Dysmetabolic iron overload syndrome (DIOS)

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Definition and epidemiology

Hyperferritinemia has been associated with metabolic syndrome, with most of its components, especially type 2 diabetes and essential hypertension, with NAFLD and with polycystic ovary syndrome. Increase in serum ferritin levels is proportional to the degree of insulin resistance and to the number of components of metabolic syndrome. Moreover, it is predictive of the onset of type 2 diabetes and NAFLD. This suggests a subtle change in iron metabolism pre-existing to overt clinical disorder and supports serum ferritin as a predictive marker of metabolic syndrome and its complications.
Metabolic hyperferritinemia does not always account for iron excess [16]. Confounding cofactors such as inflammatory syndrome, hepatitis or excessive alcohol consumption, all conditions frequently associated with metabolic abnormalities, can be responsible for hyperferritinemia with no increased body iron stores. The only way to assert iron excess is to rely upon direct measurement of hepatic iron or calculation of the amount of iron removed to obtain low serum ferritin levels (\textit{table I}).

DIOUS corresponds to mild increase in both liver and body iron stores associated with various components of metabolic syndrome in the absence of any identifiable cause of iron excess [1,17]. It is much more frequent than genetic hemochromatosis [18] and accounts for the vast majority of cases of hyperferritinemia referred to outpatient clinics. Half of patients with DIOUS have non-alcoholic fatty liver disease (NAFLD) ranging from pure steatosis to non-alcoholic steatohepatitis (NASH) [19].

### Diagnosis

Most patients with DIOUS are middle-aged males [1]. The most frequent opening symptoms are chronic fatigue and non specific joint pain resulting in the measurement of serum ferritin in the event of iron deficiency or hemochromatosis [1]. In most cases, hyperferritinemia does not exceed 1000 µg/L [1].

The diagnosis of DIOUS relies upon three criteria:

- normal or moderately increased transferrin saturation (i.e. < 60%), which allows the ruling out of hemochromatosis without ordering HFE genotyping [18]. However, due to increased production of hepcidin (see below), overweight as well as inflammatory syndrome may mask the elevation of transferrin saturation in patients with mild hemochromatosis [21,22]. In such situations, it is recommended to seek the C282Y mutation;
- one or several metabolic abnormalities including increased body mass index with android distribution of fat, elevated blood pressure, dyslipidaemia, and abnormal glucose metabolism;
- hepatic iron excess not exceeding 150 µmol/g dry weight (N < 36) at MRI or at liver biopsy:

\textbullet{} MRI has become widely used to detect and quantify hepatic iron within a range comprised between 50 and 300 µmol/g. It is a reliable tool if adequate sequences are used and the device correctly calibrated [23]. It also permits the assessment of iron deposition within the spleen, which is often increased in DIOUS and allows to distinguish it from hepcidin-deficient conditions such as hemochromatosis,

\textbullet{} liver biopsy has been supplanted by MRI to establish the diagnosis of hepatic iron overload. It is currently restricted to DIOUS cases associated with NAFLD and/or suspected fibrosis. When performed, it shows mild and mixed iron deposition in both hepatocytes and reticulo-endothelial cells [19].

In clinical practice, serum ferritin levels higher than 500 µg/L usually correspond to DIOUS in the absence of inflammation, increased levels of serum transaminases and alcoholism [24]. When hyperferritinemia exceeds 1000 µg/L, which is often the case if associated causes of hyperferritinemia coexist, the

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**TABLE I**

<table>
<thead>
<tr>
<th>Main causes of hyperferritinemia</th>
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<td><strong>Hyperferritinemia</strong></td>
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<td>Hemochromatosis</td>
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<tr>
<td>HFE</td>
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<td>Transferrin receptor 2</td>
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<td>Hepcidin</td>
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<td>Hemojuvelin</td>
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<tr>
<td>Ferroportin (type B)</td>
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<td>Others</td>
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<td>Ferroportin (type A)</td>
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diagnosis of DIOS becomes difficult. Then, the discrepancy between the marked increase in serum ferritin and the small increase in hepatic iron may help. By contrast, when hepatic iron exceeds 150 μmol/g, it may be difficult to rule out other causes of iron overload. If serum ferritin levels are not as elevated as expected, this usually corresponds to an overestimation of hepatic iron, which implies the reassessment of MRI data is needed. If serum ferritin levels are in agreement with hepatic iron, the diagnosis of type A ferroportin disease [25] has to be discussed, especially if MRI indicates iron deposition within the spleen [26].

Pathophysiology

Alteration of iron metabolism in DIOS likely results from a multifactorial and dynamic process triggered by an excessively rich diet, facilitated by environmental and genetic cofactors and implying a cross-talk between the liver and visceral adipose tissue (VAT) [3].

Iron, VAT and insulin resistance

Iron accumulation within VAT

In a mouse model of dietary iron overload, adipocytic iron accumulation has been identified [27]. Obesity has been demonstrated to alter macrophage hepatic iron content in VAT and tissue iron distribution with a shift from the liver to adipocytes [28]. Increased hepcidin gene mRNA expression and decreased transferrin receptor 1 expression, two markers of iron loading, were found in adipocytes from obese patients undergoing bariatric surgery [29]. Finally, VAT R2* signal, a putative MRI marker of iron content, was reported to be increased in subjects with obesity and to correlate significantly with hepatic iron content [30].

Modification of adipokines by iron

Gene expression of adiponectin – which exerts a protective role against insulin resistance – is reduced by iron [31]. In patients with metabolic syndrome, serum adiponectin levels are decreased and correlated negatively with serum ferritin levels [31,32]. Moreover, dietary iron loading in mice was found to induce increased expression of resistin, an adipokine associated with features of the metabolic syndrome [27], and iron was shown to down-regulate the expression of leptin, an appetite-suppressing adipokine involved in the development of insulin resistance [33]. Finally, iron was demonstrated to stimulate lipolysis in cultured cells [34].

Upregulation of hepcidin in DIOS

In streptozotocin-induced diabetic rats, hepcidin expression has been shown to be directly inhibited by insulin and down-regulated in the setting of insulin resistance [35]. In humans, serum hepcidin levels are increased following glucose administration [36] and elevated in overweight patients and in individuals with NAFLD. They are significantly increased in DIOS patients compared to overweight controls with normal serum ferritin levels [37], which suggests the persistence of the regulation of hepcidin production in these patients. Elevated serum hepcidin levels in DIOS are difficult to reconcile with the presence of iron overload. In a study of 18 de-ironed DIOS patients, Rametta et al showed that an iron challenge did not restrain iron absorption despite adequate hepcidin secretion [38]. This suggests that hepcidin activity could be reduced in DIOS and supports the concept of hepcidin resistance proposed by the authors. The pieces of the puzzle are gradually set up, but it is still too early to have a satisfactory understanding of DIOS pathophysiology (figure 1). Taken together, current data suggest that iron may accumulate within VAT with a balance between VAT and the liver, and may trigger or aggravate insulin resistance. This could contribute to explaining why serum ferritin overestimates hepatic iron stores in DIOS patients and why, contrary to overweight individuals, morbidly obese patients may have increased serum ferritin levels despite normal hepatic iron content. Moreover, DIOS could be related to a subtle impairment in the ability of hepcidin to interact with ferroportin leading to iron overload and featuring a hepcidin resistance state.

Combined effects of iron and insulin resistance on the liver

Oxidative stress

It is the main mechanism whereby both iron and insulin resistance exert a detrimental effect on the liver as demonstrated by experimental studies in both animals and humans [39]. It damages lipids, proteins and DNA, leads to energy loss, causes glutathione depletion, and then results in cell death. It enhances the production of pro-inflammatory cytokines, which triggers fibrogenesis and steatosis. Oxidative damage to DNA and its reduction after venesection have been demonstrated by immunohistochemistry in the liver of patients with NAFLD [40]. In patients with NASH, serum levels of thioredoxin [41], a marker of oxidative stress, have been shown to be elevated and to decrease after iron removal. Other mechanisms by which iron may contribute to liver injury could be its direct role in the activation of hepatic macrophages and stellate cells, generation of endoplasmic reticulum stress and up-regulation of cholesterol biosynthesis [3].

Whether hepatic iron exerts a clinically relevant role in NAFLD and DIOS remains debated

Early studies gave contradictory results. Since then, two large and well-designed Italian [10] and American [20] studies agreed upon a loose link between hepatic iron content and the development of fibrosis in 587 and 849 patients with NAFLD, respectively, but diverged as to the location of iron responsible for such a link: for Valenti et al. [10], hepatocytic iron was associated with more fibrosis than reticulo-endothelial iron which even tends to have a protective effect, whilst, for Nelson et al. [20], reticulo-endothelial iron only was associated with a higher risk of significant fibrosis. The weakness of risk level may
explain such a discrepancy together with differences in characteristics of Italian and American patients with respect to body mass index and to the severity of steatohepatitis.

**Treatment**

Venesection therapy has been advocated in DIOS and NAFLD on the basis of early and small studies conducted in heterogeneous populations and showing that the achievement of low body iron stores by bloodletting or a low iron diet [42] was associated with decreased insulin resistance. Usually, removal of 1 to 2.5 g of iron is necessary to obtain low serum ferritin levels [43]. This is much less than in hemochromatosis for a given level of serum ferritin [44] but authenticates the reality of iron excess in DIOS patients [17].

In a controlled randomised trial conducted in 28 type 2 diabetics with elevated serum ferritin, Real-Fernandez et al. found that iron removal improved both insulin sensitivity and beta cell function but had no significant effect on blood glucose [45]. Facchini et al. [46], in a randomized study of 42 patients, mainly diabetics, showed that iron depletion to near iron deficiency was associated with a decrease in both fasting and glucose-stimulated plasma insulin concentrations in a subgroup of 17 hyperferritinemic subjects with non-biopsy proven NAFLD. In a randomized study, Houshyar et al. [47] assessed the effects of phlebotomy-induced reduction of body iron stores on metabolic syndrome in 64 patients. They found that iron depletion was associated with improvement of metabolic syndrome parameters, including reduced blood pressure, blood glucose, glycosylated hemoglobin and LDL to HDL ratio. Piperno et al. [48] compared the respective effects of venesection therapy and diet restriction in 44 subjects with DIOS. They found that diet restriction only resulted in a significant decrease in blood glucose. Valenti et al. [49], in a case-control study of 128 non-diabetic patients with NAFLD and either elevated serum ALT levels or increased serum ferritin levels or both, showed that serum insulin, serum glucose and HOMA improved in iron-depleted patients. The same authors randomized 38 Italian patients with NAFLD and hyperferritinemia to venesection versus no venesection with liver histology as primary endpoint [50]. A significant improvement was observed in NAFLD activity score in the 12 evaluable venesected patients compared to controls. Beaton et al. [51] performed a phase 2 study of phlebotomy therapy with paired liver biopsies in 31 patients with NAFLD. Despite the small number of patients with liver biopsy at the end of treatment, significant improvement was observed in NAFLD activity score but not in fibrosis stage. Recently, two larger randomized controlled studies assessing the effects of phlebotomy in NAFLD and DIOS were published. The first, from Adams et al. [52] showed that iron depletion failed to improve hepatic steatosis assessed by MRI, serum ALT, blood glucose, HOMA-IR and insulin sensitivity index in 61 Australian patients with NAFLD as well as in a limited subgroup of 36 patients with hyperferritinemia. The second, from Lainé et al. [53] studied 274 non diabetic French patients with DIOS randomly assigned to receive either venesections with lifestyle and diet advice or lifestyle and diet advice only. One-year maintenance of low iron stores by bloodletting did not improve metabolic and hepatic features, was associated with weight gain, and was not as well tolerated as expected. Weight loss alone was associated with improvement in most metabolic features including glycaemia and insulin resistance, and in serum ferritin and liver tests.

**Figure 1**

Putative pathophysiology of DIOS. Excessive food intake results in iron excess within both liver and visceral adipose tissue (VAT). Adipocytic iron dysregulates the production of adipokines, especially adiponectin. This triggers/enhances insulin resistance, which stimulates hepcidin production. A hepcidin resistance state could explain the persistence of iron excess. Its differential expression according to cell types could account for a shift of iron from liver to VAT.
Based on these two randomized controlled studies, phlebotomy therapy cannot be currently considered as a valuable option in DIOS patients. Sustained modification of diet and life-style habits remains the first therapeutic intervention in these patients together with drug control of increased blood pressure, abnormal blood glucose and dyslipidemia when necessary. Pending issues in DIOS and NAFLD are:

- the comprehensive understanding of alterations in iron metabolism and of their clinical relevance;
- the assessment of long-term effects of well-conducted and sustained lifestyle and diet modifications on iron excess;
- the search for a possible benefit of iron removal in some subgroups of patients, especially those with high serum ferritin levels despite correct physical activity and dietary measures.

Disclosure of interest: The authors declare that they have no competing interest.

References


