Dysmetabolic Iron Overload Syndrome

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Dysmetabolic iron overload syndrome (DIOS) corresponds to the increase in iron stores associated with components of metabolic syndrome (MtS) and in the absence of an identifiable cause of iron excess. DIOS is usually asymptomatic and can be diagnosed by investigating MtS and steatosis. About 50% of the patients present altered hepatic biochemical tests (increased levels of γ-glutamyl transpeptidase itself or associated with increased levels of alanine aminotransferase). The liver may present parenchymal and mesenchymal iron overload, but the excess of iron is commonly mild. Steatosis or steatohepatitis is observed in half of the patients. Fibrosis is observed in about 15% of patients. Hyperferritinemia may damage the myocardium, liver, and several other tissues, increasing morbidity and mortality.

Keywords: dysmetabolic iron overload syndrome ; metabolic syndrome ; hyperferritinemia

1. Introduction

Cardiovascular diseases (CVD) are responsible for most causes of death worldwide and are strongly associated with metabolic syndrome (MtS), which comprises risk factors related to high morbidity. The primary underlying mechanism related to the onset and maintenance of CVD is atherosclerosis [1][2][3][4][5][6].

In addition to MtS, researchers have described the occurrence of another condition, the dysmetabolic iron overload syndrome (DIOS) corresponds to the increase in the body iron stores, associated with components of MtS, and in the absence of identifiable cause of iron excess [7][8][9][10][11][12][13]. Most DIOS patients also possess nonalcoholic fatty liver disease (NAFLD), a condition that is best defined as metabolic associated fat liver disease (MAFLD) [14]. Although MAFLD, which is also a result of insulin resistance and MtS, is usually but not invariably followed by expanded body iron stores, iron depletion can attenuate steatosis in MAFLD [10][15][16][17]. The histological patterns found in DIOS associates both mesenchymal and parenchymal areas. The iron deposition on the hepatic reticuloendothelial system cells is implicated with increased hepatic apoptosis in MAFLD patients, additionally to higher percentages of advanced hepatic fibrosis, higher portal inflammation, and augmented hepatocellular ballooning [18][19][20][21][22][23].

Iron is a fundamental element for the maintenance of homeostasis. It is essential to electron transport, oxygen transport, DNA synthesis, and several other actions, but it may also be toxic. Disruption in iron metabolism as observed in patients with DIOS may be multifactorial. Diets rich in iron associated with genetic factors may trigger the overload condition, related to crosstalk observed between liver and visceral adipose tissue. Macrophages seem to be especially important in the homeostasis of systemic iron levels, and ferroportin is the iron exporter and plays a role in mediating the exit of iron from macrophages to circulation [24][25][26][27].

DIOS is closely related to oxidative stress (OS), and this condition is closely associated with several pathological conditions such as inflammatory diseases, hypertension, diabetes, heart failure, and cancer [28][29][30][31].

The presence of MtS factors, hyperferritinemia, and altered transferrin saturation are disorders that represent a serious global problem. Both MAFLD and its aggressive form, nonalcoholic steatohepatitis (NASH), are linked with higher morbidity and mortality. The incidence of NASH is estimated to increase by more than 50% in the next ten years. Moreover, MAFLD incidence nowadays may vary from up to one-quarter of the world population and may be higher than 60% in diabetic patients and about 90% in patients who underwent bariatric surgery [10][32][33][34][35][36][37][38].

2. Ferritin and Hyperferritinemia

Iron is a crucial element for all living systems, essential for oxygen transport in hemoglobin and cellular energy production and serving as a cofactor or catalyst in several enzymatic processes. The iron-containing protein ferritin reflects the

homeostasis of human iron storage and iron delivery, which is crucial for the maintenance of the anteriorly mentioned biological processes [39][40][41][42].

Hyperferritinemia is a condition where excessively high levels of ferritin are observed, indirectly indicating iron overload, which damages the myocardium, the liver, and several other tissues, increasing morbidity and mortality. Nevertheless, more than 90% of hyperferritinemia cases are derived from four major causes: inflammatory conditions, cytolysis, alcoholism, and MtS. Another critical cause that should be seen separately is genetic hemochromatosis. The differentiation of these conditions can be performed with laboratory tests such as hemogram, transferrin saturation, liver function tests, creatinine phosphokinase (CPK), C reactive protein, glycemia, total cholesterol, and triglycerides. Immune and autoimmune affections can also possibly cause hyperferritinemia [39][43][44][45][46][47].

Ferritin seems to play an essential role in angiogenesis, cells proliferation, and immunosuppression. Additionally, it can also be considered as an inflammatory acute-phase protein. Some studies suggested an association between high ferritin levels and chronic diseases, such as CVD and cancer. In CVD, ferritin can lead to a dual pro-inflammatory effect because high levels can represent an acute phase similar to C reactive protein. Low levels can also precipitate inflammation and, thus, increase the pro-inflammatory cytokines. These conditions can be related to CVD progression [39][44][48][49][50]. Hyperferritinemia has also been associated with NAFLD/MAFLD and with polycystic ovary syndrome [8][16][51][52].

3. Hepcidin

Hepcidin is a peptide hormone released by liver hepatocytes involved in regulating ferroportin expression, which is the major iron export protein presented in cells. Hepcidin can bind to ferroportin, leading to its internalization and degradation, which only reduces iron export from different vias. This process inhibits cellular iron exportation from macrophages. Hepcidin also inhibits iron uptake in the gut that, together with inhibition of recycling iron from macrophages, decreases iron levels in plasma. The axis hepcidin-ferroportin has a central regulatory role in iron homeostasis. In hereditary hemochromatosis, both the expression and function of hepcidin are disturbed and lead to increase in ferroportin due to the low circulating hepcidin levels resulting in augmentation of iron absorption in the gut and pathological deposition of this element in tissues [29][53][54][55][56].

Stimulation of hepcidin in the liver reduces ferroportin levels, resulting in the inhibition of cellular iron mobilization to the plasma. Acute inflammatory and infectious conditions may also increase hepcidin expression. Induction of hepcidin resulting from inflammatory processes possibly interferes with iron metabolism in acute or chronic inflammation disorders. In case of infections, hepcidin induction is associated with sequestration of intracellular iron, depriving microorganisms of this important factor. In chronic inflammation, hepcidin expression is increased principally due to interleukin 6 (IL-6) and Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3) expressions [55][57][58].

A disrupted low synthesis of hepcidin has been associated with NAFLD and could help the iron uptake and increase predisposition for DIOS. Furthermore, both obesity and diabetes are related to augmenting hepcidin release. Marmur et al. [53], showed that in NAFLD subjects, hepcidin levels in serum and liver correlate to body iron stores. These authors found no association with body mass index (BMI), lipid parameters, the degree of steatohepatitis, or C reactive protein. In patients with DIOS and NAFLD, serum hepcidin levels are close to those observed in other hepatic diseases with iron overload, except for hereditary hemochromatosis. Researchers postulate that an adequate hepcidin production in NAFLD in comparison to iron stores and the accumulation of iron in DIOS cannot be explained by a deficiency of hepcidin, differently from what is observed in hereditary hemochromatosis.

In animal models, the expression of hepcidin is inhibited in insulin resistance conditions. After administration of glucose, levels of hepcidin are elevated as well as in overweight and patients with NAFLD. The levels of hepcidin are also increased in patients with DIOS when comparing to obese patients with regular levels of ferritin. Elevated levels of hepcidin in DIOS may suggest hepcidin resistance [59].

4. Metabolic Syndrome

MtS is a cluster of conditions associated with the development of CVD. These factors may include insulin resistance, low levels of HDL-c, high levels of triglycerides, hypertension, altered values for waist circumference (WC), and obesity. These factors are associated with a complex dysregulation of iron homeostasis. Ferritin concentrations in serum increase with the number of risk factors of the MtS, especially insulin resistance, visceral fat mass, BMI, and hypertension. For these reasons, high ferritin levels have been related to a higher risk for the development of DM2 [5][45][60][61][62][63][64][65][66].

Furthermore, in subjects with morbid obesity, ferritin is strongly associated with IR and waist circumference. This may indicate that serum ferritin levels are closely related to important insulin resistance in overweight or obesity patients independent from other risk factors of the MtS. Particularly, serum ferritin concentrations can indicate severe liver insulin resistance and a higher risk for progression of relevant clinical hard endpoints such as cardiovascular death [67][68][69].

Serum ferritin levels are moderately elevated in MtS, but serum iron and transferrin saturation are usually normal, although transferrin saturation can be increased in up to 35% of cases. It is estimated that a third of MtS patients suffer from hyperferritinemia, although with normal transferrin saturation levels. The levels of hepcidin in serum can also be elevated in MtS [70][71].

An observational study with 1391 subjects (616 men and 775 women) showed that patients with MtS present significantly higher serum levels of ferritin and hepcidin than subjects without the syndrome. Iron regulatory feedback is preserved in MtS, and hepcidin tends to progressively augment in response to the augmented iron stores [72].

Risk factors of the MtS can also be related to inflammatory processes. Regardless of its cause, acute or chronic inflammation can augment ferritin levels in serum. Transferrin saturation may decrease or remain normal depending on DIOS parameters in this condition. In inflammatory processes, several cytokines are released, and especially IL-6 has a particular role in stimulating the production of ferritin and hepcidin. When there is an increase in hepcidin levels, iron sequestration in macrophages and enterocytes results in ferritin synthesis [26][43][68][71].

5. Oxidative Stress

OS in the cells is related to a significant imbalance of a plethora of biological signaling pathways. Reactive oxygen species (ROS) release usually happens via the reduction of molecular oxygen or due to oxidation of water. In balanced conditions, mitochondria produce ROS in consequence of aerobic respiration. Three to five percent of the oxygen is converted to ROS during this process. These molecular events require endogen enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. When the ROS production surpasses the cell's antioxidant capacity, a disrupted condition (OS) starts and causes cellular macromolecules damages such as nucleic acids, lipids, and proteins may occur. Increased levels of ROS can also accelerate cell apoptosis and necrosis due to the activation of poly (adenosine diphosphate ribose) polymerase related to the development of several pathological conditions. On the other hand, ROS are needed in the heart under basal conditions for regulating myocyte growth, maintaining vascular smooth muscle tone, and other critical cellular responses. OS is also related to the development of incapacitant and degenerative conditions, such as neurological and cancer [73][74][75][76][77][78][79][80].

OS is the main reason why iron and IR damage the liver tissue in both animals and humans. The consequences are related to damage to DNA, lipids, and protein, glutathione depletion, energy loss, increased release of pro-inflammatory cytokines, fibrogenesis, steatosis, and cell death. Iron may also induce liver injury due to its role in the up-regulation of cholesterol production, stress induction in the endoplasmic reticulum, and activation of macrophages and stellate cells [8][81][82]. Furthermore, iron is also associated with an increase in the release of inflammatory cytokines, associated with fibrosis, steatosis, and hepatocellular carcinoma [8][80][83][84].

The hepatic steatosis seems to result in an environment of the augmented OS, as well as IR, and necrotic signalization in obese patients leading to hepatic damage [80][85]. DM2 and fluctuations in glycemia may be related to several micro and macrovascular complications that may result from OS and inflammatory processes leading to endothelial dysfunction and aberrant angiogenic capacity. Furthermore, atherosclerosis is a chronic process that affects large and medium-sized arteries and is also a consequence of OS [81][86][87][88].

Iron is also now related to a new non-apoptotic form of cells-death, called ferroptosis. This phenomenon is caused mainly by redox imbalance and can occur through two mechanisms: transporter-dependent (extrinsic) and enzyme-dependent (intrinsic). In resume, when a cell produces more oxidants than antioxidants, an abnormal presence of ROS. In iron-overload syndrome, the production of ROS and lipid peroxidation are all events mediated by iron ions. Extrinsic ferroptosis is caused mainly by elevation of iron uptake in consequence of decreased cysteine or glutamine uptake. The intrinsic form is caused principally by inhibition of glutathione peroxidase 4 (GPX4). All these forms lead in final analyses to the accumulation of ROS and this accumulation to oxidative damage. Ferroptosis is finished if oxidation reaches the cell membrane. Although ferroptosis is a relatively new concept, it is implicated in various human diseases, such as neurodegenerative diseases, CVD, infectious, and cancer [42][89][90].

6. Dysmetabolic Iron Overload Syndrome

DIOS was defined in the 1990s and shows a close relationship between hepatic iron overload and features of MtS in subjects without apparent cause of iron overload. It is more frequent than genetic hemochromatosis, and most patients are middle-aged males [8][12][13][22][47][91][92][93]. Now that MtS is increasing worldwide, the presence of DIOS follows this tendency.

DIOS is usually asymptomatic and can be diagnosed in the investigation of MtS and steatosis. Ferritin levels in the serum are increased (up to 1000–1200 ng/mL), but iron levels and transferrin saturation are usually normal. About 50% of the patients present altered hepatic biochemical tests (increased levels of γ-glutamyl transpeptidase itself or associated with increased levels of alanine aminotransferase). The liver may present parenchymal and mesenchymal iron overload, but the excess of iron is commonly mild. Steatosis (defined by the accumulation of triglycerides and fatty acids in the liver) or steatohepatitis was observed in half of the patients. Fibrosis or cirrhosis are observed in about 15% of patients [16][91][94][95][96].

The mechanisms of occurrence of an iron overload in DIOS are not entirely understood. Impairment in hepcidin synthesis and an imbalanced regulation of iron export are involved. The modification of metabolism of iron observed in patients with DIOS may result from a complex process triggered by the excess of iron in the diet together with environmental and genetic factors associated with a crosstalk between the hepatic tissue and visceral adipose tissue [11][12][22][59][93][94][97].

In a rat model of NAFLD, Fujiwara et al. [13] evaluated the role of iron overload. The animals were treated with a high-fat and high-fructose diet leading to hepatic steatosis, dyslipidemia and increase in the body weight. Furthermore, they observed increased hepatic inflammation represented by iron deposition in sinusoidal macrophages/Kupffer cells, together with nuclear translocation of nuclear factor-κB (NF κB) and increase of pro-inflammatory cytokines (such as tumor necrosis factor-α (TNF-α), interferon-γ (IFN γ), and interleukin (IL)-1β) due to the upregulation of TH1/M1.

Studies with dietary iron loading animals showed increased resistin expression and reduced leptin levels. Increased resistin and decreased leptin levels contribute respectively to IR and increased appetite. These two conditions together increase the chances of developing obesity and DM. The metabolism of adipose tissue results in increased resistin, TNF-α, IFN-γ, interleukins (IL-6, IL-8, and IL-12), free fat acids (FFA), and a decrease in leptin, and IL-10 levels. This secretory pattern leads to an increase in the inflammatory activity in obese patients (low-grade inflammation) [98][99] showed that leptin directly interferes with iron metabolism. These authors showed that leptin levels were lower in leptin-deficient mice and higher in leptin receptor-deficient when compared with control. These results suggest that the activation of the leptin receptor has effects on hepcidin expression. Researchers concluded that this inappropriate signaling of this hormone could nearly link obesity, MtS, CVD, autoimmunity, and cancer. In this sense, iron-mediated OS could also be contributing to this unfavorable scenario.

The iron metabolism is commonly imbalanced in obese patients in both cellular and tissue levels. Moreover, adipose tissue plays an essential role in iron regulation. The presence of obesity may modify macrophage iron content in visceral adipose tissue in the liver and adipocytes. Furthermore, iron reduces the expression of adiponectin that is related to improving IR. The level of this adipokine is reduced in MtS subjects and negatively correlated with serum ferritin levels [8][71][100][101][102].

Higher ferritin levels are associated with obesity and overweight children and may be influenced by a liver injury that, associated with hypertrophied adipocytes and low-grade inflammation, follow the clinical course of overweight and obesity to modify the circulating markers of iron status. Still, the decreased absorption of iron observed in obesity can be the consequence of higher hepcidin levels that are also triggered by inflammatory processes. On the other hand, the levels of serum transferrin and serum iron decreases during inflammation [71][103][104][105].

Modifications in iron metabolism (ferritin or serum iron) are also associated with altered lipid concentration in adults and children [106]. Gonzalez-Dominguez et al. and Zhu et al. [61][71] showed that dyslipidemic children and adolescents presented lower levels of serum iron and increased ferritin levels in the obese.

7. Future Directions

An increase in the hepatic and body iron stores and the presence of MtS components characterizes DIOS. Although increasing evidence suggests an overlap between NAFLD with iron overload and, therefore, DIOS, the pathogenic pathways involved in DIOS occurrence are still not completely understood. Due to these reasons, soon, not only animal models sharing similarities with human patients with DIOS must be designed, but also non-invasive methods for iron

overload evaluation in dysmetabolic human patients must be improved. Furthermore, there is a need to investigate how iron overload overlaps with NAFLD and causes dysmetabolic changes in the body's homeostasis [13][47]. Since a mild to moderate excess of iron in the liver can aggravate the risk of NAFLD progression to NASH, it is also necessary to unravel the mechanistic events by which pro-inflammatory cytokines, ROS, OS, and lipid peroxidation can be related to iron overload toxicity [22].

The pathways of how DIOS affects other diseases, such as inflammatory and immunomodulated diseases, must also be a field of study. Researchers highlighted that in DIOS, macrophages might present impaired polarization toward the M2 alternative phenotype, which is considered an adaptative role of the up-regulation of the TFRC in DIOS macrophages that may limit iron toxicity during the dysmetabolic process [91]. However, these events can affect the occurrence and progression of diseases other than DIOS, like atherosclerosis, arthritis, cardiometabolic affections, and other degenerative conditions. The relationship between iron status and obesity is another field that must be highlighted [107], principally because individuals with augmented visceral adiposity and waist circumference do not necessarily have increased body mass index.

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