ORIGINAL ARTICLE

Comorbidity of Iron Indices and Inflammatory Markers among Sudanese Hemodialysis Patients

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ABSTRACT

Background: Iron is critical to energy production in all cells. Patients with end-stage renal disease (ESRD) may have either functional iron deficiency (even following the intravenous iron therapy) or excess iron accumulation leads to serious health problems. Moreover, inflammation is commonly known to be associated with many complications and worsen outcome. **Materials and Methods:** A cross-sectional study was conducted in March 2016 at Port Sudan Hospital for Surgery and Hemodialysis, Sudan, to investigate iron indices and the concomitant status of inflammatory activity in ESRD patients receiving parenteral iron. Fifty ESRD patients were enrolled, 40 (80%) were male and 10 (20%) were female along with 50 normal healthy controls. Hemoglobin, serum iron, total iron-binding capacity (TIBC), unsaturated iron-binding capacity (UIBC), serum ferritin, transferrin saturation (TSAT), blood urea, serum creatinine, and C-reactive protein (CRP) were estimated. **Results:** Functional iron deficiency was present in 32% of patients and absolute iron deficiency was noticed also in the patients. Among patients receiving intravenous iron, 18 (36%) had higher levels of TSAT and 31 (62%) had higher ferritin levels ($P = 0.000$ and 0.013, respectively). In fact, 34 (68%) of CRP was significantly elevated in ESRD patients compared to the controls ($P = 0.000$). TIBC and UIBC were insignificantly lower than the controls ($P = 0.444$ and 0.273). Unexpectedly, serum iron was insignificant ($P = 0.278$) although it was higher compared to the controls. **Conclusion:** CRP elevation was more pronounced and could explain the inflammatory activity status. It is necessary to check iron indices periodically in ESRD patients under parenteral iron therapy due to being extremely prone to acquire hemochromatosis.

Key words: End-stage renal disease, iron indices, serum ferritin, Sudan, transferrin saturation

INTRODUCTION

End-stage renal disease (ESRD) is worldwide and has been estimated approximately more than 1.1 million patients.[1] ESRD is becoming a popular disease in the world, so far till now, there is no treatment that can cure the patients except either living with dialysis or kidney transplant.[2] ESRD had a high incidence in both the Middle Eastern countries (93/million populations) and the developing countries.[3] Anemia in renal disease, especially iron deficiency, plays a substantial role as a very common cause.[4] Hence, it is becoming important to regularly monitor iron profile in hemodialysis chronic kidney disease (CKD) patients receiving iron treatment to ensure that iron overload and its toxic remarks do not occur.[5] The essential major markers of iron profile are the serum iron, total iron-binding capacity (TIBC), and transferrin saturation (TSAT). Serum iron is critical and may reflect the quantity of iron immediately available for hemoglobin (HB) synthesis. The frequency of iron deficiency has been observed to be present in as many as 25–37.5% of the patients presenting with anemia of renal disease.[2] Absolute iron deficiency develops in patients with kidney disease due to frequent blood loss with gastrointestinal bleeding and this may be complicated by decreased oral iron absorption due to special

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dietary restrictions.[6] Serum ferritin generally reflects the guide on the iron stores in the bone marrow of hemodialysis patients as well as being an acute-phase material.[7] Although having a high ferritin level, ESRD patient may have functional iron deficiency even after intravenous iron therapy.[8] The goal of this study was to investigate the iron indices and the concomitant status of inflammatory activation associated with ESRD.

MATERIALS AND METHODS

A prospective study was conducted in March 2016 in patients attending the Port Sudan Hospital for Surgery and Hemodialysis. All ESRD patients on regular hemodialysis who received parenteral iron supplementation and erythropoietin as per the nephrology unit's protocol are enrolled in this study. Fifty patients with ESRD and 50 normal, healthy subjects as control were included in the study. The parameters studied are HB level, serum iron, TIBC, unsaturated iron-binding capacity (UIBC), serum ferritin, TSAT, C-reactive protein (CRP), blood urea, and serum creatinine. Those tests were performed to establish the healthy nature of the controls.

Inclusion and exclusion criteria

This study is incorporated hemodialysis patients (stage V) who were on parenteral iron therapy for a period of a minimum of 3 months' duration in Port Sudan Hospital for Surgery and Hemodialysis. Whereas excluded the patients with identified malignancy, bleeding disorders, infection or inflammation of alternative causes, history of blood transfusion for one-month, recent overt blood loss, and transplant cases.

Study specimens

Three milliliters early morning venous blood samples were collected in tripotassium ethylenediaminetetraacetic acid (K_3EDTA) and 2 ml in chilled tube. All the chemical laboratory tests were run in duplicates. All the tests were assessed on the same day by semi-automated chemistry analyzer (URIT-810). UIBC was calculated as being equal to TIBC-serum iron using the mathematical equation. HB was estimated using URIT 3010 E02211 PR China semi-automated hematology analyzer. CRP was estimated using a quantitative CRP reagent assay according to the manufacturer protocols and measured by NycoCard® method using NycoCard® READER II (SN 67498, Axis-Shield PoC AS, Oslo, Norway).

Definition of CKD Stage V

CKD (Stage V) was defined as per the National Kidney Foundation/Kidney Foundation's Kidney Dialysis Outcomes Quality Institution. CKD Stage V is defined as an estimated glomerular filtration rate <15 CKD patients for renal replacement therapy (dialysis/transplantation).[9]

Definition of iron categories

Absolute iron deficiency is defined as an acute reduction or lack of iron storage in reticuloendothelial organs (ferritin <20 µg/l).

Functional iron deficiency is defined as the shortage to competently transport iron from liver into other storage sites, despite having adequate iron stores (TSAT <20; ferritin >300 µg/l).

Iron overload is a condition that is present when too much iron is constantly absorbed than the body needs (TSAT >50; ferritin >300 µg/l).

Iron blockade is a state, in which the iron is isolated in macrophages during inflammations.[10]

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS 24.0 version, IBN, Chicago, USA). Results were presented in number, percent, mean, and standard deviation. Analysis of variance was used in statistical analysis to compare differences between groups with $P < 0.05$ considered statistically significant, when appropriate. Descriptive statistics were employed; Pearson's Chi-square test and bivariate correlation were also used.

Ethical consideration

All protocols were approved by the ethics committee of the institution (Ethics Committee, Port Sudan Hospital for Surgery and Hemodialysis, Sudan) before the initiation of the study. Informed consent was obtained from all participants.

RESULTS

One hundred adults were studied; 50 patients with ESRD and 50 healthy controls. Forty (80%) were male and 10 (20%) were female among the patients, with a mean age of 51.3 ± 13.5 years. For controls, 41 (82%) were male and 9 (18%) were female with a mean age of 33.0 ± 14.5 years. The data baseline and parameters of the study are evident in Table 1.

The findings of the present study expressed that the HB level of the patients under dialysis was significantly lower as compared to the controls as well as the serum TIBC and UIBC which were insignificant. Serum iron of the hemodialysis patients was insignificant, although it was higher when compared to the controls.

On the other hand, the parameters such as TSAT, serum ferritin, blood urea, and serum creatinine levels of the patients were significantly higher compared to the controls [Table 1].

Eighteen (36%) and 31 (62%) of ESRD patients had higher levels of TSAT and ferritin levels, respectively [Table 2].

In fact, 34 (68%) of CRP was significantly higher in ESRD patients as compared to the controls ($P < 0.000$) [Tables 1 and 2]. Twenty-three (46%) of patients had both high CRP and ferritin level. There was a statistically significant

Table 1: The characteristics baseline and parameters of the study

Parameters	ESRD (*n*=50) mean±SD	Control (*n*=50) mean±SD	*P*-value
Age (years)	52.3±13.5	33.0±14.5	0.000
Range	26–78	18–75	
Sex (%)			0.801
Male	40 (80)	41 (82)	
Female	10 (20)	9 (18)	
HB g/dl	8.64±1.99	12.99±1.76	0.000
Range	4.7–13.0	8.9–16.4	
Serum iron µg/dl	98.87±49.09	90.58±21.91	0.278
Range	40.3–212.7	60–171	
TIBC µg/dl	295.25±137.17	312.70±83.61	0.444
Range	63.6–550.8	171–500	
UIBC µg/dl	196.35±140.95	222.12±86.30	0.273
Range	12.0–509.6	79–400	
TSAT %	40.97±24.36	31.19±11.62	0.013
Range	7.5–93.0	15.6–60.3	
Serum ferritin µg/l	330.29±188.88	193.69±115.82	0.000
Range	14.8–605.7	56.3–534	
CRP	12.22±11.55	4.28±2.32	0.000
Range	2.0–48.0	1.4–15.0	
B. Urea mg/dl	123.98±40.49	27.41±8.90	0.000
Range	52–200	15–68.7	
Serum creatinine mg/dl	8.502±3.361	0.835±0.292	0.000
Range	3.0–19.3	0.4–1.60	

HB: Hemoglobin, TIBC: Total iron-binding capacity, UIBC: Unsaturated iron-binding capacity, TSAT: Transferring saturation, CRP: C-reactive protein. SD: Standard deviation

Table 2: General status of the studied parameters

Parameters/status	HB *n* (%)	Iron *n* (%)	TIBC *n* (%)	UIBC *n* (%)	Ferritin *n* (%)	TAST *n* (%)	CRP *n* (%)
High	–	4 (8)	8 (16)	–	31 (62)	18 (36)	34 (68)
Normal	11 (22)	33 (66)	22 (44)	19 (38)	18 (36)	26 (52)	16 (32)
Low	39 (78)	13 (26)	20 (40)	31 (62)	1 (2)	6 (12)	–
Total	50 (100)	50 (100)	50 (100)	50 (100)	50 (100)	50 (100)	50 (100)

HB: Hemoglobin, TIBC: Total iron-binding capacity, UIBC: Unsaturated iron-binding capacity, TSAT: Transferring saturation, CRP: C-reactive protein

difference between test and control for both CRP and ferritin levels ($P < 0.008$) and TSAT ($P < 0.036$). However, 8 (16%) of ESRD patients had high ferritin levels with normal CRP.

According to the laboratory findings, the iron indices of ESRD patients were categorized into 6 (12%) had an absolute iron deficiency, 16 (32%) had a functional iron deficiency, 9 (18%) presented with iron overload, 9 (18%) exhibited iron blockade, 6 (12%) had high iron store, and 4 (8%) were adequate [Figure 1].

There was a significant difference between HB level and TSAT ($P < 0.021$). In contrast, no significant difference was detected between HB level and serum iron, serum TIBC, UIBC, and serum ferritin ($P < 0.0055$, 0.0209, 0.118, and 0.122, respectively). A positive correlation has been statistically significant observed between the age of the patients and two parameters, serum ferritin and TSAT ($P < 0.004$ and 0.049, respectively) and a negative correlation between age of the patients and neither serum iron nor TIBC and nor UIBC with $P < 0.540$, 0.171, and 0.126, respectively. However, the TSAT levels correlated significantly with serum iron, TIBC, and UIBC ($P < 0.000$, 0.000, and 0.000, respectively). There was a good correlation between serum ferritin levels and TIBC levels ($P < 0.022$). The relevance

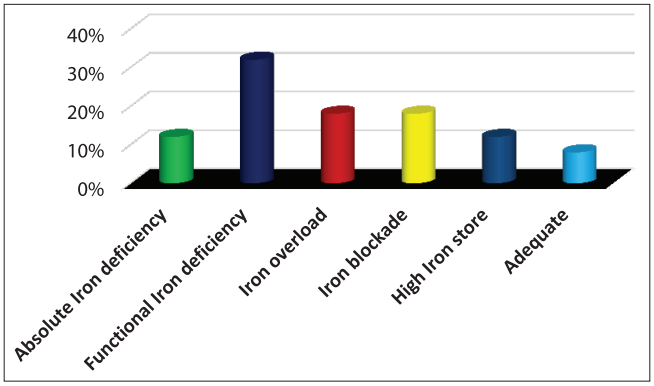

Figure 1: Iron categories proportion among the studied patients

of marked inflammatory activation was illustrated in the ESRD patients detected by significant elevations of CRP ($P < 0.000$).

DISCUSSION

In our area, this was the first study approaching the comorbidity of iron indices and inflammatory markers among ESRD Sudanese patients. Fifty patients were diagnosed as CKD Stage V.

Patients with ESRD had heightened inflammatory condition probably resulted from uremia. This inflammation may interfere with the utilization of iron by impairing the hepcidin.[10] Anemia is rampant in the general population and nutritional anemia reported about 23–98%.[11] Surprisingly, about 78% of the ESRD in our study had anemia, although most of them had administrated parenteral iron therapy. The functional iron deficiency was demonstrated in the vast majority of ESRD patients 32%, which probably stemmed from subclinical inflammation. A finding which is similar to Małyszko *et al*.[12] The iron is an essential ingredient for HB synthesis, evaluated or adequate iron stores should be present before the erythropoietin hormone is initiated. Iron therapy is important for normal response to erythropoietin in ESRD patients because the demand of iron by the precursor erythroid marrow proportionally may exceed the amount of iron that is immediately available for erythropoiesis processors (as estimated by TSAT) as well as tissue iron stores (as estimated by ferritin level).[13] It is significant to sustain the distinction between absolute (ferritin <20 µg/l) and functional iron deficiency (TSAT <20; ferritin >300 µg/l).

Parenteral iron therapy has emerged as a necessary tool in anemia management in ESRD, either by itself or combined with erythropoietin.[14] The current study demonstrates that the iron indices (serum ferritin and TSAT) were significantly different in ESRD patients with parenteral iron therapy compared to the controls ($P < 0.000$ and 0.013, respectively); this finding is in concordance with Kouegnigan *et al*.[15] who studied 85 ESRD dialysis patients and reported that a positive correlation between the iron indices and TSAT, this correlation is also documented in our study in addition to serum iron, TIBC, and UIBC ($P < 0.000$).

CRP seems to be one of the most important markers for the identification of inflammation in clinical practice.[16] The advantages of using CRP test are its low cost and wide availability especially in developing countries.[17] Serum CRP levels do not alter with changes in renal function, but in ESRD, CRP is affected by the inflammatory response.[18] CRP has been recognized to be very useful in the prediction of cardiovascular problems in kidney disease patients.[19] Moreover, it is also implicated as a potent promoter of atherosclerosis disease.[20] A study done by LaClair *et al*.[21] has shown high levels of CRP as an inflammatory marker in hemodialysis patients pointed to that the process of dialysis by itself, does not play a substantial role in the inflammation induction. Our findings in this study yielded a significant increase in CRP levels in ESRD patients compared to controls (12.22 ± 11.55 mg/l vs. 4.28 ± 2.32 mg/l, $P < 0.000$). This result was considerably similar to findings performed by Beerenhout *et al*. and Filiopoulos *et al*.[22,23] Moreover, the CRP was considered higher in patients with functional iron deficiency when compared to the patients with absolute Fe deficiency.

TSAT is a marker of the circular iron, which reflects the presence of sufficient iron in the form of transferrin bounded iron.[24] In this study, a significant value of TSAT (≥50%) was exhibited the iron overload among 18% of ESRD patients and also in 18% as iron blockade (iron sequestered in macrophages). The presence of large amounts of iron stored in most of hemodialysis ESRD patients indicates that the iron supplementation has loaded into the patients; this status was more prominent in our study as 12%. This could be attributed to the unmonitored administration of parenteral iron as well as assessing the iron indices periodically. Major limitations associated with the study were the short study period and small sample size. Serum transferrin, serum hepcidin, and serum erythropoietin should be undertaken in the future researches.

CONCLUSION

To the best of our knowledge, the average percentage of TSAT (36%) and serum ferritin level (62%) indicates increased iron availability in ESRD patients which, in turn, may cause acquired hemochromatosis. CRP elevation was more pronounced and could explain the inflammatory activity status. Estimation of CRP marker is a superior simple test in predicting the outcome of hemodialysis patients.

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