Hepcidin As an Iron Regulator and Inflammatory Mediator in Several Clinical Conditions: Narrative Review

Hisham Ali Waggiallah

Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Prince Sattam Bin Abdulaziz University, KSA.

ABSTRACT

Hepcidin plays a key role in iron metabolism control, and its activation is caused by iron or inflammatory motivations. In this review, we discussed many clinical conditions such as anemia of inflammation (AI), chronic kidney disease (CKD), Diabetes mellitus, pregnancy, and malaria. In inflammation anemia, the production of hepcidin is boosted to 100 times and that may take account of the description characteristic of this condition, the sequestering of iron in macrophages. Hepcidin may develop as an influential marker of functional iron deficiency in patients with chronic kidney ailment. Diabetes is an iron-related inflammatory condition and elevated oxidative injury. Recent research recommended that iron is a key pathogenic factor in diabetes of both type 1 and type 2 and may, therefore, be an enticing potential treatment. Normal growth and development of the fetus depend on the sufficiency of maternal iron during pregnancy, reduction of hepcidin during a healthy pregnancy enabling iron transfer to the fetus. In clinical trials, iron supplementation is associated with a higher incidence and seriousness of malaria in some studies, but not in all, while dietary iron deficiency is correlated with a reduced malaria parasitemia and Mortality.

Key Words: *Hepcidin, Iron, Inflammation, anemia, malaria, Chronic Kidney Disease, Diabetes mellitus.*

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INTRODUCTION

The main regulator of systemic iron metabolism, hepcidin, greatly influences the growth of erythrocytes. Increased levels of hepcidin block the absorption of the intestinal iron and recycling of iron by macrophage, causing iron-restricted erythropoiesis and anemia. Reduced hepcidin levels encourage the supply of bone marrow iron for the synthesis of hemoglobin and the development of red blood cells [1]. Infections and inflammatory diseases cause iron sequestration in macrophages, the characteristic of inflammatory anemia (previously called chronic disease anemia), and also reduce the absorption of iron in the small intestine. The iron sequestration response is generally believed to increase infection resistance by limiting the availability of iron to microbes, but the details remain not understood [2].

Formation, structure, and role of hepcidin:

Serum iron levels are regulated by hepcidin, a hepatic peptide hormone derived from the liver and iron metabolism master regulator [3]. It acts by binding to the iron exporter ferroportin in target cells discharging iron, particularly tissue macrophages and duodenal enterocytes but also other sorts of cells. Hepcidin binding shuts iron efflux [4] and triggers ubiquitination, internalization, and lysosomal ferroportin degradation [5]. This contributes to the retention of the intracellular iron and eventually hypoferremia. The pre-pro-hepcidin (a long precursor of 84 amino acids), which is encoded by the HAMP gene, is expressed primarily by hepatocytes in the liver, and other cells in extrahepatic tissues at much lower levels. Pre-pro-hepcidin is converted into pro-hepcidin through the elimination of its endoplasmic reticulum targeting sequence comprising 24 N-terminal amino acids. More cleavage at the C- terminus yields mature, bioactive hepcidin, an evolutionarily maintained, cysteine-rich peptide with antimicrobial-rich 25-amino acids. At the turn of a hairpin loop, it folds into a distorted β-sheet with an uncommon disulfide bridge between

Corresponding author: Dr. Hisham Ali Waggiallah
Address: Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Prince Sattam Bin Abdulaziz University.
E-mail: ✉ hishamwagg30 @ hotmail.com
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neighboring C13-C14. On the basis of this model, the structure becomes unchanging by additional disulfide bonding between C7-C23, C10-C22, and C11-C19 [6]. The connectivity of the disulfide bond between C7-C23, C10-C13, C11-C19, and C14-C22 is pre-assumed by substitutional structural model [7]. Remarkably, the core structure of hepcidin on the basis of disulfide bonding is not crucial for iron-regulatory function as cysteine substitution or the elimination of cysteine-containing segments does not damage hormonal activity [8, 9].

The release of hepatocellular hepcidin refers to multiple stimuli but the main regulators are iron, inflammation, and erythropoiesis [10]. Enhances in hepcidin transcriptional induction of serum or tissue iron activates via BMP/SMAD (Bone Morphogenetic Protein/Small Mothers Against Decapentaplegic) signaling. The crucial mechanism is the excretion of the bone morphogenetic protein 6 (BMP6) from the liver sinusoidal endothelial cells, which attaches BMP receptors on hepatocytes to type I (ALK2, ALK3, and ALK6) and type II (ActRIIA, and BMPRII), while likewise triggering the SMAD signaling cascade. Effective hepcidin iron signaling demands ancillary factors such as the BMP co-receptor hemojuvelin (HJV), BMP2, the hemochromatosis HFE protein, and the diferric transferrin sensor receptor 2 (TfR2) [11]. The route is negatively regulated by the transmembrane serine protease matriptase-2 (also known as TMPRSS6), a hepcidin suppressor that seems to cleave HJV and other hepcidin signaling pathway components [12]. Iron-dependent hepcidin upregulation helps to inhibit excess iron absorption where there are great body iron stores. (figure1)

The inflammatory cytokines support multiple pathways for hepcidin initiation. The most critical of these involves signaling JAK/STAT (Janus Kinase/Signal Transducer and Transcription Activator), which is activated in response to IL-6. A cross-talk between JAK/STAT and BMP6/SMAD signals during inflammatory hepcidin induction is increasingly evident [13-15]. Activin B, a BMP receptor ligand-induced by JAK/STAT may trigger SMAD signaling to hepcidin [16], but its role is not vital [17]. BMP6 and HJV, on the other hand, are crucial parts of the inflammatory hepcidin pathway [18, 19], which is deemed an innate immune response to deprive invading iron bacteria [20]. This is part of an expansive "nutritional immunity" tactic for iron withholding [21]. The hepcidin expression is inhibited under circumstances of raised erythropoietic drive by erythroferrone (ERFE), a hormone secreted by erythroblasts in response to erythropoietin [22] that neutralizes BMP6 [23]. This leads to iron mobilization for erythropoiesis. More hepcidin-induced erythropoietin suppressors might also be elaborate in this reaction. Dysregulation of the generation of hepcidin involves "hepcidinopathies," which are hepcidin deficiency or additional iron-related disorders [23].

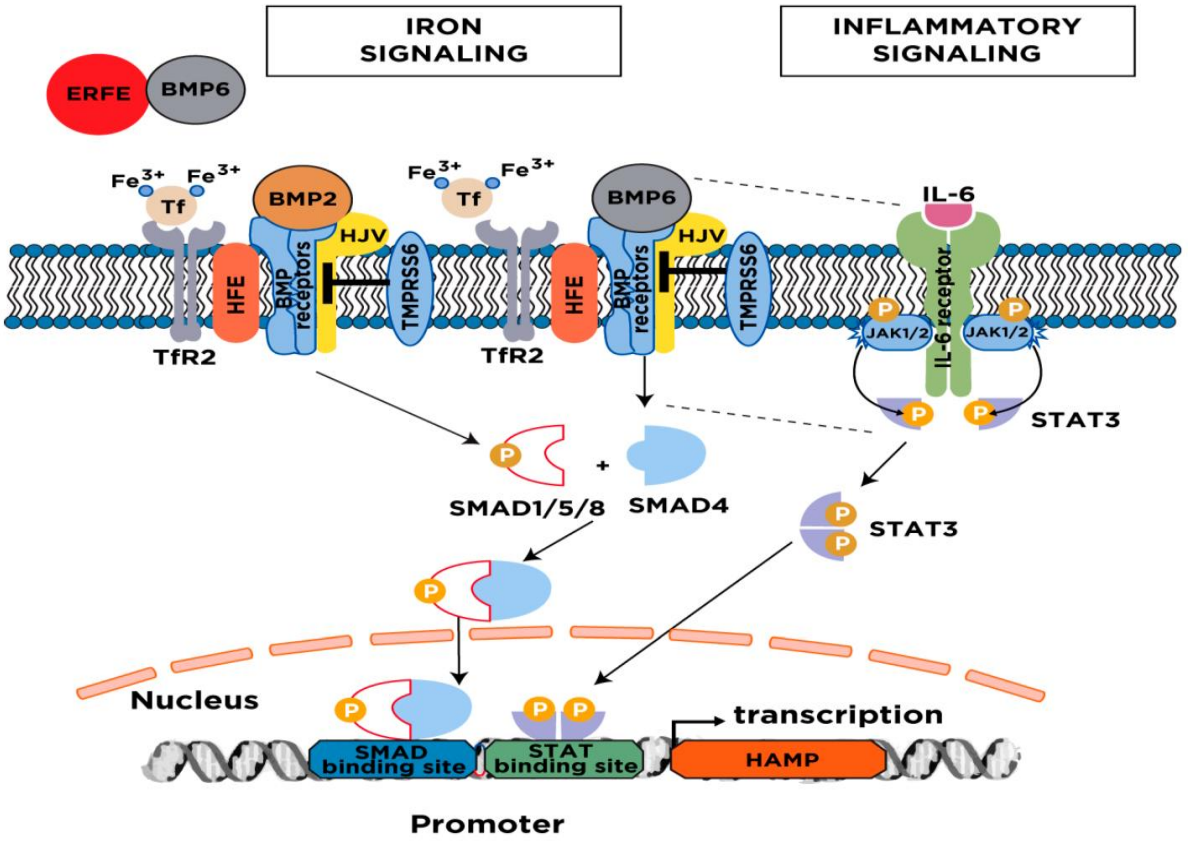

Fig 1: Hepcidin regulatory mechanism and mode of action

Hepciden as an inducer of anemia during inflammation

Anemia emerges when blood lacks enough healthy red blood cells [24-26] or hemoglobin [27]. Anemia of inflammation (AI), in the past known as chronic anemia disease, is moderate normochromic-normocytic anemia that develops under circumstances of systemic inflammation and immune response. This happens in many ailments, such as autoimmune diseases, chronic kidney disease, chronic infections, advanced cancer, chronic obstructive pulmonary disease, congestive heart failure, elderly (at least in part) anemia, and graft versus host illness. AI is one of the most widespread anemias in hospitalized patients, and the most prevalent anemia in the world. In intensive care units, acute inflammation contributes to the severity of anemia. There are numerous, and complex molecular mechanisms underlying AI. Overproduction by macrophages of cytokines such as TNF-α, IL1-β, and IL-6 by lymphocytes blunts the generation of EPO, damages the response to erythropoiesis, enhances hepcidin levels and may trigger erythrophagocytosis, mainly in the acute types [28]. Hepcidin is stimulated by signaling IL-6 through the receptor IL-6 (IL-6R) and JAK2-STAT3. Activation of complete hepcidin requires an active BMP-SMAD pathway, as inactivation of BMP signaling decreases hepcidin in inflammation of animal models [29]. The deregulation of systemic iron homeostasis results in decreased absorption and recycling and macrophage iron sequestration, leading to low transferrin saturation and iron limitation of erythropoiesis and other tissues. The common treatment of AI is centered on reversibility/control of the underlying condition, if possible. If the disease is incurable and anemia is mild, careful risk-benefit assessment is required to prevent any treatment side effects.

Treatments according to pathophysiology are restricted to erythropoietin, such as compounds, and iron. The utilization of erythropoiesis-stimulating agents (ESA) prevents hepcidin by inducing enhancement of erythropoiesis. This technique is commonly utilized in patients suffering from chronic kidney disease, low-risk myelodysplastic syndromes, and chemotherapy cancer. Nevertheless, careful clinical control is needed, as large doses have side effects on the cardiovascular.

Intravenous iron administration can relieve iron restriction, which is resulted from ESA-dependent erythropoiesis expansion. Oral iron is relatively inefficient since the high hepcidin levels mitigate its intestinal absorption. Prolyl hydroxylase inhibitors (hypoxia-inducible factor, HIF stabilizers) are experimental in chronic kidney ailment, with the objective of enhancing endogenous EPO. Chronic therapy with transfusion of red blood cells is not recommended due to transient effects and adverse reactions, and it is restricted to severe refractory anemia [28, 30].

Anemia associated with hepcidin levels

On the basis of hepcidin levels, anemias might be classified as anemia with low and high hepcidin. It is axiomatical that insistently high levels of hepcidin cause iron deficiency anemia because of a reduced source of iron to erythropoiesis by blocking the absorption of iron. In contrast, ineffectual erythropoiesis typifies the so-called iron-charging anemias with low hepcidin and iron overload. The contradictory mechanisms of pathophysiology result in these 2 groups of anemias. In the first group, anemia occurs because of the inhibitory influence of hepcidin exerts on iron absorption and recycling resulting in systemic iron deficiency. In the second group, hepcidin inhibition is because of enhanced anomalous erythropoiesis anemia [31].

Anemia with high levels of hepcidin comprises of two infrequent inherited disorders (iron-refractory iron deficiency anemia and hepcidin-producing adenomas in an inborn glucose metabolism error) and an acquired common condition: anemia of inflammation.

Iron refractory iron deficiency anemia (IRIDA) is an infrequent recessive condition described by poor transferrin saturation, hypochromic microcytic anemia, and unusually normal/high hepcidin levels. It is caused by TMPRSS6 mutations [32], a gene encoding the serine protease type II, matriptase-2 [33]. Mutations of TMPRSS6 are dispersed throughout the gene and can influence numerous domains, in particular the catalytic domain [34]. This highly expressed transmembrane protease inhibits hepcidin transcription by cleaving the BMP co-receptor hemojuvelin on the cell surface, thereby lessening the BMP signaling and hepcidin synthesis [35]. In the case of an iron deficiency, the TMPRSS6 function is vital to permit the compensatory mechanism for improved iron absorption.

Hepcidin's diagnostic role in chronic kidney diseases (CKD)

The kidney is the chief hepcidin clearance route. It is not surprising then that multiple groups have revealed that hepcidin is significantly enhanced in dialysis patients [36-41]. Most studies have found levels of hepcidin specifically associated with the serum ferritin, and some specify a correlation with C-reactive protein, an inflammation marker. Hepcidin concentrations have been significantly correlated inversely with epoetin dose [37], and decline with epoetin therapy initiation 36. These relationships are backed with the mechanisms and relationships of regulation described in animal investigations.

In CKD, most researches and assay techniques discovered hepcidin levels to be intermediate to levels found in patients with normal controls and dialysis [37-40]. In non-dialysis CKD, in some investigations hepcidin corresponds

inversely with estimated glomerular filtration rate but not in others [37-39]. This can be due to the utilization of dissimilar assays, different comorbid conditions of the patient, and relatively small sample size.

A great diagnostic concern in the management of CKD-related anemia is that patients need parenteral iron. In dialysis and non-dialysis CKD, investigations examining ferritin, transferrin saturation, combinations of such tests, and other tests have failed to find a reliable predictor for the iron response. Since hepcidin is the true regulator of iron stores, many have suggested that iron-restricted erythropoiesis may be better predicted by serum hepcidin [42-44].

Hepcidin in Diabetes mellitus

Diabetes is an iron-associated inflammatory disorder and increased oxidative damage [45]. Recent evidence recommends that iron is a crucial pathogenic factor for both type 1 and type 2 diabetes, and thus could be a looked-for therapeutic target [46]. Iron is a contentious and paradoxical factor, vivacious to living organisms, and potentially toxic at the same time [47]. The eventual significance of iron in disease pathophysiology comes from the easiness with which iron is oxidized and reduced reversibly. While vital for its metabolic functions, this feature makes iron potentially hazardous because of its capability to participate in the generation of strong oxidizing species such as hydroxyl radical [48].

Increasing evidence recommends iron metabolism disorder is strongly correlated with DM development and further induces DC complications. Iron overload in tissues can result in enhanced oxidizing stress and tissue damage [49]. Following an extensive investigation into the role of systemic hepcidin, more and more work is shedding light on the importance of local hepcidin in organ homeostasis. Numerous studies have set the function of local hepcidin in the stomach, heart, lungs, and prostate [50].

Hepcidin during pregnancy

Normal growth and development of the fetus depend upon the sufficiency of maternal iron during pregnancy. The iron needed for pregnant women is more to support compensate for intrapartum blood loss, fetoplacental growth, and expand maternal red blood cell mass. In order to come across these requirements, the absorption of dietary iron is improved along with greater utilization of existing iron stores. Hepcidin is diminished throughout a healthy pregnancy which causes the iron transfer to the fetus [51]. Obesity in the course of pregnancy can lead to excess hepcidin and diminished transfer of iron to the fetus [52, 53]. It is stated that low iron stores are more prevalent in obese pregnant women [54]. In previous investigations, the relationship between serum ferritin and hepcidin was revealed [52, 55]. While in another investigation, no relationship between serum hepcidin and iron status has been witnessed [51]. To reinforce the association between the poor iron status of obesity and hepcidin, it is interesting to note that hepcidin is expressed not only in the liver but also in adipose tissue, and that the expression of mRNA in obese pregnant patients is enhanced in adipose tissue [52]. The enhanced hepcidin may suppress iron release from the cells through influencing ferroportin expression, which is possibly correlated with diabetes complication development [56]. Iron content tends to be increased in obese patients' subcutaneous and visceral adipose tissue and negatively associated with the release of adiponectin, which may result in insulin resistance and obesity metabolic complications [57].

Hepcidin in malaria

In clinical trials, in some but not all investigations, iron supplementation is linked with elevated incidence and severity of malaria [58], whereas nutritional iron deficiency is associated with reduced malaria parasitemia and death [59]. Iron deficiency also sponsors safety against *Plasmodium berghei* infection in mice which recommends a starring role for hepcidin in this infection. As foreseen, humans and mice infected with malaria have raised plasma hepcidin levels that relate positively with IL-6 parasitemia and plasma, but patients with the most extreme *P. falciparum* anemia have decreased hepcidin levels, likely indicating negative feedback on hepcidin expression, such as the impact of compensatory erythropoiesis [60]. In vitro, *P. falciparum*-infected erythrocytes encourage hepcidin mRNA expression in human peripheral blood monocytes and monocyte-derived macrophages in an IL-6 independent but IL-10 dependent fashion [61], but the significance of leukocyte-derived hepcidin for host protection is imprecise.

The effects of hepcidin on malaria are complex [62]. On the one side, elevated hepcidin possibly contributes to anemia by inducing iron restriction. In contrast, hepcidin throughout experimental malaria can have protective influences in mice. Greater parasitemia and death in *P. berghei* infection is caused by immunoneutralization of hepcidin, while pretreatment of animals with a hepcidin-expressing lentivirus is protected against parasitemia and death in comparison with mice treated with a control lentivirus. Super-infections such as a 2nd malaria infection in endemic areas are associated with greater death. It was assumed that hepcidin functions by causing the transfer of iron from hepatocytes that can host superinfecting parasites to macrophages that cannot. Transgenic over-expression or application of hepcidin to infected mice in support of this mechanism led to protection by diminishing the burden of the parasites in the liver. Such data say hepcidin protects against malaria by reducing the supply of iron to parasites [58].

CONCLUSION

Hepcidin is an immunity mediator and an iron-regulating hormone. To convey the excitement of this emerging research, I provided the critical background information about iron metabolism and its relationship to various mechanisms for clinical conditions, and then reviewed the studies that led to our contemporary understanding of the function of hepcidin in iron metabolism and host defense.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest

The author declares that there is no conflict of interest.

Research involving human participants and/or animals

No need for ethical approval since the manuscript is a review article.

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