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SHORT COMMUNICATION article

Evaluation of hepcidin levels in end-stage renal disease patients undergoing regular hemodialysis

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Abstract: Hepcidin, a key regulator of iron homeostasis, plays a pivotal role in the pathogenesis of anemia in patients with end-stage renal disease (ESRD). ESRD patients on regular hemodialysis often experience disturbances in iron metabolism, contributing to treatment-resistant anemia. This study aims to evaluate serum hepcidin levels in ESRD patients undergoing regular hemodialysis and explore its clinical implications. To estimate and analyze serum hepcidin levels in ESRD patients on regular hemodialysis and to correlate these levels with anemia severity, iron parameters, and markers of inflammation. This cross-sectional study included hundred ESRD patients undergoing regular hemodialysis at Abass Ibrahim Dialysis Center, Kosty, Sudan. Serum hepcidin levels with relevant hematological parameters, including hemoglobin, serum ferritin, transferrin saturation, and C-reactive protein (CRP), were measured. Statistical analyses were performed to assess correlations between hepcidin levels and clinical variables. The study revealed significantly elevated serum hepcidin levels in ESRD patients compared to healthy controls (19.4±6.2, and 9.8±6.5, respectively). Hepcidin levels showed a positive correlation with serum ferritin (362.7±21.5, $p<0.05$) and CRP (16.8±19.9, $p<0.05$) while demonstrating a negative correlation with hemoglobin (8.7±1.8, $p<0.05$). These findings highlight the interplay between iron dysregulation, inflammation, and anemia in ESRD patients. Elevated hepcidin levels in ESRD patients undergoing regular hemodialysis are associated with anemia severity and inflammatory status. Targeting hepcidin dysregulation may offer novel therapeutic opportunities to manage anemia in this patient population.

Introduction

End-stage renal disease (ESRD) is a significant global health concern, characterized by irreversible loss of kidney function requiring renal replacement therapy, such as hemodialysis, to sustain life. Anemia is a common complication in ESRD patients, affecting nearly 90.0% of individuals on dialysis and substantially contributing to morbidity and reduced quality of life [1-3]. The pathogenesis of anemia in ESRD is multifactorial, involving inadequate erythropoietin production, iron deficiency, and chronic inflammation [4]. Hepcidin, a liver-derived peptide hormone, has emerged as a central regulator of iron metabolism. It controls systemic iron homeostasis by binding to ferroportin, an iron-exporting protein, leading to its internalization and degradation. Elevated hepcidin

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levels inhibit intestinal iron absorption and iron release from macrophages, resulting in functional iron deficiency despite adequate iron stores [5]. In ESRD patients, hepcidin levels are frequently elevated due to impaired renal clearance and chronic inflammation, further exacerbating anemia by limiting iron availability for erythropoiesis [6]. The role of hepcidin in ESRD-associated anemia has garnered increasing attention, as it represents a potential therapeutic target for improving anemia management. While recombinant erythropoiesis-stimulating agents (ESAs) and iron supplementation are cornerstone therapies, their efficacy is often limited in the presence of hepcidin-mediated iron dysregulation [7]. Understanding the relationship between hemodialysis, hepcidin levels, and anemia-related parameters is crucial for optimizing treatment strategies. This study aims to evaluate serum hepcidin levels in ESRD patients undergoing regular hemodialysis, analyze their association with anemia severity, and assess their correlation with iron metabolism markers and inflammation. Insights gained from this research could enhance our understanding of hepcidin's role in ESRD and guide the development of novel interventions to improve anemia management.

Materials and methods

Study design and setting: This cross-sectional study was conducted at Abass Ibrahim Center for Dialysis a tertiary care center, between March and July 2023. The study was approved by the Institutional Ethics Committee of the Applied Research, Eimam Elmahdi University, White Nile, Sudan. Verbal consent was also obtained from all the participants before enrollment.

Study population: This study included ESRD patients aged ≥20 year who were undergoing regular hemodialysis for at least 3 months. Patients with active infections, recent blood transfusions <1 month, or malignancies were excluded to minimize confounding factors. Healthy age- and sex-matched individuals were recruited as controls.

Sample size calculation: The sample size was calculated based on previous studies [6], with a confidence level of 95.0% and power of 80.0%. A total of 50 patients and 50 healthy controls were included.

Clinical and laboratory assessments: Demographic and clinical data, including age, gender, duration of dialysis, and medication history, were recorded. Blood samples were collected before the dialysis session after an overnight fast for laboratory investigation. All kits and reagents were supplied by Test Medical Co. Ltd, Sudan.

Hepcidin measurement: The levels of serum hepcidin were measured using a quantitative enzyme-linked immunosorbent assay (ELISA) kit (E01H0051) from Blue Gene Biotech Company, UK. The assay sensitivity was high and minimum inter-assay variability.

Iron parameters: Serum ferritin, transferrin saturation (TSAT), and total iron-binding capacity (TIBC) were measured using standard automated laboratory methods and kits supplied by Raheeg Medical Company, Sudan.

Inflammatory markers: The levels of C-reactive protein (CRP) were analyzed using a high-sensitivity immune-turbidimetric assay.

Anemia parameters: The levels of hemoglobin and mean corpuscular volume (MCV) were determined using an automated hematology analyzer.

Statistical analysis: Statistical analyses were performed using SPSS version 16. Continuous variables were expressed as mean±standard deviation (SD) based on data distribution. Comparisons between ESRD patients and controls were conducted using the independent t-test. Correlations between hepcidin levels and clinical/laboratory parameters were analyzed using Pearson’s correlation coefficient. A $p<0.05$ was considered significant.

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Results

Table 1 shows the characteristics data of the participants in this study. There is no statistically significant difference between male and female subjects (n=27, each subject) and with control subjects (n=23, each subject). Furthermore, there is no statistically significant difference between the mean age of the control group and the patient group. However, the body mass index (BMI) of the patients is higher than that of the control group, but statistically not significant.

Table 1: Characteristics data of subjects included in the study

	Patients (50)	Controls (50)
Males	27	23
females	27	23
Age (mean±SD)	38.6±17.6	40.8±20.4
BMI	16.8±15.5	22.6±12.8
Duration of dialysis	5.6±7.4	------

SD: Standard deviation, BMI: Body mass index

Table 2 shows the iron profiles, inflammatory markers, and hepcidin among the participants. Thus, a significant change in all the parameters investigated among the subjects between the patient and control groups. A decrease in the levels of hemoglobin, serum iron, TSAT%, TIBC, and Hct% but with an increase in the levels of serum ferritin, CRP, and hepcidin. The findings revealed significantly elevated serum hepcidin levels in ESRD patients compared to healthy controls (19.4±6.2, and 09.8±6.5, respectively). Hepcidin levels showed a positive correlation with serum ferritin (362.7±21.5, $p<0.05$) and CRP (16.8±19.9, $p<0.05$) while indicating a negative correlation with hemoglobin (8.7±1.8, $p<0.05$).

Table 2: Iron profiles, inflammatory markers, and hepcidin among study groups

Parameters	**Patients**	**Controls**	**P value**
Hemoglobin	08.7±1.8	13.37±2.4	< 0.05
Serum iron	31.6±9.6	75.38±11.7	
Serum ferritin (ng/ml)	362.7±21.5	97.3±11.6	
TSAT%	14.8±5.8	27.8±7.6	
TIBC	217.5±27.9	348.4±27.1	
Hct%	31.6±7.3	42.6±7.2	
CRP (mg/m/l)	16.8±19.9	03.4±4.7	
Hepcidin (ng/ml)	19.4±6.2	09.8±6.5	

Hb: hemoglobin, TIBC: Total iron binding capacity. TSAT: Transferrin Saturation, CRP: C – reactive protein

Discussion

This study evaluated the serum hepcidin levels in ESRD patients undergoing regular hemodialysis and explored their correlation with anemia, iron parameters, and inflammation. The findings revealed significantly elevated hepcidin levels in ESRD patients compared to healthy controls, consistent with the hypothesis that hepcidin dysregulation contributes to anemia in this population. The observed increase in hepcidin levels aligns with previous studies [6], which reported elevated hepcidin in ESRD patients due to reduced renal clearance and chronic inflammation. Similarly, a strong correlation between hepcidin levels and serum ferritin, suggesting that iron storage regulates hepcidin expression has been reported [8]. The current study corroborates these findings by showing a positive correlation between hepcidin and ferritin, as well as between hepcidin and inflammatory

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markers like CRP. However, not all the studies fully agree with the present findings. For instance, Malyszko et al. [9] found that hepcidin levels in ESRD patients varied widely, and some individuals exhibited normal levels despite chronic kidney disease (CKD). This discrepancy may stem from differences in study populations, dialysis protocols, or methods of hepcidin measurement. Unlike Malyszko's findings [9], the present study used a standardized ELISA method, which may provide more reliable and comparable results. The negative correlation between hepcidin and hemoglobin observed in this study further supports its role in anemia. Elevated hepcidin levels reduce iron availability for erythropoiesis by inhibiting iron release from macrophages and intestinal absorption [5]. This mechanism explains the persistence of functional iron deficiency and ESA resistance in ESRD patients, as previously highlighted [10]. Thus, the current findings suggest that targeting hepcidin might improve anemia management in hemodialysis patients.

Despite agreement with several studies, some controversies remain regarding the utility of hepcidin as a biomarker or therapeutic target. For instance, Kato and others argued that hepcidin measurement might be less reliable in acute inflammatory states, where fluctuations can occur [11]. In addition, interventions targeting hepcidin, such as hepcidin antagonists, remain experimental and have yet to show consistent benefits in clinical trials. This study has some limitations, including its cross-sectional design, which prevents establishing causality. The relatively small sample size may limit the generalizability of the findings. Additionally, other factors influencing hepcidin levels, such as genetic polymorphisms, were not investigated. However, more studies should focus on longitudinal analyses to assess the dynamic changes in hepcidin during different stages of anemia treatment. Clinical trials exploring hepcidin-targeted therapies, such as hepcidin inhibitors or ferroportin agonists, could offer new insights into optimizing anemia management in ESRD patients.

Conclusion: The findings reinforce the role of hepcidin as a central regulator of iron metabolism in ESRD patients undergoing regular hemodialysis. Elevated hepcidin levels are associated with anemia severity, iron dysregulation, and inflammation, highlighting its potential as a biomarker and a therapeutic target.

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