

# ASSOCIATION OF IRON DEFICIENCY ANEMIA IN PATIENTS WITH CHRONIC RENAL FAILURE

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## ABSTRACT

**Objectives:** To find out the probable association of iron deficiency anemia in patients with chronic renal failure and to find out serum hepcidin and hemoglobin levels with iron and inflammation status in patients of chronic renal failure

**Study Design:** Cross sectional study

**Place and Duration of Study:** Social Security Teaching Hospital Lahore from 1<sup>st</sup> March 2016 to 30<sup>th</sup> September 2016.

**Materials and Methods:** A total of 50 patients were included. Serum hepcidin, ferritin, high sensitivity C-reactive protein and iron levels were measured using standard methods. Statistical correlations were established.

**Results:** There were 15 (30%) females and 35 (70%) males with mean age of 50.55±14.4 years. A significant correlations was seen between hepcidin with iron status, nutritional and inflammatory markers such as ferritin, total iron binding capacity and albumin (p<0.05 respectively). An inverse relationship was seen between hepcidin and hemoglobin levels (p<0.05)

**Conclusion:** A negative correlation of hepcidin with hemoglobin level in these patients with inadequate iron stores, which could be effective in the development of an anemia in such patients.

**Keywords:** Anemia, iron status, Chronic renal failure, Heparin

## INTRODUCTION

Hemoglobin is the part of erythrocytes. Iron deficiency anemia occurs when body doesn't have enough iron to produce hemoglobin, which is more common in female because they lose blood during menstrual cycle, chronic blood loss within the from a colon polyp Or colorectal cancer, peptic ulcer, cause iron deficiency anemia. Gastrointestinal bleeding can occurs from regular use of analgesic or other pain relievers, especially aspirin. An Iron deficiency is the most common reversible cause of anemia among such patients with chronic kidney disease (CKD).<sup>1</sup> Anemia might begin to develop in the early stages of CKD, when someone has 20 to 50 percent of normal kidney function. Anemia is worsening as CKD progresses. Majority of patients, who have total loss of kidney function, or kidney failure, have anemia.<sup>1,2</sup> Especially the patient having kidney failure when he or she needs dialysis or a kidney transplant in order to live. When kidneys are

damaged or diseased they don't produce enough erythropoietin (EPO).

Blood loss from hemodialysis and low levels of the nutrients like iron, vitamin B12, folic acid low in food can lead to anemia. Inflammatory problems such as arthritis, lupus, or inflammatory bowel disease i.e. ulcerative colitis, chronic infections such as diabetic ulcers leads to iron deficiency anemia. Hemoglobin is significantly low and contributes in fatality of patients suffering with chronic renal failure and is one of the main complication.<sup>3</sup> The cause of anemia in patients of chronic renal failure has many aspects i.e. short life span of RBCs, deficiency of erythropoietin and defective erythropoiesis with accumulating BUN, contributing anemia in chronic renal failure.<sup>4,8</sup>

In a recent study, a fascinating agent have been identified which relate to gastro-intestinal iron absorption and macrophageal release of iron, the primary targets of anemia of chronic diseases (ACD) providing a molecular understanding of

erythrokinetics.<sup>4</sup> Hepcidin is one of the new agents and is most exciting and was discovered by Krause et al<sup>5</sup> and Park et al<sup>5</sup> as a 25 amino acid protein, produced in the liver and excreted in the urine with antibacterial activity and is a type II acute-phase protein similar to ferritin<sup>6</sup> and is the major cause for disturbed iron metabolism<sup>7,9</sup> because it regulate systemic balance of iron its release by lowering GIT iron absorption and release from enterocytes, macrophages and hepatocytes.<sup>10</sup> Concentration of Hepcidin increases in patients of CRF because of inflammation and reduction of its clearance.<sup>11</sup> Hepcidin production is regulated by interleukin-6(IL-6)<sup>12</sup> IL-1, interferon gamma (IFN- $\gamma$ ), and tumor necrosis factor alpha (TNF- $\alpha$ ) Resistance of erythropoietin is caused because higher Hepcidin concentration and iron limitation.<sup>13</sup> Aisne's group said that none of these agents influenced the release of iron from Kupffer cells that contained iron-labeled erythrocytes it was concluded that IL-1 may play a significant role in the anemia of inflammation by up-regulating hepcidin. So there is controversial discussion about role of hepcidin link to anemia.<sup>14,15</sup>

C-reactive protein is an acute-phase inflammatory homopentameric protein; a highly conserved plasma protein discovered in 1930 by Tillet and Francis while investigating the sera of patients suffering with acute stage of Pneumococcus infection and was named for its reaction with the capsular (C)-polysaccharide of Pneumococcus.<sup>16</sup> CRP binds to polysaccharides such as phosphocholine (PCh) on microorganisms. In the presence of calcium, and triggers the classical complement cascade of innate immunity by activating C1.<sup>17</sup> Pankow et al<sup>17</sup> also found that inter-individual variation in blood CRP levels is 35–40% heritable. Increased CRP levels are typically associated with disease, but liver failure is one condition observed to impair CRP production.<sup>18</sup>

## MATERIALS AND METHODS

This cross-sectional study was conducted from 1<sup>st</sup> March 2016 to 30<sup>th</sup> September 2016 at the Social Security Teaching Hospital Lahore includes both male and female patients suffering with chronic renal failure, coming to OPD /Medical ward of Social Security Hospital Rainwind Road, Lahore and comprised 50 patients. Adult patients ( $\geq 20$  years) with anemia who had CRF with reduced glomerular filtration rate (GFR). Adult patients of both genders with age of ( $\geq 20$  years) with low Hb% who had CRF with

glomerular filtration rate of 15-29 ml/min were included. Anemia is considered as hemoglobin concentration less than 13g/dl for men and postmenopausal women, and less than 12g/dl for premenopausal women. From the patients with CRF, blood samples were taken and GFR was estimated by the Cockcroft-Gault formula.<sup>22</sup> Hb% and hematocrit (Ht) levels were calculated on Sysmax 500. Whole blood and serum were kept at -80°C. Until samples were analyzed by using auto-analyzer (BT3000, Italy) for C-reactive protein(CRP),total iron binding capacity (TIBC), serum iron, calcium, urea, creatinine, and albumin. Serum level of PTH was estimated by using chemiluminescent method (Liaison USA). All data recorded and analyzed by using SPSS version 20 p-values less than 0.05 was considered significant statistically.

## RESULTS

There were 15 (30%) were females and 35 (70%) males with mean age was 50.55 $\pm$ 14.4 years. An inverse significant  $p < 0.05$  correlation was between hepcidin concentrations and TIBC and significant positive correlation between Hb% and ferritin levels ( $p < 0.05$  each). No significant relationship between serum hepcidin, CRP and GFR. Hepcidin in had an inverse significant relationship with albumin and PTH levels ( $p < 0.05$ ) [Table 1].

**Table 1:** Clinical characteristics of the patients

Parameter	Mean $\pm$ SE
Hepcidin (ng/ml)	258.85 $\pm$ 21.93
Total iron binding capacity ( $\mu$ g/dl)*	258.85 $\pm$ 138.75
Haemoglobin (g/dl)*	10.00 $\pm$ 0.24
Glomerular filtration rate (ml/min/1.73m <sup>2</sup> )	21.50 $\pm$ 0.73
Ferritin ( $\mu$ g/l)**	163.82 $\pm$ 24.68
Iron ( $\mu$ g/dl)**	63.4 $\pm$ 4.63
hs-CRP (mg/l)	10.53 $\pm$ 1.88
Hematocrit (%)	31.14 $\pm$ 0.68
Urea (mg/dl)	126.38 $\pm$ 7.12
Albumin (g/dl)*	4.21 $\pm$ 0.11
Total protein (g/dl)	8.10 $\pm$ 0.16
Creatinin (mg/dl)	3.65 $\pm$ 0.45
Weight (kg)	72.3 $\pm$ 1.72
Parathyroid hormone (pg/ml)*	111.92 $\pm$ 13.34
Calcium(mg/dl)	9.02 $\pm$ 0.10

\*An inverse significant relationship with hepcidin in Pearson Correlation ( $p < 0.05$ ).

\*\*A positive significant relationship with hepcidin in Pearson Correlation ( $p < 0.05$ ).

## DISCUSSION

A main complication of chronic renal failure is anemia.<sup>23</sup> Inflammation is an important factor associated with erythropoietin resistance.<sup>24</sup> Hepcidin expression emerges as a part of an inflammatory reaction and it may be involved in the pathogenesis of inflammation-associated anaemia.<sup>25</sup> In the present study, serum hepcidin concentrations were negatively associated with Hb levels. Our results are not consistent with the results of others studies in CRF patients. Studies in non-dialysis CRF patients has no correlation between serum hepcidin concentration and Hb level.<sup>26,27</sup> A study with renal insufficiency patients also had no relation between Hb levels and serum prohepcidin concentrations.<sup>28</sup> Our study results are consistent with the results of other studies in patients with dialysis and in patients with kidney and heart failure.<sup>29</sup> The results may be attributable to differences in inflammatory state, differences in the iron status of the populations studied or sample size. In CRF patients with sufficient iron stores reveals many reasons of negative association with hemoglobin.<sup>30</sup>

Iron availability is limited for erythropoiesis by hepcidin. A low renal clearance in CRF patients also elevates hepcidin serum concentration and exacerbate effects. Thus, excessive hepcidin has become as one of the key pathogenic features of inflammation associated anaemia. A significant positive correlation between hepcidin and ferritin is seen and used as marker of iron status.<sup>31</sup> In our study, it has been shown that IL-6 and other inflammatory cytokines may also change in concentrations along with serum hepcidin.<sup>32</sup> A study in patients with hemodialysis showed hepcidin level may correlate with TIBC and ferritin levels. One study in patients with chronic liver disease showed that hepcidin level correlated with ferritin level. In our results the synthesis of hepcidin is also enhanced by an increased body iron store.<sup>33</sup> A significant positive correlation between ferritin and hepcidin indicates the association between iron stores and hepcidin in CRF patients. Our study showed high hepcidin concentration may be due to elevated ferritin levels and elevated IL-6.

## CONCLUSION

A negative correlation is seen between hepcidin and hemoglobin level in chronic renal failure patients with adequate iron stores, hepcidin limits the availability of iron for erythropoiesis which can lead to the development of anaemia in these patients. Multicenter studies are needed to examine the changes in Hb, hepcidin, iron status indicators and inflammatory cytokines such as IL-6 in chronic renal failure patients.

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