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HEREDITARY HEMOCHROMATOSIS: THE ROLE OF PROTEINS IN IRON HOMEOSTASIS

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Abstract: Iron is an essential mineral for organic activities, and inadequate levels cause pathologies. A lack of it leads to iron deficiency anemia, whereas excess leads to hemochromatosis, which is a disease caused by excessive accumulation of iron, mainly in the liver. There are two types of hemochromatosis: acquired, which is caused by excessive iron intake or multiple blood transfusions, and hereditary, caused by mutations in the HFE gene, which lead to reduced hepcidin synthesis and consequent excessive iron absorption by the intestines. This accumulation of iron in the body leads to harmful consequences, such as liver cirrhosis, diabetes mellitus, atrophy, and myocardial dysfunction, among others. In both types of hemochromatosis, and especially in hereditary hemochromatosis, some proteins play a fundamental role in iron absorption and metabolism, with highlight to hepcidin. The present literature review aims to study hemochromatosis characteristics and the functions of proteins, especially hepcidin, in iron homeostasis.
Keywords: hemochromatosis, iron metabolism, proteins, hepcidin.

INTRODUCTION

Iron (Fe) is of fundamental importance for the homeostasis of the human body, being characterized as a key component in the transport and storage of oxygen molecules such as hemoglobin, myoglobin, and other enzymes that catalyze oxidation-reduction reactions. The latter are necessary for the production of energy and of various metabolic intermediates for the body's defense (ANDERSON *et al*., 2007). Fe is a mineral required for erythropoiesis and cell metabolism, but physiological mechanisms to promote the elimination of iron accumulation in the body have not yet been described. Due to this factor, Fe absorption needs to be very effective (MAST *et al*., 2013), since the levels of this micronutrient in the body must be regulated so that it is neither deficient nor excessive (BEAUMONT *et al*., 2006).

In all animal species, the concentration of Fe in the body is regulated in order for this molecule to be available when needed and for toxicity to be prevented, as an excess or accumulation of it can lead to the formation of reactive oxygen species, and its decrease can trigger diseases such as anemia (DE DOMENICO *et al*., 2007). For this reason, the maintenance of Fe stores is essential, as many human diets contain enough to replace small losses of this micronutrient. However, when Fe intake is more abundant, the absorption is adequately controlled, apparently (DE DOMENICO *et al*., 2007).

The Fe present in food can be found in two forms: as a heme group, with its absorption by the human gastrointestinal tract (GIT) occurring easily, and non-heme group, with a difficult absorption of this micronutrient by the GIT (ZAGO, 2013).

In the body, Fe is very useful in metabolic processes and, thus, the body itself has two effective ways of storing it: as ferritin and as hemosiderin (CAIRO, 1997). The concentration of this mineral in human tissues, in its turn, varies according to sex, being around 800-1,000 mg in men and around 300 mg in women (ZAGO, 2013).

Ferritin is a protein present in the cell cytoplasm and acts in the Fe storage process. It is a molecule made up of 24 polypeptide chains, forming two different types of bonds: H (Heavy) or L (Light) bond. The differentiation of bonds depends on the encoding that occurs in the chromosomes (ZAGO, 2013). The H form is the largest and is present in tissues that require a rapid exchange of iron, such as red blood cells. The smaller form, known as L, on the other hand, enters the composition of tissues that involve a long storage of iron, such as the liver (CAIRO, 1997).

Hemosiderin corresponds to the degraded form of ferritin, when the protein shell has partially disintegrated, allowing the iron to form aggregates. It can be visualized under light microscopy after staining with Prussian blue or Perl's reaction; hemosiderin stains with potassium ferrocyanide in the presence of hydrochloric acid (Fairbanks *et al*., 2001).

In the cytoplasm, iron can follow two paths: be stored by ferritin in the cell itself and later be used in cell metabolism, or proceed to the basolateral membrane, towards the plasma. The path to be followed by Fe is determined by a set of regulatory proteins encoded in DNA. These proteins, called HFE and TfR, positively or negatively alter the absorption of iron and its storage, depending on the body's needs (GROTTO, 2010).

From the moment that Fe proceeds to the basolateral membrane, it can undergo the action of two other proteins: ferroportin, which acts in the transport of iron to the blood plasma and can be inhibited by hepcidin, and hephaestin, which is used to convert iron into its divalent form, resulting in ferric Fe (Fe^{3+}), which is thus removed from the cell into the blood (ZAGO, 2013). However, if Fe takes the direction of blood plasma, it will bind to transferrin, which is capable of transporting it to any cell in the body, as needed (GROTTO, 2010).

Fe is released through mediation by the TfR receptor, which is divided into two: TfR1, expressed in most cells, and TfR2, specific to hepatocytes, erythroid cells, and duodenal crypt. When the transferrin-Fe complex comes into contact with the cell surface, there is a reaction mediated by the clathrin protein, which is transported to the cytoplasm (ZAGO, 2013).

Once inside the cytoplasm, changes occur in the endosome, and iron reverts back to ferrous iron (Fe^{2+}). Then, the transferrin-Fe complex is cleaved, and the DMT1 protein removes the iron from within the endosome, causing the structure to return to the surface of the apical membrane and the proteins inside to be reused in new processes (ZAGO, 2013). After this reaction, iron binds to protoporphyrin and is used in the synthesis of the heme group, being a part of the composition of red blood cells (GROTTO, 2008). It is observed that the human body has no effective means for dealing with the excretion metabolism of iron, and the latter is stored properly (ZAGO, 2013).

Research on iron metabolism is quite incipient in view of the wide range of blood-related diseases, as the largest portions of this mineral are concentrated in the blood. Thus, given the importance of the subject, this bibliographical review seeks to compile the findings, up to the present moment, on one of the manifestations resulting from metabolic iron deficiency, hemochromatosis, characterized as the excessive absorption and consequent excessive accumulation of iron, which, in the long term, can cause serious damage to the organism carrying this genetic disease.

MATERIALS AND METHODS

This study is characterized as a systematic literature review and was conducted through searches on scientific platforms, such as SciELO (http://scielo.org) and PubMed-NCBI (https://pubmed.ncbi.nlm.nih. gov/). It comprised studies addressing the properties of iron (Fe) in the human body, metabolism, absorption, and pathologies resulting from a low or high absorption of this micronutrient. For the search, the keywords used were iron, blood, homeostasis, hereditary hemochromatosis, proteins, hepcidin, health, combined with the Boolean operator "and", as follows: iron and hereditary hemochromatosis, proteins and iron homeostasis, and hepcidin and iron homeostasis.

A total of 72 scientific articles were found. By means of the analysis and selection strategy, free access studies published in Portuguese and English were included, totaling 59 scientific articles. Thirteen articles were excluded for not meeting the pre-established criteria, such as: not being available in full, or not being in line with the study theme.

RESULTS AND DISCUSSION

IRON ABSORPTION AND METABOLISM DISORDERS

The emergence of any situation of abnormality in Fe absorption and metabolism leads to the development of pathologies, such as anemia, which happens due to hepcidin deregulation. It can also cause cancer and ineffective erythropoiesis, as in the case of β-thalassemia and hereditary hemochromatosis.

Hepcidin production in the macrophages to control iron absorption is of great importance in situations of inflammation, such as obesity, diabetes, and metabolic syndrome. The hepcidin-ferroportin conjugation, in its turn, mediates acute and chronic alterations in Fe distribution and shows that iron distribution contributes to defense against infections. Recent studies have reported that Fe disorders are related to important pathogenic mechanisms, as well as mechanisms for protection against several human diseases. In this way, learning about hepcidin regulation is of great importance to understand the harmful consequences of iron deficiency or overload (ZHAO *et al*., 2013).

Hepcidin expression during inflammation is induced by interleukin-6, and an increase in this expression cause anemia of inflammation (NISHIMOTO *et al*., 2007). Due to its iron-regulating action, hepcidin can be used as a biomarker to evaluate patients with iron deficiency anemia (BREGMAN *et al*., 2013), and hepcidin levels can also be used to monitor treatments such as iron supplementation (AREZES *et al*., 2015).

HEREDITARY HEMOCHROMATOSIS (HH)

Hereditary hemochromatosis (HH) is an autosomal recessive disease in which there is a mutation of the HFE gene, leading to a lack of hepcidin synthesis and, consequently, to abnormal Fe absorption in the GIT. This generates serious clinical issues, such as lesions and permanent dysfunctions in tissues (CANÇADO, 2010).

In hereditary hemochromatosis, the key factor is linked to changes in the expression of the hepcidin gene (HAMP). A total or even partial loss of expression of this gene alters the entry of Fe into the circulation (PIETRANGELO, 2015).

There is a great relationship between HH and the transferrin saturation rate; from the moment that hepcidin, an important regulator of Fe metabolism, is lost, the concentration of ferric ions tends to increase rapidly, reaching a point at which there is nothing else for Fe to bind , so it moves freely in the blood. Because it is highly toxic due to its oxidative action, free Fe can cause lesions, cell destruction, tissue fibrosis, sclerosis, and even the failure of the affected organ (CANÇADO, 2010).

Clinical manifestations of HH include fatigue, arthralgia, hypogonadism, weight loss, liver cirrhosis, diabetes mellitus, cardiomyopathies, and skin hyperpigmentation. It is diagnosed through the patient's anamnesis, laboratory tests, and genetic tests that look for mutations in the HFE gene (CANÇADO, 2010). Among laboratory tests, liver biopsy is one of the best methods and is used to diagnose Fe overload. In addition to providing a histochemical demonstration of increased iron in the liver tissue, a biopsy also assesses the degree of liver lesions, when present (ANGELUCCI *et*

al., 2000).

The search for mutations in the HFE gene, especially C282Y, H63D and S65C mutations, is suggested for individuals with high values of transferrin or ferritin saturation, or even both, for individuals with increased tissue iron, and for first-degree relatives of individuals diagnosed with HH (POWELL *et al*., 1998).

A mutation in the HFE gene indicates the existence of a genetic alteration that predisposes a person to developing the phenotype of the disease, but it is not sufficient for an HH diagnosis, since the penetrance of the mutant allele and the phenotypic expression of the disease are low, which makes it difficult to predict who will or will not develop the disease (BACON *et al*., 1999).

For HH treatment, therapeutic phlebotomy is the most adequate, as it is safer and more cost-effective. It consists of a withdrawal of blood (350 to 450 ml), once or twice a week, with the aim of causing iron depletion, reaching serum ferritin concentrations below 50 μg/L and transferrin saturation below 50%. When these concentrations are reached, the patient can undergo phlebotomy within longer periods of time. Patients who initiate phlebotomy before the onset of irreversible organ damage are given a normal life expectancy (CAMASCHELLA *et al*., 2000). It is known that hepatocellular carcinoma is the most common cause of death in patients with cirrhosis (NJAJOU *et al*., 2004). If phlebotomy is not feasible due to some other organic problem of the patient, agents such as iron chelators can be used (FRANCHINI *et al*., 2004).

HH is classified according to the genetic alteration found, with its cases being divided into types 1, 2A, 2B, 3 and 4 (Table 1) (OMIM, 2022). However, this classification does not include alterations in genes other than HFE, HJV, HAMP, TRF2 and SLC40A1.

The liver is the main storage site for Fe; an accumulation in the hepatocytes is a result of excessive iron absorption via the intestine, while an accumulation in the phagocytic mononuclear system derives from an increased phagocytic activity of the macrophages. Over time, excess iron is deposited in various organs and tissues, especially the liver, spleen, endocrine glands, myocardium, and bone marrow, causing cell and tissue damage, fibrosis, and functional insufficiency (PIPERNO, 1998).

The greatest toxicity caused by iron is related to free Fe, which is not bound to transferrin. When the amount of iron absorbed exceeds the iron-chelating capacity, it leaves the macrophages and enters the circulation, and when the saturation capacity of plasma transferrin is exceeded, free and excess iron is deposited in the hepatocytes and other parachymal cells (AJIOKA *et al*., 2002).

HH is a frequent pathology in Caucasians; the first case found in the scientific literature was reported in 1865, by Trousseau, when he described a patient with liver cirrhosis, diabetes mellitus, and skin hyperpigmentation. However, the disease was recognized as being a consequence of progressive accumulation of iron in the organism in 1889, by Von Recklinghausen (PIETRANGELO, 2003). In 1935, Sheldon explained the hereditary nature of hemochromatosis, and Simon was responsible for a great advance in the understanding of genetic transmission and the molecular bases of the disease in the 1970s and 1980s. Later on, the disease was understood as an autosomal inheritance of HH and its association with the HLA-A molecule of the class I histocompatibility complex on chromosome 6 (SIMON *et al.*, 1975). Only in 1996 did Feder and his collaborators identify the HFE gene (FEDER *et al.*, 1996).

TYPE 1 HH (HFE GENE CHANGES)

It is an autosomal recessive disease caused

HH TYPES	MOLECULAR CHANGES	REFERENCES
1	HFE	FEDER *et al.*, 1996
2A	HJV	PAPANIKOLAOU *et al.*, 2004
2B	HAMP	PARK *et al.*, 2001
3	TRF2	KAWABATA *et al.*, 1999
4	SLC40A1	DONOVAN *et al.*, 2000

Table 1: Genetic alterations related to the pathophysiology of hereditary hemochromatosis (HH)

MUTATION	REPLACEMENT	POSITION	CAUSE	NUCLEOTIDE
C282Y	Cysteine by tyrosine	282	Guanine to Adenine transversion	845
H63D	Histidine by aspartate	63	Cytidine to Guanine transversion	187
S65C	Serine by cysteine	65	Adenine to Thymidine transversion	193

Table 2: Main mutations in type 1 HH and changes found.

Source: FERREIRA *et al.*, 2008

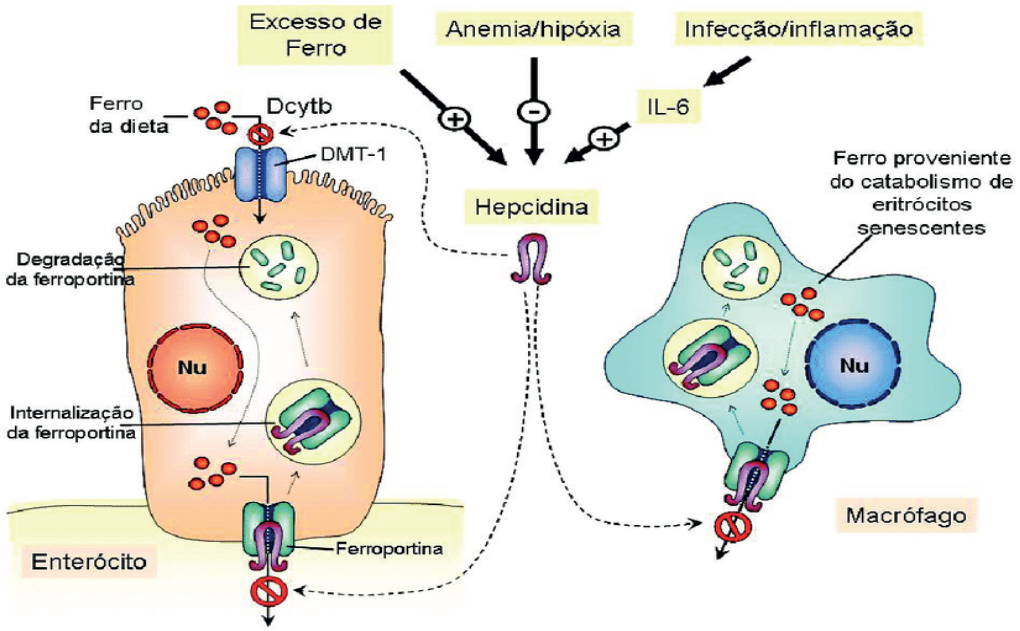

Figure 1: Action of hepcidin on iron metabolism. By forming the complex with ferroportin, it leads to its degradation. In the enterocyte, iron is not transported to the outside of the cell, and absorption is inhibited. In the macrophage, iron accumulates inside, reducing the iron available for erythropoiesis. Adapted from Grotto, 2008.

STUDY, YEAR AND LOCATION	SKIN COLOR	C282Y MUTATION (%)	H63D MUTATION (%)	S65C MUTATION (%)
AGOSTINHO, *et al*, 1999, Campinas (N = 227)	W BL BR	1.4 1.1 1.1	16.3 7.5 1.1	NR NR NR
CALADO, *et al*, 2000, Ribeirão Preto (N = 320)	W + BL + BR	2.2	14.3	NR
PEREIRA, *et al*, 2001, São Paulo (N = 395)	W BL BR	3.7 0.5 0.7	20.3 6.4 13.0	NR NR NR
OLIVEIRA, *et al*, 2003, São Paulo (N = 148)	W BL	1.4 0.0	8.6 2.4	0.6 0.3
TERADA, *et al*, 2009, São Paulo (N = 542)	NR	2.1	13.6	0.6

Table 3: Allele frequency of the C282Y, H63D and S65C mutations of the HFE gene in Brazil

by mutations in the HFE gene, which lead to excessive Fe absorption and consequent Fe overload. The HFE protein is expressed in the enterocytes and hepatocytes, and its function is to control iron in the body (PIETRANGELO, 2006). Apparently, this control starts from the moment that the HFE protein, in association with β2-microgobulin, binds to the transferrin 1 receptor and reduces the affinity of the latter with transferrin, controlling the entry of iron into the body (FEDER, 1998). A second hypothesis suggests that the HFE protein is involved in the regulation of hepcidin expression (NICOLAS, 2003).

The HFE gene is located on chromosome 6p21.3 and composed of 7 exons (FEDER, 1996). Its product is a protein with 348 amino acids. There are several mutations described in the HFE gene (V53M, V59M, H63H, Q127H, Q283P, P168X, E168Q, E168X, among others), but the most researched are C282Y, H63D and S65C (Table 2) (CAMASCHELLA *et al.*, 2002).

YPE 2A HH (HEMOJUVELIN GENE CHANGES)

The hemojuvelin (*HJV*) gene, also known as *HF2*, is made up of 4 exons found on chromosome 1q21 and encodes a protein of 426 amino acids. Said protein, in its turn, is expressed in the liver, heart and skeletal muscles (PAPANIKOLAOU *et al.*, 2004). Individuals with mutations in the *HJV* gene have lower concentrations of hepcidin, which is the iron overload mechanism (ROETTO *et al.*, 2005).

Type 2A HH, which is characterized by a mutation in the *HJV* gene and iron overload, is an autosomal recessive disease that presents severity in individuals younger than 30 years (CAMASCHELLA, 2002). There are several mutations that can occur in the *HJV* gene, such as G320V, R326X, I222N, I281T, C80R, L101P, and 4bp deletion from nucleotide 980 (LEE *et al.*, 2004).

TYPE 2B HH (HAMP GENE CHANGES)

Type 2B HH is a very rare autosomal recessive disease characterized by severe Fe overload and caused by mutations in the *HAMP* gene, which encodes hepcidin. An individual affected by type 2B HH presents cardiac symptoms for the most severe cases, with the only therapy option being heart transplantation (DE GOBBI *et al.*, 2002).

The *HAMP* gene is composed of 3 exons that encode a polypeptide of 84 amino acids and is located on chromosome 19q13. Its expression occurs in organs such as: heart, brain and liver (PARK *et al.*, 2001).

TYPE 3 HH (TRANSFERRIN 2 RECEPTOR GENE CHANGES)

An individual with iron overload caused by mutations in the *TRF2* gene presents iron absorption in the hepatocytes through endocytosis, which regulates hepcidin synthesis (KAWABATA *et al.*, 1999).

The *TRF2* gene is found on chromosome 7q22 and is composed of 18 exons, encoding a protein of 355 amino acids (KAWABATA *et al.*, 1999). Several mutations can be found in the *TRF2* gene, such as Y250X, E60X, Q690P, among others (HOFFMANN *et al.*, 2002).

TYPE 4 HH (FERROPORTIN GENE CHANGES)

It is a dominant autosomal disease caused by mutations in the *SLC40A1* gene. It is characterized by functional ferroportin alterations and a consequent overload of iron in the body. Ferroportin is expressed in the basolateral portion of the macrophages, enterocytes and Kupffer cells. This location is due to the physiological function of exporting iron from cells (DONOVAN *et al.*, 2000).

The *SLC40A1* gene is located on

chromosome 2q32 and composed of 8 exons, encoding a protein of 571 amino acids. Several mutations can be found in this gene, such as N144H, A77D, V162X, among others (MONTOSI *et al.*, 2001). These mutations cause loss of protein function, generating a decrease in iron export, mainly in macrophages of the reticuloendothelial system. As a consequence, there is an accumulation of iron in the tissues, as well as a decrease in circulating iron for transferrin, immediately causing mild anemia. Subsequently, there is an iron overload in the tissues due to the release of the mineral by macrophages, and an increase in iron absorption due to anemia (PIETRANGELO, 2004).

HEPCIDIN AS A REGULATOR OF IRON HOMEOSTASIS

Currently, it is known that hepcidin is the main protein that regulates iron absorption and metabolism. It is synthesized in the liver and, every time iron deposits increase, its production is stimulated (CANÇADO, 2010). Hepcidin is a peptide hormone consisting of 25 amino acids and synthesized in the hepatocytes. When there are iron overload, infection, lipopolysaccharides and pro-inflammatory cytokines, such as interleukin-6, this hormone is synthesized (ROY *et al.*, 2007).

Hepcidin also has antimicrobial activity, mediating innate immunity. This antimicrobial activity occurs due to the ability that hepcidin has to break microbial membranes and deplete iron availability to microorganisms during their development (PARK *et al.*, 2001). However, its greater activity in higher vertebrates is related to Fe homeostasis (NICOLAS *et al.*, 2002).

Hepcidin expression is regulated according to the amount and availability of iron in the body. Iron overload increases its expression, and other events, such as anemia and hypoxemia, lead to a reduced expression of this molecule. In inflammatory states, interleukin-6 (IL-6) plays an important role (NEMETH *et al.*, 2004). Some studies have shown that IL-6 infusion stimulates hepcidin excretion through the urine, leading to hypoferremia. In addition, IL-6 acts on hepatocytes, stimulating hepcidin production (RIVERA *et al.*, 2005).

Other studies have shown the action of hepcidin in the intestinal absorption process. Iron uptake is inhibited in the enterocytes through inhibition of DMT-1 transcription, which is induced by hepcidin, but mRNA and ferroportin levels do not change in these cells. Moreover, it has been evidenced that the effect of hepcidin is cell-dependent, and its actions are differentiated in the macrophages and enterocytes (MENA *et al.*, 2007).

Hepcidin is mainly synthesized in the hepatocytes, but lower expression levels can also be found in other cells and tissues such as: neutrophils, monocytes, lymphocytes, adipocytes, and the brain. Extrahepatic hepcidin has a little known role, but it is very likely that it is important in controlling the autocrine and paracrine system of iron flow in the body (NEMETH *et al.*, 2009).

Hepcidin binds to ferroportin and thus promotes its internalization and degradation by the cell (Figure 1). In duodenal enterocytes, the increase in hepcidin prevents ingested iron from entering the circulation through ferroportin (CANÇADO, 2010). Rapid absorption of iron by macrophages and long-term enteric iron depletion can lead to anemia. On the other hand, an absence of hepcidin leads to uncontrolled duodenal iron absorption, which generates iron overload in the body (YOUNG *et al.*, 2009).

Ferroportin, in its turn, is the hepcidin receptor, and the hepcidin-ferroportin interaction is what controls iron levels in the enterocytes, hepatocytes and macrophages. This complex is internalized in the basolateral

membrane of the macrophages, and when ferroportin is degraded, it blocks the release of iron from these cells (NEMETH *et al.*, 2004).

Once hepcidin concentrations are low, ferroportin molecules are exposed on the plasma membrane and export iron. When the concentrations of hepcidin rise, it binds to ferroportin molecules, inducing its internalization and degradation, and the released iron progressively decreases (GANZ, 2007).

ALLELE INCIDENCE AND FREQUENCY OF THE MUTATIONS THAT CAUSE HEMOCHROMATOSIS

Several studies have been carried out, especially in Brazil, to investigate the level of incidence of hemochromatosis in relation to different human races, as well as the incidence of each mutation.

A study published in 2006 established the prevalence of hemochromatosis in the white population of the United States and found that the disease is common in this demographic. HH is one of the most common genetic disorders in Caucasians, in the heterozygous form, and affects 1/10 individuals of Celtic origin or descendants of Europeans (BONINI-DOMINGOS, 2006).

The frequency of the C282Y mutation of the HFE gene is three to eight times lower in Brazilians compared to Caucasians from northern Europe. This difference is probably due to the ethnic diversity of Brazilians. The allele frequency of the H63D mutation, on the other hand, is similar between the two populations (CANÇADO *et al.*, 2006).

In a multicenter study conducted with approximately 100,000 participants of different ethnicities who were subjected to tests for mutations in the HFE gene, serum ferritin doses and transferrin saturation, homozygosis for the C282Y mutation in the HFE gene was common in Caucasians and rare in other ethnic groups, with the disease having great heterogeneity expression in C282Y homozygotes (MCLAREN *et al.*, 2009).

The C282Y mutation of the HFE gene is more common in Caucasians from northwestern Europe, North America, Australia, and New Zealand. In eastern and southern Europe, North Africa and the Middle East, its frequency is intermediate, and in Asian, African or Afro-descendant populations in Central and South America, it is rarely found (CANÇADO *et al.*, 2006).

A French study proposed dividing C282Y/C282Y individuals into five stages, according to laboratory and clinical data: stage 0: C282Y/C282Y genotype only; stage 1: C282Y/C282Y genotype and ST > 45%; stage 2: C282Y/C282Y genotype, ST > 45% and FS ≥ 300 ng/mL ≥ 200 ng/mL for males and females, respectively; stage 3: stage 2 changes and presence of clinical manifestations such as asthenia, fatigue, impotence; stage 4: stage 3 changes associated with serious clinical complications, such as liver cirrhosis, cardiomyopathy, and insulin-dependent diabetes mellitus. Stages 0 to 2 correspond to the preclinical phase, and stages 3 and 4, to the clinical phase. It can be concluded from this study that 50% of the C282Y/C282Y individuals are in stage 2, 25% in stage 3, and less than 10% are in stage 4 (BRISSOT *et al.*, 2006).

In a study carried out with patients at *Santa Casa de São Paulo*, the frequency of C282Y, H63D and S65C mutations of the HFE gene was verified in Brazilian patients with iron overload. Fifty patients with iron overload were studied – 35 men and 15 women, with an average age of 51 years, ranging from 35 to 78 years. All were Brazilian and did not have any degree of kinship. The HFE gene mutation frequency stood at 76.0% (38/50). There were no patients with the S65C mutation of the HFE gene. The allele frequency for the C282Y

and H63D mutations of the HFE gene in the patients was 43.0% and 18.0%, respectively[6]. The HFE gene mutation frequency in patients with iron overload was 76.0% (38/50). Transferrin saturation and serum ferritin were significantly higher in patients who were homozygous for the C282Y mutation, confirming the correlation between the C282Y/C282Y genotype and a higher risk of iron overload (CANÇADO *et al*., 2007).

Population studies indicate that HH originated in northern Europe, in populations of Nordic or Celtic descent. The C282Y mutation of the HFE gene is prevalent in Caucasians from northwest Europe, North America, Australia and New Zealand. In eastern and southern Europe, North Africa and the Middle East, its frequency is intermediate, and in Asian, African or Afro-descendant populations in Central and South America, it is rarely found (ASBERG *et al*., 2001).

Adams *et al*. (2005), in a study carried out with populations from the United States of America, Australia and Europe, showed that the frequency of individuals who were homozygous and heterozygous for the C282Y mutation varies between 0.2% and 0.7%, and between 7% and 14%, respectively. The H63D mutation of the HFE gene is two to three times more frequent than C282Y, and the prevalence of heterozygosity and homozygosity for this mutation ranges between 15% and 40%, and between 2.5% and 3.6%, respectively. The frequency of the C282Y/H63D genotype is approximately 2%.

The frequency of the C282Y mutation of the HFE gene is three to eight times lower in Brazilians compared to Caucasians from northern Europe. It is quite likely that this difference is due to the ethnic diversity of the Brazilian population. On the other hand, the allele frequency of the H63D mutation of the HFE gene is similar between these two populations (CANÇADO *et al*., 2010).

By observing and listing five of the main Brazilian studies, it is possible to relate the allele frequencies of the C282Y, H63D and S65C mutations of the HFE gene, as shown in the table below.

CONCLUSIONS

Iron is a mineral of great importance in maintaining the homeostasis of the human body. Balancing the levels of this mineral in the body is essential to prevent different pathologies. Iron deficiency leads to iron deficiency anemia, and an excess of it leads to hemochromatosis, which can be caused by an excessive intake of this mineral or by a genetic mutation that leads to an imbalance in iron absorption, making it cumulative in various organs, especially the liver, where it causes lesions, leading to non-functionality, as well as the onset of liver cirrhosis, carcinomas and other pathologies. To regulate iron absorption, proteins, especially hepcidin, play a very important role. Hepcidin acts as an iron regulator by inhibiting ferroportin, a protein that exports iron from the enterocytes and macrophages. Mutations in the hepcidin gene become the cause of most types of hereditary hemochromatosis. Understanding the mechanism of action of proteins in iron metabolism may be the path to a more accurate diagnosis of hemochromatosis, as well as to a satisfactory treatment that will lead to normal survival rates for patients with this disease, either in its acquired or genetic form.

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ANNEXES

Apresentação e caracterização dos artigos selecionados

AUTOR	TÍTULO DO TRABALHO	ANO
ADAMS, PC; ARTON, REBOUSSIN, DM; BARTON JC; MCLAREN, CE; ECKFELDT, JH; MCLAREN, GD	**Hemochromatosis and iron-overload screening in a racially diverse population**	2005
AGOSTINHO, MF; ARRUDA, VR; BASSERES, DS; BORDIN, S; SOARES, MC; MENEZES, RC	**Mutation analysis of the HFE gene in Brazilian populations**	1999
AJIOKA, RS; KUSHNER, JP	**Hereditary hemochromatosis**	2002
ANDERSON, GJ; DARSHAN, D; WILKINS, SJ; FRAZER DM	**Regulation of systemic iron homeostasis: how the body responds to changes in iron deman**	2007
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AREZES, J; NEMETH, E	**Hepcidin and iron disorders: new biology and clinical approaches**	2015
ASBERG, A; HVEEM, K; THORSTENSEN, K; ELLEKJTER, E, KANNELONNING, K; FJOSNE, U	**Screening for hemochromatosis: high prevalence and low morbidity in an unselected population of 65,238 persons**	2001
BACON, BR; POWELL, LW; ADAMS, PC; KRESINA, TF; HOOFNAGLE, JH	**Molecular medicine and hemochromatosis: at the crossroads**	1999
BEAUMONT, C; VAILONT, S	**Iron homeostasis**	2006
BONINI-DOMINGOS, CR	**Hemocromatose hereditária e as mutações no gene HFE**	2006
BREGMAN, DB; MORRIS, D; KOCH, TA	**Hepcidin levels predict nonresponsiveness to oral iron therapyn patients with iron deficiency anemia**	2013
BRISSOT, P; DE BELS, F	**Current approaches to the management of hemochromatosis**	2006
CAIRO, G	**La Ferritina**	1997
CALADO, RT; FRANCO, RF; PAZIN-FILHO, A; SIMÕES, MV; MARIN-NETO, JA; ZAGO, MA	**HFE gene mutations in coronary atherothrombotic disease**	2000
CAMASCHELLA, C; DE GOBBI, M; ROETTO, A	**Hereditary hemochromatosis: progress and perspectives**	2000
CAMASCHELLA, C; DE GOBBI, M; ROETTO, A	**Juvenile hemochromathosis**	2002
CANÇADO, RD; CHIATTONE, CS	**Visão atual da hemocromatose hereditária**	2010
CANÇADO, RD; GUGLIELMI, ACO; VERGUEIRO, CSV; ROLIM, EG; FIGUEIREDO, MS; CHIATTONE, CS	**Estudo das mutações C282Y, H63D e S65C do gene HFE em doentes brasileiros com sobrecarga de ferro**	2007
DE DOMENICO, I; WARD, DM; KAPLAN, J	**Hepcidin regulation: ironing out the details**	2007
DE GOBBI, M; ROETTO, A; PIPERNO, A; MARIANI, R; ALBERTI, F; PAPANIKOLAOU, G	**Natural history of juvenile haemochromatosis**	2002
DONOVAN, A; BROWNLIE, A; ZHOU, Y; SHEPARD, J; PRATT, SJ; MOYNIHAN, J	**Positional cloning of zebrafish ferroportin1 identifies a conserved vertebrate iron exporter**	2000
FAIRBANKS, VG; BEUTLER, E	**Iron metabolismo**	2001
FEDER, JN; GNIRKE, A; THOMAS, W; TSUCHIHASHI, Z; RUDDY, DA; BASAVA, A	**A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis**	1996
FEDER, JN; PENNY, DM; IRRINKI, A; LEE, VK; LEBRÓN, JÁ; WATSON, N	**The hemochromatosis gene product complexes with the transferrin receptor and lowers its affinity for ligand binding**	1998

FERREIRA, ACS; OLIVEIRA, VC; CALIXTO, FA; GOMES, KB; CASTRO, AM; PARDINI, VC	**Prevalence of C282Y and H63D mutations in the HFE gene of brazilian individuals with clinical suspicion of hereditary hemochromatosis**	2008
FRANCHINI, M; VENERI, D	**Iron-chelation therapy: an update**	2004
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GROTTO, HZW	**Fisiologia e metabolismo do ferro**	2010
HOFMANN, WK; TONG, XJ; AJIOKA, RS; KUSHNER, JP; KOEFFLER, HP	**Mutation analysis of transferrin-receptor 2 in patients with atypical hemochromatosis**	2002
KAWABATA, H; YANG, R; HIRAMA, T; VUONG, PT; KAWANO, S; GOMBART, AS	**Molecular cloning of transferrin receptor 2. A new member of the transferrin receptor-like family**	1999
LEE, PL; BEUTLER, E; RAO, SV; BARTON, JC	**Genetic abnormalities and juvenile hemochromatosis: mutations of the HJV gene encoding hemojuvelin**	2004
MAST, AE; SCHLUMPF, KS; WRIGHT, DJ	**Hepcidin level predicts hemoglobina concentration in individuals undergoing repeated phlebotomy**	2013
MENA, NP; ESPARZA, A; TAPIA,V; VALDES, P; NUNES, MT	**Hepcidin inhibits apical iron uptake in intestinal cells**	2007
MONTOSI, G; DONOVAN, A; TOTARO, A; GARUTI, C; PIGNATTI, E; CASSANELLI, S	**Autosomal-dominant hemochromatosis is associated with a mutation in the ferroportin (SLC11A3) gene**	2001
NEMETH, E; TUTTLE, MS; POWELSON, J; VAUGHN, MB; DONOVAN, A; WARD, DM	**Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization**	2004
NEMETH, E; GANZ, T	**The role of hepcidin in iron metabolism**	2009
NICOLAS, G; BENNOUN, M; PORTEU, A	**Severe iron deficiency anemia in transgenic mice expressing liver hepcidin**	2002
NICOLAS, G; VIATTE, L; LOU, DQ; BENNOUN, M; BEAUMONT, C; KAHN, A	**Constitutive hepcidin expression prevents iron overload in a mouse model of hemochromatosis**	2003
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NJAJOU, OT; ALIZADEH, BZ; VAN DUIN, CM	**Is genetic screening for hemochromatosis worthwhile?**	2004
OLIVEIRA, TM; SOUZA, FP; JARDIM, AC; CORDEIRO, JÁ; PINHO, JR; SITNIK, R	**Mutations in the HFE gene (C282Y, H63D, S65C) in a Brazilian population**	2006
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SIMON, M; PAWLOTSKY, Y; BOUREL, M; FAUCHET, R; GENETET, B	**Idiopathic hemochromatosis associated with HL-A 3 tissular antigen**	1975
TERADA, CT; SANTOS, PC; CANÇADO, RD; ROSTELATO, S; LOPREATO, FR; CHIATTONE, CS	**Iron deficiency and frequency of HFE C282Y gene mutation in Brazilian blood donos**	2009
YOUNG, B; ZARITSKY, J	**Hepcidin for clinicians**	2009
ZAGO, MA	**Tratado de hematologia**	2013
ZHAO, N; ZHANG A; ENNS CA	**Iron regulation by hepdidin**	2013