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Review Article

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Hepcidin in Hemodialysis Patients: An Update Review

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ABSTRACT

Hepcidin levels are associated with complications in chronic kidney disease patients, particularly patients on hemodialysis. However, the correlation between hepcidin levels and hemodialysis therapy is still unclear. This article will describe the physiological regulation of hepcidin and abnormalities in hepcidin levels in chronic kidney disease patients. We alsodiscusses the relationship between hepcidin levels and hemodialysis therapy in chronic kidney disease patients in this article. An increase in hepcidin can occur in patients on hemodialysis therapy, where the patient's estimated glomerular filtration rate is so low that hepcidin cannot be eliminated. On the other hand, hemodialysis can act as a substitute for the kidney to eliminate hepcidin. However, the decrease in hepcidin levels after hemodialysis did not last long. Therefore, to prevent complications, iron therapy should be given immediately.

Keywords: Anemia, chronic kidney disease, hemodialysis, hepcidin, iron metabolism

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INTRODUCTION

Hepcidin is a hormone that regulates the body's iron metabolism.[1] In patients with chronic kidney disease (CKD) on hemodialysis (HD) therapy, there is often an increase in hepcidin levels.[2] This condition will decrease the absorption and availability of iron and result in iron deficiency in the body. Iron deficiency is the main factor that causes anemia in HD patients.[3] In addition, increased levels of hepcidin can also result in the possibility of various other complications, such as cardiovascular disease.[4] Therefore, it is necessary to know the relationship between hepcidin levels and HD therapy in CKD patients to avoid thesecomplications.

CLINICAL AND RESEARCH CONSEQUENCES

Regulation of Hepcidin

Hepcidin is a peptide hormone secreted by hepatocytes in the active form hepcidin 25. Other isoforms of hepcidin (hepcidin 22 and hepcidin 20) are also present in serum in a smaller amount.[5] Hepcidin plays a role in inhibiting the release of iron into the circulation by regulating ferroportin receptors, which are iron transporters in the duodenum, macrophages, and hepatocytes.[1] The iron transported by ferroportin comes from recycled erythrocytes and food absorption in the small intestine.[6]

Hepcidin causes degradation and internalization of ferroportin. This leads to a decreased iron movement and a buildup of iron storage[7,8] (Figure 1). Several factors can influence the regulation of hepcidin, such as iron availability, erythropoiesis, and inflammatory processes.[9] For example, a decreased iron availability for the erythropoiesis process can suppress the levels of hepcidin.

Hepcidin production is regulated through the bone morphogenetic protein (BMP)–hemojuvelin (HJV) pathway involving bone morphogenetic protein 2 (BMP-2) and

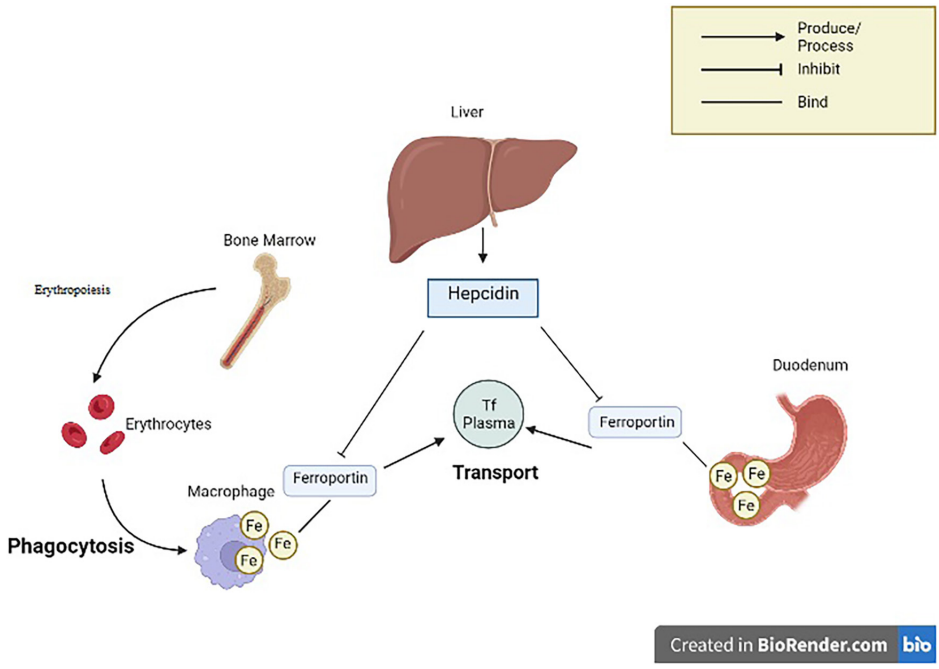

Figure 1. Iron regulation and transport mechanisms. The formation of erythrocytes occurs in the bone marrow. Through phagocytosis, iron derived from the destruction of erythrocytes is stored in macrophages. In addition to this process, iron is also produced from the absorption of food in the intestines. If needed, iron stored in macrophages and intestines will be transported to blood plasma transferrin via ferroportin. Hepcidin produced by hepatocytes inhibits the transport of iron into plasma transferrin by internalizing and degrading ferroportin. Tf, Transferrin Fe.

bone morphogenetic protein 6 (BMP-6) produced by liver endothelial cells.[10] In order to activate the BMP receptor complexes on the hepatocyte membrane, which include 2 type I receptors (ALK3 homodimers or ALK2/3 heterodimers), 2 type II receptors (ACVR2A and/or BMPR2), and coreceptor HJV, BMP-6 and BMP-2 are secreted, which work together, most likely as a heterodimer (BMP-2/6). This complex phosphorylates suppressor of mothers against decapentaplegic (SMAD) 1/5/8 proteins (SMAD1/5/8), which attach to SMAD4 and move to the nucleus to bind BMP response elements (BRE) in the hepcidin (HAMP) promoter. This causes transcription of hepcidin to occur[10-13] (Figure 2).

In addition to going through the BMP-HJV line, hepcidin is regulated by transferrin-bound iron. This pathway involves transferrin receptor 1 (TfR1), transferrin receptor 2 (TfR2), and homeostatic iron regulator (HFE).[14] The receptors of HFE do not bind directly to iron but interact with TfR1 and TfR2. Transferrin receptor 2 is a receptor for the absorption of iron transferrin by erythrocytes, mainly expressed in the liver. The interaction between HFE and TfR1 and TfR2 depends on the concentration of iron transferrin. When there is no iron transferrin, the HFE will bind to TfR1. However, in the presence of iron transferrin, the HFE will join TfR2.[15] This binding between HFE and TfR2 will induce hepcidin transcription[15,16] (Figure 2).

MAIN POINTS

- Hepcidin plays a crucial role in iron transport and regulation.
- Hemodialysis patients tend to experience elevated levels of hepcidin, leading to complications such as anemia and cardiovascular diseases.
- Hepcidin levels in hemodialysis patients should be monitored.

In the body, hepcidin levels are affected by erythroferrone (ERFE), which is the primary regulator of erythrocyte formation.[14] Erythroferrone is synthesized and secreted by erythroblasts in the bone marrow and extramedullary region.[17,18] The erythropoiesis process depends mainly on iron availability in the body. Therefore, increased erythropoiesis will be accompanied by increased ERFE production, suppressing hepcidin production through the BMP pathway.[13,19] Conversely, a decrease in hepcidin production will trigger the absorption and recycling of iron.[1,20] Thus, iron abnormalities can be treated by administering ERFE agonist and antagonist.[18,21]

Erythroferrone expression by erythroblasts will increase when there is an increase in erythropoiesis. Increased erythropoiesis in the bone marrow can be due to an increase in the production of erythropoietin (EPO). Several factors can increase the production of EPO, such as bleeding, anemia, and abnormalities that cause an increase in erythropoiesis, for example, thalassemia-β.[22] Erythroblasts release ERFE by activating the Janus kinase 2/signal transducer and activator of transcription 5 (JAK2/STAT5) pathways by EPO stimulation. This process will mediate the inhibition of hepcidin production during the

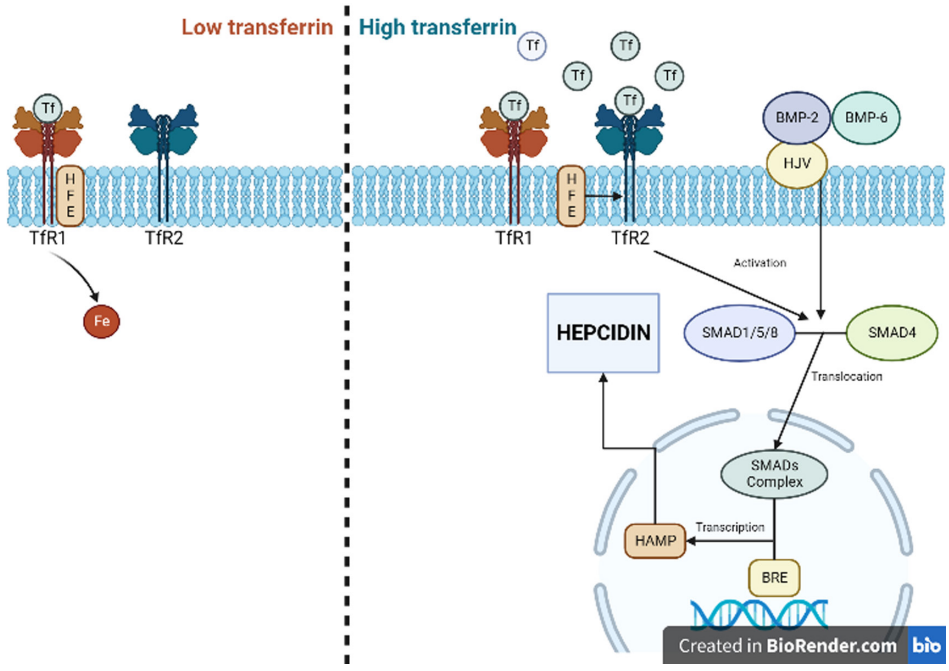

Figure 2. Regulatory pathways of hepcidin synthesis. Hepcidin synthesis is regulated through 2 signaling pathways, BMP-HJV, and iron transferrin. The BMP-2 and BMP-6 will bind to the HJV. This will activate SMAD1/5/8, which binds to SMAD4 and eventually form a complex of SMADs. Next, the SMADs complex will be translocated into the nucleus and bind to BRE. The binding between the SMADs and BRE complexes will trigger the transcription of the HAMP gene so that hepcidin is produced. Hepcidin is also regulated by iron transferrin. When iron transferrin level is low, HFE will bind to TfR1. If iron transferrin concentration is high, then HFE will be detached from TfR1 and bind to TfR2, which triggers hepcidin production. BMP, bone morphogenetic protein; BRE, BMP response element; HAMP, hepcidin antimicrobial peptide; HFE, homeostatic iron regulator; HJV, hemojuvelin; SMAD, suppressor of mothers against decapentaplegic; TfR, transferrin receptor.

erythropoiesis process.[1,23] This ensures the adequacy of circulating iron levels for the erythropoiesis process.

CAUSES OF HEPCIDIN LEVEL ABNORMALITIES IN CHRONIC KIDNEY DISEASE PATIENTS

In CKD patients, several factors can cause an increase and decrease in hepcidin levels. Increased levels of hepcidin can be caused by several circumstances, such as the following (Figure 3):

1. Decrease in estimated glomerular filtration rate (eGFR). An increase in hepcidin levels in CKD patients can be caused due to a decrease in the ability to eliminate by the kidneys. Under normal conditions, the kidneys serve to eliminate hepcidin. However, when the kidneys experience a decrease in function, then hepcidin cannot be eliminated by the kidneys and causes the levels of hepcidin to become uncontrolled.[24,25] Serum hepcidin level is inversely related with eGFR in patients with chronic kidney disease, particularly stages 3b-5.[26] On the other hand, end-stage kidney disease patients with reserved residual kidney function have lower hepcidin level, regardless of the dialysis method.[27]
2. Inflammation. An increase in hepcidin level can also be caused by inflammation. Inflammation in CKD patients results from increased urea levels and can also occur due to side effects of HD treatment [19]. An increase in the urea causes translocation of bacterial toxins into the bloodstream as well as causes systemic inflammation. The urea also induces vascular smooth muscle cell apoptosis and endothelial dysfunction, thus increasing the risk of cardiovascular disease.[28] In addition,inflammation will trigger the production of interleukin 6 (IL-6) through STAT3.[29] The production of IL-6 will stimulate hepatocytes to produce hepcidin. This leads to an increase in the level of hepcidin in the blood.

On the other hand, some factors can cause a decrease in hepcidin levels, such as the following (Figure 3):

1. Hypoxia. In CKD patients, there is a decrease in kidney function, which results in a reduced oxygen supply due to impaired blood flow in the kidneys. This decrease in oxygen delivery will alter the oxygen pressure in the tissues and result in *Hypoxia-inducible factor-α* (HIF-α) not accumulating, HIF heterodimers not forming, and EPO transcription being.[30] Hypoxia-inducible factor is a critical transcription factor in regulating erythropoiesis, iron metabolism, and various processes involved in maintaining homeostasis.[31,32] Hypoxia-inducible factor decreases hepcidin production and modulates iron metabolism so that the binding capacity of iron can increase. This can help overcome anemia in CKD patients.[25,33] In a hypoxic state, the production of platelet-derived growth factor BB (PDGF-BB) will also suppress the transcription of

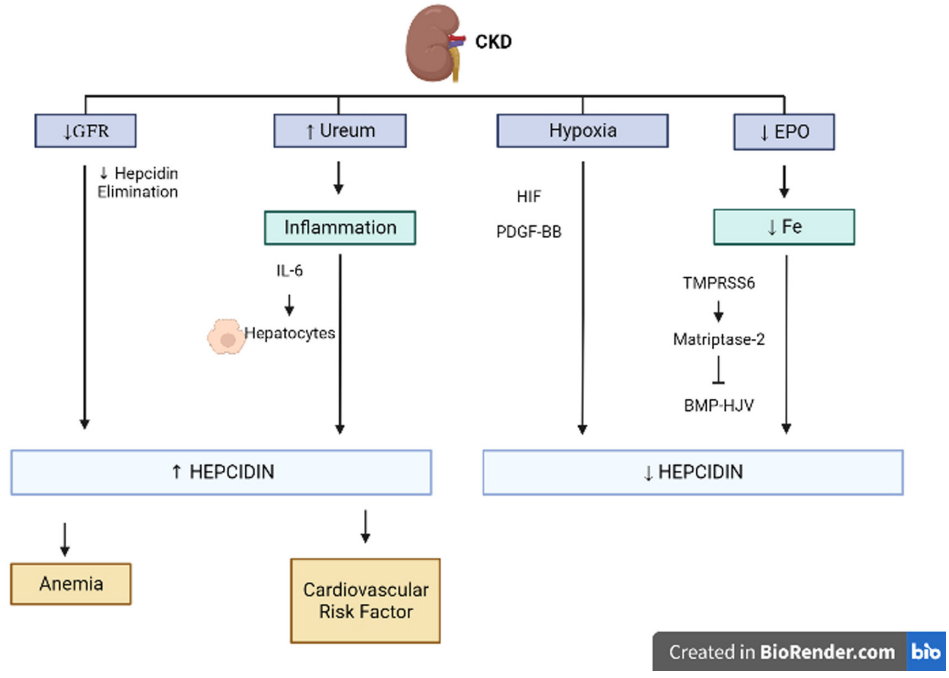

Figure 3. Abnormality of hepcidin levels in CKD patients. Several factors can trigger abnormalities in hepcidin levels. An increase in hepcidin levels can be influenced by a decrease in the glomerular filtration rate (GFR), which causes a decrease in the ability of the kidneys to eliminate hepcidin. In addition, increased hepcidin levels can also be caused by chronic inflammation due to increased urea levels in CKD patients. The inflammation will trigger the production of IL-6 and stimulate hepatocytes to produce hepcidin. Meanwhile, the incidence of hypoxia and iron deficiency conditions can cause a decrease in hepcidin levels. In hypoxia, hormones such as HIF and PDGF-BB will be produced that can suppress the production of hepcidin. Meanwhile, in iron deficiency conditions, transcription occurs in the *TMPRSS6* gene, which will produce matriptase 2 and then inhibit the binding of BMP-HJV so that there is a disturbance in the hepcidin regulation path. It can also decrease hepcidin production. CKD, chronic kidney disease; EPO, erythropoietin; GFR, glomerular filtration rate; HIF, hypoxia-inducible factor; IL-6, interleukin 6; PDGF-BB: platelet-derivative growth factor BB; BMP-HJV: bone morphogenetic protein–hemojuvelin.

hepcidin through the transcription of CREB factors (cAMP response element binding protein) and CREB-H (CREB 3-Like Protein 3)[29] so that the level of hepcidin decreases.

2. Iron deficiency. Decreased kidney function in CKD patients can lead to reduced EPO production. This leads to the occurrence of iron deficiency.[34] Iron deficiency in CKD patients is attributed to several factors: (1) reduced EPO production, which leads to decreased iron store mobilization; (2) suppression of erythropoiesis due to inflammation; (3) shortened erythrocyte life span due to inflammation and uremia; (4) increased blood loss and hepcidin-mediated decrease in intestinal iron absorption; and (5) increased hepcidin, which leads to sequestration in macrophages and iron-restricted erythropoiesis.[32] However, unlike decreased level of EPO, which happens from the early stages of CKD, increased level of hepcidin is observed in end-stage kidney disease patients with low eGFR.[26,35] In the early stages with reserved residual kidney function, decreased EPO along with other factors causes an iron deficiency state. In iron deficiency conditions, transcription occurs against the *TMPRSS6* gene, which produces matriptase 2 and then inhibits the binding of BMP and HJV so that the activation of the BMP–SMAD pathway is reduced.[29] This leads to a decrease in hepcidin levels.

Patients with CKD on dialysis tend to experience elevated levels of hepcidin. This is due to a decrease in the GFR, resulting in a reduced ability to eliminate hepcidin by the kidneys.[25] In addition, chronic inflammation is a common condition that can be encountered in CKD patients, especially after receiving dialysis therapy.[19] Both conditions can cause an increase in hepcidin levels (Figure 3). However, residual kidney function plays an important role in hepcidin level for dialyzed patients. This explains why hemodialyzed and peritoneally dialyzed patients with residual kidney function have lower hepcidin level than in anuric patients.[27] Furthermore, the type of kidney replacement therapy significantly affects hepcidin levels. Patients with peritoneal dialysis (PD) and hemodiafiltration (HDF) have lower hepcidin levels compared to HD patients.[27] This might be due to partial elimination of hepcidin by PD and HDF.

IMPACT OF INCREASED HEPCIDIN LEVELS ON CHRONIC KIDNEY DISEASE PATIENTS

An increase and decrease in hepcidin levels can impact CKD patients. Increased levels of hepcidin can lead to the occurrence of several conditions, such as the following:

1. Anemia. An increase in hepcidin levels in CKD patients can occur due to several conditions, one of which is an increase

in iron levels stored in macrophages.[4] When hepcidin levels are normal, iron from the absorption of food in the intestine will be absorbed by a divalent metal transporter 1 (DMT1). Divalent metal transporter 1 will then transport Fe^{2+} resulting from Fe^{3+} reduction by duodenal cytochrome B (DCYTB) to be delivered to circulation with the help of ferroportin. However, when there is an increase in hepcidin levels, ferroportin binds to hepcidin, resulting in the internalization and degradation of the protein. This causes ferroportin to be unable to facilitate the delivery of iron into circulation.[16] As a result, a buildup of iron reserves occurs and this causes disturbances such as obstruction of the erythropoiesis process due to the lack of iron availability in circulation. Excessive levels of hepcidin will lead to anemia, which is indicated by increased storage of iron in macrophages, a decrease in the movement of iron into the circulation, and inhibition of erythropoiesis.[36,37]

2. Increased risk of cardiovascular disease. In addition to anemia, another impact of increased hepcidin is increased risk for cardiovascular disease due to increased ferritin.[4] High levels of ferritin are associated with myocardial siderosis.[38] Myocardial siderosis happens in patients with a high level of iron load, which leads to the formation of reactive oxygen species that damage the integrity of cellular structures and result in heart dysfunction.[39] Furthermore, increased levels of hepcidin and ferritin levels in CKD patients undergoing HD therapy are associated with an increased incidence of atherosclerosis. High serum hepcidin is related to the occurrence of common carotid artery intima–media thickness.[40] The severity of plaque formation and destabilization, particularly in patients with other risk factors (i.e., gender dan metabolic syndrome), are linked to increased levels of hepcidin.[41,42] Thus, increased hepcidin level is a risk factor for increased mortality in HD patients due to increased risk cardiovascular disease.

Iron deficiency is a significant factor in anemia in HD patients.[3] Increased hepcidin levels in HD patients are due to a decrease in GFR and chronic inflammation. Both conditions have impacts on the absorption and availability of iron for the erythrocyte formation process.[2,43,44] This can result in the occurrence of iron deficinecy in the body.[45]

Apart from inflammation, kidney clearance disorders further increase hepcidin levels in CKD patients.[46] This condition can be remedied by HD therapy. However, hepcidin levels can only drop shortly after the HD process. Then, the concentration of hepcidin in the serum will increase again within a few hours.[23]

Under normal conditions, the kidneys will facilitate the elimination of hepcidin. However, in CKD patients with low eGFR values, the ability of the kidneys to eliminate hepcidin decreases. This can lead to an increase in hepcidin levels.[25] An increase in ferritin levels accompanies an increase in hepcidin levels. Ferritin itself is a molecule that functions as a place to store iron. Therefore, if there is an increase in ferritin, the number of iron reserves will increase and cannot be circulated into plasma. This can lead to the occurrence of some complications, such as anemia and atherosclerosis.[47]

Increased levels of hepcidin in HD patients can be treated with parenteral iron administration and routine ERFE supplementation. Erythroferrone suppresses hepcidin production and excess iron, so ERFE is a potential target therapy for increased hepcidin levels.[48]

CONCLUSION

In end-stage CKD patients, there is a decrease in kidney function characterized by low eGFR values. This leads to increased hepcidin levels due to a decrease in the elimination ability of hepcidin by the kidneys and chronic inflammation. High levels of hepcidin cause inhibition of iron movement, resulting in complications such as anemia and cardiovascular disease. However, on the other hand, HD also acts as a substitute for kidney function by eliminating hepcidin. However, the decrease in hepcidin levels after HD does not last long. Hepcidin levels in HD patients should be observed. Lower hepcidin level is linked to better survival outcome in CKD patients on dialysis. Hepcidin abnormalities in HD patients cause anemia that is resistant to iron supplementation. Therefore, iron supplementation in HD patients must be carefully observed to achieve the desired therapeutic goals. Additional ERFE supplementation can also be done to lower hepcidin levels.

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