

## Hepcidin Level and Iron Status in End Stage Renal Disease (ESRD) Patients

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**Abstract:** Hepcidin regulates the levels of iron in the body by preventing the body from absorbing more iron than is needed from food or supplements, and blocks the export of iron from cells. The aim of this work to assess the hepcidin level and its relation to, inflammatory status, hemoglobin level, and iron status in patients with ESRD. Seventy eight persons were included in this study. They were matched for age, sex & were divided into: 58 patients with ESRD maintained on regular hemodialysis (HDx), 4 hrs. three times weekly, 20 healthy subjects as a control group. All subjects of the study were subjected to the full history taking, including history of iron and EPO intake, complete clinical examination and laboratory investigation. Patients on regular hemodialysis Receiving intravenous iron have no significant difference in hepcidin level than those in control group. There was an inverse correlation between serum hepcidin and, Hb, AST, and S. iron. Also, there was a positive correlation between hepcidin and S.Cr., urea, calcium, phosphorous, PTH, TIBC, and serum ferritin. We concluded that the difference between level of hepcidin in the studied anemic sample has no significant difference when compared to the normal controls.

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**Key words:** Hepcidin; Level; Iron Status; End Stage Renal Disease (ESRD); Patients

### 1. Introduction

Chronic kidney disease (CKD) is a progressive disease with gradual loss of kidney functions, which leads to many complications such as disturbed electrolytes and acid base balance, hypertension, cardiovascular system affection, gastrointestinal tract affection, renal osteodystrophy, neurological manifestations, hematological affection and endocrine dysfunction (**Biff et al., 2006**).

Uremic patients usually progress and require renal replacement therapy either in the form of dialysis (hemodialysis or peritoneal dialysis) or kidney transplantation.

Hepcidin is a peptide produced by hepatocytes in response to anemia, hypoxia, or inflammation. It acts as an indicator of functional iron deficiency in those patients (**Malyszko et al., 2006**). Hepcidin regulates level of iron in the body by preventing the body from absorbing more iron than need from food or supplements, and blocks the export of iron from cells (**Jolanta, 2007**).

To properly respond to anemia treatment, the body must somehow reduce hepcidin in order to increase the iron that is needed for red blood cell production. The mechanisms of hepcidin regulation itself (**Kemna et al., 2005**).

Patients with end stage renal disease (ESRD) are in a continuous inflammatory process due to several factors. Anemia is a feature of renal failure mainly

due to insufficient production of the hormone - erythropoietin (EPO) which stimulates the bone marrow to produce mature red blood cells (**Irina et al., 2007**). However, an increased production of red blood cells also requires the absorption of adequate amounts of dietary iron. It is a common clinical observation that many renal failure patients receiving EPO require intravenous iron supplementation, despite the fact that they have adequate dietary iron. This strongly suggests an abnormality of iron absorption by the intestine (**Finberg et al., 2008**).

### 2. Patients and Methods

Seventy eight persons included in this study, matched for age, sex & divided into the following groups:

- Group I: includes 58 patients with ESRD maintained on regular hemodialysis (HDx) 4 hrs. three times weekly, at Al Hussein University dialysis unit. They were 39 males & 19 females, their age ranged between 23 & 65 yrs. This group was divided into two subgroups group IA including patients with hemoglobin reached the target level (11 gm/dl), & group IB including patients with hemoglobin lower than the target level.

- Group II: includes 20 healthy subjects as a control group. They were 11 males & 9 females, their ages ranged between 24 & 67 yrs.

All subjects of the study were subjected to the following:

1. Full history taking, including history of iron & EPO intake.
2. Complete clinical examination.
3. Laboratory investigation for:
  - a. B. urea, S. creatinine, AST, ALT, S. albumin, Calcium ( $\text{Ca}^{++}$ ), & Phosphorus ( $\text{PO}_4$ ), S. iron, total iron binding capacity (TIBC), will be measured by colorimetric technique.
  - b. Transferrin saturation (Tsat) is measured using the following formula:  $\text{Tsat} = \text{S. iron} / \text{TIBC} * 100$ .
  - c. KT/V will be calculated using The DaVita Kt/V Calculator uses the Daugirdas II equation.  $\text{Kt/V} = (-1) * \log (\text{Ratio} - 0.03) + ((4 - (3.5 * \text{Ratio})) * (\text{Ultrafiltrate Volume} / \text{Weight}))$
  - d. Where,  $\text{Ratio} = \text{Post BUN} / \text{Pre BUN}$  (**Dugirdas 1993**).
  - e. PT is measured & INR is calculated.
  - f. Serum ferritin, Parathyroid hormone (iPTH), High sensitivity C - reactive protein. (HsCRP), HBsAg, HCVAb, will be measured using immunoenzymometric sequential assay (type 4), ELISA (**DRG, (EIA-4644/2007, (EIA-3954/ 2005)**).
  - g. Hemoglobin in gm/dl using automated cell counter **sysmex k 1000**.
  - h. Hepcidin level was measured using immunoenzymometric sequential assay (type 4), ELISA (**DRG Hepcidin Elisa, EIA-4705/ 2010**).
4. Abdominal ultrasonography.

#### Exclusion criteria

- Any signs of infection such as fever within one month of the study, or during sampling.
- Any surgical procedure before the study within one month of the study.
- Temperature before hemodialysis more than  $37.2 \text{ C}^\circ$ .
- Patients with liver cirrhosis were excluded.

Two venous blood samples were collected from patients, in the middle session of the week, before the beginning of hemodialysis, one on sodium citrate to measure the Hemoglobin (Hb), haematocrit (HCT), prothrombin time (PT), prothrombin concentration (PC) & international normalized ratio (INR). Another sample which was allowed to clot for 30 minutes and the serum was obtained by centrifugation at 3000 RPM for 15 minutes. Serum was stored at  $-20 \text{ C}^\circ$  until the time of analysis, & this pre dialysis samples were used to estimate serum hepcidin.

Another sample was collected after 4 hours at the end of hemodialysis, allowed to clot, then centrifuged and stored at  $-20 \text{ C}^\circ$ , with the other samples till the time of analysis.

#### Measuring Hepcidin:

Hepcidin is a 25-aminoacid, cystein-rich peptid hormone, produced by the hepatocyte and has important role for iron hemeostasis. It is postulated that hepcidin controls plasma iron levels by regulating the absorption of iron from the intestine and the release of iron in the macrophage and hepatocyte. It is secreted in response to iron overload and inflammation. The production decreases in iron depletion. Increased hepcidin concentrations lead to decreased iron absorption and decreased hepcidin state will cause increase iron release from the enterocyte and macrophages (**Kemna et al., 2008**).

#### Statistical methodology:

Statistical evaluation was done on windows XP, results were analyzed using SPSS version 17.0 released September 2008. Paired T test for analysis of correlation between the values, Pearson correlation analyses were used. Data were expressed as mean, standard deviation, & analysis of variance (ANOVA) tests.  $\pm$  SD. Differences at the level of probability (P),  $P < 0.05$  was considered statistically significant,  $P < 0.005$  is considered highly statistically significant, and  $P < 0.0005$  is considered very high statistically significant.

#### 3. Results

The results of the study showed that there was no statistical significant difference between age and sex as regard to studied groups.

#### 4. Discussion

Hepcidin, an acute phase reactant protein produced in the liver, is a recently discovered key regulator of iron homeostasis. Hepcidin inhibits intestinal iron absorption and iron release from macrophages and hepatocytes. Because hepcidin production is increased by inflammation, and high hepcidin concentrations limit iron availability for erythropoiesis, hepcidin likely plays a major role in the anemia of inflammation and rhEPO resistance (**Ganz, 2008**).

Analysing the results between patients on regular hemodialysis with Hb reaching target level, patients on regular hemodialysis with Hb below target level, and normal individuals we found that, there is a significant decrease in Hb. level in group IB, than group IA, & group II, & there is a significant inverse correlation between serum hepcidin & Hb. Level in group IB, & group II. This can be explained by the significant increase in TIBC in patients with anemia, and raised serum iron in patients with normal Hb. Our findings are in concordance with the previous reports that have found patients with ESRD, on regular hemodialysis have a lower Hb. level than normal individuals (**Malyszko et al., 2006**).

**Table1: showing statistical analysis of the results between group IA & group II.**

	Group IA			Group II			P value
	Mean	±SD	Range	Mean	±SD	Range	
Hb gm/dl	12.9	1.3	14.9 11.0	13.9	1.6	16.5 13.6	0.0612
S. CR mg/dl	8.6250	1.99	14 6	0.665	0.18715	1.1 0.5	< 0.0001
Urea mg/dl	127.1	34.0	198 84	24.15	5.9495	34 15	< 0.0001
Ca <sup>++</sup> mg/dl	7.82	1.02	9.2 5.9	8.8	0.821	10.2 7.9	0.0121
PO <sub>4</sub> mg/dl	4.31	1.85	7.2 3	3.895	0.962	6 2.5	0.705
iPTH pg/ml	233.8	0.92	960 15	19.83	0.48	8.6 5.8	0.0009
Alb gm/dl	3.37	0.925	4.5 1.8	4.2	0.280	4.6 3.8	0.0004
ALT U/L	41.9	34.27	147 25	32.15	10.1	64 25	0.2092
AST U/L	52.9	59.3	272 22	33.55	16.65	95 22	0.1678
HsCRP mg/dl	0.071	0.0352	0.15 0.005	18.7	0.02	80 34	< 0.0001
TIBC µg/dl	334.2	193.3	841 109	293	73.7	401 192	0.4313
S. Iron µg/dl	461.95	101.855	1705 136	214	38.8	278 125	0.0109
Tsat %	217.31	141.89	1564 29.1	75.6	15.8	106.7 45.6	0.0846
S.Ferritin ng/ml	608	224.2	800 50	82.7	19.7	120 30	< 0.0001
Hepcidin ng/ml	58.15	39.78	140 31	97	18	101 40	0.0053

There was no statistically significant difference between level of Hb in group IA and group II ( $P < 0.0612$ ).

There was very high statistically significant difference between level of S.Cr. in group IA and group II ( $P < 0.0001$ ). It was higher in group IA than group II.

There was very high statistically significant difference between level of urea in group IA and group II ( $P < 0.0001$ ). It was higher in group IA than group II.

There was statistically significant difference between level of Ca<sup>++</sup> in group IA & group II ( $P = 0.0121$ ). It was lower in group IA than group II.

There was no statistically significant difference between level of PO<sub>4</sub> in group IA & group II ( $P = 0.705$ ).

There was high statistically significant difference between level of iPTH in group IA & group II ( $P = 0.0009$ ). It was higher in group IA than group II.

There was very high statistically significant difference between level of Alb in group IA & group II ( $P = 0.0004$ ). It was lower in group IA than group II.

There was no statistically significant difference between level of ALT in group IA and group II ( $P = 0.2092$ ). It was almost equal in both groups.

There was no statistically significant difference between level of AST in group IA and group II ( $P = 0.1678$ ). It was higher in group IA than group II.

There was very high statistically significant difference between level of HsCRP in group IA and group II ( $P < 0.0001$ ). It was higher in group IA than group II.

There was no statistically significant difference between level of TIBC in group IA & group II ( $P = 0.4313$ ).

There was statistically significant difference between level of S.Iron in group IA and group II ( $P = 0.0109$ ). It was higher in group IA than group II.

There was statistically significant difference between level of Tsat in group IA and group II ( $P = 0.0846$ ). It was high in group IA than group II.

There was very high statistically significant difference between level of ferritin in group IA and

group II ( $P < 0.0001$ ). It was higher in group I than group II.

There was high statistically significant difference between level of hepcidin in group IA and group II ( $P = 0.0053$ ). It was higher in group II than group IA.

**Table2: showing statistical analysis of the results between group IB & group II.**

	Group IB			Group II			P value
	Mean	±SD	Range	Mean	±SD	Range	
Hb gm/dl	8.83	1.58	10.8 4.1	13.9	1.6	16.5 13.6	<0.0001
S. CR mg/dl	7.83	3.57	14.2 2	0.665	0.18715	1.1 0.5	< 0.0001
Urea mg/dl	132.85	61.65	275 48	24.15	5.9495	34 15	< 0.0001
Ca <sup>++</sup> mg/dl	8.08	0.708	9.6 5.3	8.8	0.821	10.2 7.9	0.1346
PO <sub>4</sub> mg/dl	4.79	1.47	7 1.4	3.895	0.962	6 2.5	0.1806
iPTH pg/ml	234.45	7.1	11 1.8	19.83	0.48	78.6 8.8	0.0179
Alb gm/dl	3.43	0.77	5.2 2	4.2	0.280	4.6 3.8	0.0003
ALT U/L	34.85	13.4	83 25	32.15	10.1	64 25	0.5109
AST U/L	43.25	16.65	72 22	33.55	16.65	95 22	0.0923
HsCRP mg/dl	0.084	0.044	0.17 0.002	0.018	0.02	0.01 0.005	< 0.0001
TIBC µg/dl	633.45	2.7	1417 105	293	73.7	401 192	0.003
S. Iron µg/dl	291.4	1.9	1022 49	214	38.8	278 125	0.1938
Tsat %	62.2	5.8	314.6 10.4	75.6	15.8	106.7 45.6	0.4797
S.Ferritin ng/ml	726.5	93.5	820 250	82.7	9.7	220 10	< 0.0001
Hepcidin ng/ml	109.35	27.4	140 31	97	38	124 3	0.2048

There was very high statistically significant difference between level of Hb in group IB and group II ( $P < 0.0001$ ). It is lower in group IB than group II.

There was very high statistically significant difference between level of S.Cr. in group IB and group II ( $P < 0.0001$ ). It was higher in group IB than group II.

There was very high statistically significant difference between level of urea in group IB and group II ( $P < 0.0001$ ). It was higher in group IB than group II.

There was no statistically significant difference between level of Ca<sup>++</sup> in group IB & group II ( $P = 0.1346$ ).

There was no statistically significant difference between level of PO<sub>4</sub> in group IB & group II ( $P = 0.1806$ ).

There was statistically significant difference between level of iPTH in group IB & group II ( $P = 0.0179$ ). It was higher in group IB than group II.

There was very high statistically significant difference between level of Alb in group IB & group II ( $P = 0.0003$ ). It was lower in group IB than group II.

There was no statistically significant difference between level of ALT in group IB and group II ( $P = 0.5109$ ).

There was no statistically significant difference between level of AST in group IB and group II ( $P = 0.0923$ ).

There was very high statistically significant difference between level of HsCRP in group IB and group II ( $P < 0.0001$ ). It was higher in group IB than group II.

There was high statistically significant difference between level of TIBC in group IB & group II ( $P = 0.003$ ). It was higher in group IB than group II.

There was no statistically significant difference between level of S.Iron in group IB and group II ( $P = 0.1938$ ).

There was no statistically significant difference between level of Tsat in group IB and group II ( $P = 0.4797$ ).

There was very high statistically significant difference between level of ferritin in group IB and group II ( $P < 0.0001$ ). It was higher in group I than group II.

There was no statistically significant difference between level of hepcidin in group IB and group II ( $P = 0.2048$ ).

**Table3: showing statistical analysis of the results between group IA & group IB.**

	Group IA			Group IB			P value
	Mean	±SD	Range	Mean	±SD	Range	
Hb gm/dl	12.9	1.3	14.9 11.0	8.83	1.58	10.8 4.1	<0.0001
S. CR mg/dl	8.6250	1.99	14 6	7.83	3.57	14.2 2	0.4421
Urea mg/dl	127.1	34.0	198 84	132.85	61.65	275 48	0.7265
Ca <sup>++</sup> mg/dl	7.82	1.02	9.2 5.9	8.08	0.708	9.6 5.3	0.3676
PO <sub>4</sub> mg/dl	4.31	1.85	7.2 3	4.79	1.47	7 1.4	0.4119
iPTH pg/ml	233.8	9.8	960 15	4.5	6.1	1199 10	0.9953
Alb gm/dl	3.37	0.925	4.5 1.8	3.43	0.77	5.2 2	0.7992
ALT U/L	41.9	0.98	147 25	34.85	13.4	83 25	0.3989
AST U/L	52.9	0.76	272 22	43.25	16.65	72 22	0.5216
HsCRP mg/dl	0.071	0.0352	0.15 0.005	0.084	0.044	0.17 0.002	0.2725
TIBC µg/dl	334.2	0.546	841 109	633.45	342.7	1417 105	0.0057
S. Iron µg/dl	461.95	0.855	1705 136	291.4	241.9	1022 49	0.1019
Tsat %	217.31	0.897	1564 29.1	62.2	75.8	314.6 10.4	0.0308
S.Ferritin ng/ml	608	224.2	800 50	726.5	93.5	820 250	0.0348
Hepcidin ng/ml	58.15	39.78	140 31	109.35	27.4	140 31	< 0.0001
KT/V	1.4	0.40	2.79 0.73	1.6	0.41	0.54 2.56	0.1857

There was very high statistically significant difference between level of Hb in group IA and group IB ( $P < 0.0001$ ). It is higher in group IA than group IB.

There was no statistically significant difference between level of S.Cr. in group IA and group IB ( $P = 0.4421$ ).



There was no statistically significant difference between level of urea in group IB and group IA ( $P = 0.7265$ ). It was higher in group IB than group IA.

There was no statistically significant difference between level of  $Ca^{++}$  in group IA & group IB ( $P = 0.3676$ ).

There was no statistically significant difference between level of  $PO_4$  in group IA & group IB ( $P = 0.4119$ ).

There was no statistically significant difference between level of iPTH in group IA & group IB ( $P = 0.9953$ ).

There was no statistically significant difference between level of Alb in group IA & group IB ( $P = 0.7992$ ).

There was no statistically significant difference between level of ALT in group IA and group IB ( $P = 0.3989$ ).

There was no statistically significant difference between level of AST in group IA and group IB ( $P = 0.5216$ ).

There was no statistically significant difference between level of HsCRP in group IA and group IB ( $P = 0.2725$ ).

There was high statistically significant difference between level of TIBC in group IA & group IB ( $P = 0.0057$ ). It was higher in group IB than group IA.

There was no statistically significant difference between level of S.Iron in group IA and group IB ( $P = 0.1019$ ).

There was statistically significant difference between level of Tsat in group IA and group IB ( $P = 0.0308$ ).

There was very high statistically significant difference between level of ferritin in group IA and group IB ( $P = 0.0348$ ). It was higher in group IB than group IA.

There was very high statistically significant difference between level of hepcidin in group IA and group IB ( $P < 0.0001$ ). It was higher in group IB than group IA.

There was no statistically significant difference between level of KT/V in group IA and group IB ( $P = 0.1857$ ).

We found that there is a significant increase in serum creatinine, urea,  $PO_4$ , iPTH, HsCRP, TIBC and serum ferritin in hemodialysis patients, than normal individuals, we also find a significant correlation between increase in serum hepcidin and the increase in creatinine, urea,  $PO_4$ , HsCRP, TIBC, and serum ferritin in all groups. These results are in agreement with the reports that have found that in patients with chronic renal failure, hepcidin correlated significantly with creatinine, urea, TIBC & HsCRP. This is because the mechanism that control hepcidin secretion is affected by the iron status and

inflammatory status (**Malyszko et al., 2006**). There are no previous studies for any correlation between hepcidin,  $PO_4$  and iPTH.

We found that there is no significant difference in AST, & ALT between patients on hemodialysis in both groups, and normal individuals. We also found that there is inverse significant correlation with AST, while there is a significant inverse correlation between hepcidin & ALT in patients with anemia (group IB) on regular hemodialysis, no correlation in patients with normal Hb (group IA) on regular hemodialysis, but we found a significant positive correlation in normal individuals. **Tariq et al., 2009** found that cirrhotic liver is accompanied with reduced level of hepcidin, that's why cirrhotic patients were excluded.

We found that there is no significant difference between S.iron, in all groups, and this is explained by the regular intravenous iron therapy in the patients which has a negative feed back on hepcidin secretion. Also the effect of dialysis on hepcidin level, as adequate hemodialysis was found to be decreasing the level of hepcidin (**Joshua zarikisty et al., 2010**). This was fulfilled in our study since the mean kt/v were (1.6, 1.4) in both groups respectively. But we found that there is an inverse correlation between hepcidin level and S.iron in both patients on regular hemodialysis, & normal individuals. This is because hepcidin controls iron absorption from the gut. There was also no significant correlation between hepcidin, and Tsat in both group IA & control group, while there was a significant correlation between hepcidin & Tsat in group IB, there is also a significant correlation in all groups between hepcidin, & serum iron, and this can be explained as hepcidin decreases iron absorption from the gut.

We also found that there is a significant decrease in the level of  $Ca^{++}$  & Albumin in patients on regular hemodialysis, than normal individuals, and there was a positive significant correlation between hepcidin and  $Ca^{++}$  in both groups. But there was a strongly inverse correlation between hepcidin and Albumin in Patients on hemodialysis, but a significant positive correlation in normal individuals. There are no reported studies showing the correlation between  $Ca^{++}$  and hepcidin. While there is a reported study that agrees with our findings that increase of hepcidin is accompanied by a decrease in level of albumin (**Tariq et al., 2009**).

There was a significant difference between levels of hepcidin in anemic patients on regular hemodialysis than those with normal Hb, but no significant difference between level of hepcidin in anemic patients and control group. This can be explained by the negative feed back mechanism that iron exhibits on hepcidin as serum iron was higher in patients with normal Hb, than patients with anemia, or the effect of dialysis on its clearance (**Joshua et al.,**

**2010**) which was fulfilled in our study since the mean kt/v was 1.6 in group IA, & 1.4 in group 1B.

This observation consistent with the previous study which has found that, hepcidin is homeostatically regulated by iron and erythropoietic activity. Increased plasma and stored iron stimulate hepcidin production, which in turn blocks dietary iron absorption and further iron loading. Hepcidin is suppressed in iron deficiency, allowing increased absorption of dietary iron and replenishment of iron stores. The feedback loop between iron and hepcidin ensures the stability of plasma iron concentrations (**Ganz, 2006**).

But this is against the previous studies, that have found that pro-hepcidin is higher in hemodialysis patients, kidney transplant recipients, and patients with chronic renal failure, over controls (**Malyszko et al., 2006**).

In ESRD, hepcidin levels are elevated probably in part because hepcidin is cleared by the kidneys, and perhaps also because of increased hepcidin expression in the presence of certain inflammatory cytokines. As a result, iron uptake from the gut is diminished (iron can get into the enterocyte via an apical Fe transporter, but can't get out the basolateral surface because it needs ferroportin), and iron is trapped inside of reticuloendothelial cells. This latter phenomenon, "an inability to mobilize iron stores", has long been known to play an important role in the anemia of chronic disease. But as it was mentioned before this can be altered by efficient hemodialysis which eliminates hepcidin.

One might imagine that hepcidin inhibitors might be a successful pharmacologic intervention for CKD or ESRD patients with anemia.

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