

## Serum ferritin and liver inflammation: which come first? Chicken or egg?

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Inflammation is not the cause of an elevated serum ferritin in non-alcoholic fatty liver disease

**Beaton MD, et al.** For the clinician the serum elevation of ferritin in chronic liver diseases (CLD), with the exception of Emochromatosis, is always assumed to be a non-specific marker of hepatic inflammation and not of iron overload.<sup>1</sup> Nonalcoholic fatty liver disease (NAFLD) is now the most common cause of CLD.<sup>2</sup> The spectrum of NAFLD is ranging from simple steatosis through nonalcoholic steatohepatitis (NASH).<sup>3</sup> Iron is regarded as a putative element that interacts with oxygen radicals, and high rates of hyperferritinemia together with increased hepatic iron stores have been demonstrated in NASH.<sup>4</sup> The role of hepatic iron in the progression and in the pathogenesis of NASH remains controversial. We know that phlebotomy or iron-restricted diet reduce hepatic damage as well as insulin resistance (IR) in patients with NAFLD/NASH.<sup>5</sup> However, exact mechanisms involved in iron accumulation in NASH remain to be clarified. Genetic factors linked to IR, dysregulation of iron-regulatory molecules, erythrophagocytosis by Kupffer cells may be responsible for hepatic iron overload in NASH.<sup>6,7</sup>

Chakrabarti and Adams, in this *Annals of Hepatology* issue<sup>8</sup> reported a simple clinical study of phlebotomy treatment performed in a series of 56 patients with histology-proven NAFLD. Liver biopsy and liver iron concentration (LIC) was performed at entry and 6 months after phlebotomy. They did not find any significant correlation between LIC and the level of serum ferritin, hepatic inflammation as measured by NAS score, and other generic markers of inflammation, such as ESR and CRP.

The authors concluded that elevated serum ferritin is linked to hepatic iron accumulation, but that liver inflammation is not the cause of increased serum ferritin in patients with NAFLD. Other authors<sup>7</sup> recently demonstrated that elevated ferritin level reflects iron stores, and not hepatic inflammation, being a predictors of vascular damage in NAFLD. The mechanisms involved in iron accumulation in NAFLD, and in inducing IR, metabolic, hepatic, and vascular damage by iron accumulation are not yet well known and should be further investigated.

They may involve up-regulation of hepcidin by increased iron stores in patients not carrying HFE mutations, and iron compartmentalization into macrophages, or the hepatic expressions of the iron-export protein ferroportin-1, and of the iron-sensing molecule hemojuvelin, which have been found to be significantly lower in NAFLD patients.<sup>7,9</sup> Whatever the mechanisms should be the only certainty is that an increased serum ferritin level in NAFLD is not a marker or a cause of inflammation, but a consequence of iron accumulation inside the hepatocyte.

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