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Influence of Hepcidin in the Development of Anemia

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Abstract

Anemia presents a global public health problem. It is related to several factors, ranging from deficiency in nutrients from food to genetic alterations in iron absorption and metabolism. In this context, hepcidin is a peptide molecule that regulates iron homeostasis. Hepcidin is synthesized, in part, by hepatocytes. In physiological conditions, increased serum transferrin, serum iron, inflammation, and erythropoiesis trigger stimuli that promote hepcidin antimicrobial peptide (HAMP) gene transcription and hepcidin synthesis. However, in pathological situations, an overexpression of hepcidin occurs, an increase in the plasma concentration that damages the organism. Hepcidin contributes to the pathogenesis of iron deficiency anemia, anemia of inflammation, in hemoglobinopathies. Then, there is a restriction of the availability of iron to the tissues and the formation of new erythroid precursors, with the consequent development of anemia.

Keywords: anemia, chronic disease anemia, ferroportin, hepcidin, HAMP gene, iron deficiency, iron deficiency anemia, IRIDA, iron homeostasis, sickle cell, thalassemia

1. Introduction

The World Health Organization (WHO) characterizes anemia as a condition in which the concentration of hemoglobin is below 13 g/L for males and 12 g/L for females. Anemia is a condition in which the number of red blood cells or their oxygen carrying capacity is insufficient to meet physiological needs, which vary according to the age, gender, altitude, smoking status, and pregnancy status. Iron deficiency (ID) is considered to be the most common cause of anemia, although there are other conditions such as folate deficiency, vitamin B12 and vitamin A, chronic inflammation, parasitic infections, and hereditary disorders related to iron metabolism.
and the formation of hemoglobin [1]. Iron deficiency impairs erythroid cell formation and decreases hemoglobin synthesis. Iron has functions vital to the body, requiring daily intake through food and the constant recycling of senescent erythrocytes by macrophages to maintain adequate concentration. In view of this, the control of iron uptake and movement in the form of ferritin occur through the plasma hepcidin concentration, a peptidic hormone, which regulates iron metabolism through the negative modulation of ferroportin [2–4].

Iron deficiency and/or hypoferremia involve(s) changes in hepcidin concentration and iron metabolism markers (serum iron, transferrin and ferritin). Hepcidin has been shown to act in the direct inhibition of food absorption of iron in the duodenum, in blocking the release of iron recycled by macrophages and in controlling the movement of iron stores contained in hepatocytes, enterocytes, and macrophages [5–7]. However, the serum concentration of hepcidin assists in the prognosis of the main hematological alterations involving the iron metabolism with the development of anemia, influencing the severity of iron deficiency anemia, iron-refractory iron deficiency anemia, anemia of chronic disease, hemoglobinopathies, mainly HbS, thalassemias, and hemolytic anemia, among others.

2. Hepcidin: function and structure

The hepcidin molecule ("hep" hepatic origin, "cidin" antimicrobial activity) was described in the year 2000; it is an antimicrobial peptide that acts in parts in innate immunity and iron metabolism. It was isolated from human blood and urine [3, 4]. The relationship between hepcidin and its action on iron homeostasis was demonstrated in knockout animals for the gene encoding hepcidin, the HAMP gene, in a clinical condition compatible with hemochromatosis. However, transgenic animals with increased hepcidin expression had decreased serum iron, erythropoiesis deficiency with severe microcytic-hypochromic anemia [8, 9].

Extrahepatic production of hepcidin occurs to a lesser extent, and it is believed that at these sites it acts as an antimicrobial peptide. In the kidney, hepcidin modulates the defense barriers against urinary tract infections. In the heart, hepcidin maintains iron homeostasis in cardiac tissue by an autocrine regulation of the expression of ferroprotein on the surface of cardiomyocytes [10, 11]. Hepcidin is encoded in a molecule containing 84 amino acids, a prehepcidin, which undergoes proteolytic cleavage in one region and gives prohepcidin, composed of 64 amino acids. Prohepcidin is biologically inactive and is cleaved subsequently by the enzyme furin in a specific NH$_2$ region, resulting in biologically active hepcidin composed of 8 cysteine residues, bound by 4 bisulfide bridges containing 25 amino acids [3, 4, 8].

2.1. Iron

Iron is an integral constituent of several metalloproteins; being essential for oxygen transport, it acts on the transfer of electrons from the respiratory chain and in various catalytic reactions. The biological versatility of iron is based on its ability to act as electron donor and receptor. Thus, iron can easily convert between its oxidized state, ferric iron (Fe$^{3+}$), and reduced state,
ferrous iron (Fe$^{2+}$). Spontaneous aerobic oxidation of Fe$^{2+}$ to Fe$^{3+}$ is practically insoluble at physiological pH, which hinders the acquisition of iron by cells and tissues, requiring other proteins and enzymes that facilitate the conversion of Fe$^{3+} \rightarrow$ Fe$^{2+}$ [12].

An adult human body contains approximately 3–5 g of iron, with men presenting approximately 55 mg/kg and women 44 mg/kg. Approximately 70% of body iron is stored as heme in hemoglobin present in erythroblasts and erythrocytes. Muscle contains about 2.5% iron in the form of myoglobin; iron reserve in the macrophages corresponds to 5% and in the hepatocytes to 20%. Diet maintains the iron stores, and a diet rich in red meat provides approximately 10–15 mg iron/day as heme (Fe$^{2+}$) present in myoglobin and hemoglobin. Around 20–40% of heme and 10–20% of nonheme iron (Fe$^{3+}$) are available for absorption. This turnover maintains the iron stores for the physiological needs, since the quantities of iron required by the organism vary according to the age group and gender of each individual [12, 13].

2.1.1. Iron homeostasis

Iron in both ferrous and ferric forms is absorbed in the duodenum in different ways. In order for ferric iron to be absorbed more efficiently, it must undergo an oxidation of its state from Fe$^{3+}$ to Fe$^{2+}$. However, some factors influence the absorption of iron Fe$^{3+}$, such as a diet rich in polyphenols and phytic acid, since these molecules bind to iron from vegetables and cereals, as well as deficiency of vitamin C and antioxidant substances, gastritis caused by Helicobacter pylori, and bariatric surgery, among other factors [14].

The oxidation reaction, Fe$^{3+}$ $\rightarrow$ Fe$^{2+}$, is performed by the enzyme cytochrome b duodenal (dCytB), present on the plasma membrane of enterocytes. Thereafter, ferrous iron is mobilized via the divalent metal-1 type metal transporter (DMT-1) to the intracellular medium. However, heme iron from the diet is internalized by the heme-1 carrier protein (HCP-1) into the cells. Both forms of iron derived from the diet may be stored as ferritin or transported to different tissues and organs (Figure 1) [15, 16].

2.1.2. Transport and delivery of iron to the cells

Transferrin transports iron into tissues. It is necessary that the iron in its iron state be oxidized to ferric iron through the oxidizing action of the enzymes hephaestin and ceruloplasmin [17]. Transferrin is a beta-globulin, which has an ellipsoidal shape, with two iron-binding sites. Transferrin saturation (TS) determines its functional status. In healthy subjects, about 30% of transferrin is saturated with iron. When the two iron-binding sites are occupied, it is termed diferric transferrin; when only one site is connected to iron, it is called monoferric transferrin; and when no site contains iron, it is called apotransferrin [18].

Under physiological conditions, transferrin saturation determines its affinity to cells and cell receptors; the less saturated and/or iron-bound, the greater the affinity of apotransferrin to enterocytes. On the other hand, the diferric transferrin has a greater affinity to the transferrin receptors (TfR1 and TfR2) than the monoferric transferrin receptors. The ability of apotransferrin is to prevent the accumulation of free iron not bound to transferrin (NTBI), which is a redox-active and toxic [12, 18].
Transferrin binds the TfR1 and TfR2 receptor subunits on the cell surface to form a ferrocarbonate-transferrin complex. The cell internalizes this complex by endocytosis. After the internalization of the complex, the acidic pH present in the intracellular medium favors the release of Fe$^{3+}$, and then it is reduced to Fe$^{2+}$ by the ferroreductase, Steap3 (six-transmembrane epithelial antigen of prostate 3) and transported in the intracellular medium by DMT1. The receptor-transferrin complex returns to the cell surface and the apotransferrin is released to a new cycle. Replenishment of transferrin occurs through iron stored in macrophages [12, 18–20].

### 2.1.3. Recycling and storage of iron

Each erythrocyte contains approximately $1.2 \times 10^9$ molecules of the heme group associated with hemoglobin, with approximately 200 billion erythrocytes reaching senescence and intravascular hemolysis each day. Hemoglobin released from senescent erythrocytes can be easily oxidized, releasing the heme group, which can promote protein oxidation, generate lipid peroxides, and damage DNA through the formation of reactive oxygen species [21]. The heme group is metabolized within the splenic macrophages by the activity of heme oxygenase (HO-1 and HO-2). The intracellular concentration of HO-1 increases after heme phagocytosis. The breakdown of heme by HO-1 gives rise to Fe$^{2+}$ and the remaining portion is biliverdin, which after the action of the enzyme biliverdin reductase gives rise to bilirubin. About 70% of body bilirubin comes from erythrophagocytosis [15].

Iron is stored in the body in the form of ferritin. All the cells of the organisms have reserves of irons. Ferritin is a complete molecule composed of a protein, apoferritin, and iron. Apoferritin
has a shell shape of 24 subunits, which stores about 4000 iron atoms. Three different genes encode apoferritin: the heavy chain (H) is encoded by the FTH gene, located on chromosome 11; the light chain (L) is encoded by the FTL gene located on chromosome 19; and the mitochondrial apoferritin is encoded by the FTMT gene and is on chromosome 5. In situations that decrease serum iron and erythropoietic activity, stored iron is mobilized from the interior of ferritin by the action of natural chelating and reducing agents such as glutathione and cysteine, into the intracellular medium, into the cell’s cytosol and then exported to the extracellular medium through the ferroportin [22].

2.1.4. Export of stored iron to the extracellular medium

Ferroportin is a transmembrane protein that mediates the stored iron efflux of macrophages, enterocytes, and hepatocytes into plasma, maintaining systemic iron homeostasis. Through stimuli originated by the increase of serum iron, serum transferrin, erythropoiesis, and proinflammatory cytokines, the HAMP gene transcription occurs, increasing the plasma concentration of hepcidin, which binds to ferroportin in the extracellular medium through its portion N-terminal, promoting its phosphorylation, internalization, and ubiquitination in lysosomal endosomes. As with other receptors that undergo ligand-induced endocytosis, the interaction of hepcidin with ferroportin causes a conformational change in ferroportin and covalent modifications of one or more cytoplasmic segments to initiate endocytosis. The specific interaction between hepcidin and ferroportin, when altered, favors the iron accumulation of the organism [23, 24].

2.2. Regulation of hepcidin expression

Serum hepcidin concentration is regulated by several factors that may increase or decrease its serum concentration. Among the main factors that increase the serum concentration of hepcidin are infections and chronic diseases, hepatic diseases, alcohol abuse, genetic alterations in the TMPRSS6 gene, blood transfusion, dialysis in renal disease, and administration of iron by orally or intravenously. The factors that decrease the serum concentration of hepcidin are erythropoiesis, erythropoietin, and erythropoietin-stimulating agents in order to allow the movement and delivery of iron in the bone marrow. Genetic alterations are related to the development of hemochromatosis, hypoxia, and steroid hormones, among others [25–29].

These factors activate the HAMP gene, located on chromosome 19q13 to transcribe the hepcidin mRNA. Literatures have described several HAMP signaling pathways, without much evidence. However, two pathways are described as the main ways of regulating and activating the HAMP gene. These pathways are related to increased serum iron and the production of inflammatory cytokines. The first signaling pathway occurs through the induction of the pathway related to bone morphogenetic proteins (BMPs), being activated by the concentration of circulating iron. Second, the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway is activated by inflammatory stimuli. Increased transferrin saturation and its binding to the TfR1 and TfR2 receptors cause a displacement of the HFE protein to its receptor, TfR2, where activation of hemojuvelin (HJV), a BMP coreceptor occurs. Then, intracellular signaling proceeds until the activation of HAMP gene [30].
The BMP cytokines are proteins that are part of the great family transforming growth factor-β (TGF-β). Activation of the BMP path requires interaction with its BMP-r receptor and with the BMP-R receptor coreceptor, the HJV protein. The integration between HIV-BMP-R induces phosphorylation of the BMP receptor, thus activating it. This activation generates an intracellular signaling cascade through the binding of a threonine/serine kinase type I and type II receptor complex [31–33].

The activated receptor type II activates the type I receptor. This action may activate other receptors and other intracellular proteins, such as the R-SMAD protein, which regulates the phosphorylation of SMAD-1/5/8 proteins, leaving them active. However, these proteins cannot promote the transcription of the HAMP gene but are necessary for union with the SMAD-4 factor. After formation of the SMAD1/5/8/−SMAD4 complex, migration to the nucleus commences. These proteins bind to the promoter region of the HAMP gene by initiating its transcription. The negative intracellular feedback of the SMAD pathway is performed by the SMAD-7 protein, which prevents phosphorylation and formation of the SMAD-1/5/8/−SMAD4 complex. Currently, it has been thought to use SMAD-7 as a therapeutic target to suppress hepcidin mRNA in diseases where hepcidin overexpression occurs. The BMP/SMAD pathway has shown promise in the development of candidate hepcidin suppressors [34–37].

Inflammatory mediators influence the expression of HAMP gene through the JAK/STAT signaling pathway. Initially, a conformation shift on the subunits of the JAK receptors is required. JAK receptors are present in the intracellular medium coupled with other transmembrane receptors. When the inflammatory cytokines, interleukin-6 (IL-6), IL-1β, IL-22, activin-B, and interferon-α bind to their receptors, they activate the cytoplasmic JAK. As an example, IL-6 binds to its receptor, which is formed by two subunits: one alpha subunit (IL-6-R) and another beta subunit (GP130). When IL-6 binds to IL-6-R, a dimerization of gp130 occurs, which recruits the cytoplasmic JAK to phosphorylate the gp130 protein. After phosphorylation, the STAT-1 and STAT-3 proteins bind to gp130 and autophosphorylate soon after the formation of a complex that migrates to the nucleus and induces the transcription of the HAMP gene (Figure 2) [38–43].

2.3. Hepcidin and anemia

2.3.1. Iron deficiency and iron deficiency anemia

Iron deficiency (ID) and iron deficiency anemia (IDA) are distinct forms, even though they are often used as synonyms. Capellini et al. [44] define “iron deficiency is a health-related condition in which iron availability is insufficient to meet the body’s needs and which can be presented with or without anemia.”

ID defines a condition in which iron stores are reduced (ferritin <12 μg/L) in the absence of anemia, but the supply of iron to erythropoiesis is maintained. IDA occurs when there is no iron available for erythropoiesis, characterizing a decrease in hemoglobin synthesis. When IDA is the result of progressive ID, it usually develops slowly and can be well tolerated by organisms, making its diagnosis difficult. The diagnosis of IDA requires laboratory tests, since the symptoms may be present, but they are nonspecific and often ignored [45].
The treatment for ID/IDA is done with oral iron replacement; however, when the serum concentration of hepcidin is increased, this iron is not absorbed in the duodenum and it is necessary to use injectable iron. ID is commonly reported in obese individuals due to their elevated serum concentration of hepcidin and reduction of iron absorption due to inflammation developed by adipose tissue [46, 47]. Serum hepcidin, ferritin, and iron content in hepatic and skeletal muscle are increased in obese individuals, and after weight loss, values tend to normalize [48].

2.3.2. Chronic disease anemia

Chronic disease anemia (CDA) or anemia of inflammation (AI) refers to the impaired production of erythrocytes associated with chronic inflammatory conditions, including cancer, chronic infection, or autoimmune diseases. Recent data indicate that anemia can also occur in situations of severe and acute inflammation, or with persistent inflammatory signs that occur in obesity, aging, and renal failure. Anemia of inflammation is defined by low concentration of serum iron (<60 μg/dL) with normal or elevated serum ferritin (>12 ng/mL) and saturation of transferrin around 15% [49].

The clinical picture of anemia, established in the AI, is due to the production of cytokines as IL-1β, INF-γ, and TNF-α, which influence negatively on erythropoiesis, by inhibiting the production of erythropoietin (EPO). In addition, when the erythropoietin concentration is decreased, there is an increase in hepatic synthesis of hepcidin. Other factors that influence the alteration of iron metabolism through modulation of hepcidin expression are interleukin IL-6, IL-1β, IL-22, INF-γ, and TNF-α. These cytokines act on the HAMP gene through the activation
of the signaling pathway JAK-STAT. Due to the intense production of inflammatory media-
tors, the serum concentration of hepcidin is high, restricting the mobilization of iron stores of
ferritin in enterocytes and hepatocytes and making it difficult for the delivery of iron by mac-
rophages in the bone marrow to generate new precursors erythroid. Due to this fact, serum
ferritin is elevated and transferrin is decreased [49, 50].

Morbid obesity is considered a chronic inflammatory state with altered iron metabolism. ID
may initially occur due to malabsorption of iron in the duodenum, as well as increased hepci-
din due to the chronic inflammatory process. Most obese individuals present serum transferrin
saturation below 20%, and after weight loss, markers of iron metabolism normalize over a period of up to 4–6 months. This evidence supports the hypothesis that obesity favors iron
sequestration with the development of anemia of inflammation, but AI in obesity may or may
not be preceded by ID [50, 51].

In some more serious situations, such as patients with chronic kidney disease (CKD), the ane-
emia is mainly due to the lack of erythropoietin. During the development of CKD, the kidneys
lose the ability to produce erythropoietin, causing less red blood cell production, resulting
in anemia. Another interesting fact is that the inflammation generated by CKD stimulates
the synthesis of hepcidin, which prevents the mobilization of iron stores in the macrophages
present in the marrow. These facts alone or together contribute to the development of anemia
in CKD. Besides that, the renal function plays a role in clearance of hepcidin. Renal dys-
function results in decreased clearance of hepcidin and consequent storage of hepcidin with
development of anemia. As CKD progresses, the serum concentration of hepcidin increases
independent of the inflammatory state. In this clinical context, it is common to develop an
anemia of inflammatory disease with ID anemia, since several compartments involved in the
metabolism and maintenance of iron stores are compromised [50, 52–54].

2.3.3. Iron-refractory iron deficiency anemia

Iron-refractory iron deficiency anemia (IRIDA OMIM # 206200) is an autosomal recessive dis-
ease characterized clinically by microcytic and hypochromic congenital anemia, unresponsive
to treatment with oral iron and partial response to treatment with parenteral iron, and has
low transferrin saturation, low iron concentration, high serum ferritin, and excess hepcidin.
Mutations present in the TMPRSS6 gene, which encodes the matriptase-2 protein, confer the
pathogenesis of IRIDA. The matriptase-2 protein is a type II transmembrane serine protease,
expressed in hepatocytes, enterocytes, and other cells. The biological function of matriptase-2
is to regulate hepcidin expression in liver cells [55–57].

The polymorphism of rs855791 (p.Ala736Val) of the single nucleotide polymorphism (SNP)
type is the most frequent underlying pathology. In this genetic alteration, the amino acid
alanine is replaced by a valine at position 736, in the serine protease domain of matriptase-2.
Thus, the protein matriptase-2 does not undergo proteolytic cleavage, losing its function of
negatively regulating the action of hepcidin. Another variant is T287N, which inactivates
hemojuvelin cleavage. Cleavage of the hemojuvelin is required so that it binds to the BMP
receptors inactivating the signaling pathways of the HAMP gene [58–60].
The appearance of anemia in IRIDA occurs in early childhood; there are reports that the process of instituting anemia begins in the intrauterine life. The most serious cases of IRIDA reported are in children. The clinical-laboratorial picture presents as characteristics of the disease congenital hypochromia, microcytic anemia with very low MCV, low transferrin saturation (<15–5%), and abnormal iron absorption with the use of defective iron. IRIDA can develop with varying degrees of anemia, ranging from severe to moderate or mild; the common feature among all is resistance to oral iron therapy and genetic inheritance with changes in the TMPRSS6 gene. Initially, the concentration of hepcidin in mild and moderate IDA and IRIDA is high, restricting the iron absorption in the duodenum and making it impossible to mobilize the iron stores. However, in the treatment of IDA with iron replacement, the serum concentration of hepcidin decreases rapidly, facilitating the absorption and replacement of the iron stores [61, 62].

2.3.4. Sickle cell anemia

Hemoglobinopathies are hereditary changes that affect hemoglobin. These changes may be structural or deficient synthesis. In structural hemoglobinopathies, the change in one or more hemoglobin chains occurs. In the vast majority of cases, such changes are caused by point mutations, which determine the exchange of one amino acid by another. Among structural hemoglobinopathies, hemoglobin S is the most common inherited hematological abnormality in human being. Its etiology is genetic, with an autosomal recessive pattern and due to mutation in the beta globin gene, producing a structural alteration in the molecule. Approximately 300,000 infants are born per year with sickle cell anemia globally [63].

In its homozygous form, it is called sickle cell anemia and, where at least one gene is HbS, is called sickle cell disease. The hemoglobin S (HbS) variant results from the substitution of valine for glutamic acid in the sixth amino acid of β-globin. Sickle cell disease or anemia is characterized by reduced blood hemoglobin concentration, susceptibility to infections, recurrent vaso-occlusion, tissue infarction, and complications such as stroke, avascular necrosis of the joints, or nephropathy. Tissue hypoxia of vessel obstruction facilitates the deoxygenation of HbS, its crystallization, hepatic eruption, and chronic hemolysis. The iron overload present in sickle cell anemia is due to blood transfusions, requiring the use of oral chelants, since free iron is toxic. The high concentration of inflammatory cytokines increases the retention of cellular iron stores and in the endothelial reticulum, due to the high serum hepcidin. Use of iron chelators in the treatment of sickle cell anemia lowers the serum concentration of hepcidin and mobilizes iron stores for erythropoiesis [64–66].

2.3.5. Thalassemias

The thalassemias are derived from partial or total deficiency in the synthesis of one or more types of globin chains, leading to defective production of hemoglobin. Thalassemia is an autosomal recessive genetic disorder. In the literature, alpha thalassemia, thalassemia intermediary, and beta-thalassemias have been described. Mediterranean population is most affected by the disease. Among the main symptoms are fatigue and weakness, due to the development of anemia; pale or yellowish skin; increased direct bilirubin; facial bone deformities and slow
growth; lack of iron in hemopoiesis; abdominal bloating, due to the increase of blood and iron deposition in the organs of abdominal cavity; and dark urine, due to the presence of hemoglobin, urobilinogen, and iron. Individuals with thalassemia also develop serious heart problems. Thalassemia is an anemia with iron overload. The iron overload results from the blood transfusions patients often receive and the hemolysis of the red blood cells [67].

The relationship between thalassemia and hepcidin was initially observed in mice with thalassemia. These animals had a low expression of hepcidin and severe anemia. Decreased serum hepcidin concentration favors increased iron uptake from diet and iron overload. Anemia, tissue hypoxia, and increased erythropoietin production observed in beta-thalassemia promote suppression of hepcidin. Another mitigating factor in the thalassemia clinical framework is the overexpression of the erythroid hormone erythroferrone (ERFE). ERFE regulates the synthesis of hepcidin, together with erythropoietin, during erythropoiesis [68, 69].

3. Conclusion

The development of anemia is complex and requires better understanding and studies related to iron metabolism. Hepcidin controls the metabolism of iron, but when an imbalance occurs in its serum concentration, it causes serious damage to the organism, it is necessary to consider hepcidin level for the laboratory diagnosis of anemias, a practice that is not performed, and to establish a reference value for hepcidin.

Conflict of interests

The authors state that there are no conflicts of interest.

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