Hepcidin - A novel biomarker with changing trends

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Submitted: 09-05-2014 Revised: 23-05-2014 Published: 05-05-2015

ABSTRACT

Hepcidin is a novel peptide hormone of hepatic origin. It has a crucial role in iron metabolism. The causative association of this peptide in anemia and iron overloading states has been well established. Current research has expanded the diagnostic implications of hepcidin in other medical conditions. Increased serum hepcidin has been reported in neoplastic diseases, inflammation, and sepsis. However, the clinical use of hepcidin as a biomarker is limited owing to nonavailability of an appropriate diagnostic test. Assays for serum and urine hepcidin estimation have been developed recently, which are likely to facilitate the use of hepcidin in research as well as in patient care in the near future.

Key words: Biomarker, hepcidin, iron metabolism, malignancy, sepsis

INTRODUCTION

Hemoglobin and several other hemoproteins contain iron as their indispensable component. Iron homeostasis is important for erythropoiesis and normal cellular functions. As there is no specific physiological mechanism of elimination of iron from the body apart from loss of skin and mucosal epithelial cells and menstrual blood loss, iron uptake from a dietary source and utilization from internal iron reserves are the main determinants of extracellular iron balance.[1] Although several iron transport proteins and enzymes have been implicated, it was found that the metabolism of iron is closely regulated by a novel liver-derived peptide, hepcidin. It exerts its action by interacting with a ferroprotein, a transmembrane protein implicated in iron efflux from the body iron stores.[2] The current research supports the association of hepcidin with the pathophysiology of iron-related disorders.[3-5] Hepcidin excess may result in anemia refractory to iron therapy, whereas reduced serum hepcidin may lead to iron overload with widespread deposition of iron in the tissue.[5,6] Increased serum hepcidin has been reported increasingly from diverse clinical states, namely, neoplastic diseases, inflammation, and sepsis.[1,7,8] The availability of efficient detection modalities will increase the prospect of hepcidin being considered as a biomarker in these conditions in future.

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Access this article online

Quick Response Code:

Website: www.phcogrev.com

DOI: 10.4103/0973-7847.156333

Physiological functions of hepcidin

Hepcidin is a peptide hormone with 25 amino acids. Owing to antibacterial and antifungal properties, hepcidin was initially designated as a liver-expressed antimicrobial peptide.[9] The current nomenclature reflects both its hepatic origin and antimicrobial action. Although the liver is the main source, extra-hepatic production of hepcidin in the heart, kidney, retina, monocytes and macrophages, alveolar cells, adipocytes, and pancreatic β-cells has also been described.[10] However, these tissues have been found to have a considerably lower level of hepcidin gene expression in comparison to the liver and its significance still remains uncertain.

Chromosome 19 contains the *hepcidin antimicrobial peptide* (*HAMP*) gene, which codes for hepcidin. It codes for the 84 amino acid precursor, preprohepcidin, which subsequently undergoes two enzymatic cleavages in the hepatocyte cytoplasm and in the blood, to liberate the 25 amino acids containing the biologically active form (hepcidin-25). Hepcidin produced in the liver enters the systemic circulation and achieves wide distribution in the tissues. Hepcidin-25 along with two isoforms, namely, hepcidin-20 and hepcidin-22, are excreted by the kidneys.[1] These two peptides are considered as the degradation products of hepcidin.

The molecular structure of human hepcidin, as revealed by spectroscopy studies, contains one beta-sheet within the peptide backbone, which has a hairpin loop with eight cysteine molecules forming four disulfide bonds. The cysteine molecules and N-terminal amino acids that form the Copper and Nickel ion binding (ATCUN) motif are considered to be essential for its biological activity.[9] Hepcidin exerts its action on three main target

cell types associated with iron metabolism, namely, enterocytes, hepatocytes, and reticuloendothelial (RE) phagocytes. These are the three major sources of plasma iron (transferrin-Fe^{2+}). About 66% iron in the human body is attributed to the hemoglobin that is incorporated inside the erythrocytes. RE macrophages engulf senescent erythrocytes and release the iron into circulation or store it as ferritin. Likewise, intestinal epithelial cells absorb both dietary heme- and nonheme iron and contribute to plasma iron and intracellular ferritin store. Cells that express transferrin receptors take up transferrin-bound iron from the circulation by endocytosis.[1] Bone marrow erythroid cells utilize this iron for erythropoiesis, whereas, liver cells use it for storage. Ferroportin (FPN) is the transmembrane iron exporter responsible for the efflux of iron from the tissue to the serum, so that it can be utilized for erythropoiesis. Hepcidin combines with FPN and exerts a negative effect on erythropoiesis by inducing internalization and the subsequent destruction of FPN.[2,5,11]

Regulation of hepcidin

Although several factors interplay at a genetic level, three discrete mechanisms, namely, regulation by iron store, erythropoietic activity, and inflammation, are mainly implicated in the control of liver hepcidin production [Figure 1].[9] Increased erythropoiesis suppresses hepcidin production, whereas, iron loading and inflammation induce its production. Blood loss, anemia, increased erythropoietin or hypoxia stimulate bone marrow erythropoiesis and are found to reduce hepcidin.[1,9,12] However, the bone marrow-derived signals that decrease hepcidin production in response to erythropoietic expansion remain unidentified.[12] Erythropoietin and erythropoiesis-stimulating agents (ESAs) probably decrease hepcidin expression by stimulating the hypoxia-inducible factor (HIF). The regulatory mechanisms of both erythropoiesis and iron stores are mediated by the bone morphogenetic protein (BMP), hemochromatosis (HFE), and hemojuvelin (HJV) at the surface of hepatocytes.[9,11] This is also known as the mandatory signaling pathway. HJV is a BMP coreceptor. The BMP6 ligand binds to the BMP receptor-HJV forming a multiprotein complex on the hepatocyte cell surface, which activates SMAD 1/5/8 phosphorylation. This phosphorylated molecule interacts with SMAD4, inducing translocation of the SMAD complex to the nucleus for activation of hepcidin synthesis.[11] Tmprss6 (serine protease) on the hepatocyte cell membrane decreases the expression of hepcidin as a result of hypoxia and acute iron deprivation by cleaving HJV on the cell surface.[11] Inflammatory cytokines, especially IL-6, was found to promote *HAMP* gene expression via the interleukin receptor and JAK2 - STAT3 pathway.[9,11]

Diagnostic assays

Although assays for the estimation of serum and urine hepcidin have been developed in recent years, their availability and affordability is limited to only a few centers. Furthermore, it is important to differentiate other isoforms of hepcidin from the biologically active hepcidin-25.[13] Most commercially available assays are used for the detection of serum and urine hepcidin. Mass spectrometry-based assay such as Surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS), and Weak Cation Exchange

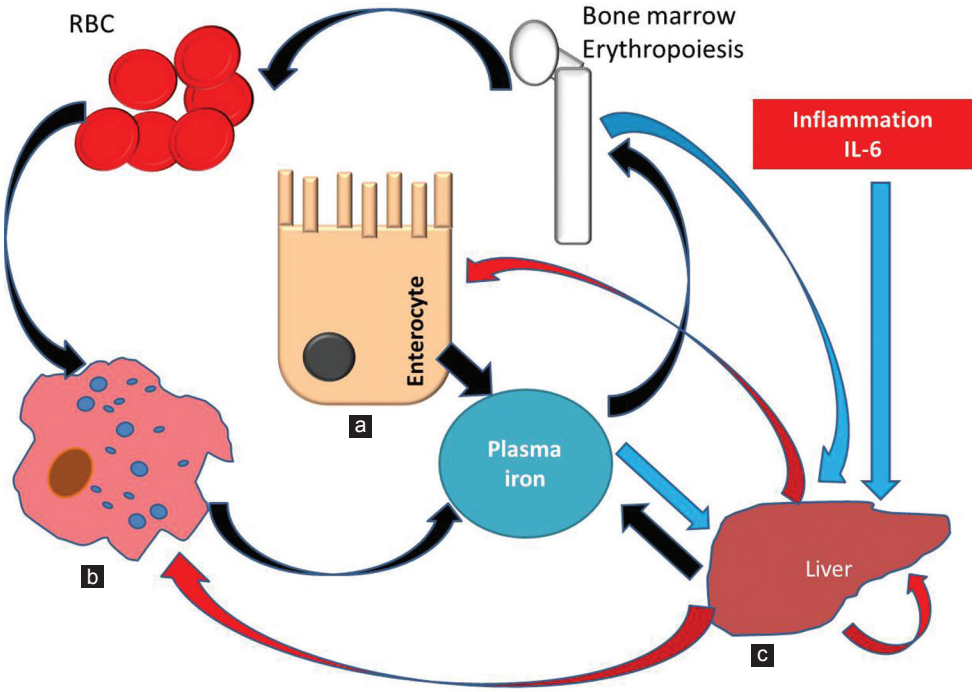

Figure 1: Regulation of iron absorption, distribution, and recycling by hepcidin. Enterocyte (a), macrophage (b), and liver (c) contribute to the plasma iron pool by iron efflux, which is utilized for erythropoiesis (black arrows). Plasma iron loading, decreased erythropoiesis in bone marrow and inflammatory cytokines (IL-6) induce hepatic hepcidin production (blue arrows). Hepcidin inhibits intestinal iron absorption and iron mobilization from hepatic and reticuloendothelial iron stores (red arrows)

time-of-flight mass spectrometry (WCX-TOF MS) are superior to the antibody-based assays (ELISA, chemiluminescence, and dot blot assay), as they can discriminate between different isoforms.[13,14] Different studies have reported substantial intraindividual variability and diurnal variability in serum hepcidin, which may preclude its use.[13,15]

Hepcidin in hematological disorders

Both acquired and hereditary hepcidin deregulation have been found to play a vital role in the pathogenesis of hematological disorders. Genetic defect in *HFE, HJV, HAMP, transferrin receptor 2 (TFR2),* and *FPN g*enes have been implicated in hereditary hemochromatosis where the underlying pathology is either impaired hepcidin synthesis or resistance to its biological actions.[3,11] Hemochromatosis is classically described as 'bronze diabetes'. Dysregulated deposition of iron in the liver parenchyma, pancreas, and skin are the pathognomonic features of hemochromatosis. Among the different types, hereditary hemochromatosis associated with *HFE* genes is the most familiar form.[11] Genetic hepcidin overexpression occurs as an autosomal recessive disease. This unusual condition presents with iron-refractory iron-deficiency anemia (IRIDA). In this condition, unopposed activation of hepcidin expression is because of the impaired cleaving of cell surface HJV, as the Tmprss6 enzyme is inactivated by molecular defects.[11]

The acquired hepcidin deficiency is an important feature of the so-called 'iron-loading anemias'. Beta thalassemia is the most common entity in this group. Pertaining to the low hepcidin level, intestinal iron absorption remains high to support the erythropoiesis needs, despite the iron overload. It is postulated that the mandatory signaling pathway mediated by BMP-SMAD is downregulated by chemical mediators.[5,10,11] However, the mediators involved in this process are yet to be identified. Current research suggests that Transforming growth factor beta (TGF-beta), hypoxia-induced factor (HIF), Growth differentiation factor 15 (GDF15), and twisted gastrulation protein homolog 1(TWGS1) may play an important role.[11] The acquired disorder of hepcidin overexpression occurs most commonly in anemia of chronic diseases (ACD). However, hepcidin-producing benign hepatic adenoma is also reported.[16] Inflammatory cytokines namely IL-6, IL-1, TNF-alpha, and gamma-IFN are involved in the JAK-STAT3 signaling pathway-mediated activation of hepcidin production in ACD.[11] IL-6 is the most important cytokine in the pathogenesis of ACD. Elevated hepcidin explains iron sequestration and iron-restricted erythropoiesis, whereas, the blunted erythropoietic response to erythropoietin seen in ACD may be related to the effect of inflammation.

New diagnostic implications of hepcidin

Malignancies

The relevance of the hepcidin-ferroportin axis in neoplastic disease is multidimensional. Hepcidin overexpression is not only associated with various cancers, but also responsible for anemia in cancer patients. Hematological malignancies such as leukemia, both Hodgkin's and non-Hodgkin's lymphoma, and multiple myeloma as well as solid organ tumors such as cancers of breast, prostate, kidney, brain, ovary, and lungs were reported to display hepcidin overexpression.[1,17-20] Increased hepcidin and anemia in cancer are because of inflammatory cytokines, especially IL-6. However, an IL 6-independent mechanism mediated by increased BMP-2 has also been described in hematological malignancies.[21] Radiation-induced inflammatory cytokines also contribute to hepcidin production and consequent worsening anemia in cancer.[22] Iron is an essential cofactor for cancer cell proliferation.[23] Thus, restriction of iron uptake from the dietary source and utilization from internal iron reserves by hepcidin may have an anticancer effect.

Cirrhosis is considered a precancerous lesion and a sequel of iron-loading anemia and hemochromatosis because of chronic hepatic inflammation. The iron-derived reactive oxygen species (ROS) commonly seen in these conditions, play a major role in inflammation and hepato-carcinogenesis. Although the exact mechanism is not well understood, hepcidin expression is suppressed in all cancerous liver tissues regardless of the degree of tumor differentiation, although it remains unchanged in the normal tissues.[1,24] TFR 1 and TFR 2 may have implications in hepcidin suppression and increased iron uptake by cancer cells in this condition.[24]

In renal cell carcinoma, higher hepcidin levels were reported in metastasis in comparison to patients with nonmetastatic carcinoma. Current studies showed a lack of correlation of serum hepcidin with hepcidin mRNA expression, tumor stage, and tumor differentiation. In renal cell carcinoma, the level of hepcidin mRNA expression reportedly reflects the metastatic potential of the tumor, and hence, it may be employed as a prognostic marker.[1,24]

Breast cancer patients were reported to display elevated serum hepcidin and a ferritin light chain in association with decreased levels of FPN in comparison to healthy controls.[17,25] These provide a noninvasive diagnostic modality for the follow-up of diagnosed cases. Furthermore, baseline hemoglobin and hepcidin levels could predict development of anemia in early breast cancer cases treated by chemotherapy.[26]

Inflammation and sepsis

The pathogenesis and progression of atherosclerosis, coronary artery disease, neurodegenerative diseases, allergic, and autoimmune diseases are essentially attributed to inflammation. It also constitutes an important component of host response to infective agents, grafted tissues, and tumor cells. Hepcidin synthesis in the liver is induced by IL-6 in response to inflammation. Current research has enlightened the prospect of hepcidin as a potential acute-phase biomarker in inflammation and sepsis. In febrile children, an increased serum hepcidin has been noted during acute infection, which tends to fall during convalescence.[27] A recent single center prospective study on patients with acute pancreatitis reported the superiority of hepcidin over C-reactive protein (CRP) and the leucocyte count in assessing the severity of this condition.[28] Anemia often complicates Inflammatory Bowel Disease. Serum and urine

hepcidin were found to have a strong correlation with the IL-6 and hemoglobin values in Crohn's disease.[29] Sepsis in neonates is the most important factor contributing to neonatal mortality in developing countries. Owing to nonspecific and diverse clinical presentations, diagnosis of neonatal sepsis is often challenging. As collection of an adequate blood sample from a neonate is difficult and a negative blood culture does not rule out sepsis, culture negative sepsis constitutes a significant problem. Hence, acute-phase markers (erythrocyte sedimentation rate (ESR), CRP, and Procalcitonin) are commonly used for the identification of sepsis. Recently, hepcidin was also found to be a reliable biological marker of early- as well as late-onset sepsis in neonates.[7,30] The serum hepcidin values were in keeping with the disease process in late-onset neonatal sepsis. A four-fold rise of serum hepcidin during sepsis returned to normal levels following therapy.[30] A significantly increased level of hepcidin in the cord blood was observed in early-onset neonatal sepsis, which could allow rapid nonculture detection of sepsis in the newborn.[7]

Low-grade inflammation

The hepcidin level was found to rise in low-grade inflammatory conditions associated with obesity and following severe exertion. In severe obesity, a persistent elevation of acute-phase proteins as well as cytokines such as tumor necrosis factor, IL-6, and plasminogen activator inhibitor have been observed. This reflects a low-grade systemic inflammatory state, which persists chronically in severely obese individuals as a result of adipocyte derived proinflammatory adipokines. The adipose tissue is currently considered as an endocrine organ, which produces biologically active peptides including hepcidin. Obese individuals suffer from iron deficiency more commonly than nonobese individuals. Stimulation of hepcidin synthesis as evident from an increase in both hepcidin mRNA and protein was reported in severe obesity, which may explain this iron deficiency.

A similar low-grade inflammation with elevated acute-phase proteins has been observed following severe exertion, with transient dysregulation of iron homeostasis attributed to increased serum hepcidin. However, the extent and duration of exertion that can induce inflammation and hepcidin expression is not clear. High blood hepcidin concentrations were reported in participants of tennis tournaments at the end of the season and in military personnel after a seven-day training exercise.[31,32] However, running a 100-km ultra-marathon was not associated with elevated blood hepcidin.[33]

Insulin resistance, diabetes, polycystic ovary syndrome

Insulin resistance is the main pathological feature of type 2 diabetes mellitus (DM) as well as polycystic ovary syndrome (PCOS).[34,35] The connection between an elevated iron store and resistance to hypoglycemic effects of insulin is currently under investigation. Evidence suggests that iron influences glucose metabolism and a low hepcidin level with consequent elevated iron stores that may contribute to insulin resistance in DM and PCOS. A decreased hepcidin: Ferritin ratio suggests inadequate production of hepcidin, which is not proportionate to the degree of iron load. Hence, it can be used as a reliable marker of insulin resistance in these conditions.[35]

Obstructive sleep apnea syndrome

Obstructive sleep apnea is characterized by a reoxygenation and reperfusion period resulting from intermittent hypoxia during sleep. This leads to activation of inflammatory cytokines, which induce hepcidin production. On the other hand, hypoxia simultaneously downregulates hepcidin production. A significant reduction of serum hepcidin found in obstructive sleep apnea is essentially related to hypoxic episodes and evidence suggests that serum hepcidin could be a prognostic marker.[36]

New therapeutic implications of hepcidin

Antimicrobial properties

Although iron homeostasis is a prominent physiological function of hepcidin, its initial isolation is not a result of studies on metabolism of iron. On the contrary, its discovery is a consequence of a research on antimicrobial molecules in a plasma ultrafiltrate.[37] The *in vitro* antibacterial and antifungal activity of hepcidin has been demonstrated by several authors. However, its mechanism of antimicrobial action is not yet recognized. Bacteria and fungi require iron as an essential factor for their growth as well as virulence. Iron acquisition from the host transferrin or lactoferrin is mediated by high-affinity iron-binding molecules (siderophore) in several pathogenic bacteria.[5] Increased expression of hepcidin in response to infection limits the availability of iron to the invading pathogen. Apart from this, a mechanism of direct antimicrobial effect has been proposed. The motif of numerous cationic residues of hepcidin is similar to the well-recognized antimicrobial peptides.[5] Owing to its amphipathic structure, hepcidin may have the ability to combine with negatively charged membrane phospholipids of the bacteria and fungi resulting in the subsequent disruption of the membrane, penetration into cells or immune response through chemotactic properties.[5]

Therapeutic option in hematology

Hepcidin is currently not available for treating human medical illnesses. However, its vital role in the regulation of iron homeostasis and in the development of disorders of iron metabolism, has initiated research on novel therapeutic approaches targeting the hepcidin–ferroportin axis. Hepcidin agonists or agents that stimulate hepcidin expression could be used for the treatment of hereditary hemochromatosis and iron-loading anemia. A small peptide, composed of nine N-terminal amino acids of hepcidin has shown direct *in vivo* bioactivity.[38] Indirect hepcidin agonistic action has been achieved in mice models of hereditary hemochromatosis using pharmacological doses of BMP6 and inactivation of the Tmprss6 enzyme on the hepatocyte membrane, in two different studies.[39,40]

On the other side of this spectrum, iron-restrictive anemia associated with infection, inflammation, cancer, and renal disease might be amenable to therapy, using hepcidin antagonists. Along with a monoclonal antibody against hepcidin, various natural and modified antagonists of BMP (noggin, soluble HJV, dorsomorphin), IL-6 antagonists (antibody directed against IL-6 receptor), activators of HIF (erythropoietin and

erythropoiesis-stimulating agents), and siRNAs and antisense oligonucleotides raised against genes involved in hepcidin or its regulatory pathways are the novel approaches to achieve hepcidin antagonistic actions currently under research and development.[38]

CONCLUSION

Hepcidin is a novel hepatocyte-derived peptide hormone. It has a vital function in iron homeostasis. In recent years, the focus of interest on hepcidin has been shifted from iron regulation to a broader perspective. It has shown prospects of being considered as an important diagnostic as well as a prognostic marker in a wide spectrum of hematological and nonhematological disorders. The current research on the mechanism of action and regulation of hepcidin has enabled the understanding of newer pathological associations as well as development of newer diagnostic assays and therapeutic options.

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How to cite this Article: Kali A, Charles MP, Seetharam RK. Hepcidin - A novel biomarker with changing trends. Phcog Rev 2015;9:35-40.

Source of Support: Nil, **Conflict of Interest:** None declared