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Assessment Of Iron Status In End Stage Renal Disease Patients On Hemodialysis.

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ABSTRACT

Chronic kidney disease is a pathological condition that results from a gradual, permanent loss of kidney function. Anemia is a common comorbidity of End Stage Renal Disease patients who are on maintenance hemodialysis. This study aims to find out the iron status in maintenance hemodialysis patients. Serum iron, Ferritin and Transferrin saturation are widely used together to assess iron status. A total of 80 End Stage Renal Disease patients of age 18-80yrs on Hemodialysis were included. Serum iron,Total iron binding capacity(TIBC) and Serum Ferritin were measured . We found that, the mean level of serum ferritin was 365.91 ±198.3 µg/l . Although the serum ferritin levels were within the normal range, hemoglobin and serum iron levels were lower which indicates poor iron status. Also serum iron levels had a significant negative correlation with Ferritin (p-value 0.04) . This indicates, high ferritin in hemodialysis is due to non iron related factors such as inflammation. Periodic assessment of iron status is necessary while managing anemia in hemodialysis patients and this probably will help in reducing morbidity and mortality.

Keywords: Chronic Kidney Disease, End Stage Renal Disease, Hemodialysis, Serum Ferritin, Serum Iron, Total iron binding capacity.

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INTRODUCTION

Chronic Kidney Disease (CKD) refers to the entire continuum of renal disease that progresses from mildly impaired kidney function to significant deterioration or End Stage Renal Disease (ESRD), requiring dialysis or kidney transplant[1]. ESRD is a major cost driver for health care systems. One well-known complication associated with CKD and ESRD, including those undergoing maintenance hemodialysis (MHD) treatment is anemia. As renal function declines, the incidence of anemia increases[2,3]. Several factors have been implicated in the development of anemia in ESRD which include erythropoietin deficiency, iron deficiency, decreased lifespan of red blood cells, chronic blood loss, secondary hyperparathyroidism, chronic inflammation, oxidative stress, nutritional folate deficiency, uremia and chronic suppression of erythropoiesis etc[4,5]. Of these, inflammation and chronic inflammatory state are considered to be the major causes[6]. Untreated anemia can significantly decrease a patient's quality of life and can increase morbidity and mortality.

Moreover, inflammation is closely related to protein energy wasting in dialysis patients[7] and the simultaneous occurrence of these two conditions, also referred to as malnutrition-inflammation cachexia syndrome (MICS), is observed frequently in CKD patients[8]. Concurrent to the poor clinical outcomes, MICS may also lead to moderate hyperferritinemia and refractory anemia[9] . The most commonly used markers of monitoring iron management in MHD patients are Transferrin saturation ratio, and serum ferritin[10]. Although serum ferritin is the main storage molecule for iron[11], it's also an acute phase reactant, *i.e.*, its serum concentration tends to increase moderately in the presence of inflammation which occurs commonly in MHD patients[8,11,12,13] .

We hypothesised that, in MHD patients, moderately high ferritin levels is more strongly associated with inflammation than with iron stores. Therefore, the present study was aimed to evaluate the relative contribution of inflammation and iron stores to high serum ferritin in MHD patients.

MATERIALS AND METHODS

The present cross sectional study was conducted in the dialysis unit of Nephrology department after obtaining ethical committee clearance. 80 ESRD patients who were on twice weekly hemodialysis therapy were included in the study after getting written informed consent. Among them sixty four were males and 16 were females, aged 18 – 80 years. Subjects with recent bleeding episodes, clinically evident inflammatory or infectious diseases, coronary vascular disease (CVD), chronic obstructive pulmonary disease, peripheral vascular disease and neoplasm were excluded from this study. After obtaining informed consent 5ml of venous blood drawn from the patients prior to the hemodialysis sessions for measuring serum Iron, TIBC, ferritin and Hemoglobin. S.Iron and TIBC were estimated by Ferrozine method, S.Ferritin by Turbilatex turbidimetry method and Hemoglobin estimation by cyanmethemoglobin method. Statistical analysis was done using SPSS version 16 software. The quantitative data were reported as mean ± SD. Correlation between the variables was evaluated by Pearson's correlation with P value < 0.05 considered being statistically significant.

RESULTS AND DISCUSSION

Anemia is a common complication in hemodialysis patients, mainly due to the insufficient production of erythropoietin by the failing kidneys[14]. Anemia itself can worsen cardiac function, cognitive function, exercise capacity and quality of life, and it has been independently associated with progression of renal disease and increased morbidity and mortality[15,16].

The present study was conducted on 80 MHD patients Among the 80 patients 64 (80%) were male and 16 (20%) were female . This could be due to the increased prevalence of CKD in males and also may be due male dominance in seeking treatment in this part of the country[17,18]. In our study, around 85% of study subjects were anaemic with an average hemoglobin level of 7.5gms% which is very much below the target range (11gm %) recommended by KDOQI guideline[Fig.1]. The observed lower hemoglobin level could be attributed to a variety of reasons, mainly, due to the insufficient production of EPO by the failing kidneys. However, other factors contribute to anemia in these patients, as reduced RBC life span in the presence of uremia, deficiencies in iron, folic acid, and vitamin B_{12}, blood loss due to frequent laboratory draws as well as loss during hemodialysis[19], and inflammation[10,20,21,22,] Likewise, hypo-responsiveness to erythropoietin may also be one of the cause for low hemoglobin level observed in some of our patients, and this was also supported by Kalantar-Zadeh et al., and Rossert et al.

Inflammation, a very common condition seen in dialysis patients may be attributed to occult infection of old, non-functioning, arteriovenous grafts (AVGs). Recent evidences suggest that the HD procedure itself may cause an inflammatory response[8,23]. In patients with ESRD, serum iron, TSAT and ferritin are widely used to determine iron deficiency and dictate iron management. In our study, we found that serum iron and TIBC levels were significantly low[Table.1] . Also we found that serum TIBC had the strongest positive correlation with serum iron[Fig.4] and negative correlation with serum ferritin concentrations [Fig.3]. The positive association of TIBC with iron in our current study, as well as in previous studies in CKD patients[24], appears to be in sharp contradiction to its known reverse association with iron in the general population. In the non-CKD populations, iron deficiency is associated with concurrent decreased serum iron and increased TIBC levels, so that iron divided by TIBC, also known as transferrin saturation ratio, is usually quite low[11]. In dialysis patients, on the contrary, TIBC could be low in the setting of malnutrition, inflammation or iron deficiency. Hence, use of traditionally calculated transferrin saturation ratio, to rule out iron deficiency may be misleading, since this simple algebraic fraction may erroneously be high, which is observed in our study subjects.

Similarly, the mean level of serum ferritin was 365.91 ± 198.3 µg/l which was well within the expected range. Although the serum ferritin levels were within the normal range, hemoglobin and serum iron levels were lower which indicates poor iron status in CKD patients. We also found that patients who had significantly low serum iron had a significant negative correlation (p-value 0.04) with ferritin [Fig 3]. This indicates that such moderately high ferritin concentrations in MHD patients can happen due to non iron related factors, including inflammation. The level of ferritin in plasma represents the balance between its secretion, which is directly related to intracellular iron synthesis, and its clearance, mainly in liver and other organs[25]. However, liver dysfunction and inflammatory factors may interfere with the synthesis and clearance of ferritin, thereby increasing serum ferritin levels due to circumstances not related to iron metabolism[26]. Negative Iron balance[27] in these patients could be attributed to functional iron deficiency(FID). FID reflects impaired iron mobilisation from stores to bone marrow as in different settings of infections and inflammation leading to high, normal or low ferritin values. This process of "Inflammatory block" increases the ferritin level[28,29,30]. Several studies have suggested that during the acute phase response, inflammatory cytokines such as interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) increase the synthesis of both H and L subunits of ferritin[31].

Erythropoiesis stimulating agent(ESA) and iron are the mainstays of treatment for anemia associated with CKD. It is well known that patients receiving erythropoietin therapy require a large amount of iron for the process of erythropoiesis, but giving more iron to patients with adequate iron stores and the inability of that iron to be used by bone marrow could create a problem of iron overload. In these patients most of the intravenous iron will deposit in the tissue and little is used by the bone marrow[32]. Both the American and Australian guidelines[10,33] recommend caution with the routine administration of intravenous Fe if the serum ferritin is >500µg/L. However, the upper limit of a safe serum ferritin level remains unresolved[11]. The findings insist that, inflammatory status should also be taken into account when interpreting and monitoring iron status in hemodialysis patients. Since the seemingly paradoxical combination of serum ferritin > 500µg/L and low iron in MHD patients is associated with increased level of inflammation.

Table 1: Parameters of Iron metabolism

Variables	Mean ± SD
Hb(gm/dl)	8.09 ± 1.58
Ferritin (µg/l)	365.9 ± 198.2
Iron (µg/dl)	53.56 ± 35.74
TIBC (µg/dl)	111.66 ± 61.34

Hb, serum iron and TIBC levels were lower than the normal range.[Hb->11gm/dl, Iron-50-175 µg/dl, TIBC-250-425 µg/dl, Ferritin-20-250 µg/l]

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Table 2: Correlation of variables with ferritin

Variables	Ferritin	
	r-value	p-value
Hb(gm/dl)	- 0.2	0.06^{ns}
Iron(µg/dl)	-0.23	0.04*
TIBC(µg/dl)	-0.27	0.01**

*P<0.05, **P<0.01, ns – non significant. Serum ferritin was negatively correlated with hemoglobin, serum iron as well as TIBC.

Figure 1: Distribution of patients by mean Hb levels.

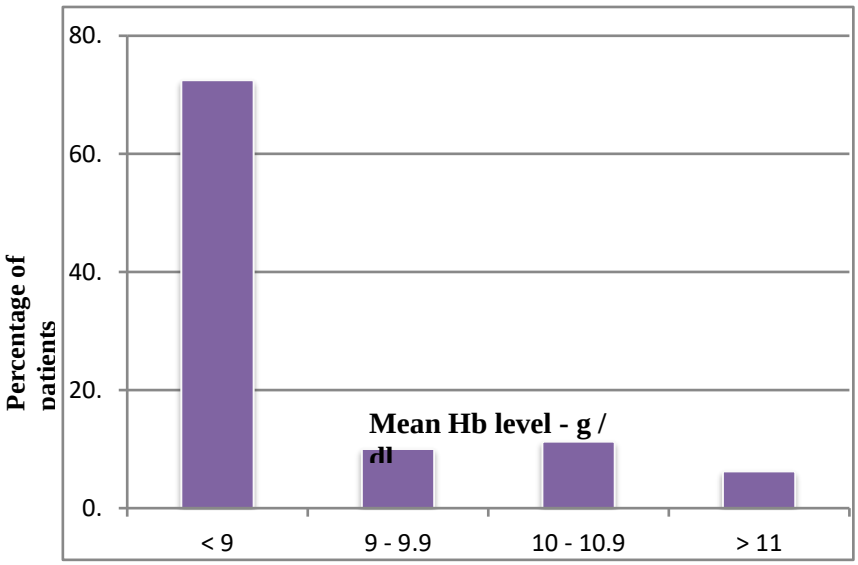
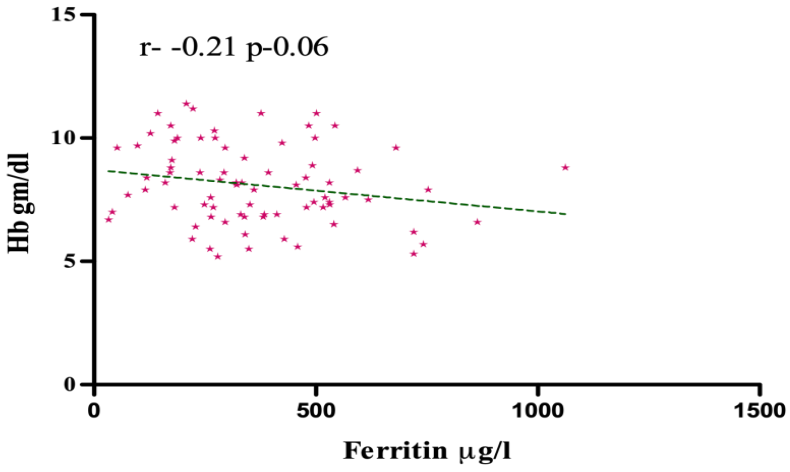


Figure 2: Correlation of Hb with ferritin.



The above scatter plot matrix shows that the Hb levels decrease as ferritin increases, though this was not statistically significant. Rho = -0.2106 (p- value = 0.0607)

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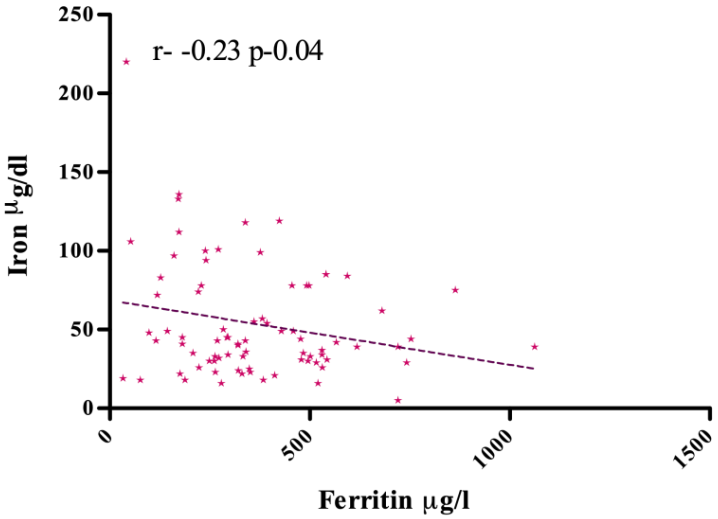
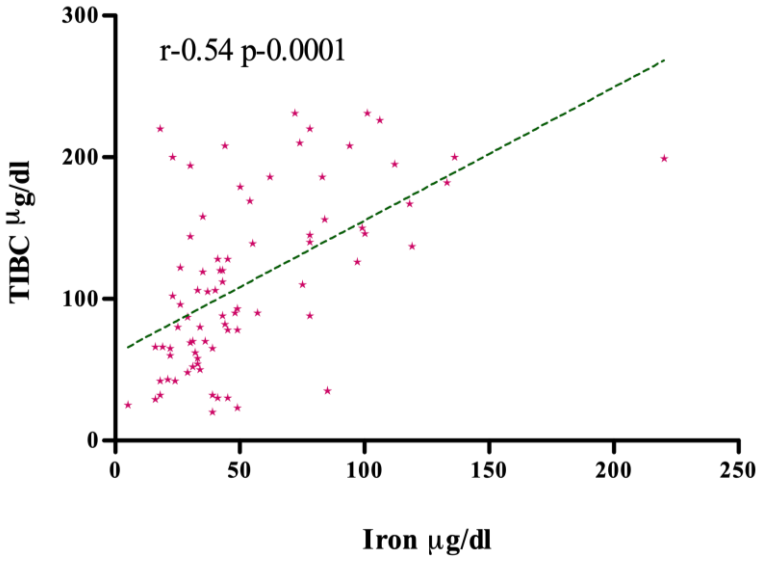
Figure 3: Correlation between serum iron and ferritin.



The above scatter plot shows the significant negative correlation between serum iron and ferritin.
Rho = -0.23 (p- value = 0.04)

Figure 4: Correlation of serum Iron with TIBC



The above scatter plot matrix shows that TIBC had statistically significant positive correlation with serum iron.
Rho: 0.5483 (p-value 0.0001)

CONCLUSION

To conclude, the effect of inflammation on iron metabolism may be a major factor in creating functional iron deficiency. Variability in iron status, or perhaps more specifically, altered ferritin values, often above target range, is associated with more of acute phase reaction rather than adequate iron store. Thus, periodic assessment of iron status and inflammatory markers is necessary while managing anemia in hemodialysis patients and this probably will help in reducing the morbidity and mortality.

Limitations: The study was a cross sectional not a prospective longitudinal study, conducted in small sample size.

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