ORIGINAL ARTICLE

IRON PROFILE AND HEMATOLOGICAL PARAMETERS IN PATIENTS WITH ADVANCING CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: Iron deficiency anemia is the most common and early complications of chronic kidney disease (CKD) patients. On the other hand, excess iron supplementation induced iron overload, oxidative stress, hypersensitivity reactions and a permissive environment for infectious processes among CKD. Hence this study aims to determine the association of iron profile and hematological parameters with advancing CKD

Method: This descriptive cross-sectional study was carried out among 80 CKD patients attending Manmohan Teaching Hospital, Kathmandu. Demographics, anthropometry, blood glucose, RFT, Serum iron profile and complete blood count were measured. Glomerular filtration rate (GFR) was estimated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) criteria for staging CKD.

Findings: The study included 80 participants out of which 48 (60%) were females and 32 (40%) were males. Overall, 82.5% of CKD patients were presented with anemia. Among the study population, 50% of CKD patients had normal iron status, 41.3% had iron deficiency, and 8.8% had iron overload. Out of total iron deficient individuals, 69.7% was found to have functional iron deficiency and 30.3% was found to have absolute iron deficiency. WBC and platelets were significantly decreased with increased availability of circulating iron and iron stores.

Conclusion: The functional iron deficiency worsens the severity of anemia with advancing CKD. However, iron overload in CKD patients is also associated with leucopenia and thrombocytopenia. Thus, regular investigation and monitoring of serum iron profile is required in CKD patients for the prevention from various complications.

Keywords: ***CKD, Hematological Profile, iron Profile, Iron deficient anemia, Iron overload***

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Received 12 March 2024; Received in revised form 15 April 2024; Accepted 02 June 2024

https://doi.org/10.3126/jmmihs.v9i1.68636

INTRODUCTION

Chronic kidney disease (CKD) is defined as decreased kidney function with glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m2, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause (1). End-Stage Renal Disease [ESDR] is the final stage [stage 5] of CKD where only less than 10% of nephron is functioning and there is marked reduction in eGFR resulting in imbalance in body fluid and electrolyte concentration followed by uremia (2). Most severe form of CKD is kidney failure and it is fatal if not treated by renal replacement therapy (kidney transplantation or dialysis) (3). Risk factors of CKD includes hypertension, Diabetes mellitus, glomerulonephritis, history of cardiovascular disease, family history of CKD, older age, smoking, excessive alcohol consumption, use of analgesic medication, experiencing acute kidney disease, hyperlipidemia, metabolic syndrome e.tc (4).

Chronic kidney disease (CKD) is a leading public health problem worldwide increasing at an annual growth rate of 8% (5). The global estimated prevalence of CKD is 13.4% (11.7-15.1%), and patients with end-stage renal disease (ESRD) needing renal replacement therapy is estimated between 4.902 and 7.083 million (6). The prevalence of CKD in Nepal is estimated around to be 6% (7). Globally, in 2017, 1·2 million people died from CKD(8). According to WHO, in Nepal, the death rate due to CKD was found to be 2.74% in 2018 (9).

With the progression of kidney disease, kidney function become severely impaired leading to different hematological and biochemical dysfunction (9). Anemia is the most common complication of CKD patients that start to appear at GFR below 60ml/min, but more prevalent when it falls below 30ml/min (or stages 4 and 5 of CKD) (10). The primary cause of anemia in patients with CKD is insufficient production of erythropoietin by diseased kidneys followed by distorted iron homeostasis, folate & B12 deficiency due to nutritional insufficiency or increased blood loss, acute and chronic inflammation, severe hyperparathyroidism and shortened red cell survival in the uremic environment (11). Other affected hematological parameters in CKD include total leukocytes and its differential counts, platelet count, bleeding time and prothrombin time (2).

Iron deficiency is common in patients with CKD which may be absolute, often due to poor dietary intake or sometimes occult bleeding, or functional, when there is adequate iron stores in the body but insufficient iron availability for incorporation into erythroid precursors due to increased hepcidin level (12, 13). Iron deficiency is common problem in hemodialysis patients that mainly results from excessive blood loss due to dialysis filter, frequent blood testing, access bleeding, and surgical blood loss (14-16). Iron deficient anemia is the most common complication which is associated

with increase morbidity and mortality in CKD patients. Similarly patients undergoing iron supplement and frequent blood transfusion may develop iron overload which can cause iron toxicity, oxidative stress, hypersensitivity reactions, and a permissive environment for infectious processes(17). Furthermore, iron chelating agents have been reported to decrease creatinine clearance. Level of iron in the body plays a significant role in pathogenesis of anemia and other possible risks due to iron overload. Hence adjusting iron status in normal level is a prerequisite for effective treatment of anemia and to avoid possible risks of iron overload(18). This study aims to find any association of hematological and iron profile with advancing CKD

MATERIAL AND METHODS

Study Design and Participants

This laboratory-based cross-sectional study was conducted in Manmohan Memorial Medical College and Teaching Hospital (MMTH), Kathmandu, Nepal, and Manmohan Memorial Institute of Health Sciences, Kathmandu, Nepal, from October 2021 to March 2022. A total of 80 participants were included in the study.

Inclusion and Exclusion Criteria

All the patients diagnosed with CKD attending nephrology ward of MMTH were included in the study. Known hematological disorders or malignancy, recent hemorrhagic episode, pregnancy, and covid-19 cases were excluded from the study.

Informed consent

The participants in the study provided written informed consent after being fully informed on the procedures about the research.

Experimental protocol

5ml fasting (8-12 hours) blood sample was collected by venipuncture method in a EDTA and Serum Separator Tube (BD Vacutainer® SST™ Tubes). CBC was analyzed using EDTA blood and separated serum from SST vial through centrifugation process was used for estimation of Glucose, Urea, Creatinine, Serum Iron, TIBC in a fully automated chemistry analyzer (VITROS® 350 Chemistry System, USA). TSAT was calculated using the equation TSAT = (Fe/TIBC) x 100%. Sodium and Potassium were analyzed using ISE electrolyte analyzer (Joko. Japan), Ferritin level was estimated using a fully automated (SNIBE, China). MAGLUMI® 800, Chemiluminescence Immunoassay (CLIA) System

GFR was calculated using CKD-EPI equation (19). CKD-EPI: 141× min (Scr/κ,1) α × max (Scr/κ, 1)-1.209 × 0.993Age × 1.018 (if female) × 1.159 (if black). [Scr is serum creatinine (mg/dl), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.]

CKD cases with Transferrin Saturation (TSAT) ≤20% and the serum ferritin concentration ≤100 ng/mL among predialysis and peritoneal dialysis patients or ≤200 ng/mL among hemodialysis patients were categorized under 'Absolute Iron Deficient' group and CKD cases with TSAT ≤20% and elevated ferritin levels were categorized under 'Functional Iron Deficient" group (13). CKD cases with TSAT>50% and Ferritin>300µg/L were categorized under 'Iron Overload' group.

Statistical analysis

The data were entered in Microsoft Excel 2013 and analyzed using SPSS version 23 (IBM corporation, Armonk, NY, USA). Mean (± standard deviation), and frequency and percentage were reported. Bivariate analysis was performed using Independent t-test and ANOVA. Post-hoc analysis was performed among the variables which showed significant association in ANOVA tests. Correlation analysis was performed to examine the relationship between variables. A p-value less than 0.05 was considered statistically significant.

RESULTS

This study was conducted among 80 patients diagnosed with CKD attending Manmohan Memorial Teaching Hospital (MMTH). In this study majority of the cases were male (60%). Among CKD cases majority males (53.8%) were non vegetarian and only 32.5% females were non vegetarian. Regarding the risk factors among males, 46.3% were alcoholics, 43.8% had hypertension, 43.8% were smokers, 27.5% were diabetics and 3.8% had family history of CKD whereas in female majority (27.5%) had hypertension followed by diabetes (10%) as shown in Table 1.

The CKD cases were categorized into five groups based on eGFR. Level of urea, creatinine and ferritin were found to be significantly increased with increasing severity of CKD. Similarly, level of RBC and hemoglobin were found to be significantly decreased with increasing severity of CKD. Though WBC level had shown difference between different stages of CKD but there was no statistical significance found in this study as shown in Table 2 below.

Table 1: Characteristics of the Participants

Characteristics	Male	Female	Total
	N (%)	N (%)	
Gender	48 (60.0)	32 (40.0)	80 (100.0)
Family history of CKD	3 (3.8)	1 (1.3)	4 (5.0)
History of Diabetic	22 (27.5)	8 (10.0)	30 (37.5)
History of Hypertension	35 (43.8)	22 (27.5)	57 (71.3)
Habit of smoking	35(43.8)	14 (17.5)	49 (61.2)
Habit of alcoholism	37 (46.3)	3 (3.8)	40 (50.1)
Vegetarian	5 (6.3)	6 (7.5)	11(13.8)
Non- vegetarian	43(53.8)	26(32.5)	69(86.3)

Post Hoc was applied to the variables that show significant changes in different stages of CKD. The level of urea was found to be significantly increase in stage 4 and stage 5 in comparison with earlier stages. Similarly, level of creatinine and ferritin was found to be significantly increase in stage 5 in comparison with earlier stages. Also, level of RBC and hemoglobin was found to be significantly decrease in stage 5 in comparison with earlier stages as shown in Table 3 below

Urea and Creatinine had significant negative correlation with the Hb level and RBC count and positive correlation with ferritin level. Creatinine solely was found to be negatively correlated with WBC count and positively correlated with total iron saturation at a significant level. Sodium level was found negatively correlated with WBC count significantly. Whereas potassium level was found positively correlated with iron, ferritin and total iron saturation at a significant level as shown in Table 4.

The RBC count had significant negative correlation with ferritin and positive significant correlation with TIBC. Hemoglobin level had significant negative correlation with serum ferritin. The WBC count had significant negative correlation

Table 2:Comparision of Different Parameters between different stages of CKD

Variables	Stage I	Stage II	Stage III	Stage IV	Stage V	p Value
Glucose (mg/dl)	167±101	150±65	149±67	125±47	124±47	0.258
Urea (mg/dl)	27±5	31±9	58±19	99±51	131±64	0.000
Creatinine (mg/dl)	0.7±01	0.96± 0.2	1.7± 0.4	3.1± 0.7	8.4± 3.5	0.000
Sodium (mEq/L)	138±4	139.4±3	138.5± 5.1	140.1± 4.6	138± 4.7	0.635
Potassium (mEq/L)	4.31±0.5	4.19± 0.28	4.42± 0.62	4.52±0.54	4.85±0.80	0.429
Iron (µg/dl)	60±23	70±48	85±41	66 ±23	73 ±35	0.393
Ferritin (ng/ml)	126± 87	74±59	258±184	315±285	612±679	0.002
TIBC (µg/dl)	329±123	302±71	293±103	293±81	250±91	0.171
TSAT (%)	18±8	23±14	27±11	27±11	33±20	0.058
RBC (millions/mm^3)	4.67± 0.97	4.52± 0.1	3.99 ±0.84	3.99± 0.84	2.91± 0.53	0.000
Hb (gm/dl)	12.84 ±2.2	12.54± 2.3	10.86± 2.55	10.48 ±2.55	8.28 ±1.47	0.000
WBC (/mm^3)	7950 ±2288	7062±2297	8925±3561	8899±3227	6530±2041	0.025
Platelets (/mm^3)	282100±60768	291273±86627	293063±131123	293000±61952	257269±96350	0.677

Table 3:Post hoc anaysis of different significant variables

Variables	Stages of CKD	95% Confidence Interval		p Value
		Lower Bound	Upper Bound	
Urea (mg/dl)	Stage 1 & Stage 4	-123.1	-20.1	0.001
	Stage 1 & Stage 5	-159.24	-63.07	0.000
Urea (mg/dl)	Stage 2 & Stage 4	-117.88	-17.87	0.002
	Stage 2 & Stage 5	-153.91	-60.95	0.000
	Stage 3 & Stage 5	-123.34	-39.218	0.000
Creatinine (mg/dl)	Stage 1 & Stage 5	-9.9	-5.4	0.000
	Stage 2 & Stage 5	-9.64	-5.28	0.000
	Stage 3 & Stage 5	-8.7	-4.85	0.000
	Stage 4 & Stage 5	-7.22	-3.44	0.000
Ferritin (ng/ml)	Stage 1 & Stage 5	-942.58	-30.72	0.028
	Stage 2 & Stage 5	-979.33	-97.90	0.007
RBC (millions/mm^3)	Stage 1 & Stage 5	0.98	2.52	0.000
	Stage 2 & Stage 5	0.86	2.35	0.000
RBC (millions/mm^3)	Stage 3 & Stage 5	0.42	1.73	0.000
	Stage 4 & Stage 5	0.34	1.63	0.000
Hb (gm/dl)	Stage 1 & Stage 5	2.31	6.8	0.000
	Stage 2 & Stage 5	2.09	6.43	0.000
	Stage 3 & Stage 5	0.66	4.48	0.002
	Stage 4 & Stage 5	0.32	4.07	0.011

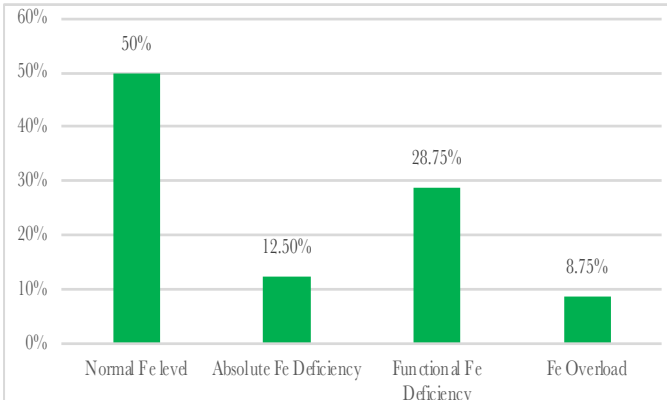
Table 4: Correlation between hematological, biochemical and iron profile parameters

Variables	Urea		Creatinine		Sodium		Potassium	
	r	p	r	p	r	p	r	p
RBC	-0.55	0.000	-0.580	0.000	0.2	0.05	-0.205	0.069
Hemoglobin	-0.53	0.000	-0.541	0.000	0.16	0.163	-0.152	0.179
WBC	-0.13	0.242	-0.220	0.049	-0.27	0.014	-0.179	0.112
Platelets	-0.07	0.539	-0.194	0.085	-0.07	0.559	-0.615	0.142
Iron	0.54	0.636	0.159	0.159	-0.01	0.936	0.229	0.041
Ferritin	0.44	0.000	0.461	0.000	-0.13	0.27	0.328	0.003
TIBC	-0.17	0.131	-0.199	0.077	-0.09	0.443	-0.07	0.539
TSAT	0.29	0.052	0.390	0.000	-0.001	0.97	0.272	0.014

Table 5: Correlation between iron profile and hematological parameters

Variables	Iron		Ferritin		TIBC		TSAT	
	r	p-value	r	p-value	r	p-value	r	p-value
RBC	0.021	0.851	-0.380	0.001	0.258	0.021	-0.178	0.115
Hb	0.614	0.147	-0.312	0.005	0.166	0.141	-0.058	0.611
WBC	-0.229	0.041	-0.04	0.724	0.134	0.237	-0.255	0.023
Platelets	-0.243	0.030	-0.038	0.737	-0.021	0.085	-0.248	0.027

Figure 1: Status of iron (Fe) in CKD



with serum iron and TSAT. The platelet count has significant negative correlation with serum iron and TSAT as shown in Table 5.

Furthermore, on the basis of iron status the CKD cases were distributed into different groups: 1. Normal iron status, 2. Absolute Iron deficient, 3. Functional iron deficient and 4. Iron overloaded Where, 50% participants had normal iron status, 12.5% participants had absolute iron deficiency, 28.75% participants had functional iron deficiency and 8.75% participants had iron overload as shown in Figure 1.

Hematological and biochemical parameters were compared between CKD cases with normal iron profile, Iron deficient and Iron overloaded groups. Creatinine, Potassium, Iron, ferritin, TIBC and TSAT were significantly increased whereas WBC and platelets were significantly decreased among CKD patient with normal iron, iron deficiency and iron overload as shown in Table 6.

Table 6: Comparison of hematological and biochemical parameters between CKD cases with normal iron profile, Iron deficient and Iron overloaded groups.

Variables	Normal Iron	Iron deficiency	Iron overload	P value
Glucose	152.9±81.5	129.9±42.6	117.5±21.7	0.183
Urea	73.1± 63.8	88.4±60.2	121.9±54.5	0.149
Creatinine	2.74±2.65	4.13±3.89	8.75±4.46	0.000
Sodium	138.15±4.6	139.5±4.4	137.4±3.05	0.290
Potassium	4.34±0.51	4.41±0.6	5.13±0.77	0.008
Iron	45.27±16.25	84.63±28.23	124.4±38.6	0.000
Ferritin	264.4±293.01	286.04±292.2	1042.8±1072.8	0.000
TIBC	305.13±108.4	283.4±79.5	208.4±78.2	0.047
TSAT	14.65±4.18	30.03±6.9	61.6±14.6	0.000
RBC	3.85±0.99	3.82±0.91	3.24± 1.01	0.294
Hemoglobin	10.44±2.49	10.52± 2.66	9.71± 3.55	0.762
WBC	8847.27±3404.2	7137±2205.7	6228.6±1741.6	0.012
Platelets	311909.9±107172.9		221714.3±51399.5	0.017

DISCUSSION

CKD has become a major global health problem and the major risk factors for CKD include hypertension, diabetes mellitus, glomerulonephritis and obesity (10, 21). Most severe form of CKD is kidney failure and it is fatal if not treated by dialysis or renal transplant (3). Anemia is the most common complication of CKD patients and it is significantly associated with morbidity and mortality (10, 22). Deficiency and dysregulation of iron in CKD also plays central role in pathogenesis of anemia (18). Adjusting iron status in normal level is a prerequisite for effective treatment of anemia and to avoid possible risks of iron overload (18).

In this study the majority of the CKD cases were male than female with the primary etiology hypertension (71.3%) followed by diabetics (37.5%). This findings is similar to a cross sectional study conducted in Vietnam by Thang et al. (23). Furthermore, habit of smoking and alcoholism was observed in 61.2% and 50.1% CKD patients. Study conducted in US adult by Stengel et al. shows cigarette smoking as a risk factor for the development and progression of CKD (24). Hypertension causes the vascular damage leading to further renal insufficiency (25). Increased glucose level cause alterations in glomerular permeability, glomerular hyperfiltration, glomerular basement thickening, mesangial matrix synthesis and ultimately glomerulosclerosis and interstitial fibrosis (26). Alcohol may cause kidney injury by inducing oxidative stress and inflammation(27). Similarly, smoking causes CKD progression via increased oxidative stress (28).

This study shows the grade of anemia proportionally higher with increasing stages of CKD. Hemoglobin and RBC counts are significantly decreasing with increasing stages of CKD. The findings of this study are similar with the study of Habib et al., Shrestha et. al., Islam et. al., (2, 9, 29). The impaired erythropoietin production and shortened red cell survival in CKD patients is the essential cause of decrease RBC counts and consequent decrease in the Hb concentration. Furthermore, the RBC count and Hb concentration has shown significant negative correlation with urea in this study. RBC survival is decreased in uremic patients in proportion to the blood urea nitrogen concentration. Uremic plasma increases the expression of phosphatidyl serine on the outer cell surface in RBCs which enhances the recognition of damaged red blood cells by macrophage, leading to their subsequent destruction and decreased survival (30). Substantial publications have revealed that the thrombocytopenia and leukocytosis as other conditions which is seen in majority of the CKD cases but in this study the association is not statistically significant and the less sample size may be the reason behind this. Leukocytosis in CKD is due to up regulation and presence of cytokines such as tumor necrosis

factor –α (TNF-α) and interleukin-6 (IL-6) in blood contribute to chronic inflammation in the uremic state (31). Whereas due to decreased thrombopoietin level and interaction of platelet with dialysis membrane leads to the platelet's adhesion, aggregation and activation may cause thrombocytopenia (32).

The iron profile in CKD cases in this study revealed that the 50% of cases were normal, 12.50% were absolute iron deficient, 28.75% were functional iron deficient and 8.75% were Iron overloaded.

Absolute iron deficiency (severely reduced or absent iron stores where; TSAT: ≤20% and the serum ferritin: ≤100 ng/mL among predialysis and peritoneal dialysis patients or ≤200 ng/mL among hemodialysis patients) may be a result of poor dietary iron absorption in the GI tract, malnutrition, hematuria, frequent tests or hemodialysis in CKD. Whereas, functional iron deficiency (TSAT ≤20% and elevated ferritin levels; Adequate iron stores but insufficient iron availability for incorporation into erythroid precursors) is a result of increased hepcidin level. Highly inflammatory state in CKD chronically elevates hepcidin levels and result in dysregulation of iron homeostasis by preventing release of stored iron from absorptive duodenal epithelial cells, macrophages and hepatocytes, reducing the availability of iron for erythropoiesis. This leads to high ferritin level and low TSTAT (33, 34). Erythropoiesis-stimulating agents (ESAs), such as epoetin alfa and darbepoetin alfa stimulates rapid RBC production and quickly depletes the available pool of iron which also may lead to functional iron deficiency (35). In this study, serum iron level, TIBC and TSAT were not found statistically significant with increasing stages of CKD. This may indicate that these indices may not be specific enough and may falsely identify too many subjects as being iron deficient. On another hand, many patients were also under iron supplement therapy (either oral or intravenous) and may be because of this reason no significant changes were seen in these parameters among CKD patients. Whereas, the ferritin level was found to be significantly increased with increasing severity of CKD. Similar finding was observed in study conducted by Thang et al. (23). The increase ferritin level is due to nonspecific protein synthesis for compensation of protein loss in advanced CKD as well as the progression of inflammation in CKD patients(23).

In this study a small fragment of CKD cases was reported with iron overload. Secondary Iron overload with CKD may happen due to frequent intravenous iron use, especially in patients on hemodialysis. However, the risk of iron toxicity in ESRD patients is usually insignificant because other factors minimize iron accumulation, including the concurrent use of erythropoiesis-stimulating agents (ESA) and the distribution of hepatic iron by the reticuloendothelial cells. However, the iron overload has been reported to also be associated with high mortality in patients undergoing HD. This could result from increased infection risks due to an abnormal immune response and cardiovascular complications caused by endothelial dysfunction or myocardial iron deposits (36). In this study secondary iron overloaded CKD groups were significantly associated with high creatinine level, hyperkalemia and thrombocytopenia as compared to normal iron group and iron deficient group which suggest that the severity of CKD is associated with iron overload. As the severity of the CKD increases the frequency of blood transfusion also increases resulting in iron overload (37,38,39). Iron overload has also been associated with renal disease progression and associated with increased mortality. Most chelating agents have been reported to increase creatinine level by decreasing its clearance (40).

CONCLUSION

The hematological and iron profile are deranged in CKD reflecting the majority of the cases with functional iron deficiency. The severity of anemia and iron overload as well worsens with advancing or severity of CKD. Therefore, regular screening and monitoring for iron status in CKD is crucial in medical interventions. Iron supplementation in anemic and use of proper chelating agents in iron overload is recommended for CKD patients in order to alleviate the complications.

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ACKNOWLEDGEMENTS

We would like to acknowledge all the participants involved and MMTH staff for their support in this study

AUTHOR CONTRIBUTIONS

Principal author designed the study. Dr. Archan Shumsher Rana and Sahara Bista had major contribution in patient selection and data collection and Sudip Khanal in statistical analysis. Other all authors have equally contributed in drafting and finalizing manuscript.

COMPETING INTERESTS

Authors declare no any conflict of interests