Correction of insulin resistance syndrome does not cause normalization of hyperferritinemia

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SUMMARY
The consequences of iron overload from dysmetabolic hyperferritinemia are a strong motivation for an active medical care program. Venesection therapy is known to be effective in controlling iron overload parameters although no study has evaluated the impact of the normalization of metabolic dysfunction on iron overload.

Aims — To evaluate the impact of normalization of metabolic dysfunction on iron overload.

Methods — Sixty consecutive patients with dysmetabolic hepatosiderosis were included in a prospective study. Patients with hyperferritinemia above 1 000 µg/L were excluded. Multidisciplinary care was offered to all patients to normalize metabolic disorders (body mass index, arterial hypertension, fasting and postprandial hyperglycemia, hyperuricemia, hypercholesterolemia and hypertriglyceridemia) every three months. All patients were followed for one year. At clinical examinations, ferritinaemia concentrations were measured and all dysmetabolic parameters evaluated. MRI was performed at the beginning of the study and at the one year follow-up, to measure hepatic iron load.

Results — Despite efficient medical care of insulin resistance syndrome, ferritinaemia remained stable. In two thirds of the study population, hyperferritinemia reached at least one and a half times the baseline value, although the dysmetabolic disorders of 40% of the patients were strictly normalized. In this group of 44 patients with strict normalization of metabolic functions, 24 (54%) had hyperferritinemia at one year follow-up whereas 16 other (36%) normalized this parameter. Only 4 patients who had a ferritinaemia below 450 µg/L at baseline, normalized this value at one year. Intra-hepatic iron overload, evaluated by MRI imaging remained stable except for 2 patients who normalized ferritinaemia.

Conclusion — Although efficient handling of dysmetabolic disorders is essential, it is not sufficient to normalize dysmetabolic hyperferritinemia. Only patients with a ferritinaemia value below a baseline of 450 µg/L had normalization of iron overload. Therefore venesection must be offered to all patients with a hyperferritinemia above this value.

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Introduction
Dysmetabolic hepatosiderosis was defined by Moirand et al. [1] in 1997. This new entity associates hepatic iron overload with signs of insulin resistance in the absence of other causes of iron overload, particularly genetic hemochromatosis and chronic alcoholism. Serum ferritin is elevated and, in 10% of patients, there is an increase in the transferrin coefficient of saturation [2]. This iron overload can have serious mid- and long-term consequences with probable increased risk of fibrosis and thus cirrhosis [3]. Furthermore, a few cases of hepatocellular carcinoma have been reported [4]. Iron overload is also associated with an increased risk of sepsis and cancer [5] and could accelerate the development of atheroma complications [6]. It must be reduced. Venesection has proven efficacy and is well tolerated [7, 8] but requires careful surveillance for these patients often taking many medications.

Conversely, the impact of treating the metabolic diseases on iron overload has not been studied. We therefore analyzed changes in iron overload before and after correction of the metabolic syndrome in order to determine whether this necessary attitude is sufficient for treatment of dysmetabolic hepatosiderosis.

Patients and Methods
We included in this prospective study all consecutive patients aged less than 65 years, hospitalized between January and December 1998 with dysmetabolic hyperferritinemia who had at least one risk factor for insulin resistance, i.e. type 2 diabetes mellitus according to the WHO clasi-
Changes in serum ferritin level in the 44 patients whose metabolic disorders were controlled during the study are presented in figure 3. Normalization of the risk factors in these 44 patients was not correlated with a decrease in serum ferritin at one year: 830 g/L (220-990) in comparison with the serum ferritin level at one year in the group of 16 patients who did not normalize their risk factors: 905 g/L (590-980) (NS). At inclusion, the serum ferritin cut-off level of 450 g/L separated patients who achieved or not a normal serum ferritin level at one year after correction of metabolic disorders. All patients whose baseline serum ferritin was below 450 g/L achieved a normal level at one year and none of the patients whose baseline serum ferritin was greater than 450 g/L presented a normal or decreased level at one year. Considering BMI < 27 kg/m² as normal instead of the < 30 kg/m² defined as normal, changes in serum ferritin were different in the subgroup of 44 whose metabolic disorders were controlled (figure 4). The number of patients with a stable ferritin level at one year was significantly higher if BMI < 27 was achieved than if BMI remained above 27 (14 patients versus 2 patients, P < 0.05). Conversely, serum ferritin increased more often among patients whose BMI was in the 27-30 range than in those with BMI < 27 (P = 0.05). But the median serum ferritin level at one year was comparable: 610 g/L (220-880) for BMI < 27 at one year and 840 g/L (240-990) for 27 < BMI < 30 at one year (NS). The time course of serum ferritin did not exhibit any rapid phase of improvement. There was on the contrary a rather constant progression in the number of patients whose serum ferritin level worsened (figure 5) despite management of their polymetabolic syndrome.

Hepatic iron overload

Hepatic iron overload as determined by MRI was assessed before and after the one-year study in 45 patients. In this subgroup, two patients achieved a normal serum ferritin level. In these two patients, iron concentration in the liver was 75 g/kg before treatment and < 36 µg/g at one year. For the other 43 patients, including 25 whose serum ferritin level stabilized and 18 whose serum ferritin level worsened despite normalization of metabolic parameters, iron concentration in the liver was com-

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**Results**

**Patient characteristics**

Sixty patients were included in the study: None were lost to follow-up. Patient characteristics are presented in table I. Forty-eight patients (80%) presented at least two risk factors. At inclusion, 32 patients had elevated serum aminotransferase levels. The transferrin coefficient of saturation was normal (< 35%) in all patients except five who had a serum ferritin levels > 800 g/L associated with elevated aminotransferase levels (> 3 times ULN).

**Time course of serum ferritin**

After one year of management, median serum ferritin remained unchanged at 880 g/L (range 220-990) (NS) (figure 1). Among the 40 patients whose serum ferritin increased during the course of the study, 24 had normalized all of their risk factors (figure 2). Among the 16 patients who serum ferritin remained unchanged at one year, all had normalized the risk factors present at inclusion.

**Statistical analysis**

Results are reported as median and range and were compared with the non-parametric Wilcoxon test. Differences were considered significant for P < 0.05. Spearman's coefficient of correlation was used to search for correlations between variables.

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**Table I. – Characteristic features of 60 patients with dymetabolic hyperferritinemia at inclusion and at last follow-up (one year).**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>One year</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>55 (30-66)</td>
<td>56 (31-65)</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Type 2 diabetes(1)</td>
<td>(N, %)</td>
<td>39, 65%</td>
</tr>
<tr>
<td>Dyslipidemia(2)</td>
<td>(N, %)</td>
<td>24, 40%</td>
</tr>
<tr>
<td>Obesity(3)</td>
<td>(N, %)</td>
<td>30, 50%</td>
</tr>
<tr>
<td>Serum ferritin*</td>
<td>680*(360-990)</td>
<td>880 (220-990)</td>
</tr>
<tr>
<td>ALT (ULN &lt; 30 µ/l)</td>
<td>68 µ/l* (34-110)</td>
<td>65 µ/l (22-105)</td>
</tr>
<tr>
<td>AST (ULN &lt; 30 µ/l)</td>
<td>54 µ/l* (31-83)</td>
<td>51 (48) (18-61)</td>
</tr>
</tbody>
</table>

(1) Type 2 diabetes: fasting blood glucose (twice) > 1.27 g; blood glucose at any time > 2 g.
(2) Hypercholesterolemia > 200 mg/dl; hypertriglyceridemia > 2 G/L.
(3) Body mass index > 30 kg/m².
(4) Systolic pressure > 150 mmHg, diastolic pressure > 90 mmHg.
* median.
* P : non significant.

**ULN**: upper limit of normal.
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parable before and after treatment (median 100 g/L [72-122] before treatment and median 98 g/L [74-119] at one year) (NS).

Serum aminotransferase levels

At inclusion serum aminotransferase levels were not correlated with serum ferritin level. Among patients whose aminotransferase levels were elevated at inclusion, only three achieved normal levels at the end of the study. These three patients also normalized their metabolic parameters during the study and were classed stage 0 at the baseline abdominal ultrasound.

Search for HFE gene mutation

HFE gene mutation was observed in half of the patients: 18 H63D heterozygous patients and 12 C282Y heterozygous patients. At inclusion, serum ferritin was not correlated with the presence or absence of HFE gene mutation. Median serum ferritin levels were comparable between patients with and without HFE gene mutation (NS).

Hepatic steatosis at abdominal ultrasound

At inclusion, the abdominal ultrasound identified stage 0 steatosis in 19 patients, stage 1 in 32, stage 2 in six and stage 3 in three. There was no correlation between the severity of steatosis defined ultrasonographically and serum ferritin or serum aminotransferase levels. Thirty-six patients who did not achieve normal serum ferritin levels after treatment of their polymetabolic disorders underwent a control ultrasound before initiating venosection at one year. The stage of steatosis was unchanged in all 36. At inclusion, liver biopsy was performed in 15 patients who did not have a baseline MRI. Besides the iron overload, histology revealed hepatic steatosis in six patients, steatohepatitis in four, and fibrosis in three. There were no cases of cirrhosis.

Discussion

Management practices for patients with dysmetabolic hyperferritinemia are not clearly defined. Although there is no prospective evidence demonstrating that normalization of serum ferritin level and reducing hepatic iron overload has a beneficial effect, this appears to be a rational approach. Even moderate iron overload is known to favor hepatic [4] and extrahepatic [5] cancer. Several case-control and longitudinal studies have demonstrated a significant relationship between iron overload and cancer morbidity and mortality [11]. Moreover, iron overload could worsen risks of atherosclerosis which are already significant in patients with polymetabolic syndromes [12]. The presence of iron overload might also be associated with more severe fibrosis in patients with non-alcoholic steatohepatitis [3].

Our work clearly demonstrated that if serum ferritin is greater than 450 g/L, careful regular control by a pluridisciplinary team of the polymetabolic disorders is not sufficient to normalize the ferritin level, which can even rise significantly in more than half of patients. It was noted however that among patients whose ferritin did increase, metabolic control did not achieve the objectives in four out of ten patients. According to these results,
hyperferritinemia patients. There has been just one report by hyperinsulinism syndromes linked to insulin receptor mutations [16]. The same type of iron overload as on the surface of hepatocytes and inversely transferrin has an anti-insulin action [16]. The same type of iron overload as on the surface of hepatocytes and inversely transferrin has an anti-insulin action [16]. The same type of iron overload as on the surface of hepatocytes and inversely transferrin has an anti-insulin action [16]. The same type of iron overload as on the surface of hepatocytes and inversely transferrin has an anti-insulin action [16]. The same type of iron overload as on the surface of hepatocytes and inversely transferrin has an anti-insulin action [16].

The fact that normalizing metabolic levels in patients with polymetabolic syndrome has no impact on dysmetabolic hyperferritinemia is compatible with the lack of impact on steatosis or nonalcoholic steatohepatitis. This is partly in contradiction with the fact that weight loss in patients with steatosis or nonalcoholic steatohepatitis can sometimes lead to normal aminotransferase levels [17] and improved histology [18]. Furthermore, it is known that hyperferritinemia in polymetabolic syndrome leads to an underestimation of hepatic tissue overload [7].

Our findings demonstrate that while achieving normal metabolic levels for the different risk factors in dysmetabolic syndrome, particularly BMI < 27 kg/m², is crucial, it is not sufficient to reduce the iron overload. On the contrary, iron overload continues to progress if the existing metabolic disorders are not rigorously controlled. It thus appears logical to propose the classical solution of venesection [8]. The 450 g/L level for serum ferritin appears to be an important cut-off. Above this level one cannot expect improvement without blood removal. This level might be a sign of shorter duration of the disease that could be useful to detect dysmetabolic hyperferritinemia in patients with risk factors.

**REFERENCES**


**Fig. 5** - Changes in serum ferritin over time (N = 60).

The longer metabolic control cannot be expected to alleviate the iron overload. Forty-four of our 60 patients achieved control of their metabolic disorders. This is better than in routine practice but we were working with selected patients seen every three months. In the group of patients whose ferritin level increased and who did not achieve normal metabolic levels, the insulin resistance phenomenon which caused the dysmetabolic hyperferritinemia was probably not improved. We did not however perform an objective insulin resistance test (e.g. HOMA) for confirmation. The majority of the patients achieved metabolic levels within normal ranges but for most of them, serum ferritin remained unchanged or even rose in 44%. We retained BMI > 30 as the cut-off level for obesity, but this level may be too high. We therefore readied the analysis setting the cut-off at 27. Under these conditions, 95% of our patients who achieved normal metabolic levels had stable ferritin levels. Serum ferritin increased in only 5%. For these 5%, the metabolic levels may have been set too high for their individual metabolic situation. On the other hand, none of the patients whose serum ferritin was > 450 g/L at inclusion normalized their metabolic disorders. Even though the insulin resistance phenomenon was probably blocked in these patients, this was not sufficient to alleviate their excessive iron overload. Once iron has been deposited in the liver, it can probably not be eliminated spontaneously since hepatic clearance is extremely low. Venesection subsequently proposed for 36 patients in our study appears to be the only way to normalize ferritin level with very good clinical tolerance [7]. The normal ferritin levels achieved in four patients with a baseline level < 450 g/L would appear to be related in part to strict normalization of the metabolic levels and in part to the shorter duration of the disease in these patients and their shorter history of diabetes and hypertension (less than one year). Physiological clearance of excess iron would appear to be insufficient in patients with significant tissue overload. The 450 g/L ferritin level might correspond to a threshold of physiological iron overload clearance capacity.

Although we did not perform precise tests, our results confirmed a strong link between insulin resistance and iron overload. Several pathophysiologcal mechanisms argue in favor of such a relationship. Hepatic iron overload has been observed in hyperinsulinism syndromes linked to insulin receptor mutations [13, 14]. A correlation between the level of hyperferritinemia and blood glucose levels has also been reported in insulin resistance patients [15]. Insulin increases the expression of transferrin on the surface of hepatocytes and inversely transferrin has an anti-insulin action [16]. The same type of iron overload as observed in dysmetabolic hyperferritinemia is reported in nonalcoholic steatohepatitis [3].

To our knowledge, there has been no other study reported to date demonstrating that normal metabolic levels are necessary but not sufficient to obtain a normal iron level in dysmetabolic hyperferritinemia patients. There has been just one report by Guillygomar’ch et al. [8] who observed similar results in a group of ten control patients in a study of insulin resistance after phlebotomy. These authors did not design their study to assess iron levels in patients treated for their dysmetabolic syndrome, but the ferritin level did not improve in the control group: 679 g/L (range 476-979) before treatment and 708 g/L (range 544-849) after treatment (NS). These authors did not describe the patient characteristics at inclusion, so the associated medical treatments and the metabolic results make it difficult to draw any clear conclusion concerning this subgroup.

Our findings demonstrate that while achieving normal metabolic levels in patients with polymetabolic syndrome has no impact on dysmetabolic hyperferritinemia, the ferritin level did not improve in the control group: 679 g/L (range 476-979) before treatment and 708 g/L (range 544-849) after treatment (NS). These authors did not describe the patient characteristics at inclusion, so the associated medical treatments and the metabolic results make it difficult to draw any clear conclusion concerning this subgroup.
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