EVALUATION HEPCIDIN FUNCTION IN CHRONIC RENAL FAILURE STAGES AND DIALYSIS

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ABSTRACT

Chronic kidney disease (CKD) may present with anemia of chronic disease (ACD), iron-deficiency anemia. Common hematologic parameters may not distinguish type of anemia in CKD. Hepcidin is a new variable considered to guide management of anemia in CKD. and the discovery of hepcidin about a decade ago has brought new light to the pathogenesis of iron deficiency in renal anemia. In chronic kidney disease patients, functional iron deficiency due to inflammation and elevated serum hepcidin (hep) contribute to erythropoietin-resistant anemia. The relationship between inflammations, iron metabolism. Hepcidin is being extensively studied for anemia and inflammation in chronic kidney disease (CKD) patients. Hepcidin is thought to regulate iron metabolism by iron blockade through various mechanisms. Patients with CKD have early cardiac mortality due to anemia and subclinical inflammation.

Keywords: CKD (chronic kidney disease), hep (hepcidin)

Conclusion

Elevated levels of serum hepcidin have been associated with an increased risk of anemia in CKD patients.

Introduction

Chronic kidney disease (CKD) is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m², persisting for three months or more, irrespective of the cause (Vaidya SR. 2020).

Anemia is a frequent complication in many patients suffered from chronic kidney disease (Soni et al., 2010). Relative deficiency of erythropoietin (EPO) is the predominant cause of anemia in CKD. EPO is the hormone essential for maintaining the survival, proliferation and differentiation of erythroid progenitor cells in the bone marrow, acting by binding the EPO receptor (EPOR) homodimer on the cell surface of erythroblasts (Cheung and Miller 2001). Mechanisms responsible for impaired EPO production are defect in the function of renal EPO-producing cells (REPs) and perturbations of the hypoxia-sensing system in the kidney. Additionally, inflammatory cytokines, as TNF-α and IL-1β (Souma et al., 2016).

More recently, it has become apparent that disordered iron homoeostasis is another crucial factor contributing to renal anemia (Panwar and Gutiérrez 2016). Recent work has elucidated that hepcidin excess may account for this iron deficit (Babitt and Lin 2012). Hepcidin, the central regulator of systemic iron homeostasis, restricts the release of recycled iron in macrophages and stored iron in hepatocytes into plasma, resulting in inadequate iron supply for erythropoiesis (Wilkinson et al. 2016).

In CKD patients, hepcidin levels have been found to be highly elevated, presumably due to induction by inflammation and reduced renal clearance (Ashby et al. 2009).

In chronic kidney disease, plasma hepcidin is increased by inflammation and impaired renal clearance, which prevents the absorption of duodenal iron and sequesters iron in macrophages. These effects of hepcidin can lead to systemic iron deficiency, reduced iron availability for erythropoiesis, and endogenous and exogenous erythropoietin resistance. Hepcidin-mediated iron restriction, combined with decreased renal development of erythropoietin, leads to chronic kidney disease anemia (Ganz
and Nemeth, 2016). In systemic inflammation, this usually happens and leads to anemia due to underuse of iron. Hepcidin production is regulated transcriptionally by the concentration of plasma iron, liver iron reserves, erythropoietic activity, and inflammation. In CKD, plasma hepcidin increases inflammation and impaired renal clearance, inhibits duodenal iron absorption and sequesters iron in macrophages. (Kim, 2020).

**Materials and Methods**

141 patients with Chronic Kidney Diseases were study investigating various clinical courses and risk factors for the progression of CKD in Baghdad teaching hospital. patients aged between (25-78) years with CKD Stage 1-5, stage 2 (34) patients (20 Men 14 and female),and in Stage 3(35) patients (25 Mans 10 and female), Stage 4 (35) patients(25 Mans10 and female) stage dialysis (37) (patients 23 Mans and 14 Women's) compared with (34)17 Mans and 17 Women's healthy control group for the period from April 2019- July 2019. Were all admitted to the IbnSina center for dialysis in Baquba teaching hospital. Fully informed consent was obtained from patients and controls. Hepcidin was determined in serum of all subjects by using a commercially ELISA Micro wells kit (from LDN, Germany).

**Statistical Analysis**

The program Statistical Analysis System- SAS (2012) has been used to detect the influence of differential variables on research parameters. LSD test, the least important difference. A substantial distinction between means was used (Analysis of Variation-ANOVA). Estimation of the coefficient of association between parameters in this study.

**Results and Discussion**

Anemia is one of the most common complications of CKD, and its prevalence gradually increases as kidney function deteriorates. A significant difference (P ≤ 0.01) is shown in Table 1. in red blood cells counts (4.81 ± 0.10, 4.28 ± 0.09, 4.02 ± 0.11, 3.49 ± 0.08 and 3.08 ± 0.07) x 10^6 and hemoglobin levels (14.19 ± 0.24, 12.17 ± 0.34, 11.37 ± 0.31, 9.67 ± 0.24 and 9.21 ± 0.19) g/dl for control and stages 2, 3, 4, dialysis respectively (table -1).

Table 1: Shows the hematological parameters and ferritin, hepcidin, TIBC in patients with CKD

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Dialysis</th>
<th>LSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC x 10^6</td>
<td>4.81 ± 0.10 a</td>
<td>4.28 ± 0.09 b</td>
<td>4.02 ± 0.11 c</td>
<td>3.49 ± 0.08 d</td>
<td>3.08 ± 0.07 e</td>
<td>0.263 **</td>
</tr>
<tr>
<td>Hb</td>
<td>14.19 ± 0.24 a</td>
<td>12.17 ± 0.34 b</td>
<td>11.37 ± 0.31 c</td>
<td>9.67 ± 0.24 d</td>
<td>9.21 ± 0.19 d</td>
<td>0.762 **</td>
</tr>
<tr>
<td>Ferritin [ng/dL]</td>
<td>184.81 ± 12.24</td>
<td>205.74 ± 10.41</td>
<td>236.08 ± 30.81</td>
<td>244.27 ± 15.45</td>
<td>396.40 ± 27.00</td>
<td>59.225 **</td>
</tr>
<tr>
<td>Hepcidin [ng/dL]</td>
<td>14.44 ± 2.10 d</td>
<td>29.39 ± 1.82 c</td>
<td>31.16 ± 1.57 c</td>
<td>44.49 ± 2.64 b</td>
<td>52.73 ± 3.54 a</td>
<td>6.941 **</td>
</tr>
</tbody>
</table>

Means having with the different letters in same column differed significantly. ** [P≤0.01].

The large reduction in the number of RBCs in CKD patients may be due to the fact that patients with impaired renal function have reduced bone marrow development of erythropoietin [EPO], Having a contribution to anemia (Eschbach et al., 1987). Our results were in agreement with many other studies since Hb is contained only in RBCs, a low number of them would lead to low level of Hb (Sonora Quest, 2018). In general, the concentration of Hb and hematocrit provide an accurate representation of the degree to which the mass of red cells circulating is decreased. This decreased Hb level could be attributed to reticuloendothelial cell iron blockage due to inflammation. Inflammation has been implicated in many complications in CKD, including malnutrition, atherosclerosis, and decreased iron utilization (Reddy et al., 2013).

**Relationship between hepcidin and anemia**
Table 1 show a significant increase in hepcidin levels (P ≤ 0.01) between stages of CKD and control and between stages of CKD each other except stages 3 and 4( 14.44± 2.10 , 29.39 ± 1.82 , 31.16± 1.57 , 44.49 ± 2.64 and 52.73± 3.54 ) ng / dl for control and stages 2,3 and dialysis respectively. Hepcidin can serve as an essential mediator of chronic disease anemia pathogenesis (Roy and Andrews, 2005). Iron-free anemic-state diet production and hypoxia are associated with reduced hepcidin production, while acute inflammation shows increased hepcidin production. (Bushbridge et al., 2009). This study showed that there is a negative relationship between hepcidin and hemoglobin where acute inflammation was observed. The correlation between Hecpidin and Hb showed Negative significant (r = - 0.26 [P ≤ 0.01] figure (1).

![Figure 1. Relationship between Hepcidin and Hb](image)

Hepcidin is a primary peptide in iron sequestration and serum hepcidin levels are higher in CKD patients compared to healthy volunteers (Troutt et al., 2013). Hepcidin serum levels increased as they developed. This is in line with the study conducted by CKD (Lee et al., 2017).

An inverse correlation was shown between hepcidin and Hb, similar results were reported by Sabău et al. The serum hepcidin level is found to be a significant predictor for Hb level. Hepcidin concentration was significantly and inversely correlated with serum iron, a result which is comparable to the study of (Sabău et al., 2013) It is found that experimental hepcidin increase in humans, induced by IL-6 infusion, is accompanied by a decrease in serum iron levels (Swellam et al., 2013). The mechanism of anemia in CKD is mainly due to the inability to develop erythropoietin (EPO) in response to a decrease in hemoglobin concentration (Escbach, 1989). The pathogenesis of renal anemia also leads to other possible causes such as chronic inflammation, iron deficiency, malnutrition, increased red blood cell destruction, and vitamin D deficiency (Patel et al., 2010). These results were consistent with the recent National Health and Nutrition Examination Survey, found that anemia in people with CKD was twice as common (15.4%) in the general population (7.6%) in the United States (Stauffer & Fan, 2014). Regarding correlation of Hb with serum hepcidin, Our findings are consistent with the outcomes of other dialysis patient reports (Tessitore et al., 2010) as well as With studies of patients with non-dialysis CKD (Zaritsky et al., 2009). Hepcidin levels are regulated by iron status and erythropoietin activity, hepcidin levels are reduced by anemia and hypoxia and increased by inflammation and intake of food rich in iron without overload (Sanad et al., 2011). Suppression of hepcidin appears to occur possibly due to the increase of erythropoiesis in response to anemia, which is characteristic of the disease and, consequently, could lead to increased intestinal absorption of iron (Omena et al., 2018).

Hepcidin can serve as an essential mediator of chronic disease anemia pathogenesis (Roy and Andrews, 2005). Iron-free anemic-state diet production and hypoxia are associated with reduced...
hepcidin production, while acute inflammation shows increased hepcidin production. (Busbridge et al., 2009). This study showed that there is a negative relationship between hepcidin and hemoglobin where acute inflammation was observed. The correlation between Hepcidin and Hb showed Negative significant (r = - 0.26 [P≤0.01] figure (1).

### Table 2: Correlation coefficient between Hepcidin, Ferritin, RBC and HG

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Correlation-r</th>
<th>Level of sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepcidin &amp; Ferritin</td>
<td>0.21</td>
<td>**</td>
</tr>
<tr>
<td>Hepcidin &amp; RBC</td>
<td>-0.40</td>
<td>**</td>
</tr>
<tr>
<td>Hepcidin &amp; HG</td>
<td>-0.26</td>
<td>**</td>
</tr>
<tr>
<td>Ferritin &amp; RBC</td>
<td>-0.24</td>
<td>**</td>
</tr>
<tr>
<td>Ferritin &amp; HG</td>
<td>-0.31</td>
<td>**</td>
</tr>
<tr>
<td>RBC &amp; HG</td>
<td>0.35</td>
<td>**</td>
</tr>
</tbody>
</table>

** [P≤0.01].

### Relationship between hepcidin and ferritin

The level of Ferritin was significantly the highest in the dialysis group (396.40 ± 27.00 ng/dL) when it compared with stages (2, 3, 4, and control) (P<0.01). While the stages 2(205.74 ± 10.41ng/dL) and stage 3(236.08 ± 30.81 ng/dL) don’t show any significant different except stage 4(244.27 ± 15.45ng/dL) when compared with control (184.81 ± 12.24 ng/dL) as presented in (table - 1).

There is a significant association between hepcidin and serum ferritin because both are reactants in the acute phase (Dallalio et al., 2003). Several studies now report that circulating levels of hepcidin increase in patients with CKD, with dialysis being the best in patients (Zaritskit AL, 2009). Hepcidin concentration was further positively correlated with serum ferritin (Adam, 2017).

### References


