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Preponderance Of Iron Deficiency Anemia And Low Iron Status In Patients Of Chronic Kidney Disease [CKD]

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Abstract

Background: Anemia is the most characteristic and visible manifestation of renal failure caused mainly due to erythropoietin deficiency. However in a developing country like India where there is a higher prevalence of iron deficiency. Iron deficiency can thus be a major determinant contributing to anemia in chronic kidney disease.

Aims and Objectives: (i) To study hematologic abnormalities in cases of CKD with special reference to Hemoglobin, Peripheral blood smear, Red cell indices, Reticulocyte count etc. **(ii)** To study the ferrokinetics in cases of chronic kidney disease with special reference to Serum Iron, TIBC and Transferrin saturation.

Methodology: This was a prospective study carried out in a tertiary care hospital in India over a period of two years. A total of fifty cases were selected randomly. Evaluation was done with special emphasis on hematologic complications of CKD along with relevant biochemical investigations.

Observations and Results: Anemia was predominantly normocytic normochromic on indices in (76%), microcytic anemia (22%). Serum iron was reduced in 28 % and TIBC was increased in 20 % of cases. Transferrin saturation was also reduced in 20 % cases in our study.

Conclusion: In present study, the frequency of iron deficiency was slightly more than Western studies but definitely lower than other Indian studies. Singh et al have shown that iron supplementation reduces requirement of erythropoietin therapy, thereby reducing the cost of management. Hence it is important to note that iron deficiency in anemia of CKD is believed to be the primary cause of unresponsiveness to erythropoietin therapy.

Keywords: Ferrokinetics, Reticulocyte, Erythropoietin, CKD

Introduction

Hematological manifestations like anemia and bleeding are the most characteristic and visible manifestations of renal failure and can substantially contribute to morbidity[1,2]. The close relationship between hematopoiesis and kidney is well recognized for more than a century. Since then, innumerable studies have been done to study this aspect of disease. Many symptoms of end stage renal disease are a consequence of antecedent hematological manifestations. Classical anemia of renal failure is normocytic normochromic and is attributed to deficiency of erythropoietin which is predominantly produced by the kidney[1].

In a developing country like India, there is a higher prevalence of iron deficiency, etiopathogenesis of

which is multifactorial. Iron deficiency can thus be a major determinant causing anemia in chronic kidney disease. The preponderance of iron deficiency anemia and low iron status in patients of CKD has been described in Indian patients by some authors. It has been shown that more than 50% of anemia of CKD is secondary to iron deficiency[3].

Iron Metabolism[4,5,6,7]

The total body iron contentof a normal adult varies from 3-5 gms, hemoglobin being around 2.3 gms, storage iron (ferritin and hemosiderin) around 1gm, non-available (myoglobin, enzymes) around 0.5 gms and the remaining 3-4 mg in circulating plasma iron. This circulating iron is bound to transferrin, a β globulin which serves as a means by which iron absorbed from the alimentary tract is transported to the tissue stores and then to bone marrow erythroblasts. When transferrin reaches the storage sites, it binds to transferrin receptors and liberates ferric ions which pass into the cell to be stored or utilized. Transferrin is present in the serum in a concentration which enables it to combine with iron. This is called total iron binding capacity (TIBC) of the serum. The percentage of total iron binding protein to which iron is attached is known as the percentage saturation of the iron binding protein, calculated by dividing serum iron by TIBC and expressing the result as a percentage. The average normal value of TIBC is about 33%[8]. Ferritin is a valuable indicator to diagnose iron deficiency because it is generally the first laboratory test to become abnormal when iron stores begin to decrease[6]. However, the serum transferrin receptor assay has been suggested to be the most sensitive and specific test for iron deficiency.

Iron deficiency affects a significant fraction of patients treated with hemodialysis when transfusions are restricted. Absolute iron deficiency may result from the loss of blood associated with the dialysis process and diagnostic tests. Gastrointestinal blood losses may also be substantial, averaging 6.27 ml/day in one study. Telangiectasias are among the most common bleeding gastrointestinal lesions in patients with renal failure. Other factors contributing to negative iron balance include reduced dietary iron intake and malabsorption of iron caused by the aluminum hydroxide used to control hyperphosphatemia.

Administration of erythropoietin may result in a "functional iron deficiency" even when body iron stores are replete. The intense, periodic erythropoietic stimulus resulting from erythropoietin treatments can drive red blood cell production in such a way that adequate transferrin-bound iron is not available. For this reason, parenteral iron supplementation is often provided as an adjunct to erythropoietin therapy.

Aim And Objectives

1. To study hematologic abnormalities in cases of CKD with special reference to Hemoglobin, Peripheral blood smear, Red cell indices.
2. To study the ferrokinetics in cases of chronic kidney disease with special reference to Serum Iron, TIBC and Transferrin saturation.

Materials And Methods

This was a cross-sectional study was carried out in a tertiary care hospital in India over a period of two years. A total number of fifty cases were selected randomly (i.e., indoor patients and OPD patients).

Inclusion Criteria:

All patients with/without symptoms of fluid overload i.e., breathlessness etc. who on investigations were found to have elevated blood urea and serum creatinine with normal or decreased creatinine clearance.

Patients with deranged renal biochemical parameters who on ultrasonography show kidneys with hyperechoic cortex and decreased size [<9cm] except diabetes mellitus and patients with a creatinine clearance <15ml/min who need dialysis.

Exclusion Criteria:

All pregnant women showing signs/symptoms of CKD with deranged renal parameters of blood urea and serum creatinine.

All patients with signs/symptoms of CKD who have;

1. Recent history of an upper or lower G.I bleed i.e. h/o malena, bleeding piles etc.
2. H/o a primary G.I. malignancy
3. Patients with a primary hematologic abnormality e.g., leukemia who later on develop CKD

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Clinical evaluation was done with special emphasis on clinical presentation of hematologic complications of CKD. Results of renal function tests and pertinent investigations

COLLECTION OF BLOOD AND INVESTIGATIONS DONE			
Type	Anticoagulant	Amount	Investigations
Capillary	--	Drop	Peripheral blood smear
Venous	EDTA	1.8cc	- Automated cell count - Hemoglobin
	Plain Bulb	1.8cc	- Blood urea level - Serum creatinine - Serum Iron, TIBC

Automated cell counter used was SYSMEX XS-800i and SYSMEX KX-21, automated chemistry analyser was EM 360. Glass slides / Leishman's stain / Reticulocyte stain (Brilliant cresyl blue), serozyme manual method [Raichem USA], plan of analysis of results based on: (i) Morphological classification of anemia on PBS and RBC Indices], (ii) Correlation of RBC Indices with ferokinetics of patients of CKD

Observations And Results

50 patients of CKD were evaluated clinically and with hematological investigations which included Peripheral blood smear, Complete blood count, Serum iron and TIBC. Following observations were noted and conclusions were drawn.

1. Anemia was predominantly normocytic normochromic on indices in (76%). Microcytic hypochromic anemia was seen in 22% cases whereas macrocytic anemia was seen in 2% cases of CKD.
2. Serum iron was reduced in 28% cases of CKD. TIBC was increased in 20% cases. Transferrin saturation was also reduced in 20% cases of CKD. (Table 2)
3. Hemoglobin, RBC count and Hematocrit correlated positively with each other and also with Transferrin saturation and Serum iron. Platelet count showed negative correlation with PDW and MPV. (Table 3&4)

Table – 1			
Parameter with range		**Number (n)**	**Percentage (%)**
ESR (mm at the end of 1 hour)	Within normal range Male (0-9), Female (0-20)	0	0
	Above higher limit of normal range	50	100
	Total	50	100
Corrected ESR	Within normal range	12	24

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	Male (0-9), Female (0-20)		
	Above higher limit of normal range	38	76
	Total	50	100
Reticulocyte count (%)	<0.5	0	0
	0.5-2.5	50	100
	>2.5	00	00
	Total	50	100
Corrected Reticulocyte count (%)	<2	47	94
	>2	3	6
	Total	50	100
Sr. Iron (ug/100ml)	<60	14	28
	60-160	36	72
	Total	50	100
Transferrin saturation (%)	Below lower limit of normal range	12	24
	Within normal range M (18-40), F (13-37)	38	76
	Total	50	100
TIBC (□g/100ml)	<300	11	22
	300-360	29	58
	>360	10	20
	Total	50	100

Table 2: Summarization of ferrokinetics in CKD		
Biochemical iron parameters	**Number (n)**	**Percentage (%)**
↓S. Iron, ↑ TIBC	06	12
↓Transferrin saturation , ↑ TIBC	07	14

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↓S. Iron , ↓ Transferrin saturation, ↑ TIBC	07	14
↓Transferrin saturation	10	20
↑TIBC	10	20
(N) Transferrin saturation , (N) or ↓ TIBC	33	66

Table 3: Correlation of RBC indices with the Ferrokinetics

'p' value	**Iron**	**TIBC**	**TS**
MCV	0.020	0.050	0.048
MCH	0.011	0.012	0.075
MCHC	0.101	0.062	0.447

P< 0.05 is significant

MCV and MCH showed a statistically significant positive correlation with the means of Serum iron and Transferrin saturation.

Table 4: Correlation of PBS with means of Indices and Ferrokinetics

PBS	**MCV**	**MCH**	**MCHC**	**IRON**	**TIBC**	**TS**
'p' value	0.000	0.000	0.003	0.005	0.144	0.019

P<0.05 is significant

PBS correlated positively with the means of Indices and with Ferrokinetics

(Serum iron and Transferrin saturation)

Discussion:

The discussion on association of kidney diseases with hematological abnormalities can be dated back to previous century where Richard Bright described anemia in renal failure[9]. This was followed by innumerable studies on various aspects of this issue. Unlike present study, most of the studies have restricted themselves to certain hematological aspects which predominantly included study of RBC or platelet parameters[8,10,11-14]. Very few studies have comprehensively studied various hematological parameters[3,15,16]. The present study has comprehensively dealt with hematological manifestations of CKD.

It must be emphasized that while evaluating USG findings for the diagnosis of CKD, the cases of Diabetes Mellitus should be considered separately as it may be associated with normal kidney size[17]. Incidentally, 6 patients of Diabetes Mellitus in present study showed normal kidney size.

Present study included one pediatric patient presenting with chronic renal failure due to chronic pyelonephritis following urethral valve obstruction while rest of the patients were adults.

The predominant age range for chronic kidney disease was 41-60 years. There was slight male preponderance in our study. Similar findings are noted by others[8,12,18,19.]

The predominant clinical presentation in present study of CKD was edema(72%) followed by oliguria (32%). Interestingly the edema was predominantly pedal edema (56%) and periorbital edema was seen in 16.0% cases. Experience is shared by others[3]. In present study, we have classified effusion as separate manifestation though in most of our cases it was a part of congestive cardiac failure. In 11 cases, there was pericardial rub suggestive of uremic pericarditis.

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23.4% cases showed electrolyte imbalance in the forms of hyponatremia (19.1%) and hypokalemia (8.5%). Thrombocytopenia was noted in 32% of our cases. None of our patients presented clinically with bleeding.

Hematological manifestations: In present study, hematological manifestations of CKD were dominated by anemia. It was present in all cases. The anemia was determined according to the criteria set by The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative[20].

On peripheral smear, anemia was predominantly normocytic normochromic (58%), followed by microcytic hypochromic anemia (28%) and macrocytic (14%). However on RBC indices, macrocytosis was not that frequent. Burr cells were seen in 29.6% cases of renal failure in well made peripheral smear after ruling out artifacts. MCHC was elevated in 12% cases of CKD even in those who had a normal MCV and MCH. Thus high values of MCHC on indices are usually artifactual and automated MCHC has a limited clinical utility[21].

Those patients who had decreased serum iron levels, the RDW was increased only in 6% and MCV was reduced in 8% patients. Similarly, in all those patients who had a high TIBC, an increased RDW-CV and low MCV were seen in only 9% cases each. This shows that serum iron and TIBC are sensitive markers to detect latent (stage 2) iron deficient erythropoiesis and should probably be the early investigations done when suspecting latent iron deficiency in a laboratory restricted setting. RDW was increased in 24% cases even in those patients who had a normocytic normochromic anemia on smear.

Serum iron and transferrin saturation were reduced in 26% cases and TIBC was raised in 20% cases. It could be inferred from Table 9 that normal transferrin saturation with a normal to decreased TIBC, suggesting anemia of chronic renal failure was noted in 66% cases. The classical triad of iron deficiency with decreased Serum iron, decreased transferrin saturation and raised TIBC was seen in 14% of cases. But when resorted to raised TIBC which is recently considered a very reliable marker of iron deficiency, we could categorize 20% cases of CKD as having iron deficiency[21].

In a study by Gupta et al, the iron deficiency was observed to be underlying 50% cases of CKD with anemia[10]. This increased frequency of underlying iron deficiency can be attributed to the nature of the study which was quite comprehensive and included serum ferritin and serum transferrin receptor assay in addition to serum iron studies.

Talwar et al have noted iron deficiency in 62% cases of CKD by doing serum ferritin, and noted reduced iron stores in 81% of cases[3].

In a study by Singh et al[22] 22.5% to 25% cases of CKD showed decreased bone marrow iron stores.

In western countries, prevalence of iron deficiency in CKD is 20% which is thought to be lower as compared to Indian patients of CKD[10]. It has been thought that iron deficiency is widespread in India and may be a contributory factor to anemia of CKD. The commonest cause of iron deficiency apart from increased requirements is poor availability of iron in vegetarian diet which contains high phytates and increased loss due to parasitic infestations[6].

Singh et al have shown that iron supplementation reduces requirement of erythropoietin therapy, thereby reducing the cost of management[22]. Incidentally, only 11 cases were receiving hematinics.

In present study, the reticulocyte count was normal in all cases. However on correcting the reticulocyte count for the degree of anemia, corrected reticulocyte count (CRC) was decreased in 94% cases. This indirectly indicates the possibility of erythropoietin deficiency and bone marrow inhibition in anemia of CKD. 22% cases in present study had leucocytosis. This could be attributed to sepsis which was seen in some cases, stress, concurrent illness or circulating toxic uremic substances[15].

Thrombocytopenia was seen in 32% cases of which 60% had mild thrombocytopenia. Studies of Aboo suggest that thrombocytopenia appears to be a common presenting feature in AKI as opposed to CKD. However none of our patients presented with bleeding as the first manifestation of renal failure.

In present study, ESR was raised in all cases. However on correcting for the degree of hematocrit, the corrected ESR turned out to be normal in 24 % cases.

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The peripheral smear findings correlated positively with the means of RBC indices and Ferrokinetics (Serum Iron, Transferrin saturation). The RBC indices (MCV, MCH) also correlated positively with Ferrokinetics (Serum Iron, Transferrin saturation).

On taking a holistic view of observations noted in present study , it will not be too pragmatic to state that present comprehensive study of clinicohematological aspects of chronic kidney disease was fruitful and provided a couple of interesting observations and assumptions.

Conclusion

In present study, the frequency of iron deficiency was slightly more than Western studies but definitely lower than other Indian studies. However this may not be a true reflection of low iron deficiency status as we have not used any new investigations and have not resorted to bone marrow aspiration to study bone marrow iron. Hence this relatively low frequency of iron deficiency noted in present study needs to be taken with a pinch of salt. Singh et al have shown that iron supplementation reduces requirement of erythropoietin therapy, thereby reducing the cost of management[22]. Incidentally, only 11 cases were receiving hematinics. Hence it is important to note that iron deficiency in anemia of CKD is believed to be the primary cause of unresponsiveness to erythropoietin therapy.

References

1. Caro J, Erslev AJ. Anemia of Chronic Renal Failure. *Williams Hematology* 6th International ed. McGraw Hill Company, 2001:399-405.
2. Shattil SJ, Abrams CS, Bennett JS. Acquired Qualitative Platelet Disorders due to Diseases, Drugs and Foods. *Williams Hematology* 6th International ed. McGraw Hill Company, 2001: 1583-602.
3. Firkin F, Chesterman C, Penington D, Rush B. *de Gruchy' s Clinical Haematology in Medical Practice* 5th ed. Blackwell Science, Inc, 1997.
4. Mezzano D, Tagle R, Panes O et al. Hemostatic disorder of uremia: the platelet defect, main determinant of the prolonged bleeding time, is correlated with indices of activation of coagulation and fibrinolysis. *Thromb Haemostat* 1996; 76(3):312-21.
5. Talwar VK, Gupta HL, Shashinarayan K. Clinicohematological Profile in Chronic Renal Failure. *J Assoc Physicians India* 2002; 50:228-33.
6. Sabatini S. The acidosis of chronic renal failure. *Med Clin North Am* 1983; 67(4):845-58.
7. Green R. Disorders of inadequate iron. *Hospital practice symposium* 1991; 13: 41.
8. Fairbanks VF, Klee GG. Biochemical aspects of hematology. In Burtis CA, Ashwood ER eds. *Teitz' Textbook of Clinical*
9. Gupta M, Kannan M, Gupta S, Saxena R. Contribution of iron deficiency to anemia in chronic renal failure. *Indian J Pathol Microbiol* 2003; 46(4):563-4.
10. Bright R. Cases and observations, illustrative of renal disease accompanied with the secretion of albuminous urine. *Guys Hosp Rep* 1836; 1:338.
11. Loge JP, Lange RD, Moore CV. Characterization of anemia associated with Chronic Renal Insufficiency. *Am J Med* 1958; 4:17-26.
12. Guenter W, Lawrence TG. Anemia of chronic disease. *N Eng J Med* 2005; 352:1011-23.
13. Skorecki K, Green J, Brenner BM. Chronic Renal Failure. *Harrison Principles of Internal Medicine* 16th International ed. McGraw-Hill Company, 2005:1653-67.
14. Varma PP, Kumar R, Prasher PK, Roy ND. Hypochromic anemia in chronic renal failure-role of aluminium. *J Assoc Physicians India* 1999; 47(7):690-3
15. Singh NP, Aggarwal L, Singh T, Anuradha S, Kohli R. Anemia, Iron studies and Erythropoietin in Patients of Chronic Renal Failure. *J Assoc Physicians India* 1999; 47:284-90.
16. Akinsola A, Durosinmi MO, Akinola NO. The haematological profile of Nigerians with chronic renal failure. *Air J Med Med Sci* 2000; 29(1):13-6.
17. Fernandez-Rodriguez AM, Guindeo-Casasus MC, Molero-Labarta T et al. Diagnosis of Iron

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Deficiency in Chronic Renal Failure. *Am J Kidney Dis* 1999; 34:508-13.

18. Kazmi WH, Kausz AT, Khan S et al. Anemia: An early complication of Chronic Renal Insufficiency. *Am J Kidney Dis* 2001; 38:803-12.
19. Jovanovic N, Lausevic M, Stojimirovic B. Residual renal function and blood count in patients on continuous ambulatory peritoneal dialysis. *Srp Arh Celok Lek* 2006; 134(11-12):503-08.
20. Robinson BE. Epidemiology of chronic kidney disease and anemia. *J AmMed Dir Assoc* 2006; 7(9 Suppl):S3-6; quiz S 17-21
21. Brittenham GM, Koepke JA. Red Blood Cell Volume Distributions and the Diagnosis of Anemia. *Arch Pathol Lab* Med 1987; 111: 1146-8.
22. Singh NP, Aggarwal L, Singh T, Anuradha S, Kohli R. Anemia, Iron studies and Erythropoietin in Patients of Chronic Renal Failure. *J Assoc Physicians India* 1999; 47:284-90.

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