IRON INDICES IN PATIENTS WITH FUNCTIONAL ANEMIA IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: Despite high ferritin level, HDCKD patients may have functional iron deficiency even after intravenous iron (iv) therapy. The aim of this study was to test the hypothesis that lowered serum transferrin level may contribute to functional anemia and erythropoietin hypo responsiveness by the failure to transport accumulated tissue iron to the relevant target tissue.

Materials and methods: The study subjects were divided into four groups. Group-A: HDCKD Patients receiving iv iron (n=290). Group-B: Patients not initiated on to hemodialysis (NDCKD), and received oral iron (n=38). Group-C: HDCKD patients with erythropoietin hypo responsiveness (n=9). Group-D: Healthy controls (n=36). The group-A, patients were sub-divided into five groups (A-1 to A-5) based on their serum ferritin levels.

Results: Serum ferritin and tissue iron levels in group-A and C patients were significantly greater than the group-D(p<0.0001) and group-B patients(p<0.001). Transferrin level of group-A and C showed lowered values and consequently a higher %TSAT when compared to group-D. The percent of patients with iron overload was 2.6%, 31%, and 44% in group-B, group-A and group-C respectively. Serum transferrin level significantly correlated with TIBC in group-A and B patients (p<0.0001;p<0.05 respectively). Transferrin level significantly correlated with TIBC in all subgroups of HDCKD(p<0.05) with the exception in subgroup-A2 and with hemoglobin in subgroups A3 (p<0.05) and A5(p<0.01) respectively.

Conclusions: The lowered transferrin level prevents the proper transport of the iron to the hematopoietic sites, which may be a reason for the low hemoglobin synthesis and also for the development of erythropoietin hypo responsiveness in some of the dialysis patients.

INTRODUCTION

The treatment of anemia in Chronic Kidney Disease patients on hemodialysis (HDCKD) as per the NKF-DOQI guidelines is by giving intravenous(iv) iron , where as in non hemodialysis CKD patients(NDCKD), oral iron is generally administered (1). The iv iron administration in HDCKD patients may lead to iron overload with deposition of iron in tissues even in the post erythropoietin (EPO) era has been accompanied by growing concern about iron overload (2). Hence, it becomes important to regularly monitor iron indices in HDCKD patients receiving iron therapy to ensure that iron overload with its toxic manifestations do not occur.
The main markers of iron status are serum ferritin, TSAT and TIBC. By determining both the serum ferritin concentration and the transferrin saturation, are used to direct anemia therapy in chronic kidney disease (CKD) and are associated with clinical outcomes in patients on dialysis (3). Serum Ferritin adequately reflects iron stores in bone marrow of HD patients and also functions as an acute phase reactant (4). Despite the ferritin values ranging from approximately 80 - 480ng/mL, the iron stores were absent on bone marrow aspiration in ESRD patients starting dialysis and may have functional iron deficiency (FID) (5).

Indian patients with CKD have evidence of iron overload similar to those in developed countries (6). Despite the accumulation of tissue iron and elevated serum ferritin which occurs in HDCKD patients on iv iron therapy, the hemoglobin levels continue to be low, which point to the prevalence of FID anemia seen in CKD patients. We have examined the accumulation of tissue iron and elevated serum ferritin in HDCKD and NDCKD patients receiving iv and oral iron therapy respectively. The serum iron levels were correlated with tissue iron and ferritin levels to gauge the occurrences of functional and absolute iron deficiency. The aim of this study was to test the hypothesis that lowered serum transferrin levels may also significantly contribute to functional anemia and erythropoietin hypo response by the failure to transport accumulated tissue iron to the relevant target tissue. The cause of such a reduced synthesis of iron transporting protein may be traced to the concomitant presence of the malnutrition and inflammation syndrome seen in hemodialysis patients. Recognizing and treating functional iron deficiency and transferrin deficiency is therefore an important concept in the management of anemia in both HDCKD and NDCKD patients.

**MATERIALS AND METHODS**

**Patients:** The study groups comprised of CKD patients attending the Nephrology department of Kamineni hospital during the period June 2008 to September 2010. The ethical committee of Kamineni Hospital approved the study. In this study the hemodialysis (HD), non dialysis (ND) cohort of CKD patients taken into study and compared themselves and also compared with healthy controls. The inclusion criteria are the stable CKD patients on MHD at least 3 months period and the CKD stage iv and v NDCKD patients who were on oral iron therapy for a period of minimum 3 months duration. The exclusion criteria are patients with known malignancies, bleeding disorders, infection or inflammation of other cause and transplant cases. Some of the HDCKD patients remained persistently anemic with no increase in Hb% with EPO dosage of more than 500 IU/kg/wk and were labeled as hypo responsive to erythropoietin. Indices of iron metabolism were studied in this EPO hypo responsive subgroup to detect biochemical evidence of iron overload. Antibodies for EPO were also estimated in this group. The study subjects were divided into four groups.

**Group-A:** HDCKD patients receiving iv iron therapy (n=290).

The group-A, hemodialysis patients were further sub-divided into five groups (A-1 to A-5) based on their serum ferritin levels.

| Sub groups       | N   | Serum Ferritin levels |
|------------------|-----|-----------------------|
| Sub group A-1    | n=94| 20 - 300 ng/mL        |
| Sub group A-2    | n=65| 300 - 500 ng/mL       |
| Sub group A-3    | n=58| 500 - 1000 ng/mL      |
| Sub group A-4    | n=44| 1000 - 2000 ng/mL     |
| Sub group A-5    | n=29| > 2000 ng/mL          |

**Group-B:** NDCKD stage-4 & 5 patients who were not initiated on to hemodialysis and on oral iron supplementation (n=38).

**Group-C:** Suspected EPO resistant HDCKD patients tested for EPO antibodies (n=9).

**Group-D:** Healthy controls (n=36).

**METHODS**

A prospective study from June 2008 to September 2010 was carried out with the patients attending the Nephrology Department at Kamineni Hospital. All HDCKD patients received iv iron supplementation and erythropoietin as per the Nephrology unit’s protocol. The study parameters included serum iron, unsaturated iron binding capacity (UIBC), serum ferritin, transferrin, percent saturation of transferrin, blood urea and serum creatinine. The blood samples collected after 2 weeks of iv iron supplementation in HDCKD patients and at random for NDCKD and controls subjects. All the tests were assessed on the same day by automated chemistry analyzer, Cobas Integra 400+ (Roche). TIBC was calculated as being equal to serum iron + UIBC and tissue iron levels were calculated by using the mathematical equation (7), (8). EPO antibodies were analyzed by ELISA. Hemoglobin was estimated by using BC-3000-plus Mindray auto hematology analyzer.
STATISTICAL METHODS

All relevant statistics were performed using the Statistical package for social sciences (SPSS Ver-11.0, SPSS Inc, Chicago) software. The mean and standard error (SE) of all parameters were expressed. Analysis of variance (ANOVA) was used for comparison of mean between the groups. The relationship between the parameters obtained by Pearson’s correlation matrix (r) and a value of P< 0.05 was considered (at 95% CI) to be statistically significant(9).

RESULTS

The mean age of subjects was 50±12 years. Among these, 51% had type-2 diabetes and 61% had hypertension as a co-morbid disease. The demographics of the study patients were shown in Table-1. Serum ferritin levels in group-A (HDCKD patients receiving iv iron therapy) and group-C (HDCKD tested for EPO antibodies) patients were significantly greater than in group-D (healthy controls) and group-B (NDCKD) patients (p<0.0001, p<0.001 respectively). Similarly, tissue iron was also significantly elevated in group-A and C patients when compared to group-D and B patients (p<0.0001 for both). Transferrin levels and its saturation (% TSAT) in group-B NDCKD patients who received oral iron were not significantly different from group-D healthy subjects. However, there was a significant difference in the mean levels of transferrin between the group-A, group C HDCKD patients and the group-B NDCKD patients (p<0.0001). Transferrin levels in HDCKD patients of both groups-A and C showed lowered values and consequently a higher %TSAT when compared to group-D controls. Hence transferrin levels were lower in patients on hemodialysis who also had a higher incidence of iron overload. Hemoglobin levels were low in all groups of CKD patients when compared to the healthy controls (p<0.0001). As per NKF-K/DOQI guidelines, which define iron overload as serum ferritin >800ng/mL, 2.6% of NDCKD (Group-B) patients and 31% of HDCKD (group-A) patients had iron overload in this study. Among the EPO resistant cases (Group-C), 44% had iron overload. Absolute iron deficiency was identified by two parameters: i)
serum iron <35µg/dL ii) ferritin <100ng/mL. Functional iron deficiency was measured either as iron <35µg/dL or serum ferritin <100ng/mL (10). Among the group-A HDCKD patients, 18% had serum iron less than 35µg/dL and 11% of them had ferritin <100ng/mL. However, only 1.5% of these patients had absolute iron deficiency.

As per the NKF/Kidney Early Evaluation Programmed guidelines, a hemoglobin level below 11g/dL is defined as anemia. Ninety four (94%) percent of all the CKD patients in this study were anemic having hemoglobin level less than 11g/dL. The prevalence of iron deficiency by serum iron levels less than 35µg/dL revealed only 19% of the total CKD patients had iron deficiency. Hence the cause of anemia could be factors other than iron deficiency alone.

Tissue iron deposits were significantly increased in all CKD patients when compared to the controls (p<0.0001). In group-C suspected EPO resistant HDCKD patients, serum was examined for the presence of antibodies to recombinant erythropoietin. However, none of the studied patients had any antibodies to erythropoietin. Overall, the picture that emerges in this population is one of sufficient serum and tissue iron and paradoxically low hemoglobin levels combined with very high serum ferritin levels.

**CORRELATION ANALYSIS IN STUDY GROUPS**

Serum transferrin levels significantly positively correlated with TIBC in group-A HDCKD and group-B NDCKD patients (r=0.409, p<0.0001; r=0.394, p<0.05 respectively) (Table-2). There was no significant association between these two parameters in group-

| Parameter | HDCKD (Group A) | NDCKD (Group B) | EPO-Hypo responsive HDCKD (Group C) |
|-----------|----------------|----------------|--------------------------------------|
| % TSAT    | 0.282 <0.0001  | 0.366 <0.05    | 0.314 NS                               |
| Ferritin  | 0.879 <0.0001  | 0.896 <0.0001  | 0.982 <0.0001                         |
| Urea      | 0.039 NS       | 0.462 <0.004   | 0.388 NS                               |
| Creatinine| -0.01 NS       | 0.309 NS       | -0.101 NS                              |
| Ferritin  | 0.879 <0.0001  | 0.896 <0.0001  | 0.982 <0.0001                         |
| % TSAT    | 0.314 <0.0001  | 0.379 <0.05    | 0.318 NS                               |
| Urea      | 0.145 <0.05    | 0.444 <0.01    | 0.450 NS                               |
| Creatinine| 0.098 NS       | 0.311 NS       | -0.010 NS                              |
| Ferritin  | 0.601 <0.0001  | 0.815 <0.0001  | 0.972 <0.0001                         |
| % TSAT    | 0.039 NS       | 0.462 <0.01    | 0.388 NS                               |
| Urea      | 0.097 NS       | 0.429 <0.01    | 0.166 NS                               |
| Tissue iron| 0.145 <0.05   | 0.444 <0.01    | 0.450 NS                               |
| Creatinine| 0.690 <0.0001  | 0.812 <0.0001  | 0.691 <0.058                          |
| %TSAT     | -0.14 <0.05    | -0.141 NS      | -0.004 NS                              |
| Hemoglobin| -0.17 <0.05    | -0.172 NS      | -0.181 NS                              |
| Transferrin| 0.158 NS      | 0.276 NS       | -0.297 NS                              |
| Creatinine| -0.06 NS      | -0.179 NS      | -0.697 <0.055                         |
| Tissue iron| -0.22 <0.0001 | -0.345 <0.05   | 0.271 NS                               |
| Transferrin| 0.409 <0.0001 | 0.394 <0.05    | 0.280 NS                               |
| % TSAT    | -0.05 NS       | -0.273 NS      | 0.780 <0.05                           |
| Urea      | 0.023 NS       | -0.242 NS      | 0.099 NS                               |

P<0.05 considered as significant.; NS= Not significant.; Entered p values are against the controls. %TSAT= Percentage Transferrin Saturation.; TIBC= Total Iron Binding Capacity.; Hb= Hemoglobin.
C EPO resistant and group-D control subjects. It was observed that hemoglobin and transferrin did not correlate each other in all study groups. Serum ferritin significantly positively correlated with tissue iron in controls, HDCKD and NDCKD patients. In group-A HDCKD patients, hemoglobin did not correlate with serum ferritin, % TSAT, tissue iron. In group-B NDCKD patients who were on oral iron supplementation; hemoglobin correlated with serum ferritin, tissue iron levels. Therefore, while in NDCKD patients, serum ferritin is an index of iron availability, in HDCKD patients; ferritin may not an appropriate marker of iron status. TIBC correlated negatively with ferritin and tissue iron in HDCKD and NDCKD (group A&B) patients and controls (p<0.001 for all groups). TIBC also correlated with % TSAT in NDCKD and controls subjects but not in HDCKD patients (Table-2).

The iv iron receiving group-A HDCKD patients were distributed into 5 different sub-groups based on their serum ferritin levels. When serum ferritin was less than 500ng/mL (group A-1 and A-2), ferritin levels correlated significantly with %TSAT (r = 0.288, 0.453 and p <0.05, p<0.0001) respectively. Tissue iron deposits correlated with % TSAT when ferritin was less than 500ng/mL (groupA-1and A-2), but as serum ferritin increased further, there was no correlation between ferritin and transferrin or % TSAT, indicating that factors other than iron were responsible for elevation of serum ferritin levels beyond 500ng/mL. The serum iron significantly positively correlated (p<0.0001) with the %TSAT in all the subgroups (A-1 to A-5), with hemoglobin in subgroup A-3 and with transferrin in subgroups A-3 (r=0.441,p<0.05) and A-5 (r=0.620,p<0.01) respectively (Table-3). TIBC and %TSAT correlated significantly positively with %TSAT and tissue iron deposits with (p<0.0001 for all groups). TIBC also correlated with % TSAT in HDCKD and controls subjects but not in HDCKD patients (p<0.05).

Table 3
Correlation between the indices of iron status in sub-groups of HDCKD patients.

| Parameter | Subgroup | A-1 | A-2 | A-3 | A-4 | A-5 |
|-----------|----------|-----|-----|-----|-----|-----|
|           | r        | p   | r   | p   | r   | p   |
| %TSAT     | 0.288    | <0.01 | 0.453 | <0.0001 | 0.055 | NS | 0.017 | NS | NS | NS |
| Ferritin  | 0.942    | <0.0001 | 0.996 | <0.0001 | 0.794 | <0.0001 | 0.997 | <0.0001 | NS | NS | NS |
| Urea      | 0.268    | <0.01 | 0.039 | NS | 0.011 | NS | -0.03 | NS | NS | NS |
| Creatinine| 0.242    | <0.05 | 0.117 | NS | 0.012 | NS | 0.023 | NS | NS | NS |
| Ferritin  | 0.942    | <0.0001 | 0.996 | <0.0001 | 0.794 | <0.0001 | 0.997 | <0.0001 | NS | NS | NS |
| Tissue iron| 0.263    | <0.01 | 0.449 | <0.0001 | -0.12 | NS | 0.005 | NS | NS | NS |
| Urea      | 0.254    | <0.05 | 0.055 | NS | 0.087 | NS | -0.02 | NS | NS | NS |
| Creatinine| 0.007    | NS | 0.935 | <0.0001 | 0.276 | <0.05 | 0.775 | <0.0001 | 0.521 | <0.01 |
| S.Iron    | 0.321    | <0.05 | 0.180 | NS | 0.362 | <0.05 | 0.537 | <0.05 | 0.512 | <0.05 |
| TIBC      | 0.364    | <0.0001 | 0.449 | <0.0001 | -0.33 | <0.01 | 0.033 | NS | -0.01 | NS |
| Urea      | -0.16    | NS | -0.10 | NS | 0.419 | <0.001 | 0.197 | NS | -0.40 | NS |
| Creatinine| -0.02    | NS | -0.11 | NS | 0.454 | <0.0001 | 0.150 | NS | -0.31 | NS |
| Iron      | -0.08    | NS | -0.08 | NS | 0.525 | <0.001 | -0.02 | NS | 0.120 | NS |
| Transferrin| -0.19    | NS | 0.134 | NS | 0.441 | <0.05 | 0.345 | NS | 0.620 | <0.01 |
| Creatinine| -0.23    | NS | -0.30 | <0.05 | 0.274 | NS | 0.389 | <0.05 | 0.205 | NS |

P<0.05 considered as significant.; NS= Not significant.; Entered p values are against the controls. %TSAT= Percentage Transferrin Saturation.; TIBC= Total Iron Binding Capacity.; Hb= Hemoglobin.
in this study were anemic having hemoglobin level less than 11g/dL. Hemoglobin levels in patients receiving iv iron still remained of iv iron. The target hemoglobin for HDCKD patients at present is between 11-12 g/dL (17). Majority of the CKD patients (94%) had ferritin levels elevated more than 500ng/mL (16). However, other factors need to be considered while stopping administration. Of the total 299 HDCKD subjects, 131 (44%) had ferritin levels more than 500ng/mL. K/DOQI guidelines of the year 2006 say that iron not to be supplemented when hematocrit ranges within target levels, as per K/DOQI guidelines published in 2006 (16). Of the total 299 HDCKD subjects, 131 (44%) had ferritin levels more than 500ng/mL. K/DOQI guidelines of the year 2006 say that iron not to be supplemented when ferritin levels elevated more than 500ng/mL (16). However, other factors need to be considered while stopping administration of iv iron. The target hemoglobin for HDCKD patients at present is between 11-12 g/dL (17). Majority of the CKD patients (94%) in this study were anemic having hemoglobin level less than 11g/dL. Hemoglobin levels in patients receiving iv iron still remained low (<9g/dL) while tissue iron deposits and serum ferritin levels increased in this study. Though there was significant rise in the average hemoglobin levels (~12g/dL) in the same population of western studies (18), the rise in hemoglobin levels in this study was negligible. This prompt the need of hour to look into various factors resulted in low hemoglobin levels.

The percentage of patients who had absolute iron deficiency was only 1.5% indicating the majority of dialysis patients exhibits FID with high serum ferritin levels. (19) et al showed that FID associated with elevated ferritin levels in dialysis patients, and there was significant improvement in FID status with iv iron supplementation. The estimation and regular monitoring of iron indices is an important requirement in the management of anemia of CKD patients. While serum iron, TIBC and ferritin are regularly estimated in patients, the estimation of tissue ferritin and transferrin are not widely done. The average range of serum iron levels in all the CKD groups is within the normal range (66-139 μg/dL). The two fold increase of tissue iron than controls, leading to iron overload state and normal serum iron levels observed with decreased transferrin synthesis due to associated inflammation and malnutrition in CKD cases may be the reason for lack of significant correlation between TIBC and % TSAT observed in HDCKD and NDCKD patient groups. Hemoglobin is an important indicator of iron status alone, and also how well the tissue iron is being mobilized to target cells and being utilized for heme synthesis. TSAT is an indicator of circulating iron and the positive association with serum iron, serum ferritin and tissue iron (p<0.0001) reflects that the availability of sufficient iron in the form of iron bound with transferrin. The presence of large quantities of tissue iron in all patients of dialysis indicates that iron therapy has loaded iron into the patients, which may result in other complexities associated with MIA syndrome. Our study shows that estimation of hemoglobin or ferritin alone does not give the correct picture of the iron status which supports many of previous studies. Ferritin levels below 500ng/mL may be considered as expressing the stored iron levels. However, only about 16% of (45 out of 299) the total HDCKD patients in this study had serum ferritin levels above 500ng/mL and TSAT <3% are probably an indication of an inflammatory response. Within the sub groups of HDCKD patients, as ferritin levels increased, the hemoglobin levels decreased, indicating that ferritin was not a reliable iron status marker in HDCKD patients as also supported by atomic absorption studies (20).

Soluble transferrin receptor (sTfR) is a product of the transferrin receptor and its concentration in plasma is proportional to the total concentration of cellular TfR. A number of factors may affect the concentration of sTfR in plasma or sera: acute or chronic inflammation and the anaemia of chronic disease and malnutrition. sTfR may be a good indicator of iron deficiency anemia in iron deficient thalassemic patients and in subjects without inflammation (21), (22). However, diagnostic accuracy of sTfR as an indicator of iron deficiency anemia is not well established and it may be an appropriate marker for erythropoiesis than iron deficiency (23). Transferrin saturation and ferritin currently remain better methods for the evaluation of iron status in rHuEPO-treated chronic hemodialysis patients(24;25).

Human hepcidin is a 25–amino acid peptide. The hepatocytes are the main sources of hepcidin, while the bacteria-activated neutrophils and macrophages are other sources. The structure of the bioactive hepcidin is a simple hairpin with 8 cysteines that forms 4 disulfide bonds in a ladder-like configuration. The regulation of iron export from cytosol to plasma is controlled by hepcidin and it has no effect on the iron dynamics of reticulocytes (26). Transferrin circulates iron in a soluble, non-toxic form and delivers it to developing reticulocytes in bone marrow and play a key role in iron metabolism. Individual cells modulate their uptake of transferrin-bound iron depending on their iron requirements (27). Transferrin regulates the iron homeostasis as
component of a plasma iron sensing system that modulates hepcidin expression. Transferrin synthesis by the liver in experimentally induced acute inflammation rats is normal (28) and in HDCKD patients on one year MHD, concentration of total serum transferrin remained constant (29), though there was 2.5 fold decrease in serum transferrin levels when compared with healthy controls.

In this study, transferrin levels decreased significantly (p<0.0001) in HDCKD patients on iv iron (184±5 mg/dL) and in group-C EPO hypo responsive patients (31±5 mg/dL) when compared to controls. There was also significant difference (p<0.0001) in transferrin levels between the HDCKD, EPO-resistant HDCKD and NDCKD patients. The significantly lowered transferrin levels prevent the proper transport of the iron to the hematopoietic sites, which may be a reason for the low hemoglobin synthesis and also for the development of erythropoietin hypo responsiveness in some of the dialysis patients (Fig 1). The absence of EPO antibodies in serum group-C HDCKD patients, against the supplemented rHuEPO, may reflect the other factors like decreased iron availability due to significantly reduced transferrin levels may involved in resulting EPO hypo responsiveness seen in these patients. Lowered transferrin results from the presence of the Malnutrition-Infammation–Atherosclerosis syndrome which decreases protein synthesis in the liver. This action is mediated by IL-6, a pro–inflammatory cytokine (30) (31). Hence it is important to ensure adequate mobilization of tissue iron deposits to increase hemoglobin levels rather than repeatedly administering iron to CKD patients. Recognizing functional iron deficiency and transferrin deficiency is therefore an important concept in the evaluation of anemia in CKD patients.

CONCLUSION

The existence of functional iron deficiency anemia, characterized by low hemoglobin levels in the presence of elevated serum ferritin and tissue iron levels observed in HDCKD patients. The average %TSAT in HDCKD patients is 44%, which indicates the adequate iron availability. The excess iron increases the tissue iron deposits and elevates the pro-inflammatory cytokines, causing decreased transferrin levels. The lack of correlation between TIBC and %TSAT in HDCKD, NDCKD groups may need further study to establish the possible causes. Serum transferrin levels decreased in all CKD patients, leading to decreased tissue iron mobilization to erythroid cells, which in turn may cause decreased hemoglobin synthesis and elevated tissue iron levels.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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