Evaluation of Iron Status in Diabetic CKD Stage 5 Pre-Dialysis Patients

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Abstract

Objective: To evaluate the iron status among patients with diabetes mellitus and CKD stage 5, who have not started dialysis yet. Methodology: This cross-sectional study was carried on a total of 50 adult diabetic patients with stage 5 CKD, in the Department of Nephrology, BIRDEM General Hospital, Dhaka over 6 months. Results: Total number of patients was 50. Sixty two percent were male and 38% were female. Mean age was 55.22 (range 33-75) years. Mean± SD hemoglobin and ferritin levels were 7.61±2.54 mg/dl and 155.22±92.32 ng/ml respectively. Seventy percent of the study subjects had haemoglobin level d" 9 mg/dl. In 48% of the study subjects, ferritin level was less than 100ng/ml. Fourty six percent of the study subjects had TSAT level below 20%. Haemoglobin, serum ferritin and TSAT level in the study subjects had negative relationship with duration of CKD. Haemoglobin and serum ferritin levels were positively correlated with eGFR of the study population. 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 and TSAT level was statistically significant. Statistical analysis showed relationship between eGFR with haemoglobin and serum ferritin level was significant (P<0.05). Conclusion: Most of the diabetic CKD stage 5 patients had reduced hemoglobin level and iron deficiency is one of the contributory factors and TSAT is the better indicator for iron deficiency than serum iron, TIBC and ferritin level.

Key words: *Iron status, CKD stage 5, diabetes mellitus.*

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Introduction

Anemia is common in chronic kidney disease (CKD) and contributes to many adverse clinical outcomes. The World Health Organization (WHO) defines anemia as hemoglobin <13 gm/dl for men and <12 gm/dl for women. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) defines anemia in adult men and postmenopausal women as hemoglobin <12 g/dl or <11 g/dl in a pre-menopausal woman.[1] Renal anemia becomes more common and severe with deteriorating renal function. Anemia develops in chronic renal failure (CRF) when the glomerular filtration rate drops below 20-30 ml/min.[2] Over 40% of patients with CKD are anemic and anemia in this population is often under-recognized and under treated.[3]

The vast majority of patients with CKD seem to be iron-deficient, as evaluated by the usual parameters and by iron staining on bone marrow biopsy. Multiple forms of interference with all phases of iron metabolism are the causes. Anemia in patients with CRF is multifactorial, with an absolute or functional iron deficiency prevailing in 60-80% of patients.[4] Therefore, the need for iron supplementation in CKD becomes obvious. Other factors contributing to renal anemia are a moderately reduced red cell life span, blood loss resulting from dialysis, diagnostic sampling and occult gastrointestinal bleeding and an inadequate increase in erythropoietin relative to the fall in hemoglobin.[2]

The NKF-K/DOQI Practice Guidelines recommend maintaining ferritin > or =100 ng/ml and transferrin

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saturation (TSAT) > or =20% to ensure adequate iron supply for erythropoiesis among patients with CKD, whether they are dialysis dependent or not. Iron status should be routinely monitored in patients receiving erythropoietin stimulating agents (ESA), as many patients will eventually require iron supplementation for ESA hypo-responsiveness or resistance.[5] Much has been written on the important contribution of iron deficiency towards anemia and erythropoietin resistance among end-stage renal disease (ESRD) patients, but there are few studies of iron status among chronic renal insufficiency (CRI) subjects not yet requiring dialysis.[6] Iron deficiency afflicts anemic patients at all stages of CKD[7] and is one of the important contributory factors of renal anemia that can be measured and treated effectively.

Materials and methods

This cross-sectional study was carried out in the Nephrology Department, BIRDEM General Hospital, Dhaka from April 2011 to September 2011 with the aims to describe the frequency of iron deficiency anaemia (IDA) among patients with diabetes mellitus and CKD stage 5 before the first dialysis, to describe the levels of haemoglobin, ferritin and transferin saturation (TSAT) among these patients, to compare the duration of CKD with the levels of haemoglobin, ferritin and TSAT. A total of 50 Stage 5 CKD patients with diabetes mellitus of any duration and of either sex were included in the study. CKD stage 5 was evaluated by eGFR<15 ml/min, which was calculated at bedside byusing Cockcroft and Gault equation. Patients with acute kidney injury (AKI) on CKD, with history of recent blood loss or hematological disorders and those who were already on dialysis were excluded.

Results

Total number of patients was 50. Male were 31 (62%) and female were 19 (38%). The mean (±SD) age was 55.22 (±10.30) years (range 33 - 75 years). The mean (±SD) duration of CKD was 3.50 (±2.27) years (range 1 - 8 years). Twenty percent of the study subjects had peripheral vascular disease, 26% had diabetic neuropathy and 44% had diabetic retinopathy. Regarding co-morbidities, 37 (74%) of the study subjects had hypertension, 22 (44%) had ischaemic heart disease, 31 (62%) had dyslipidemia and 9 (18%) patients had history of stroke. Among the study subjects 38% had history of blood transfusion, 60% had history of iron supplementation and 12% subjects received erythropoietin. (Table I)

Table I

Clinical history of the study subjects (n=50)

History	Responses	Frequency	Percentage
Blood Transfusion	Yes	19	38
	No	31	62
Iron Supplementation	Yes	30	60
	No	20	40
Erythropoietin Supplementation	Yes	12	24
	No	38	56

All the study subjects had eGFR level < 15 ml/min. Mean (±SD) eGFR was 9.44 (±02) ml/min (range 6 - 14). Mean (±SD) serum creatinine and urea levels were 8.60 (±6.04) mg/dl (range 3.30 - 26.80) and 36.28 (±09.89) mg/dl (range 26.31 - 54.83) respectively.

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 II)

Table II

Haemoglobin level of the study subjects.

Haemoglobin level (mg/dl)	Number	Percentage	P- value	β- value
≤9	35	70	0.036[S]	0.289
>9	15	30		
Mean± SD	07.61±02.54			
Range	04.80-10.60			

β= Regression coefficient, S= significant, P value reached from t – test

In the present study, mean (±SD) serum iron level was 15.59 (±07.39) µ mole/ lit. In 46% of the study subjects, iron level was d" 7.3µ mole/ lit and 52% had iron level between 7.3 to 23.6 µmole/ lit. (Table III)

Table III

Serum iron level of the study subjects.

Serum iron level (µ mole/ lit)	Number	Percentage
≤ 7.3	23	46
>7.3-23.6	26	52
≥ 23.6	01	02
Mean± SD	15.59±07.39	

Mean (± SD) ferritin level of the study subjects was 155.22 (±92.32) ng/ ml. In 58% of the study subjects ferritin level was d" 100ng/ml and 42% had e" 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 serum creatinine, haemoglobin (Figure 1), serum urea and serum ferritin (Figure 2). (P<0.05). (Table V)

Table IV

Ferritin level of the study subjects.

Ferritin level (ng/ml)	Number	Percentage	P-value	β-value
≤ 100	29	58		0.041^{S}
0.517				
>100	21	42		
Mean± SD	155.22±92.32			
Range	50.00-255.36			

β= Regression coefficient, S= significant, P value reached from t – test

Table V

Correlation of the eGFR with several variables.

Variable	Level (mean± SD)	r-value	P-value
Haemoglobin level (mg/dl)	07.61±02.54	0.684	0.012^{S}
Serum ferritin (ng/ml)	153.22±92.32	0.491	0.041^{S}

r= Correlation coefficient, S= significant, NS= not significant

Forty six percent of the study subjects had 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). (Table VI).

Table VI

TSAT level of the study subjects.

TSAT level (%)	Number	Percentage	P-value	β-value
≤ 20	23	46	0.001^{S}	0.743
>20	27	54		

β= Regression coefficient, S= significant, P value reached from t-test

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 VII)

Table-VII

Correlation of total duration of CKD with haemoglobin, serum ferritin and TSAT level in the study subjects (n=50).

Correlation traits	r- value	P- value
Haemoglobin level (mg/dl)	-0.652	0.046^{S}
Serum ferritin (ng/ml)	-.0251	0.059^{NS}
TSAT (%)	-.0781	0.036^{S}

r= Correlation coefficient, S= significant, NS= not significant, P value reached from t – test

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 VIII).

Table VIII

Correlation of haemoglobin level with serum iron, serum TIBC, serum ferritin level and TSAT level in the study subjects (n=50).

Correlation traits	r- value	P- value
Serum iron level (mg/dl)	0.458	0.001^{S}
Serum TIBC	-.0204	0.015^{S}
Serum ferritin (ng/ml)	0.120	0.057^{NS}
TSAT (%)	0.769	0.001^{S}

r= Correlation coefficient, S= significant, NS= not significant, P value reached from t – test

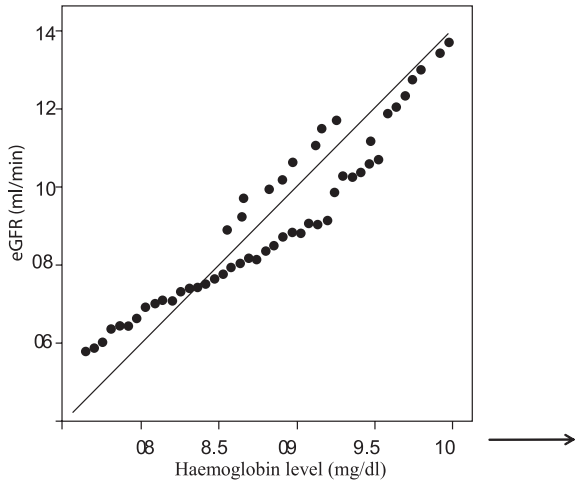

Fig.-1: *Scatter diagram showing correlation of the eGFR with haemoglobin level.*

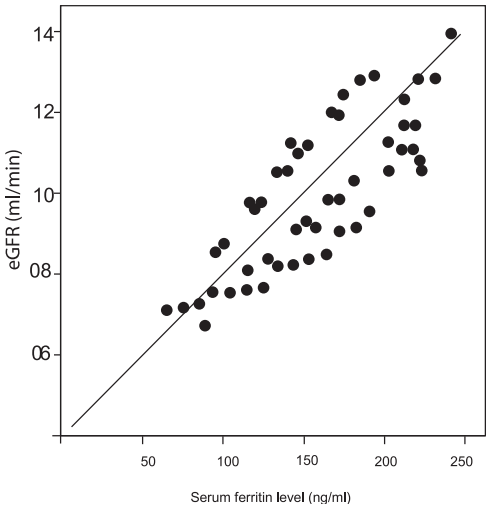

Fig.-2: *Scatter diagram showing correlation of the eGFR with serum ferritin level.*

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 is 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.[8] It ameliorates left ventricular hypertrophy and improves quality of life and various health measures.[9] 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 stage 5, 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 were in the age group above 41 years. Among 50 subjects 62% were male. The USRDS 2004 Annual Data Report showed that the incidence of ESRD was higher for males.[10] The age and gender distribution of this present study corresponds with the epidemiology of CKD (Stage 5).[4,7,11]

Mean haemoglobin level was 7.61 gm/dl which had the similarity with the studies conducted by Hsu et al.[12]and Levin et al.[13] Seventy percent of the present study subjects had haemoglobin level d" 9gm/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.[14] and Eschbach et al.[15] and proved that low serum ferritin level is an

indicator of iron deficiency in CKD. 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.[12,13] 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. This results reflects the similar result of the study carried out by Mc Clellan et al.[16] 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.[11] The development of effective therapeutic options, such as blood transfusion, iron supplementation and erythropoietin therapy etc. has provided for the effective treatment of anemia. An earlier KDOQI Clinical Practice Guideline is devoted to this topic[17] however, that guideline focused primarily on patients treated by dialysis. This guideline addresses anemia in the earlier stages of CKD. 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 al.[7]and Johnson et al.[18]

Conclusion

In this study it was observed that most of the diabetic CKD stage 5 patients who were not yet receiving haemodialysis were anaemic irrespective of their previous blood transfusion, iron or erythropoietin supplementation and many of them were iron deficient. From the finding of the present work, it can be 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. It is can also be recommended that iron deficiency anaemia should be corrected with iron supplementation along with other measures. However further study can be carried out by including large number of study subjects and in multiple centers.

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