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# Review on iron regulatory hormone Hepcidin

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***Abstract:****To study a review on iron regulating hormone Hepcidin. Hepcidin is a major regulator of iron metabolism. This review is done on Hepcidin and its role in regulation of iron in our body.Hepcidin is a 25-amino acid peptide that is synthesized in hepatocytes. Liver derived hepcidin peptide is secreted in response to iron and inflammation and interacts with the iron export protein ferroprotein.Hepcidin can control both the total body iron by modulating intestinal iron absorption as well as promote iron available for erythropoiesis by affecting the efficiency with which macrophages recycle iron from red blood cells.This review will give information about the hormone Hepcidin and regulation of iron in the humanbody.*

***Keywords:*** *Hepcidin, Hormones, Metabolism, Anemia*

## 1. INTRODUCTION:

Hepcidin - a iron regulatory hormone synthesized in hepatocytes, which is a 25- amino acid peptide. It regulates the iron transport from dietary sources, for extra cellular maintenance of iron concentration. Iron gets transported from recycled senescent red cells in macrophages, in the duodenum and are stored in hepatocytes. Hepcidin is responsible for the interaction of iron with its receptors ferroportin - a transmembrane export protein. Ferroportin is abundant in cell surface of reticulo endothelial macrophages and on base lateral membrane of duodenal enterocytes [1]

Hepcidin synthesis can be increased and decreased by iron loading, anaemia and hypoxia respectively[2].. Hepcidin is considered as a negative regulator of iron absorption and recycling, because it inhibits the release of iron at both the sites by binding to cell surface ferroportin and causing internalization and subsequent degradation [3]. The iron store in our can be indicated by hepcidin [4].. Liver iron stones and hemoglobin levels are unaffected by Hepcidin injection.However, no data measuring the direct effect of injection Hepcidin on iron absorption rates are available [5]. Hemochromatosis genes which encode molecules that regulate hepcidin synthesis any change or mutation in this gene will modify ferroportin and make it less responsive to Hepcidin[6]. Hepcidin interacts directly with the intestinal epithelium. It controls the amount of iron absorbed from the diet by modulating the uptake mechanism of apical membrane [7].

## 2. Discovery:

Hepcidin, a peptide associated with inflammation was discovered in human blood and serum in the year 2000 and was named since it was produced in the liver and it had bactericidal properties[8][9] . Hepcidin is a key regulator of circulation of iron in humans. During inflammation the hepcidin level is high since there is a fall in the serum iron and it us because of trapping of iron in the macrophages and liver cells[10].

Hepcidin was first isolated from human urine and named on the basis of its site of synthesis and its in-vitro

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antibacterial properties. In human urine, the predominant form contains 25 amino acids, although shorter 22 and 20 amino acid peptides are also present [11].

Soon after this discovery, researchers discovered that Hepcidin production in mice increases in conditions of iron overload as well as in inflammation. In the lab of Nancy Andrew in Boston. Liver tissue of two patients with liver tumors showed severe microcytic anaemia that does not respond to iron supplements. These tumors over produces Hepcidin and contained large quantities of mRNA. This Anaemia was cured by surgical removal of these tumors. This is the first clinical condition that linked Hepcidin with anaemia. These discoveries suggested that hepcidin regulates the absorption of iron into the body [12].

**3. Importance of iron in our body:**

Iron is a major component of hemoglobin and myoglobin and other enzymes involved in redox reactions and energy metabolism. Most of the iron in plasma is destined for erythropoiesis in the bone marrow. The daily loss of iron from the body is small (1-2 mg/day) and Western diets usually contain more iron than is necessary to replace the losses. Dietary iron is absorbed predominantly in the duodenum and absorption increases in response to increased iron requirements due to systemic iron deficiency, anemia or hypoxia. Iron is very important for all living organisms from small microorganisms to humans. Available in a variety of food stuffs like; beef, chicken, oysters, mussels, mollusks, etc. Iron is essential to life due to its unusual flexibility to serve as both an electron donor and acceptor. Iron can also be potentially toxic. Free radicals are produced by donating or accepting an electron, when iron is free inside the cell, causing damage to intracellular organelles resulting in cell death. This binding allows cells to benefit from iron while also limiting its ability to do harm [13][14].

Iron is present at the center of the heme molecule of iron binding protein. Humans and most bacteria carry out redox reactions and electron transport processes. These reactions are required for oxidative phosphorylation. The iron sulphur proteins are another important group of iron-containing proteins. Some of these proteins are also essential parts of oxidative phosphorylation. Iron in the haemoglobin of red blood cells, transport oxygen from the lungs to the tissues. Iron is a main component of myoglobin to store and diffuse oxygen in muscle cells. The human body needs iron for oxygen transport. That oxygen is required for the production and survival of almost all cells in our bodies (mature erythrocytes being one exception). Human bodies tightly regulate iron absorption and recycling. Humans have no physiological mechanism for excreting iron. Iron overload is prevented by iron absorption. If the body can't regulate the absorption then the person ends up in the toxicity of iron, which is because of iron overload [15].

**4. Regulation of hepcidin:**

Hepcidin production by the liver is controlled by iron stores within macrophages, inflammation , hypoxia, and erythropoiesis . Macrophages communicate with the hepatocyte to regulate hepcidin release into the circulation via eight different proteins: hereditary hemochromatosis protein, transferrin, bone morphogenetic protein 6 (BMP6), matriptase-2, neogenin, BMP receptors, and transferrin [9].

Systemic iron homeostasis is regulated by Hepcidin. Hepcidin controls plasma iron concentration and tissue distribution of iron by inhibiting intestinal iron absorption. Synthesis of hepcidin is homeostatic ally increased by iron loading and decreased by anaemia and hypoxia. Hepcidin is also elevated during infections and inflammation, causing a decrease in serum iron levels and contributing to the development of anaemia of inflammation, probably as a host defense mechanism to limit the availability of iron to invading microorganisms. At the opposite side of the spectrum,

hepcidin deficiency appears to be the ultimate cause of most forms of hemochromatosis, either due to mutations in the hepcidin gene itself or due to mutations in the regulators of hepcidin synthesis. The emergence of hepcidin as the pathogenic factor in most systemic iron disorders should provide important opportunities for improving their diagnosis and treatment [16].

Most of the iron absorbed from the diet or recycled from hemoglobin is destined for developing erythrocytes whose production is increased after such erythropoietic stimuli as blood loss or hypoxia. It is therefore not surprising that hepcidin production is also homeostatically regulated by anemia and hypoxia [17] . In principle, the hepcidin response to anemia could be mediated by tissue hypoxia, increased erythropoietin levels, increased erythropoietic activity, or decreased plasma or tissue iron consequent to its consumption by the expanded pool of erythrocyte precursors [18]. Hepcidin is not only an iron-regulatory hormone but also an important link between host defense and iron metabolism. During infection and inflammation, hepcidin synthesis is markedly increased by a mechanism that is independent of iron status or erythropoietic activity [1]. Hypoferrima developed so rapidly within hours of an inflammatory stimulus. The plasma transferring compartment contains about 3 mg of iron and functions as a transit compartment through which about 20 mg of iron flows each day, largely generated by recycling of senescent erythrocytes. In simplified terms, this means that plasma iron turns over every 3-4 hours. If hepcidin could completely block iron recycling, this would result in about a 30% drop in plasma iron in an hour. Because of the shorter lifespan of their erythrocytes, hypoferremia develops even more rapidly in mice. The hypoferremia response is likely to have a role in host defense but it remains to be shown which microbes are effectively targeted for by this mechanism [19].

## 5. Role of hepcidin:

Hepcidin is a regulator of iron metabolism. Hepcidin inhibits iron transport by binding to the iron export channel ferroportin which is located on the basolateral surface of gut enterocytes and the plasma membrane of reticuloendothelial cells (macrophages). Hepcidin ultimately breaks down the transporter protein in the lysosomes. Inhibiting ferroportin prevents iron from being exported and the iron is sequestered in the cells [20] . By inhibiting ferroportin, hepcidin prevents enterocytes from allowing iron into the hepatic portal system, thereby reducing dietary iron absorption. The iron release from macrophages is also reduced by ferroportin inhibition. Increased hepcidin activity is partially responsible for reduced iron availability seen in anemia of chronic inflammation such as renal failure [21] . Any one of several mutations in Hepcidin result in juvenile hemochromatosis. The majority of juvenile hemochromatosis cases are due to mutations in hemojuvelin [22].

Inflammation has a major effect on iron homeostasis, reducing intestinal iron absorption, sequestering iron in macrophages, and thereby results in decreasing serum iron levels. There is now substantial evidence that these effects of inflammation are also mediated by hepcidin. In Wild-type mice there was increased hepcidin-1 mRNA and produced hypoferremia in response to turpentine-induced inflammation, but in USF2/Hamp knockout (KO) mice, the hypoferremia response was lost [23]. These experiments were confounded by the severe iron overload in Hamp KO mice, which could by itself provide enough iron to relieve hypoferremia, so they need to be replicated in hepcidin-deficient humans or Hamp KO mice that are depleted of iron. In favor of the role of hepcidin in inflammatory hypoferremia, IL-6 and supernatants of lipopolysaccharide stimulated macrophages readily induced hepcidin in human hepatocytes and hepatic cell lines [14]. Moreover, urinary hepcidin level rose within hours of IL-6 or lipopolysaccharide infusion into human volunteers, on the average 7-fold, and hypoferremia coincided with the rise of Hepcidin [19][19]. The stimulatory effect of IL-6 on hepcidin is transcriptional and depends on STAT3 interactions with a STAT3-binding element in the hepcidin promoter [24][25][26] . Other cytokines and direct effects of microbial molecules on hepatocytes may also contribute to the inflammatory increase in hepcidin.

**6. Hepcidin deficiencies:**

Hepcidin deficiency causes a lot of disorders which result from lesions in the genes that encode Hepcidin, ferroportin, or their physiologic regulators and as "secondary" those disorders that are caused by disease that originate outside the iron homeostatic system.

Hereditary hemochromatosis - is a hepcidin deficiency disorder.

The gene mutated in this is HJV, Hepcidin, HFE. These are groups of disorders which are characterized by excessive absorption of iron from the daily diet and storage of this iron in the liver and in other body parts like adrenal glands, heart, skin, gonads, joints, and the pancreas. Patients with this disorder are susceptible to disease like poly arthropathy, adrenal insufficiency, heart failure or diabetes and Cirrhosis which are due to increased absorption of iron from our diet . The hereditary form of the disease is most common among those of Northern European ancestry, in particular those of Celtic descent [27] . It is an inherited disease, where mutation is present in both the genes [28] .

The disease is protean in nature and many of the signs and symptoms below are uncommon and most patients with the hereditary form of haemochromatosis do not show any overt signs of disease nor do they suffer premature morbidity [29]. The disease presents the following signs and symptoms malaise, fatigue, joint pain, liver cirrhosis, insulin resistance, congestive heart failure, arrhythmia or pericarditis , dysfunction of endocrine organ, and damage to adrenal gland [30][31].

HH disorder can also be caused by autosomal dominant mutations in ferroportin that cause resistance to hepcidin. It is a very rare disorder. Of several ferroportin mutations that give rise to this syndrome, the one best characterized is C326S, which causes early-onset parenchymal iron overload with documented high or high-normal hepcidin levels [32].

Hypotransferrinemia - is an autosomal recessive metabolic disorder due to deficiency in ferroportin which is a plasma protein present in our blood for iron transport. It is also called Atransferrinemia. It affects organs like liver, heart, pancreas, thyroid , kidney, and bone joints. In severe cases arthropathy, hypothyroidism and heart failure in severe cases. Treatment with infusions of plasma or purified Apo transferrin may stabilize or correct the anemia.

A case study was done in 1961 on a 7-year-old girl who died of heart failure with atransferrinemia. The half-normal levels of transferrin in her parent’s bloodstream supported the notion that this disorder is transferred in an autosomal recessive pattern [33]. Anaemia of inflammation - Anaemia of inflammation is also known as anaemia of chronic diseases. It is the second commonest anaemia. The common chronic diseases presenting with anaemia of inflammation being Chronic infection - tuberculosis, lung abscess, endocarditis, Hodgkin’s diseases, breast cancer, lung cancer. Autoimmune diseases - rheumatoid, arthritis, lumps, Crohn's diseases. Symptoms are pale skin, lack of energy,fatigue,headache,lethargy, shortness of breath during exercise and dizziness

Normally our body recycles iron from old red blood cells and uses it to use it to make new red blood cells. In anaemia of inflammation, the body's recycle mechanism does not occur properly and it is held up as macrophages in the cells and macrophages are a type of red blood cell.

Other diseases - Beta thalassemia is one of the most common congenital anemia arising from lack of β-globin synthesis. In beta thalassemia one of the main features is the excessive iron absorption, which leads to morbidity and mortality. In the serial analyses β thalassemia haemoglobin level decreases and concentration of iron in organs like liver, spleen and kidney increases. The overload of iron is associated with low levels of hepcidin. It was found that patients with Beta thalassemia also have low hepcidin levels [33]. The researchers hypothesized that more iron is absorbed in Beta thalassemia than is required for production of red blood cells (erythropoiesis) and whether increasing the concentration of hepcidin in the body of such patients might have some therapeutic effect on this condition by

limiting iron overload. It was demonstrated that a moderate increase in expression of hepcidin in β-thalassemic mice limits iron overload, decreases formation of insoluble membrane bound globins and reactive oxygen species, and improves anemia. Increased hepcidin expression in mice demonstrated an increase in the lifespan of their red cells, reversal of ineffective production of red blood cells andincrease in the size of spleen (splenomegaly), and an increase in total blood haemoglobin levels. This data suggests that therapeutics that would increase hepcidin levels or act as hepcidin agonists might help treat the abnormal iron absorption in individuals with beta thalassemia and related disorders [34].

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