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The Relationship between Serum Hepcidin Level and Serum Iron Parameters in Chronic Hepatitis C Virus Hemodialysis Patients

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Abstract

Background: Anemia is a major clinical problem in patients on dialysis and has substantial impact on morbidity and mortality. Anemia in these patients is a multifactorial one on of these factors is iron hemostasis and one of its regulator is hepcidin.

Aim of Study: The aim of this work is to evaluate hepcidin levels, identify the relation of hepcidin with various iron parameters and to assess the correlation of hepcidin with hepatitis C virus sero-positivity in a population of prevalent hemodialysis patients in Egypt.

Patients and Methods: This study included 40 patients, who have end stage renal disease (ESRD), on regular hemodialysis divided into two groups Group 1 (HCV–ve) and Group II (HCV+ve). Patients selected from Tanta University Hospitals, Internal Medicine Department, Nephrology and Hemodialysis Unit and 20 control healthy individuals age and sex cross matched. All were subjected to history taking, physical and clinical examination, routine laboratory investigation and hepcidin level using ELISA Kit.

Results: The study showed significant higher hemoglobin level in (HCV+ve) group than (HCV–ve) group. Also (HCV+ve) group showed significant higher level in iron, TFS and ferritin in comparison with (HCV–ve) group. The study showed significant higher level of hepcidin and CRP in (HCV–ve) group in comparison with (HCV+ve) group and between dialysis groups with control one. There was positive significant correlation between hepcidin and CRP, ferritin and also there was negative significant correlation between hepcidin and hemoglobin.

Conclusion: The Level of serum hepcidin is associated with values of hemoglobin and hematocrit, which led to lowering of the necessary erythropoietin dose and iron therapy specifically in patients with anemia of end stage renal disease.

Key Words: *End stage renal disease (ESRD) – Hepatitis c virus (HCV) – Hemoglobin (Hb) – C-reactive protein (CRP).*

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Introduction

ANEMIA is a common problem in patients with end stage renal disease (ESRD) and this type is multifactorial: Inadequate production of endogenous erythropoietin (EPO) for the degree of anemia, iron deficiency, blood loss, shortening of life span of erythrocytes, presence of inhibitors of erythropoiesis in plasma and vitamin deficiency **[1]**.

This peptide hormone (Hepcidin) is the homeostatic regulator of intestinal iron absorption, iron recycling by macrophages and iron mobilization from hepatic stores. Hepcidin acts by inhibiting the efflux of iron through ferroportin (FPN), the sole known iron exporter of enterocytes, macrophages and hepatocytes. As befits an iron-regulatory hormone, hepcidin synthesis is increased by iron loading and decreased by anemia and hypoxia. Hepcidin is markedly induced during infections and inflammation, causing iron to be sequestered in macrophages, hepatocytes and enterocytes. The resulting decrease in plasma iron levels eventually contributes to the anemia associated with infection and inflammation. These alterations in iron metabolism probably have a role in host defense by limiting the availability of iron to invading microorganisms **[2]**.

At the opposite extreme, early studies indicate that hepcidin deficiency due to the dysregulation of its synthesis or mutations in the hepcidin gene itself is the immediate cause of most forms of hemochromatosis **[3]**.

Hepatitis C virus (HCV) infection is the most common cause of chronic liver disease in the world and also common among chronic hemodialysis (HD) patients. HCV positive HD patients have been found to have low levels of serum hepcidin

which might account for iron accumulation together with lower iron and erythropoietin (EPO) requirements in those patients [4].

The mechanisms responsible for disturbed iron homoeostasis in hemochromatosis (HH) are poorly understood. However, results of some studies indicate a link between serum hepcidin, and intestinal iron absorption, suggesting that this molecule could play a part in hepatic iron overload toxicity [5].

Patients and Methods

The study was carried out on:

40 patient on regular hemodialysis at hemodialysis Unit at Tanta University Hospital. And 20 subjects act as control group. This study was carried out from June 2017 to December 2017.

An informed consents was taken from all participants and the privacy of the data will be greatly considered.

Study design:

It is cross sectional study.

Inclusion criteria:

Patient on hemodialysis >6 months, 3 time per week 4 hours per session each session with bicarbonate dialysate, low flux with heparin as anticoagulant.

Exclusion criteria:

Patients on peritoneal dialysis, patient on hemodialysis not fit with times or duration of sessions, Patients with other causes of hepatitis as (HBV, alcoholic, autoimmune, Patients with Child Pugh C chronic liver disease, Patients with non-renal anemia as (GIT bleeding, anti-coagulant, autoimmune, hemolytic), Patients with active infection or inflammatory disease, Patients with acute cardiovascular co-morbid conditions, Patients who received blood transfusion within the former 4 months and Patients with malignancy or on immunosuppressive therapy.

All patients included in the study were subjected to:

• Full history and detailed clinical examinations: Stressing on clinical signs of either anemia or infection.

• Investigations including:

Laboratory investigation:

- Complete blood picture.
- Liver function tests and hepatitis markers: (Serum Alanine transaminase-serum Aspartate transaminase-serum albumin-prothrombin time-hepatitis C virus antibodies-hepatitis B surface antigen).
- Renal bio-chemical tests: (Serum creatinine - blood urea nitrogen-Creatinine clearance-serum sodium-serum Potassium-serum phosphorus-serum calcium).
- High-sensitive serum C-reactive protein.
- Iron Parameters: (Serum iron-serum ferritin-total iron binding capacity-transferrin saturation)
- Serum hepcidin level (using ELISA technique).

Radiological investigation:

- Abdominal ultrasound examination.

Statistical analysis of the data:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

A one-way analysis of variance (ANOVA) when comparing between more than two means for parametric variants and (Mann-Whitney U) for non-parametric variants.

Post Hoc test: Least Significant Difference (LSD) was used for multiple comparisons between different variables.

Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.

Spearman's rank correlation coefficient (*rs*) was used to assess the degree of association between two sets of variables if one or both of them was skewed.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p*-value was considered significant as the following:

• Probability (*p*-value):

- *p*-value <0.05 was considered significant.
- *p*-value <0.001 was considered as highly significant.
- *p*-value >0.05 was considered insignificant.

Results

This is a cross-sectional study conducted on 40 on regular hemodialysis who were divided to two groups group I (HCV–ve) and group II

(HCV+ve) and 20 healthy subjects act as control group.

Group I which were 20 patients with ESRD on regular hemodialysis, negative for hepatitis C virus markers. Their mean age 40.05 ±7.26 years, (13 males and 7 females).

Group II which were 20 patients with ESRD on regular hemodialysis, positive for hepatitis C virus markers. Their mean age of 39.98 ±7.26 years, (6 males and 14 females).

Group III which were 20 healthy subjects cross matched age as patients groups. Their mean age of 39.89±7.14 years (14 males and 6 females).

The study showed a significant difference in hepcidin and CRP levels between dialysis groups and control group as the hepcidin and CRP levels tends to be significantly higher in the dialysis groups. Between the dialysis groups hepcidin tend to be significantly higher in group I (HCV-ve) while there insignificant difference as regard CRP. As shown in (Table 1).

Also in our study, we found that there is a significant difference in hemoglobin level between dialysis groups and control group as the hemoglobin level tends to be significantly higher in the control groups. Between the dialysis groups hemoglobin tend to be significantly higher in group II (HCV +ve). As shown in (Table 2).

The results showed a significant difference in ferritin, iron, TFS and TIBC levels between dialysis groups and control group as these levels tends to be significantly higher in the control group except TIBC tend to be significantly higher in dialysis groups. Between the dialysis groups ferritin, iron and TFS tend to be significantly higher in group II (HCV+ve) but TIBC tend to be significantly higher in group I (HCVve). As shown in (Table 3).

The study showed a significant difference in BUN and serum creatinine levels between dialysis groups and control group as these levels tends to be significantly higher in the dialysis groups. Between the dialysis groups there is insignificant difference according BUN and serum creatinine. Also, we found that there is a significant difference in corrected calcium and serum phosphorous levels between dialysis groups and control group as corrected calcium level tends to be significantly higher in the control group while serum phosphorous tend to be higher in dialysis groups. Between the dialysis groups there is insignificant difference according corrected calcium and serum phosphorous. As shown in (Table 4).

The results showed a significant difference in ALT and AST levels between group II (HCV +ve) in one hand and group I (HCV–ve) and control group in the other hand. However, there is insignificant difference between group II (HCV +ve) and control group. There was no significant difference among all studied groups regarding serum albumin and PT. As shown in (Table 5).

Correlation between the level of hemoglobin, CRP and ferritin with hepcidin levels in dialysis groups showed significantly positive correlation between CRP and ferritin with hepcidin as CRP and ferritin levels increased with the increased of hepcidin while it showed significantly negative correlation between hemoglobin and hepcidin as hemoglobin level increased with the decrease of hepcidin. As shown in (Table 6).

Table (1): Comparison between all the studied groups as regard acute phase reactants.

	Group I (N=20)	Group II (N=20)	Group III (N=20)	*p*-value	p_1	p_2	p_3
Serum Hepcidin (ng/mL) [Mean, Standard Deviation]	1772.8±510.33	1402.8±318.58	433.55±81.90	<0.001	0.026	<0.001	<0.001
Hs Serum CRP (µg/mL) [Mean, Standard Deviation]	8.5±2.69	7.6±1.65	1.5±0.37	<0.001	0.737	<0.001	<0.001

Table (2): Comparison between all the studied groups as regard hemoglobin level.

	Group I (N=20)	Group II (N=20)	Group III (N=20)	*p*-value	p_1	p_2	p_3
Hb (gm/dL) [Mean, Standard Deviation]	8.42±1.73	9.80±0.90	12.59±0.73	<0.001	0.028	<0.001	<0.001

Table (3): Comparison between all the studied groups as regard Bio-chemical renal parameters.

	Group I (N=20)	Group II (N=20)	Group III (N=20)	*p*-value	p_1	p_2	p_3
Creatinine (mg/dL) [Mean, Standard Deviation]	9.90±0.72	10.19±0.63	0.59±0.13	<0.001	0.431	<0.001	<0.001
Urea (mg/dL) [Mean, Standard Deviation]	188.16±29.68	179.46±28.1	24.90±4.6	<0.001	0.375	<0.001	<0.001
Phosphorus (mg/dL) [Mean, Standard Deviation]	5.89±0.88	6.08±0.83	3.82±0.62	<0.019	0.117	0.048	0.022
Corrected Calcium (mg/dL) [Mean, Standard Deviation]	6.64±0.47	6.06±0.24	9.21±0.53	<0.001	0.396	<0.001	<0.001

Table (4): Comparison between all the studied groups as regard Bio-chemical renal parameters.

	Group I (N=20)	Group II (N=20)	Group III (N=20)	*p*-value	p_1	p_2	p_3
Creatinine (mg/dL) [Mean, Standard Deviation]	9.90±0.72	10.19±0.63	0.59±0.13	<0.001	0.431	<0.001	<0.001
Urea (mg/dL) [Mean, Standard Deviation]	188.16±29.68	179.46±28.1	24.90±4.6	<0.001	0.375	<0.001	<0.001
Phosphorus (mg/dL) [Mean, Standard Deviation]	5.89±0.88	6.08±0.83	3.82±0.62	<0.019	0.117	0.048	0.022
Corrected Calcium (mg/dL) [Mean, Standard Deviation]	6.64±0.47	6.06±0.24	9.21±0.53	<0.001	0.396	<0.001	<0.001

Table (5): Comparison among all the studied groups as regard liver parameters.

	Group I (N=20)	Group II (N=20)	Group III (N=20)	*p*-value	p_1	p_2	p_3
ALT(IU/L) [mean, Standard Deviation]	24±13.55	44±20.42	19±3.82	0.003	0.008	0.641	0.031
AST (IU/L) [mean, Standard Deviation]	37±17.72	53±25.28	28±4.32	<0.001	0.031	0.678	0.035
PT (seconds) [Mean, Standard Deviation]	11.96±1.89	11.86±1.31	11.97±2.99	0.756	–	–	–
Albumin (gm/dL) [Mean, Standard Deviation]	4.12±0.42	3.95±0.30	4.02±0.27	0.059	–	–	–

Table (6): Correlations between serum Hepcidin and all studied parameters in dialysis groups.

Parameters	Hepcidin	
	r-value	*p*-value
(Hs) CRP (µg/mL)	0.528	0.023 *
Hb (gm/dL)	–0.538	0.035*
Iron parameters:		
Ferritin (ng/mL)	0.465	0.017*
TIBC (µg/dL)	0.247	0.311
TFS %	–0.120	0.617
S.Iron (ug/dl)	–0.177	0.395
Liver profile:		
ALT (IU/L)	–0.221	0.320
AST (IU/L)	–0.147	0.414
Albumin (gm/dL)	0.433	0.117
PT (seconds)	–0.388	0.149
Bio-chemical renal parameters:		
Creatinine (mg/dL)	0.416	0.128
BUN (mg/dL)	0.437	0.113

Discussion

Renal anemia is a major complication in patients with end stage renal disease (ESRD), and it is a complex pathophysiological disorder which causes a significant increase in morbidity and mortality, cost of care, and decrease in quality of life **[6]**.

In the current study, there was no statistically significant difference in age (*p*-value 0.832) and sex (*p*-value 0.084) distribution in the three groups of our study.

In the current study, serum ALT, was statistically significantly higher in HCV+ve group than both HCVve (*p*-value 0.003) and control groups (*p*-value 0.031) and serum AST was statistically significantly higher in HCV+ve group than both

HCVve (p-value 0.031) and control groups (p-value 0.035).

Our results in agreement with results of Lemos et al., [7] who found that HCV-infected patients had significantly higher ALT levels compared with the non-infected patients; they also suggested that the serum ALT level in pre dialysis patients may be a good marker of HCV infection.

In contrast with our results, Fabrizi et al., [8] showed that patients on dialysis in general tend to have lower ALT levels Cotler et al., [9] also found that the serum ALT levels were significantly lower in patients with ESRD and this might be attributed to liver cell protection by hepatocyte growth factor, which showed higher concentration in patients with ESRD on HD.

The lower ALT activity in hemodialysis patients might also be a consequence of a smaller serum HCV viral load either due to the adsorption of the virus genome in the dialyzer membrane or due to the induction of endogenous interferon caused by hemodialysis [10].

In our study, serum creatinine was significantly higher in dialysis groups than control group (p-value <0.001) and no significant difference between dialysis patients (p-value 0.431). Serum BUN was significantly higher in dialysis groups than control group (p-value <0.001) and no significant difference between dialysis patients (p-value 0.375).

Serum corrected calcium was significantly lower in dialysis groups than control group (p-value <0.001) and no significant difference between dialysis patients (p-value 0.396). Serum phosphorous was significantly higher in dialysis groups than control group (p_2-value 0.048) (p_3-value 0.022) and no significant difference between dialysis patients (p-value 0.117).

In the current study, hemoglobin was significantly higher in HCV+ve group than HCV–ve group (p-value 0.028) and significantly higher in control group than HCV+ve group (p-value <0.001) and HCV–ve group (p-value <0.001).

Our findings were in agreement with those of Sahin et al., [11], who concluded that 49 patients had higher hemoglobin levels in HCV infected patients compared with HCV non infected patients, and this attributed to increased production of erythropoietin from HCV-infected patient's hepatocyte. [12] and Saifan et al., [13] reported that higher Hb levels in HCV +ve HD compared to HCV –ve patients.

Hemoglobin in HCV+ve patients was higher and needed lower erythropoietin and iron doses than HCV–ve patients. This data supported by Khurana et al., [14] and Kranthi et al., [15].

In contrast to our study, Abdalla et al., [16] and Sabry et al., [17] reported a higher erythropoietin requirement in HCV-infected versus HCV non infected patients, which was a result of altered iron metabolism induced by chronic infection; however, the mechanism by which infection and inflammatory disease impaired erythropoiesis was still poorly understood.

In the current study, serum ferritin is significantly higher in HCV+ve group than HCV–ve group (p_1-value <0.001) and control group (p-value <0.001). Also, significantly higher in HCV-ve group than control group (p_2-value 0.017). Serum iron is significantly higher in HCV+ve group than HCV–ve group (p_1-value 0.034). Also, dialysis groups is significantly lower than control group (p_2-value <0.001) (p_3-value 0.041).

TIBC is significantly higher in HCVve group than HCV+ve group (p_1-value 0.048) and control group (p_2-value <0.001). Also, HCV+ve group significantly higher than control group (p_3-value <0.001). TFS is significantly higher in HCV+ve group than HCV–ve group (p_1-value 0.014). But control group is significantly higher than dialysis groups (p_2-value <0.001) (p_3-value 0.021).

In agree with our study, Shan Yet et al., [18] reported that patients with chronic hepatitis C infection tended to have a higher ferritin level when compared with non-HCV-infected patients. This can be explained by ferritin is an acute phase reactant that is released by the liver with inflammation. Also Naoki et al., [19] and Schmid et al., [20]. Also Xu Y [21] found that elevated serum levels of ferritin in the HD group could be attributed to serum ferritin being a potent acute phase reactant and usually is associated with elevation of CRP levels and inflammation.

In contrast to our study, Nemeth et al., [22] and Nabila et al., [23] reported that serum ferritin levels in the HCV-positive group were statistically significantly lower than those in the HCV negative group.

In the current study, serum hepcidin was statistically significantly higher in HCV–ve group than HCV+ve group (p_1-value 0.026) and control group (p_2-value <0.001). Also, HCV+ve group significantly higher than control group (p_3-value <0.001).

Our results in agreement with Ganz et al., [24], Rubab et al., [25] and (Mohamed et al., 2014) [26] who reported that hepcidin level in dialysis patients is higher than healthy subjects and there is a possibility that the HD procedure itself may increase hepcidin production in the liver. Also Ganz et al., [27] demonstrated that loss of kidney function could decrease hepcidin clearance and lead to the accumulation of hepcidin.

Our present data disagrees with the results of Pelusi et al., [28] who suggested that anaemia and hypoxia override the effect of iron and inflammation and decrease hepcidin m-RNA expression in the liver.

On the other hand, we found that hepcidin was significantly higher in the HCV negative group compared to the HCV positive one. The scientific explanation could be that hepcidin is exclusively synthesized in the liver.

Similarly, in the study of Caliskan et al., [4] hepcidin levels of HCV positive patients were significantly lower than HCV negative. Also the study the study of Toima et al., [29] which was conducted on 70 patients showed reduced expression in diseased groups compared to non-diseased.

Lower hepcidin in dialysis patients with hepatitis C may be due to impaired induction of hepcidin by IL-6 in chronic hepatitis C and the down regulation of hepcidin expression by erythropoietin via inhibiting hepcidin transcription in liver cells Girelli D et al., [30]. Our results disagree with Fujita et al., [31].

In the current study, Serum CRP was significantly higher in HCV-ve group than control group (p_2-value <0.001) and insignificantly higher than HCV +ve group (p_1-value 0.737). Also, HCV+ve group significantly higher than control group (p_3-value <0.001). This agree with Fujita et al., [31], who reported that CRP is an acute phase reactant that is elevated during infections and inflammation.

In our study there is significant positive correlation between serum hepcidin and CRP (*r*-value 0.528) (*p*-value 0.023). Which agree with Ibrahim et al., [32] and Mercadel et al., [1] and in contrast to our results, Rasheed et al., [33] and Kato et al., [34].

In the current study, serum hepcidin shows significant negative correlation with hemoglobin (*r*-value –0.538) (*p*-value 0.035). Our results agree with Mercadel et al., [1], and Ibrahim et al., [32] and disagree with Silva et al., [35].

In the current study, serum hepcidin shows significant positive correlation with serum ferritin (*r*-value 0.465) (*p*-value 0.017). Our results agree with Jelic´ et al., [36], Mercadel et al., [1] and Ibrahim et al., [32] and disagree with Mahmoud T [37] and Damien et al., [38]. The difference could be explained by the fact that ferritin levels of patients in the former study were very high.

We are aware that our study had some limitations, as it was a single-center study on a small sample of patients; therefore, it may be underpowered for evaluating the role of the different biomarkers in predicting iron status.

Conclusion:

- Dialysis is associated with elevation of Serum hepcidin level due to decline of its clearance or inflammatory status itself related to dialysis.
- Hepatitis C patients tend to have low level of serum hepcidin suggested by decline of its synthesis by diseased liver.
- The Level of serum hepcidin is associated with values of hemoglobin and hematocrit, which led to lowering of the necessary erythropoietin dose and iron therapy specifically in patients with anemia of end stage renal disease.

Recommendations:

1- Further studies to investigate the benefits of using serum hepcidin levels in evaluation of anemia in patients with ESRD on HD since serum hepcidin provides useful information about the level and availability of iron.

2- Further studies to investigate the relation between serum hepcidin level and the response to ESA as hepcidin is higher in non-responders to EPO than the responders and can be used as an important marker to assess the response to ESA.

3- Further studies to evaluate the role of Hepcidin antagonists such as vitamin C, erythropoietin and mono-clonal antibodies and their benefits in treatment of hypo-responsiveness to ESA therapy in ESRD patients and IRIDA.

4- Further studies to investigate hemojuvelin which is suspected to have a role in hepcidin control which offer alternative mechanisms to management of ESA hypo responsiveness. Hepcidin antagonist may reverse the iron restricted erythropoiesis contributing to anemia. In anemic patients with chronic kidney disease where erythropoietin synthesis is disturbed, hepcidin antagonist might be useful as a supplement to ESA therapy, particularly for patients with a low response to them.

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العلاقة بين مستوى مصل الهيبسيدين ومصل دلائل الحديد لدى مرضى الإستصفاء الدموى المصابين بالإلتهاب الكبدى الفيروسى المزمن (سى)

أجريت هذه الدراسة على ٦٠ شخصاً وقد تم تقسيمهم إلى ثلاث مجموعات بحثية هى كالآتى:

المجموعة الأولى: تشمل ٢٠ مريضاً معتمدين على الاستصفاء الدموى ومصابين بالالتهاب الكبدى الفيروسى سى.

المجموعة الثانية: تشمل ٢٠ مريضاً معتمدين على الاستصفاء الدموى وغير مصابين بالالتهاب الكبدى الفيروسى سى.

المجموعة الثالثة: تشمل من الأشخاص الأصحاء ظاهرياً كمجموعة ضابطة.

من تقييم نتائج هذه الرسالة ومقارنتها بنتائج الباحثين الآخرين فى نفس المجال فإننا نوصى بدراسة إمكانية استخدام نسبة الهيبسيدين لتقييم حالة فقر الدم لدى مرضى الاستصفاء الدموى ومدى تأثيره على استجابة نخاع العظم لهرمون الاريثروبيوتين.