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The Role of Hepcidin on Iron and Ferritin Levels in Hemodialysis Patients

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Abstract

Background: *Anemia is a common complication in dialysis patients, the most important of which are decreased erythropoietin, iron deficiency, blood loss, dialysis, and chronic inflammation. Hepcidin plays a key role in iron homeostasis in dialysis patients and acts as a natural regulator of hemostasis. Given the importance of the subject and the high frequency of iron homeostasis disorders in hemodialysis patients, as well as the lack of sufficient documentation in this regard, the present study aimed to the role of hepcidin on iron and ferritin levels in hemodialysis patients in Shahroud city in 2024.*

Methods: *This study was a descriptive-analytical study that was conducted cross-sectionally on hemodialysis patients in Shahroud city at Imam Hossein Hospital during 2024. In this plan, after initial measures and obtaining written and informed consent, eligible patients were asked to stop taking iron compounds two weeks before the study and not to use any iron supplements without coordination with the administrators. For all patients, iron factors and ferritin were measured using standard laboratory methods, and then hepcidin was measured using ELISA.*

Results: *In the present study, out of 85 patients studied, 45 (52.9%) were male and 40 (47.1%) were female. The mean age of the patients was 54.31±12.59 years (28-79 years). The mean hepcidin level was 60.39±4.22 mg/dL. It was also found that the level of hepcidin was significantly associated with the duration of dialysis (P-value=0.001) and the number of dialysis sessions per week (P-value=0.006) and had no significant relationship with other variables.*

Conclusion: *The results of this study showed that there was a significant relationship between hepcidin levels, dialysis duration, and the number of dialysis sessions per week. It is necessary to control iron levels before starting hemodialysis, and to adjust the dialysis program for each patient specifically.*

Keywords: Hemodialysis, Hepcidin, Serum iron, Ferritin.
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Introduction

Chronic kidney disease (CKD) impairs the ability of the kidney's functional units to filter waste and regulate blood water and acid. The prevalence of this disorder is increasing[1, 2]. Currently, more than 1.5 million people worldwide are surviving on dialysis[3]. In Iran, 25,600 hemodialysis patients in 375 hemodialysis units in the country are undergoing chronic hemodialysis, with an annual increase of about 8% in the number of these patients[4, 5].

Anemia is a common complication in hemodialysis patients. Among the types of anemia, normocytic normochromic anemia and mild hypochromic anemia, which result from insufficient red blood cell production, are most commonly seen and occur in these patients[1, 2]. Many factors play a role in the development of these anemias, the most important of which include decreased erythropoietin, iron deficiency, blood loss, dialysis proses, chronic inflammation, and factors that negatively affect erythropoiesis[3, 4]. Erythropoietin deficiency is the most common cause of anemia in dialysis patients[5]. Anemia in patients with CKD due to any cause can lead to negative iron balance, resulting in severely reduced ferritin, iron, and iron saturation levels[6, 7].

Hepcidin is an antibacterial peptide that is regulated by iron and inflammatory markers and plays a key role in iron homeostasis[8]. Hepcidin in humans is encoded by a 0.4 kb mRNA consisting of a 2.5 kb, three-exon gene located on chromosome 19[9]. The active form of hepcidin is a 25-amino acid peptide. Hepcidin is synthesized as a larger molecular precursor (preprohepcidin, 84 amino acids) and is subsequently converted to the 64-amino acid prohepcidin by enzymatic cleavage at the C-terminus, and then to the active form of hepcidin by the loss of 39 amino acids[10]. This peptide is produced in the liver and acts as a natural regulator of homeostasis and a negative regulator of iron absorption under normal conditions. High levels of hepcidin inhibit iron absorption from the duodenum and release of iron from macrophages[8-10].

Type II acute inflammatory mediators associated with interleukin-6 (IL-6) are responsible for the production of hepcidin in the liver[11]. Anemia, decreased erythropoietin, and hypoxia lead to increased iron absorption and decreased hepcidin production[12, 13].

Given the level of anemia, normal hepcidin levels are considered high in patients with CKD[14]. Hepcidin is increased in dialysis patients, but there is no association between increased hepcidin levels and IL-6 levels or lack of response to treatment. However, the increase in hepcidin is reversed after erythropoietin treatment[15]. Hepcidin levels also decrease after dialysis[16]. Therefore, dialysis and inflammation have different effects on decreasing or increasing hepcidin in dialysis patients with anemia[17]. Despite research on the effects of hepcidin on blood parameters in hemodialysis patients, there is still no definitive evidence in this regard[15-17]. Given the importance of

the topic and the high frequency of iron homeostasis disorders in hemodialysis patients, as well as the lack of sufficient documentation in this regard, the present study aimed to the role of hepcidin on iron and ferritin levels in hemodialysis patients in Shahroud city in 2024.

Materials and Methods

This study was descriptive-analytical research that was conducted cross-sectionally on hemodialysis patients in Shahroud city at Imam Hossein Hospital in Shahroud between January and December 2024.

The inclusion criteria included: age over 18 years; having regular dialysis at least three times a month to three times a week; Stable vital signs; and withdrawal from participating in the research.

The exclusion criteria included: history of severe and moderately severe cardiovascular disease; presence of acute infection (acute infections were excluded via C-reactive protein (CRP)<5 mg/L); presence of active inflammatory disease; pregnancy; blood transfusion in the past 6 months; any evidence of active or occult bleeding; presence of liver disease; presence of any active malignancy; use of immunosuppressive drugs for at least the past two months; and withdrawal or regret from participating in the study at any stage of the study.

All patients were selected in an accessible and easy way and after full explanation of the research objectives and obtaining informed consent, they were included in the study.

In this plan, eligible patients were asked to discontinue iron compounds 2 weeks before the study and not to use any iron supplements without coordination with the investigators. For all patients, iron and ferritin were measured using standard laboratory methods. Hepcidin was quantified using the DRG® Human Hepcidin ELISA Kit (EIA-5729) following manufacturer protocols.

To estimate the sample size, considering the number of hemodialysis patients in Shahroud city as well as the research objectives and taking into account the formula for calculating the sample size of cross-sectional studies, 88 eligible hemodialysis patients were selected and studied in an accessible and easy manner. It should be noted that during the study, 3 patients were excluded from the study for various reasons, and the study was completed with 85 patients.

Descriptive statistics including mean, standard deviation and relative frequency were used to describe the data. For data analysis, chi-square test (for correlation between qualitative variables) and t-test (for correlation between quantitative variables) were used. All analyzes were performed using SPSS version 23 software at a significant level (P-value<0.05). All participants gave oral and written consent and cooperated in the research. No additional costs were imposed on the subjects and their right to stop the study was guaranteed. Ethical approval of the study was obtained from the Institutional Review Board of Shahroud University of Medical Sciences (IR.SHMU.REC.1403.158) based on the Declaration of Helsinki.

Results

Of the 85 patients studied, 45 people (52.9%) were male and 40 (47.1%) were female. The mean age of patients was 54.31±12.59 years. The average duration of dialysis was 3.61±1.43 years, the average number of dialysis in week was 2.65±0.48 times, and the average dialysis adequacy was 1.15±0.14 liters. The results of the demographic, clinical and para clinical factors of the patients are shown in Table 1.

Table 1. The results of the demographic and clinical factors of the patients

Variable	Mean±SD or Number (%)
Sex	
Male	45 (52.9)
Female	40 (47.1)
Average dialysis duration (years)	3.61±1.43
Age group	
<50	32 (37.6)
50-65	34 (40.0)
>65	19 (22.4)
Average number of dialysis times (per week)	2.65±0.48
Dialysis duration group (years)	
<2	27 (31.8)
2-5	49 (57.6)
>5	9 (10.6)
Dialysis adequacy group (liters)	
Good	37 (43.5)
Poor	48 (56.5)
Average ferritin level group (mg/dl)	
≥200	75 (88.2)
<200	10 (11.8)
Mean hemoglobin level (mg/dl)	10.38±1.18
Mean serum iron level (ng/dl)	47.13±15.91
Average age of patients (years)	54.31±12.59
Average BMI of patients (kg/m²)	25.76±1.74
BMI group	
<20	0 (0)

20-25	44 (51.8)
>25	41 (48.2)
Dialysis adequacy (liters)	1.15±0.14
Average number of dialysis times group (times)	
2	30 (35.3)
3	55 (64.7)
Average hemoglobin level group (mg/dl)	
≥12	8 (9.4)
<12	77 (90.6)
Average serum iron level group (ng/dl)	
≥50	38 (44.7)
<50	47 (55.3)
Mean ferritin level (mg/dl)	595.12±200.65
Mean hepcidin level (mg/dl)	60.39±4.22

Information on the variables of demographic, clinical and para clinical factors in terms of hepcidin is shown in Table 2. As can be seen, the amount of hepcidin was significantly associated with the duration of dialysis (P-value=0.001) and the number of dialysis sessions per week (P-value=0.006), and had no significant relationship with other variables.

Table 2. Association of demographic, clinical and laboratory variables with hepcidin

Variable	Mean±SD of Hepcidin level	P-value
Sex		
Male	60.78±3.92	0.375
Female	59.95±4.54	
Age Group		
<50	60.02±4.39	
50-65	60.47±4.20	0.872
>65	60.86±4.11	
BMI (kg/m2)		
<20	0	
20-25	60.30±5.42	0.837
>25	60.49±3.93	
Duration of dialysis		
<2	57.61±3.25	
2-5	61.48±4.02	0.001
>5	62.79±3.96	
Dialysis frequency per week		
2	58.85±3.18	0.006
3	61.23±4.50	
Dialysis adequacy		
Good	60.18±3.83	0.681
Poor	60.55±4.53	
Hemoglobin level		
≥12	61.08±1.83	0.366
<12	60.32±4.39	
Ferritin level		
≥200	60.65±4.15	0.150
<200	58.38±4.41	
Serum Iron level		
≥50	60.82±4.14	0.392
<50	60.03±4.29	

Discussion

The results of the study showed that there was a significant relationship between hepcidin levels and the duration of dialysis (P-value=0.001) and the number of dialysis sessions per week (P-value=0.006), but no significant relationship was found with the other variables studied. This finding is largely consistent with the results of the studies by Kuragano and Kato, but since other factors were also examined in those two studies, a complete comparison between the above articles cannot be made[18, 19].

In their study, van der Putten et al., stated that increased hepcidin levels were associated with iron load markers, such that hepcidin reflects iron load and response to erythropoietin resistance, but has no significant relationship with the levels of

elements such as ferritin, reticulocyte count, and serum albumin[20].

Ghahramanfard et al., showed in their study that in the presence of anemia in hemodialysis patients, hepcidin levels are significantly reduced. They also showed that there was no significant relationship between TIBC, iron, ferritin, CRP, and ESR levels and hepcidin levels, and that hepcidin assessment is not appropriate for the management of anemia in hemodialysis patients[21]. The results of the above two studies are completely consistent with the findings of our study and show that the use of hepcidin marker is useful for assessing iron and ferritin status in hemodialysis patients[20, 21].

Hepcidin has emerged as a multifunctional hormone that essentially coordinates iron metabolism and mediates its response to stresses such as dietary iron deficiency, infection, hemorrhage, and pregnancy. Dysregulation of hepcidin has been implicated in many iron disorders, including anemia of inflammation, hereditary hemochromatosis, and iron overload in anemias of ineffective erythropoiesis, stimulating the development of many diagnostic and therapeutic applications[22].

Poles et al., stated that hepcidin can be very effective in regulating body iron levels, especially in patients with chronic diseases such as CKD and those undergoing hemodialysis, and can play a decisive role, but this effect varies depending on the patient's conditions such as gender, duration of kidney disease and dialysis, as well as underlying diseases[23].

Cardiovascular disease, dysregulation of some vital body factors such as iron, changes in circulating volume, electrolyte disorders, and severe inflammation in some organs such as the liver and spleen exacerbate morbidity and mortality in hemodialysis patients. The use of some regulatory factors such as hepcidin can largely regulate circulating iron levels and reduce these complications[24].

Rosansky et al., demonstrated that failure to accurately monitor vital signs such as heart rate, blood pressure, iron levels, and serum albumin levels in hemodialysis patients can result in significant complications. Hepcidin has been shown to be useful in determining the severity and progression of renal failure, with hepcidin levels being significantly correlated with ferritin levels less than 10 mg/dl[25].

In the study by Cooper et al., it was also shown that starting dialysis regardless of factors such as electrolyte levels, serum iron, and cardiovascular status of patients will be associated with severe complications[26]. These findings are completely consistent with the results of the present study and, while demonstrating the importance of hepcidin, show the lack of relationship between iron elements and hepcidin[25, 26].

Our understanding of the control of iron metabolism has increased dramatically over the past 5 years due to the discovery of hepcidin[27]. Agents that reduce hepcidin or inhibit its function may be effective strategies to restore normal iron homeostasis and overcome the anemia of CKD[28].

Conclusions: Finally, the results of the present study showed that there is a significant relationship between hepcidin levels and the duration of dialysis and the number of dialysis sessions per week, and it is necessary to control all patient conditions such as iron and ferritin levels before starting hemodialysis and specifically adjust the dialysis program for these patients. Also, physicians should prioritize inflammation control to optimize iron therapy in dialysis patients. To generalize this finding to the entire population, further studies with larger sample sizes and, if possible, multicenter studies are needed.

Limitations: The most important limitations of the present study include the relatively small number of patients and the single-center nature of the study. Due to the death of a number of patients, the instability of clinical symptoms in some of them, which made it impossible to continue the study, and the withdrawal of a number of others, the present study ended with a limited number of patients. Small sample size may limit the generalizability of our findings. It is hoped that these problems will be resolved in future studies.

Ethical Considerations

This study has an ethics code number (IR.SHMU.REC.1403.158) from the research deputy of Shahroud University of Medical Sciences. Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest

The authors declared that they have no conflict of interest.

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