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Review Article

Hepcidin as a Regulator of Iron Homeostasis: A Review

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ABSTRACT

Iron is an essential element for all the cells of the organism. The balance of the levels of iron must be regulated so that the metal is not with low or in surplus levels. The aim of this review was to evaluate the action of hepcidin in the iron homeostasis and its clinical application. Bibliographic survey was carried out on PUBMED, LILACS and Scielo databases, in the period from 2000 to 2015, relating to the hepcidin as a biomarker of iron homeostasis. A total of 76 studies published in international and national magazines were selected. The understanding of the hepcidin function, a small peptide hormone, produced by the liver, contributed for a better understanding of the various mechanisms involved in the iron homeostasis, positioning itself as an important regulator and a pathogenic factor in common disorders of iron. The hepcidin disruption in involved in the several pathologic processes related to the iron disorders. The hepcidin deficiency causes the iron overload in the hereditary hemochromatosis and iron loading anemia, while the surplus of hepcidin contributes for the development of anemias due to iron restriction in inflammatory diseases, infections, some types of cancer and chronic kidney disease. For this reason, the hepcidin can become a useful tool for the diagnostic and provide new therapeutic approaches for diseases associated with the iron deregulation. However, more researches are necessary to clarify the mechanisms of hepcidin in the iron regulation and to outline the contribution in the different disorders of the metabolism of iron.

Keyword: Hepcidin, Iron homeostasis, anemia, iron overload.

INTRODUCTION

The iron is a necessary nutrient for erythropoiesis and cellular metabolism. As there is no exist physiological mechanism to iron overload excretion, the iron dietetic absorptionis a process that need to be well regulated. [1] The evolution of molecular information about the iron transport and homeostasis provided a comprehensive understanding of complicated mechanisms involved in this process. It is known that the iron levels must be strictly regulated to supply the essential nutrient that is involved in oxygen distribution, ensuring that this metal not be deficient neither excessive. [2,3]

By being an essential element for cellular homeostasis, the iron capacity to donate and receive electrons makes it indispensable to many cellular reactions. It is a functional key component by oxygen transport and storage and participates of many proteins formation. [4,5] Evidences suggest that the primary mediator of iron homeostasis is the hepcidin. Discovery independently by three laboratories and related for the first time in 2000 and 2001, [6] the hepcidin is a peptidic hormone, constituted by 25 aminoacids, synthesize

at the hepatocytes, induced by iron overload, infection, lipopolysaccharides (LPS) and pro-inflammatory cytokines, such as Interleukin–6. [7-9]

The hepcidin principal action is internalizes and degrades the ferroportin, protein responsible to the iron transference for circulation through enterocytes and monocytes. [10,11] Thus, a high level of hepcidin take to intestinal iron absorption suppression and iron release from macrophages and hepatocytes, while a low concentration of hepcidin take the acceleration of iron release from these cells. [12]

The hepcidin interaction with the ferroportin and your works in iron transport regulation has enabled an understanding at a molecular level of absorption homeostatic regulation andiron distribution and to your behavior in hereditary hemochromatosis and anaemia of inflammation. [13] are available for research tests of mass spectrometry and immunochemical serum hepcidin. These tests would be useful in anaemia diagnostic by iron deficiency and hereditary hemochromatosis stratification and diagnostic, being that hepcidin deregulation is the reason this disease and genetic tests many times are inconclusive. The tests also can help to guide treatment with iron in the anaemia. [14]

The hepcidin seems to be the central regulator of homeostasis systemic of iron. The deregulation of your production results in a variety of diseases associated to iron disturb. Techniques for your dosage and therapeutic applications about hepcidin are beginning to arise. Many researches are in progress to clarify the hepcidin mechanisms in iron regulation and to outline your contribution of their changes in iron disorders. [15]

The objective this study is to discuss the hepcidin importance as primary regulator in iron homeostasis and your clinical application.

Iron Metabolism

The iron is a very important metal for all cells. The lack of iron results in cell death, but the iron overload can be also harmful. [16] The human beings not have effective mechanisms to eliminate the iron overload, so, the only way to keep the balance is through intestinal regulation. [13] The two main mechanisms involved in iron homeostasis are regulated by intracellular levels, according to the iron quantify that cell has, and another systemic, where the hepcidin has crucial role. [17,4]

The human beings have about 3 to 5 grams of iron in organism; the most of them are connected to hemoglobin. Largely, the iron is strictly preserved through your recycling, from hemoglobin of de senescent erythrocytes. The greatest storage of iron occurs in the liver, or more specifically in hepatocytes, where the majority iron is connected with ferritin. [16]

The liver contributes to repair of iron homeostasis by iron storage and regulation of hepcidin secretion. The iron of diet is absorbed by intestinal epithelium and then is carried for circulation through ferroportin. The iron absorbed is quickly linked to protein of iron connection, transferrin. The iron linked to transferrin is transmitted to erythroid precursor cells. Another important source of iron is iron recycling to de senescent erythrocytes by macrophages. The iron overload in plasma will be stored in hepatocytes, under the form of ferritin. [18]

The regulation of intracellular iron metabolism is coordinated by expression or activity by protein involved in iron absorption changes, use and storage. The IRE-IRP (iron-responsive elemento - iron-regulatory protein) is the central regulator to iron cell metabolism, because allows fast changes in protein synthesis answering to variations in intracellular iron concentrations. The synthesis protein control enabled by IRE-IRP system occurs in translation level in cytoplasm, including the transcription initiation, the core

processing and mRNA exportation to cytosol. The protein exportation also can be transcriptionally regulated by iron in a HIF-dependent (hypoxia-inducible factor). Moreover, many inflammatory cytokines, including the interferon-C and interleukins 1, 2 and 6 can change them RNA transcription to protein iron metabolism. [19]

The regulation of iron metabolism by cytokines, particularly in relation to IL-6, is the responsible for anemia pathogenic mechanism chronic disease. Whereas in inflammation anemia the hepcidin production is stimulate by cytokines increase. [20,8] In general, the cytokines link to the surface receptors starts a cascade of signaling that regulates the transcription in core inside. As example, the IL-6 increases the genes expression - key, like the HAMP (hepcidin) that codifies the hepcidin by JAK (Janus kinase)/STAT (signal transducer and activator of transcription). The ferritin regulation by cytokines corresponds with your behavior protein of acute phase, being secreted in liver for answer to inflammation. [21,19]

In relation to regulation iron systemic, the last decade checked that hepcidin discharged a central role. This small peptide made by 25 amino acids is synthesized by liver. [14] The hepcidin is central regulatory hormone that controls the iron absorption by intestine and irons recycling senescent erythrocytes can cause the internalization of ferroportin protein. [18] The ferroportin is the only iron protein exporting in mammals that contributes for systemic level iron homeostasis. Increases the iron availability through release from duodenum, spleen and liver cells, of absorption locals, recycling and iron storage respectively. [22]

The hepcidin acts blocking the main iron flows in plasma, like the iron absorption in intestine, the recycling iron release through macrophages and the iron mobilization from hepatic repository. A hepcidin increase causes a reduction of iron levels concentrations in plasma, limiting the iron availability for hemoglobin synthesis. [23] Consequently, when the iron is deficient the hepatocytes do not synthesize the hepcidin, allowing more iron input in plasma. [24]

Hepcidin

The hepcidin was isolated independently in three studies. Firstly Krause et al. [25] described the isolation in blood ultra filtrate a new human peptide abundant in cysteine with 25 amino acids, with antimicrobial activity, which called LEAP-1 (liver-expressed antimicrobial peptide). At the same time, Park et al [26] isolated the same peptide from the human sample which called hepcidin due your liver origin and your antimicrobial properties. In the same year, Pigeon et al. [27] reported that this new peptide discharged a role specific while the iron overload and showed different functions to your antimicrobial activity, and almost simultaneously Nicolas et al. [28] demonstrated that a defect in expression by hepcidin gene was responsible for iron overload in liver of mice, similar to human hemochromatosis. Later the same authors observed that hepcidin over expression resulted in severe anemia by iron deficiency showing the fundamental role that hepcidin have in iron homeostasis. [29]

The hepcidin is synthesized predominantly in hepatocytes, but your low levels of expression can be find in others cells and tissues, including the neutrophils, [30] monocytes, [31,32] lymphocytes, [33] adipocytes [34] and brain. [8] The hepcidin extra-hepatic role still is not completely clarified, [3] but probably have more relevance to control of autocrine and paracrine system of flows of body iron. [8]

The biggest molecular event unleashed in plasma by hepcidin is the lisossomal ferroportin internalization and degradation that quickly results after the hepcidin-ferroportin connects plasma membrane. [14] Inside the plasma the hepcidin can circulate connected with the carrier protein, α-2-macroglobulin. [35] The

ferroportin is the greatest iron exporting in macrophages and in basolateral membrane of duodenal enterocyte. [36] It is expressed from duodenals enterocytes, macrophages involved in iron recycling from senescent erythrocytes and e hepatocytes involved in iron storage. [8]

The hepcidin biological actions were facilitated by your ferroportin connection, the main efflux duct by cell iron. [37] In case of duodenals enterocytes, the hepcidin growth prevents the diet iron circulation to circulation through ferroportin. The fast iron kidnapping in macrophages and the enteric reduction to long term absorption of iron, can eventually to take to anemia, decreasing the iron availability for erythropoiesis. On the other hand, the hepcidin lack takes to iron duodenal absorption do not regulated and subsequent the iron overload. [38]

The hepcidin expression is mediated by bone morphogenetic protein (BPM) and signaling pathways JAK2/STAT3, [39,40] under non-pathological conditions the organism iron levels regulate your expression. The hepcidin production is homeostatically regulate through the anemia, hypoxia and inflammation, [13,41] the regulation by inflammation likely developed as a host defense mechanism to limit the iron availability for microorganisms. [38,15]

According to Ganz, [42] when the hepcidin concentrations are decreased, the ferroportin molecules exposed in plasma membrane and export iron, even as when the hepcidin concentrations raise, this links with ferroportin inducing your internalization and degradation, progressively decreasing the released iron. This way, the hepcidin regulation by iron is a complex process that needs the multiple proteins coordination, including the BMP6 (bone morphogenetic protein 6), hereditary hemochromatosis protein, transferrin 2 receptor, matriprase-2, BMP receptors and transferrin. [39]

Nowadays, two hepcidin ways has been identified (hepcidin-20 and hepcidin-22). [38,26] Due to be small, the hepcidin is probably filtered in kidney sat first passage and reabsorbed in proximal tubule. Moreover, has been detected and quantified in urine samples, because your fast excretion implies in greater regulation of serum levels, modulating your synthesis. [43,38]

Iron disorders diagnosis

The disarrangement of cellular or systemic iron metabolism can follow many pathological processes. The hepcidin deregulation is found in anemia of chronic illness, anemia by iron deficiency, cancer, hereditary hemochromatosis, and ineffective erythropoiesis, like the β-thalassemia. The hepcidin production by inflammatory macrophages to control the local iron availability is a relevant phenomenon in disorders characterized by low degree inflammation, such as obesity, diabetes and metabolic syndrome. The hepcidin-ferroportin route has been proposal to mediate chronics and acute changes in iron distribution that contribute for host defense in large infections. The studies realized with iron rare genetic disorders were beginning to clarify the important phatogenic or protection mechanisms in main human diseases. So, the hepcidin regulation is the interested theme to improvement of harmful effects of any iron deficiency or overload. [40,39]

Recent studies showing that the dosage of hepcidin levels are useful to evaluate the iron reservations in lactating women, [44] classification and diagnosis of hemochromatosis rare forms, in distinction between ferritin rise by iron overload or inflammation and in clinical diagnosis of iron deficiency. Your levels also can to be used to monitor with iron supplementation, even before the hemoglobin levels growth to be observed. [15]

Another relevant aspect is that the interleukin-6 is a powerful inductor of hepcidin expression during the inflammation, and an increase of hepcidin synthesis is involved in etiology in inflammation anemia. [45,46] In a study in

patients with rheumatoid arthritis and anemia was evaluated the IL-6 effects and blocks therapies about anemia. Before the treatment, the level of serum hepcidin of patients with rheumatoid arthritis showed signisicative positive relation with serum ferritin levels, reactive protein, factor of vascular endothelial growth. These correlations suggest that exist a link between hepcidin, homeostasis unusual of iron and inflammation. Thus, speculated that the hepcidin excessive production take to increase in iron storage and reduces the blood iron quantify available for hemoglobin synthesis and erythrocytes production, what takes to iron-deficiency anemia in rheumatoid arthritis. [47]

The anemia is also being in patients with chronic renal disease (CRD), actually the treatment for this condition involves the administration of higher doses of erythropoiesis stimulators agents. Studies have shown that the effects of erythropoiesis stimulators agents were powered by iron parenteral administration that suggests an iron restrictive component is implicated in pathogenesis of anemia. The patients with CRD have hepcidin growth levels that probably results from a combination of inflammation and inadequate hepcidin clearance by kidney. [15] Due to your renal elimination and regulation by inflammation, is possible that the progressive renal insufficiency changes the hepcidin metabolism, affecting subsequently the iron enteric absorption andiron reserves availability. [38]

Due your action in iron regulation, the hepcidin can be used like a biomarker for patients clinical evaluation with anemia by iron deficiency. Studies have shown that the hepcidin levels demonstrate higher predictive value than saturation transferring or ferritin levels for patients in supplementation with iron. [48]

The key factor in etiology of hereditary hemochromatosis is associated to changes in hepcidin gene expression (HAMP). The partial or total expression loss by gene HAMP restrict the iron input to circulation, so, the therapy with hepcidin hormone would be useful to avoid the excess iron deposition, particularly in young hemochromatosis severe forms. Alternatively, the uses of hepcidin agonists can be a valuable therapeutic strategy to raise the hepcidin serum levels or the favouring to internalization and ferroportin degradation. [49,50]

The ferroportin-hepcidin route regulation contributes substantially in iron regulation in systemic level and also has a role key in cancer. [51] The cancerous cells increase the metabolically available iron not only to increase the iron absorption and decrease your storage, but also by lowering iron efflux, also the ferroportin correlated metabolically with iron available. In patients with breast cancer have been shown that the high and low hepcidin-ferroportin was associated with favorable prognosis, even in women with lymph nodes metastases, that shows the ferroportin and hepcidin laboratory evaluation can be used in breast cancer prognosis, as well as in many others malignant tumors. [52]

Thalassemia syndromes and others anemias with erythropoiesis ineffective are characterized by hepcidin synthesis reduction caused by a erythroid signal still not identified, [53] however, although the iron overload has in β-thalassemia, the hepcidin levels are not high. [54]

In β-thalassemia the hepcidin deficiencies enable the increase of iron intestinal absorption with similar rates with described in severe hereditary hemochromatosis. In anemia with iron overload the hepcidin like to be regulated by influences to erythropoietic activities which suppress your expression. [55] Pasricha et al. [56] showed that in patients with β-thalassemia which have high levels of iron overload, the hepcidin levels are lower than the hoped because exuberant erythropoiesis. The erythropoietic reduction activity by erythrocytes

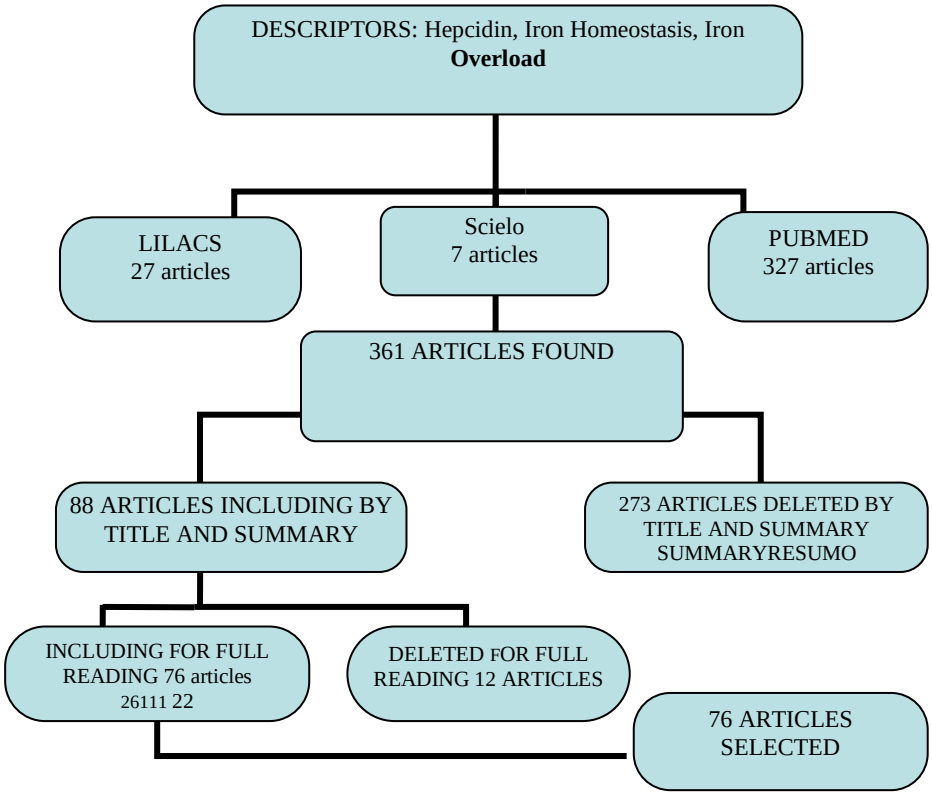
transfusions relieve partly the hepcidin suppression, thus, the transfusions effects about hepcidin is due to anemia correction associated for erythropoietin decrease concentrations and is not related to iron level from erythrocytes transfused.

Although the relevance hepcidin sérum levels to your diagnostic application, methodologies for your dosage are still limited. Recently, many validated kits are commercially available; however, the results from different assessments evidenced the necessity of techniques validation as well as the respective values of reference, [44] the majority of essays published were realized in small group of patients and in large part in animals models. [57, 41,53]

MATERIALS AND METHODS

Descriptive review of the scientific literature, addessing themes regarding to iron homeostasis and hepcidin and your relation with the iron disorders metabolism.

The review process was realized by a search in electronic database base, Pubmed (National Lybrary of Medicine's Biomedical Literature), in 2015, using the descriptors Hepcidin (hepcidin), Iron Homeostasis (iron homeostasis) and iron Overload (iron overload). Were found 361 articles in total, which passed by title and summary review to select which were associated with researched theme "hepcidin with regulator of iron homeostasis "and were published from 2000 years. After this analysis were selected 88 articles. After full reading, were selected 76 articles. The others twelve articles, were deleted due are not related to search objectives.



Picture 1–Flow chart analysis of articles.

RESULTS AND DISCUSSION

The iron is essential for human life, but become toxic if in overload. To prevent the iron overload and to keep your homeostasis all cells are able to regulate your levels through post-transcriptional control of iron genes. To systemic level, the iron homeostasis is regulate by peptide

hormone hepcidin, being that the your regulation loss control predisposes mightily for pathologies characterized by iron deficiency or overload. Changes in iron metabolism control are also found in obtained disorders, such as anemias by ineffective erythropoiesis and chronic diseases anemia associated with common inflammatory conditions. The hepcidin deficiency causes the iron overload in hereditary hemochromatosis andiron-loading anemias, whereas the hepcidin excess contributes to iron restriction anemia development in inflammatory diseases, infections, some kind of cancer and chronic renal disease. In these terms many studies point that hepcidin can become a useful tool for diagnosis and open ways for new therapeutic interventions in iron disorders. [54, 15]

The hemochromatosis ways more clinically severes are caused hemojuvelin (HJV) gene mutations, transferrin 2 receptor (TFR2) or hepcidin (HAMP), [58,59] however in the most hereditary hemochromatosis cases are identified gene mutations HFE (C282Y). Wu et al. [60] described the molecular function of HFE gene, that prevent the morphogenetic bone protein degradation (BPM) and receptor type I (ALK 3), increasing the expression of this desse receptor in hepatocytes cell surface, consequently is activate the hepcidin transcription. In studies with animals model knock out for hepcidin gene showed the hereditary hemochromatosis induction, which hepcidin serum levels are undetectable and observed the iron plasma increase andiron massive accumulation of parenchyma. [61] Although the red blood cells concentrated transfusions being often the iron predominant source in thalassemic patients, nowadays was described that the patients who not transfusion dependents also develop the iron overload. The main contributor for iron total load in these patients is the increasing intestinal absorption instead blood transfusion. [62] But in iron overload anemias the hepcidin seems to be regulated by erythropoietic influences that suppress your activity and occur the iron load increase. [63] According to Nemeth, [23] inpatients with β-thalassemia or iron overload anemia, the erythroblasts stimulated by erythropoietin produce suppressors that act on liver to suppress the hepcidin production. Kautz et al., [64] demonstrated that the hepcidin levels also can be suppressed inβ-thalassemia by bone marrow factors derived through erytroferrone (ERFE) hormone that controls the hepcidin suppression during the erythropoiesis stress.

In African children anemic the hepcidin was the main predictor of iron incorporation in erythrocytes, suggesting that the hepcidin can be used as control way of oral iron use in diet. [65] In low weight newborns the serum hepcidin answered well with iron supplementation, in which hepcidin concentrations increased significantly with an answer to iron load and were significantly lower in children with iron deficiency being associated with serum ferritin and with others iron status indicators. [44,66]

The iron homeostasis disbalance is characterized like a key element for inflammation anemia pathogenesis. Eijk et al., [67] investigated the hepcidin antagonist (lexaptepid) effectiveness in prevention of iron loss in serum patients during the systemic inflammation to evaluate this drug effect about innate answer. The treatment with lexaptepid was well tolerated and effective in blockade of serum iron reduction by inflammation during the systemic inflammation. Ready Sasu et al., [68] to explore the hepcidin role in inflammation anemia, in animal model, demonstrated that hepcidin over expression was enough to cause iron deficiency and anemia and the hepcidin neutralization reversed this effect. The modulation in inflammation anemia was examined by mRNA from hepcidin suppression through an antibody antihepcidin therapy that reversed the

inflammation anemia proving to be able to iron redistribute from storage locals as well as to permit the iron absorption from normal diet. [69]

In the patients oncological group the hepcidin was inversely correlated with hemoglobin, particularly in patients with more advanced disease, also found high hepcidin levels associated with ferritin growth, serum iron and transferrin saturation lower to level. Furthermore, the more lower levels of hemoglobin were associated with interleukin pro-inflammatory elevation, mainly, the IL-6, showing a positive correlation with the IL-1, hepcidin and ferritin. [70] Durigova et al., [71] also demonstrated a positive correlation between hepcidin and hemoglobin levels in cancer patients, associating the lower hepcidin levels with predictive to anemia development.

In patients with chronic renal disease (DRC) the hepcidin levels and your is forms are increased, [72] which hepcidin levels showed positively associated with iron stocks, ferritin, inflammation and diabetes, and inversely correlated with erythropoiesis, residual renal function and male gender. According to Weerd et al., [73] the hepcidin is involved in pathophysiological way from renal anemia andiron availability.

Although the hepcidin potential for iron disorders diagnostics, the laboratory tests methodologies to measure hepcidin concentrations are limited. Actually, the hepcidin tests are available only for search, [15] being that the majority of studies in humans was based in hepcidin urinary excretion. [74] However, still is not established the relation between the urinary and serum hepcidin levels and the reference values between age group and population genre. Many mass spectrometry immunoassays and assays were demonstrated to evaluate the serum hepcidin, plasma and urine. Immunoassays like ELISA has potential for large diffusion in clinical places being more appropriate for large scale quantification due your high efficiency and low-cost when compared with mass spectrometry assays. However, in ELISA methodology lost the absolute specificity for hepcidin isoforms in function of many grades of antibodies cross reactions. [75, 76,15]

CONCLUSION

The iron is essential for all body cells and is not limited by erythropoiesis or liver diseases. Recent researches contributed for knowledge about the principal regulatory ways of iron homeostasis in organism, showing the hepcidin role in this process that is appointed with potential laboratory biomarker to iron metabolism disorders.

The hepcidin discovery and your iron homeostasis role revolutionized the understanding about the iron overload pathogenesis and iron restriction anemia sand has promoted the new therapeutic diagnostics methods development for these disorders. However, the laboratory tests methodologies to determine the hepcidin concentrations are limited, where as the majority of human studies are not still standard neither your respective reference values in population. This way, more studies are needed to clarify the hepcidin mechanisms in iron regulation and to delineate your specific contribution in different disorders of iron metabolism, as well as to determine your reference values to your laboratory routine insertion.

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