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ORIGINAL ARTICLE

HAEMOGLOBIN, SERUM IRON LEVEL AND CARDIOVASCULAR STATUS IN ADVANCED STAGES OF CHRONIC KIDNEY DISEASE PATIENTS ADMITTED IN A TERTIARY CARE CENTRE

MD. YOUSUF ALI[1], MD. EHSANUL ALAM[2], AMINUR RAHMAN[3], NADIRA MAJID[4]

Abstract:

***Background**: Anaemia due to advanced stages of chronic kidney disease increases morbidity of patients. Early detection and correction of anaemia may be helpful in preventing the progress of the disease & its cardiovascular outcomes. The objective of this study was to evaluate hemoglobin, serum iron level and cardiovascular status in advanced of CKD patients. **Methods:** This was a cross sectional observational study on 150 cases of diagnosed advanced stages (3B,4 &5) of CKD patients in indoor of department of medicine of Mitford Hospital, Dhaka from July 2019 to January 2020. Convenience sampling was done. Data were analyzed with SPSS 26. **Results:** Total number of patients were 150. Male were 93 (62%) and female were 57 (38%). The mean (±SD) age was 55.22 (±10.30) years (range 33 - 75 years). Among the study subjects 38% had history of blood transfusion, 60% had history of iron supplementation and 12% subjects received erythropoietin. Mean (±SD) haemoglobin level was 7.61 (±2.54) g/dl. Seventy percent of the study subjects had haemoglobin level < 9 g/dl and rest had ≥9 g/dl. Significant difference was found in between these two groups (p = 0.036). In the present study, mean (±SD) serum iron level was 15.59 (±07.39) µmol/l. In 46% of the study subjects, iron level was 7.3µ mol/l and 52% had iron level between 7.3 to 23.6 µmole/ lit. Mean (± SD) ferritin level of the study subjects was 155.22 (±92.32) ng/ ml. In 58% of the study subjects ferritin level was < 100ng/ ml and 42% had >100 ng/ml. Significant difference was found in between these two groups (p = 0.041) (Table-IV). Ferritin level had significant positive relationship with blood transfusion, iron and erythropoietin supplementation on logistic regression analysis. Haemoglobin and serum ferritin level was positively correlated with eGFR of the study subjects. Statistical analysis showed significant relationship between eGFR with haemoglobin and serum ferritin. Forty six percent of the study subjects had Transferrin saturation (TSAT) level below 20%. Fifty four percent subjects had a TSAT level above 20%. Significant difference was found in between these two groups (p = 0.001). In correlation analysis, haemoglobin, serum ferritin and TSAT level in the study subjects had negative relationship with duration of CKD in years. Relationship of haemoglobin and TSAT level with duration of CKD was statistically significant. In correlation analysis, serum TIBC level had negative relationship with haemoglobin level which was statistically significant. Serum iron, ferritin and TSAT level in the study subjects were positively correlated with haemoglobin level. Relationship of haemoglobin with serum iron level and TSAT level was statistically significant. Twenty percent of the study subjects had peripheral vascular disease, 111 (74%) of the study subjects had hypertension, 66 (44%) had ischaemic heart disease, 27 (18%) had a history of acute myocardial infarction, 24 (16%) had chronic heart failure, 93 (62%) had dyslipidemia and 27 (18%) patients had history of stroke. **Conclusion:** In this study it was observed that TSAT appears to be a more useful indicator for measuring the frequency of iron deficiency than serum iron, TIBC and serum ferritin. The cardiovascular comorbidities plagued significant number of patients with advanced CKD.*

***Key words:** Hemoglobin, serum iron, cardiovascular status, chronic kidney disease.*

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1. Indoor Medical Officer, Dept. of Medicine, Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh.
2. Resident, Department of Physical Medicine & Rehabilitation, Dhaka Medical College & Hospital, Dhaka, Bangladesh
3. Assistant Professor, Department of Neurology, Sir Salimullah Medical College, Dhaka, Bangladesh.
4. Associate Professor, Department of Pathology, Delta Medical College and Hospital, 26/2 Principal Abul Kashem Road, Mirpur-1, Dhaka-1216, Bangladesh.

Address of Correspondence: Dr. Md. Yousuf Ali, Indoor Medical Officer, Department of Medicine, Sir Salimullah Medical College, Mitford Hospital, Dhaka, E-mail: yousufssmc@gmail.com

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 chronic kidney disease; nowadays, infections have become a less important cause for kidney disease, at least in the western world.[4] Current evidence suggests diabetes and hypertension to be the major causes of chronic kidney disease worldwide.[5,6] Aneamia refers to state in which level of haemoglobin in the blood is below the normal range appropriate for age & sex.[5] According to WHO, anaemia is defined as Haemoglobin <13g/dl in men and <12g/dl in women. Anaemia in CKD results from following different causes: deficiency of erythropoiten, toxic effect of uraemia on bone marrow precursor cells, reduced red cell survival, blood loss due to capillary fragility, poor platelet function, and reduced intake, absorption and utilization of dietary iron.[2]

Iron deficiency has been identified as a major factor for anaemia in CKD patients, with a 43-90% prevalence in different series.[6,7] Hence, the periodic monitoring of iron status is crucial in both CKD and end stage renal disease (ESRD). There are two forms of iron deficiency, absolute iron deficiency and functional iron deficiency. Reduction of reticuloendothelial system iron in the bone marrow is referred to as absolute iron deficiency. Absolute iron deficiency may occur from impaired intestinal absorption, blood loss through the dialysis circuit, vascular access surgeries, repeated phlebotomies and increased iron utilization with erythropoietin therapy. In clinical practice, absolute iron deficiency is determined by serum ferritin less than 200ng/ml and TSAT less than 20%. In the non-ESRD population, "functional" iron deficiency is ascribed when iron reserves in the bone marrow are adequate, but iron mobilization is impaired as in states of chronic inflammation.[8] The reduced Kidney function (eGFR), low Haemoglobin and low serum iron level are independently associated with cardiovascular disease (CVD) risk, which are important complications of CKD. The therapeutic goal of this study was early detection & correction of iron deficiency in CKD which may prevent cardiovascular outcome.

Methods:

This cross sectional observational study was conducted in the Department of Medicine, Sir Salimullah Medical College & Mitford hospital, Dhaka from July 2019 to January 2020. Convenience sampling was used and sample size was duly calculated and total number of cases

were 150. Adult patients above 18 years of age, who met the inclusion criteria and attended the outpatient department of medicine or were admitted in medicine ward of Mitford Hospital were selected. Inclusion criteria involved adult patients above age >18 years of either sex diagnosed as advanced CKD (stage 4 & 5) who were yet not on dialysis and patients who were willing to give informed written consent. Exclusion criteria were: (1) CKD with bleeding disorder, recent haemorrhage, CLD or malignancy, (2) CKD patients on dialysis, (4) psychological abnormality, and (5) patients refusing to give consent to take part in the study.

Data collection was done through face to face interview with the selected patients with the help of a structured questionnaire. The patients were examined for certain clinical signs and those were recorded in the check-list. Relevant investigations were done within 24-72 hours of admission.

Variables included were: clinical examination findings (blood pressure, anaemia level), serum creatinine, haemoglobin level, creatinine clearance rate, serum iron profile, ECG and echocardiography findings.

Collected data were checked carefully for any error and processing works were done. Statistical analysis was done using SPSS 25 on windows 10. Then data were entered in IBM Statistical package for Social Science (SPSS) 25 for Windows 10. An analysis plan was developed keeping the objectives of the study in mind. To establish relationship in between variables chi-square analysis, student t test and Fisher's Exact test were done and in all cases. P value < 0.05 considered significant.

Before the commencement of the study, the protocol for the following study was approved by Institutional ethical review committee (ERC). The informed consent of the patients was taken. They were also given freedom to withdraw themselves from the study whenever they want and were ensured that the information obtained from them will be kept confidential. Furthermore, they were clearly informed that participation of the study had no effect on their treatment and management process, and they would not get any kind of financial benefits.

Operational definitions:

Chronic kidney disease (CKD):

Chronic kidney disease (CKD) was defined as an irreversible deterioration in renal function that usually develops over a period of years. Initially it manifests only as a biochemical abnormality but eventually loss of excretory, metabolic and endocrine functions of kidney leads to clinical symptoms and signs of renal failure, collectively referred to as uremia.[9]

CKD staging:

CKD staging was done according to the US National Kidney Foundation Kidney Disease Quality Outcomes Initiative 2002. Stage 1: eGFR e^90 mL/min with normal kidney function and patients remained asymptomatic. Stage 2: eGFR 60-89 mL/min, with a mild decline in kidney function and patients remained asymptomatic. Stage 3A: eGFR 45-59 mL/min with mild to moderate decline in kidney function and patients remained asymptomatic. Stage 3B: eGFR 30-44 mL/min with a moderate decline in kidney function and patients were anaemic where anaemia was non progressive or very slowly progressive in most cases. Stage 4: eGFR 15-29 mL/min with a severe decline in kidney function and appearance of symptoms begins when GFR<20 mL/min. Stage 5: eGFR<15 mL/min or patients on maintenance dialysis with kidney failure or end-stage renal disease (ESRD) requiring dialysis and having significant symptoms and complications.[9]

Results:

The study was done on 150 patients diagnosed as cases of CKD. We took necessary history and ran relevant investigations. The pertinent results are shown below. 93 of the participants were male and 57 were female.

Table-I

Distribution of study patients according to Serum Iron Levels (n = 150)

Iron (µmol/L)	Frequency n (%)
≤7.3	69 (46)
> 7.3 – 23.6	78 (52)
≥23.6	03 (02)
Mean ± SD	15.59 ± 7.39

Mean (±SD) haemoglobin level was 7.61 (±2.54) g/dl. Seventy percent of the study subjects had haemoglobin level d" 9 g/dl and rest had e" 9 g/dl. Significant difference was found in between these two groups (p = 0.036) (Table I).

Table-II

Distribution of study patients according to serum Ferritin levels (n = 150)

Ferritin (ng/mL)	Frequency n (%)	Percent	P-value	ℜ-value
≤ 100	87 (58)	58	0.041	.517
> 100	63 (42)	42		
Mean ± SD	155.22 ± 92.32			
Range	50 – 255.36			

Significant difference was found in between these two groups (p = 0.041) (Table II). Ferritin level had significant positive relationship with blood transfusion, iron and erythropoietin supplementation on logistic regression analysis.

Table-III

Correlation of the eGFR with Hemoglobin & serum Ferritin levels (n = 150)

Variable	Level (Mean ± SD)	r-value	P-value
Hb level (mg/dL)	07.61±02.54	0.684	0.012
Ferritin (ng/mL)	153.22±92.32	0.491	0.041

Haemoglobin and serum ferritin level was positively correlated with eGFR of the study subjects. Statistical analysis showed significant relationship between eGFR with haemoglobin and serum ferritin.

Table-IV

Distribution of study patients according to TSAT level (n = 150)

TSAT %	Frequency, n (%)	P Value	B Value
≤ 20	69 (46)	0.001	0.743
> 20	81 (54)		

Significant difference was found in between these two groups (p = 0.001) Table IV.

Table-V

Correlation of total duration of CKD with haemoglobin, serum ferritin and TSAT level in the study subjects (n = 150)

Traits	r-value	P-value
Hb (mg/dL)	0.652	0.046
Ferritin (ng/mL)	0.0251	0.059
TSAT (%)	0.0781	0.036

In correlation analysis haemoglobin, serum ferritin and TSAT level in the study subjects had negative relationship with duration of CKD in years. Relationship of haemoglobin and TSAT level with duration of CKD was statistically significant (Table V).

Table-VI

Correlation of haemoglobin level with serum iron, serum TIBC, serum ferritin level and TSAT level in the study subjects (n = 150)

Traits	r-value	P-value
Iron (mg/dL)	0.458	0.001
TIBC	- 0.0204	0.015
Ferritin (ng/mL)	0.120	0.057
TSAT (%)	0.769	0.001

In correlation analysis, serum TIBC level had negative relationship with haemoglobin level which was statistically significant. Serum iron, ferritin and TSAT level in the study subjects were positively correlated with haemoglobin level. Relationship of haemoglobin with serum iron level and TSAT level was statistically significant (Table VI).

Table-VII

Prevalence cardiovascular comorbidity in study patients (n = 150)

Comorbidity	Frequency, n (%)
PVD	30 (20)
Hypertension	111 (74)
IHD	66 (44)
Acute MI	27 (18)
Chronic Heart Failure (EF <50%)	24 (16)
Dyslipidemia	93 (62)
Stroke	27 (18)

Twenty percent of the study subjects had peripheral vascular disease, 111 (74%) of the study subjects had hypertension, 66 (44%) had ischaemic heart disease, 27 (18%) had a history of acute myocardial infarction, 24 (16%) had chronic heart failure, 93 (62%) had dyslipidemia and 27 (18%) patients had history of stroke (Table:VII).

Discussion:

Anemia in CKD is often encountered by the clinicians and has many adverse clinical outcomes in these patients. One of the most common contributory factors of anemia is iron deficiency. Iron deficiency can be easily measured in laboratory by doing iron profile and iron replacement can correct anemia and improve quality of life in CKD. Treatment of anemia prior to initiation of dialysis confers a survival advantage after the start of dialysis.[3] It ameliorates left ventricular hypertrophy and improves quality of life and various health measures.[3] Therefore, it can be assumed that correction of iron deficiency in advanced CKD will provide correction of anaemia (in those who have iron deficiency anaemia) and thus will improve quality of life, morbidity and mortality. This study was carried out with the aim to see the hemoglobin status and frequency of iron deficiency among diabetic patients with CKD, who have not received any dialysis. In the United States, the highest incidence of ESRD occurs in patients older than 65 years. As per NHANES III data, the prevalence of CKD was 37.8% among patients older than 70 years. Similar result was seen in this present study, where it was observed that mean age was 55.22 years and 70% patients in the age group were above 41 years. Among 150 subjects, 62% were male. The USRDS 2004 Annual Data Report showed that the incidence of ESRD was higher for males and the age and gender distribution of this present study corresponded with the epidemiology of CKD (Stage 5).[8,10,] Mean haemoglobin level was 7.61 gm/dl which had the similarity with the studies conducted by Hsu et al. and Levin et al.[11] Seventy percent of the present study subjects had haemoglobin level <9 gm/dl. Multiple logistic regression analysis showed haemoglobin level had relationship with blood transfusion, iron and erythropoietin supplementation in this present study. This relationship reflects that CKD results in low haemoglobin level due to iron and erythropoietin deficiency. In 58% of the current study population, serum ferritin level was < 100 ng/ml. Similar results were found in the studies conducted by Garneata et al. and Eschbach et al. and proved that low serum ferritin level is an indicator of iron deficiency in CKD.[20] Forty six percent subjects had TSAT level below 20% and 54% subjects had a TSAT level above 20%. Like serum ferritin level, multiple logistic regression analysis showed TSAT level had relationship with blood transfusion, iron and erythropoietin supplementation as was seen in other studies.[10,11] Difference between these two groups on basis of serum ferritin level (p=0.041) and TSAT level (p=0.001) were significant. But statistically TSAT level was in higher position than serum ferritin level. This reflects that in CKD patients, TSAT level is a better indicator of anaemia and a better predictor of the necessity for iron supplimentation than other indicators of anaemia like haemoglobin and serum ferritin level. In correlation analysis haemoglobin,

serum ferritin and TSAT level in the study subjects had negative relationship with duration of CKD in years. Only relationship of haemoglobin and TSAT level with duration of CKD was statistically significant. These results reflect the similar result of the study carried out by McClellan et al. In correlation analysis serum TIBC level had negative relationship with haemoglobin level which was statistically significant. Serum iron, ferritin and TSAT level in the study subjects were positively correlated with haemoglobin level. Relationship of haemoglobin with serum iron level and TSAT level was statistically significant. It is well established that development of anemia is nearly universal in patients with CKD.[12] The development of effective therapeutic options, such as blood transfusion, iron supplementation and erythropoietin therapy etc. has provided for the effective treatment of anemia. In this current study, 38% patients had positive history of blood transfusion, 60% had iron supplementation and 12% received erythropoietin supplementation. The prevalence of anaemia correction in several ways is very much similar with the study result conducted by Mc Culloughet et al. and Johnson et al[13].

Twenty percent of our study subjects had peripheral vascular disease, 111 (74%) of the study subjects had hypertension, 66 (44%) had ischaemic heart disease, 27 (18%) had a history of acute myocardial infarction, 24 (16%) had chronic heart failure, 93 (62%) had dyslipidemia and 27 (18%) patients had history of stroke. Half of the participants (n = 42) were at CKD Stage 5, while 33.7% (n = 28) were at Stage 3 and 15.7% (n = 13) at Stage 4 and. Mean SBP and DBP were 144.8 ± 24.1 mmHg and 89.1 ± 14.1 mmHg respectively and showed a non-significant increase across CKD stages. Hypertension (37.35%), diabetes (20.48%) and chronic glomerulonephritis (12.05%) were the main causes of CKD. The etiology was undetermined in 10% of patients. The mean number of cardiovascular risk factors CVRF in the study population was 5.19 ± 1.64 and the number increased although not significantly with severity of CKD[14,15]. The mean number of non-traditional CVRF significantly increased with stage of CKD (p=0.004). Hypertension (90.3%), abdominal obesity (79.5%), dyslipidemias (69.8%), and diabetes (42.1%) were the most frequent traditional CVRF, while anemia (78.3%), hyperuricemia (69.8%) and proteinuria (44.5%) were frequent non-traditional factors. Alcohol use decreased significantly with the stages of CKD, while anemia and proteinuria increased significantly with the severity of disease. The mean number of CVD per patient was 1.5 ± 0.6 with an overall prevalence of 69.8% (n = 58). LVH (48.2%) and CHD (30.1%) were the most frequent CVD found. Prevalence of CVD (p = 0.022), LVH (p = 0.009) and CHD (p = 0.02) increased significantly with the severity of CKD. The cardiovascular comorbidities were is very much similar with previous studies[16-18].

Conclusion:

In this study, it was concluded that TSAT may appear to be a more useful indicator for measuring the frequency of iron deficiency than serum iron, TIBC and serum ferritin levels. Therefore it can be recommended that TSAT should be further measured in terms of sensitivity and specificity as a marker of iron deficiency. Cardiovascular comorbidities persecuted significant number of patients with advanced CKD. Early screening and attention to the cardiovascular status should be attributed for these patients.

Limitations of the study:

The study was done on 150 cases only due to time and resource constraint. It was done in only one centre in Dhaka, which may not be attributable to the total population with CKD in the country. Further studies should be carried out with large number of study subjects and in multiple centers.

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Declaration of interest:

The authors report no conflict of interest.

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Ethical consideration:

The study was conducted after approval from the ethical review committee. The confidentiality and anonymity of the study participants were maintained.

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