CKD5	
Hb(gm/dl)	9.23 \pm 1.36	8.32 \pm 1.7	7.0 \pm 1.54	0.0002 Significant
RBC (million/cumm)	3.45 \pm 0.53	3.22 \pm 0.72	3.01 \pm 0.73	0.0892 Not significant
PCV %	27.88 \pm 3.82	26.61 \pm 4.29	23.52 \pm 3.89	0.0059 Significant
MCV (fL)	81.5 \pm 8.9	82.4 \pm 9.3	81 \pm 11.8	0.9704 Not significant
MCH (pg)	27.4 \pm 5	25.7 \pm 5.7	25.9 \pm 4.8	0.5124 Not significant
MCHC (g/dL)	30.2 \pm 3.4	31.2 \pm 4.5	32.1 \pm 4.0	0.3517 Not significant
RDW %	16.1 \pm 4.6	16.5 \pm 5.5	15.3 \pm 3.1	0.7476 Not significant
Duration (in months)	6.25 \pm 3.28	8.47 \pm 3.92	9.87 \pm 4.44	0.0264 Significant

There were statistically significant associations between Hb% (p= 0.0002), PCV (p<0.005) and duration of illness and CKD stages. (p< 0.05). As the CKD stage increases, the level of hemoglobin, packed cell volume decreases. These relationships have got statistical significance.

SERUM IRON INDICES AND CKD STAGE

CKD stage	Value (Mean \pmSD) of			
	Iron(μg/l)	TIBC(μg/l)	TSAT%	Ferritin(μg/l)
3	70.7 \pm 32.8	269.9 \pm 76.2	31.6 \pm 23.5	357.9 \pm 519.8
4	69.3 \pm 39.4	300.3 \pm 77	25.3 \pm 16.7	254.8 \pm 254.5
5	67.2 \pm 25.2	286 \pm 80.5	25.4 \pm 11.6	256.1 \pm 294.4
'p'	0.7939 Not significant	0.4799 Not significant	0.7688 Not significant	0.9591 Not significant

Serum iron indices and severity of CKD did not have statistically significant relationship with serum iron profile.

%TSAT and CKD Stage

CKD STAGE	TSAT %					
	< 20%		\geq 20%		Mean	SD
	No	%	No	%		
3 (12)	6	50	6	50	31.6	23.5
4 (19)	9	47.4	10	52.6	25.3	16.7
5 (23)	9	39.1	14	60.9	25.4	11.6
Total (54)	24	44.4	30	55.6	26.7	16.5
'p'	0.7688 Not significant					

Prevalence of Transferrin saturation (TSAT) < 20% is 44.4% of study cases. No significant relation between CKD stage and Transferrin saturation. Transferrin saturation (TSAT) >20% was present in 55.6% cases.

FERRITIN (μG/L) AND CKD STAGE:

CKD STAGE	Ferritin					Mean	SD
	< 100microg/L		≥ 100microg/L				
	No	%	No	%			
3 (12)	5	41.7	7	58.3	357.9	519.8	
4 (19)	9	47.4	10	52.6	254.8	254.5	
5 (23)	7	30.4	16	69.6	256.1	294.4	
Total (54)	21	38.9	33	61.1	278.3	340.4	
‘p’	0.9591 Not significant						

Prevalence of Serum ferritin level <100 micro gm/L is 38.9% of the study cases. No significant relation between CKD stage and serum ferritin. Serum ferritin level > 100 micro gm/L was present in 61.1% cases. 9 cases (16.67%) had serum ferritin >500 micro gm/l.

DISCUSSION:

Chronic kidney disease is a major public health problem and major cause of morbidity and mortality worldwide. The actual prevalence of the initial stages of CKD is much more than the late stages. However in clinical practice prevalence of stage 4 and 5 appears to be more because initial stages are asymptomatic and people present themselves when severity of symptoms increases. Anemia of chronic kidney disease is multifactorial in origin. The renal community has long recognized that anemia can impair the quality of life of patients and lead to irreversible cardiac consequences. (Levy AS et al).

Anemia, an easily reversible feature of end-stage renal disease, is an independent risk factor for cardiac disease, as well as mortality in end stage renal disease patients^{9,10}

Available evidence demonstrates that: Both iron and erythropoietin are needed to produce red blood cells; as a result, unless adequate iron is available, Erythropoietin will be relatively ineffective. Although no tests are perfect indicators of the adequacy of iron stores, the TSAT and serum ferritin are the best measures of the body's iron status that we currently have^{11,12,13}. Given the prevalence of iron deficiency in CKD patients, and the sensitivity and specificity of TSAT and serum ferritin in detection of iron deficiency, the likelihood of iron deficiency is sufficiently high when TSAT is <20% and the serum ferritin is <100 ng/mL. Therefore, the TSAT and serum ferritin should be maintained at a level of >20% and >100 ng/mL, respectively, in all non dialysis chronic kidney disease patients.

This study was undertaken with the aim to study the haematological profile and identifying the prevalence of iron deficiency anemia (according to NKF- K/DOQI Guidelines) in non dialysis chronic kidney disease patients. Among the 54 patients selected for the study the sex distribution was 42 male and 12 females and the mean age of the study group was 43.3yrs. In assessing the risk factors of chronic kidney disease in our patients, diabetes were prevalent in 20.4% meanwhile 50% of them had hypertension. Afshar et al¹⁴ in their study found 49.1% patients were diabetic and 28.3% were hypertensive among CKD patients.

In our study mean duration of illness was 8.57 months. Applying the NKF staging of CKD, most of our patients came under stage 3, 4 or 5 who were awaiting some form of renal replacement therapy as the last treatment option. Mean Glomerular Filtration Rate was 18.77 ml/min/m².

At the time of presentation in our study, about 40.7% had left ventricular hypertrophy as per ECG criteria. Anemia and hypertension are the most important causes of left ventricular hypertrophy in chronic kidney disease patients. Hypertension and left ventricular hypertrophy are the major risk factors for cardiovascular death in patients with CKD.

The relationship between anemia and cardiac disease in CKD was studied by Levin and co-workers,⁹ in their study Echocardiograms were performed in 175 patients attending a renal insufficiency clinic. LVH was found to be present in 38.9% of patients. The prevalence of LVH progressively increased with declining levels of renal function; 26.7% of patients with creatinine clearance (CrCl) greater than 50 mL/min, 30.8% with CrCl of 25 to 49 mL/min, and 45.2% with CrCl less than 25 mL/min. Each 1 g/dL decrease in Hb was associated with a 6% increase in risk for LVH.

Furthermore, these investigators performed two echocardiograms 1 year apart on 246 patients with early stages of CKD to determine factors responsible for subsequent worsening of LVH. Worsening anemia proved to be an important predictor, with Hb decreasing 0.85 g/dL in patients with ventricular growth compared with a decrease of 0.11 g/dL among patients with stable LVH. Among study and control group there was a statistically significant difference present between Hemoglobin, Red Blood Cell count, Packed Cell Volume, and Erythrocyte Sedimentation Rate.

Anemia was universal in our study and it showed direct linear relationship with reduction in the GFR. The mean Hemoglobin in our patients was 8.01 gm/dl. There was a significant reduction in Packed Cell Volume with progressive increase in stage of Chronic Kidney Disease. Afshar et al¹⁵ and Khanam et al¹⁶ also found same linear relationship between Hb and GFR. Khanam et al¹⁹ also found reduction in PCV with decreasing GFR. Ijoma et al found mean haemoglobin 10.57 gm/dl in stage 3, 8.84 gm/dl in stage 4, 7.33 gm/dl in stage 5 chronic kidney disease. This states that anemia is very well correlated with severity of chronic kidney disease

The lower GFR or EPO production, greater loss of haematopoietic elements and inflammation can

lead to lower haemoglobin and hematocrit level in CKD patients. As anorexia, nausea, vomiting are the common features of CKD patients, less dietary intake of nutrients needed for erythropoiesis might also be a factor for anemia. In developing countries like India, parasitic infestation, low socioeconomic status may play a role in nutritional deficiency and anemia. More over CKD patients are on protein restricted diet which might also have some role for occurrence of anemia in these patients.¹⁷

Peripheral smear was done in our patients with the aim to classify the type of anemia. As the conventionally taught normocytic normochromic anemia was found in 70.4 % of the patients and microcytic hypochromic anemia in another 20.4%, and 9.2% had both type of morphology in peripheral smear picture. Afsar et al ¹⁷also found normocytic normochromic anemia in 80% patients and microcytic hypochromic anemia in 15% patients. Talwar et al¹⁸ found 60% patients with microcytic hypochromic anemia, 30% patients normocytic normochromic anemia in their study. MCV, MCH, MCHC of the patients with normocytic normochromic anemia were normal and low in hypochromic microcytic anemia. There was a statistically significant relationship between peripheral smear type and TSAT and also between the peripheral smear type and ferritin. Serum ferritin level and transferrin saturation was low in microcytic hypochromic anemia. Increased bleeding time was present in 3 cases (5.6%). Akisola et al¹⁹ reported increased bleeding time 25.6% in their study. So increased bleeding time in some of the patient calls for caution in surgical procedure in CKD patients and correction of anemia may improve the bleeding time abnormality.

In our study 7 cases had neutrophilic leukocytosis, 3 cases had lymphocytosis and 6 cases had eosinophilia. No patients had leukaemia or lymphoma. Talwar et al¹⁸ found in their study found increased leukocyte and eosinophil count in 32% patients. The presence of uremic toxins itself can lead to such changes, in addition to the presence of infection. A raised ESR in 64.8% patients may be due to presence of low grade chronic inflammation and anemia in Chronic Kidney Disease. Afshar et al¹⁸ found elevated ESR in more than half of patients in their study. There has long been a great interest in iron tests and iron status in hemodialysis patients^{20,21}. In contrast, far less is known regarding iron status of patients with nondialysis Chronic Kidney Disease. It should be noted that our results are most applicable to patients with estimated GFR<60 ml/min in which CKD is most likely to be present.

Hsu et al. studied iron status in CKD in the NHANES III survey (1988 to 1994) and found iron indices suggestive of iron deficiency to be present and to contribute to anemia in many subjects. Typical markers of iron deficiency used in CKD are serum ferritin < 100 ng/ml and TSAT < 20%. Clinicians often use these thresholds to base iron treatment decisions, and NKF-K/DOQI guidelines recommend these levels in nondialysis CKD. Specifically, the NKF- K/DOQI guidelines indicate that if either of the above value is low then iron treatment is recommended.

Steven fishbane et al primary finding was that between 57.8 and 72.8% of subjects with CKD have either serum ferritin <100 ng/ml or TSAT <20%. In contrast to these relatively high values of serum ferritin (100 ng/ml) and TSAT (20%) that indicate insufficient iron in CKD, in the general population lower thresholds of serum ferritin (15 to 30 ng/ml) and TSAT (15%) are often used. In our study TSAT <20% in 24 cases (44.4%) and serum ferritin <100 ng/ml in 21 cases (38.9%) was present. According to NKF-K/DOQI Guidelines⁸ up to 44.4% of patients in our study are in iron deficient state.

Chronic inflammation is common in patients with CKD, and up to 40 to 70% of patients with CKD may have increased C-reactive protein (CRP) levels on a chronic basis. Hence inflammation probably is the most common confounder in CKD-associated hyperferritinemia and may contribute to it more strongly than Iron (Jairam et al).

Serum ferritin value was measured in our patients and healthy controls and found to exist a significant difference between them. (P value 0.047). There existed no relationship between Glomerular filtration rate and serum ferritin. As expected those patients with microcytic hypochromic anemia had lower serum ferritin and low transferrin saturation (TSAT) when compared to the normocytic normochromic anemia.

CONCLUSION:

In our study, we have found that chronic kidney disease affects predominantly middle aged population. All the patients in this study were in the stage 3, 4 or 5 of Chronic Kidney Disease (CKD). Profound anemia was universal in our patients, which is an important contributor to the high mortality and morbidity in patients with End Stage Renal Disease (ESRD).

There was a significant reduction in Hemoglobin, and Packed Cell Volume with progressive increase in severity of CKD stage. Bleeding time increased in 5.6% patients and elevated Erythrocyte Sedimentation Rate was present in more than half of patients.

Normocytic normochromic anemia was found in 70.4 % of the patients and microcytic hypochromic anemia in another 20.4%, and 9.2% had both type of morphology in the peripheral smear picture.

Patients with microcytic hypochromic anemia had relatively low serum ferritin and low transferrin saturation (TSAT) when compared to the normocytic normochromic anemia patients. Applying the NKF-K/DOQI guidelines for nondialysis chronic kidney disease to our population it was found that nearly 38.9% of the study population did not have target serum ferritin of 100 ng/ml and 44.4% of study population did not have target TSAT of >20%. So it is vital to address this issue of iron deficiency in patients with chronic kidney disease so that necessary investigations can be undertaken to find the cause of iron deficiency if any.

Adequate supplementation of iron should be given either as oral or parenteral route before initiation of dialysis or erythropoietin therapy to attain the goals according NKF guidelines. So every effort should be done to identify the cause of anemia in CKD patients and treat the coexistent iron deficiency anemia in chronic kidney disease patients and other haematological parameters should be monitored to find out coexisting abnormality. Even though treating the complication of CKD like anemia, will reduce the mortality and improve the survival, our ultimate aim should be focused on the preventive strategies for CKD. This include screening high risk population, control of hypertension, DM, limiting the use of nephrotoxic drugs like NSAID'S so that a large section of our population escape the burden of this killer disease.

LIMITATIONS OF THE STUDY

As the study population was small, larger studies are required to validate the results of this study. Iron deficiency in CKD should be assessed by using other newer methods which include soluble transferrin receptors, zinc protoporphyrin, percentage of hypochromic cells, reticulocyte hemoglobin concentration and the gold standard method, the bone marrow examination for stainable iron. Hepcidin level was not done. Also in our patients the probable causes of iron deficiency like occult Gastro intestinal blood loss were not excluded by upper gastrointestinal endoscopy. Folic acid and vitamin B12 assays are not done.

As this was a cross-sectional study, we could not document if the findings were persistent. Finally, this study only shows an association, and cannot prove the causality. Interventional studies will be needed to finally nail down a cause-and-effect relationship.

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