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Hepatology highlights

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Castiella A, *et al.* Liver iron concentration is not raised in patients with dysmetabolic hyperferritinemia

In this issue of *Annals of Hepatology,* Castiella, *et al.* examined the relationship between liver iron concentration (LIC), hyperferritinemia and metabolic syndrome in a Spanish cohort of patients.

Metabolic syndrome is defined by the presence of at least three of the following: obesity (increased waistline circumference), atherogenic dyslipidemia (hypertriglyceridemia and/or low high-density lipoprotein), hypertension or insulin resistance (elevated glucose levels or frank diabetes).[1] Metabolic syndrome is increasing in prevalence in Western societies and is on the order of 25% of the adult population.[2] Nonalcoholic fatty liver disease (NAFLD) is often observed in concert with metabolic syndrome with similar prevalence rates.[3] Hyperferritinemia is commonly associated with both metabolic syndrome and NAFLD; a recent report from Chen, *et al.* found this association in the context of normal hepatic iron concentrations.[4] However, this as well as other reports has been relatively limited in accuracy by the imaging and calculation methods for determining liver iron concentration (LIC). To date, there is conflicting evidence from large-scale randomized clinical trials regarding the clinical importance of treating iron overload in improving histologic or biochemical parameters in metabolic syndrome associated with hyperferritinemia as is commonly seen in NASH/NAFLD.

In this paper, the authors conducted a prospective cohort of 132 consecutive adult patients, of which 97 patients were included with complete data, over twelve months from two centers in Basque Country, Spain. Included subjects were referred for evaluation of hyperferritinemia. The authors attempted to determine LIC with greater diagnostic certainty in an effort to compare patients with and without metabolic syndrome. Hyperferritinemia was defined as serum ferritin > 200 ug/L in women and > 300 ug/L in men. LIC values were extracted from magnetic resonance imaging (MRI) by one trained investigator; normal LIC was < 36 umol/g, iron overload 37-80 umol/g and high iron overload > 80 umol/g. The cohort was predominantly male (82%) and 60% (n = 54) met criteria for metabolic syndrome. Patients with metabolic syndrome were similar to those without metabolic syndrome in baseline characteristics (age, alcohol use, concurrent viral hepatitis) and reported laboratory values including ferritin, transferrin saturation index, iron hepatic index, and hemochromatosis predisposing mutations. Thirty-six patients with metabolic syndrome underwent MRI and were compared to 18 without metabolic syndrome. Interestingly, the primary endpoint of LIC approached statistical significance with lower mean mean values observed in the metabolic syndrome group (28.8 ± 20.9 umol/g *vs.* 33.2 ± 19.6 umol/g, p = 0.067). No patients had high iron overload and the hepatic iron index was < 1.5 in all patients.

This work confirms that of Chen, *et al.*[4] and provides further evidence that LIC may not be elevated in patients with hyperferritinemia and metabolic syndrome. Given the trend towards statistical significance, the differences in LIC in bothin the metabolic syndrome and non-metabolic syndrome patient populations should be further studied on a large scale, greater powered basis to further define this relationship. Nonetheless, this study is thought provoking in that patients with metabolic syndrome had lower levels of LIC in the setting of comparable markers of iron saturation. This points towards the importance of ferritin as a marker of inflammation rather than clinically important iron deposition in the liver and provides caution when interpreting these values and making subsequent clinical management decisions.

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Fan J, *et al.*
Association of HLA-DQ and IFNL4 polymorphisms with susceptibility to hepatitis B virus infection and clearance

Fan, *et al.* investigated human leukocyte antigen (HLA)-DQ and interferon (IFNL-4) gene polymorphisms and their relationship with clearance of chronic viral hepatitis ina cohort of 1,069 Chinese subjects enrolled between 2011-2014 at a single academic center in this issue of *Annals of Hepatology*.

Chronic HBV infection is associated with 5% of all deaths in China and 400 million people are infected worldwide.[5] Chronic HBV is a leading cause of hepatocellular carcinoma (HCC) in both patients with and without cirrhosis. Genome-wide association studies in the HBV population have identifiedHLA-DQ rs9275319as a single nucleotide polymorphism (SNP) that is associated with improved HBV outcomes including lower rates of HCC.[6] IFNL-4 is a SNP that is associated with varying degrees of HCV clearance with treatment.[7] The role of this SNP in patients with chronic HBV without HCC and in those patients who have cleared prior HBV remains unknown.

In their paper, Fan, *et al.* compared three distinct groups of patients: 397 with HBV (which the authors defined as chronic HBV, HBV-associated cirrhosis or HBV-associated HCC), 434 with spontaneous clearance of viral hepatitis and 238 healthy controls. Subjects who were vaccinated against HBV were excluded. Not surprisingly, baseline serum aminotransferases and total bilirubin were significantly higher in the chronic HBV group when compared to the other two groups, otherwise the populations were interchangeable in demographics. HLA-DQ rs9275319 TT was the most frequently identified allele across all three groups (76-86%). Carriage of the HLA-DQ rs9275319 C allele was protective against chronic HBV infection with OR 0.51, 95% CI 0.36-0.74 ($p < 0.001$) and was also associated with greater odds of HBV clearance (OR 1.66, 95% CI 1.20-2.30, $p = 0.002$). Utilizing multifactor dimensionality reduction, the interaction between HLA-DQ SNPs and IFNL-4 was also found to play a role in HBV susceptibility, however IFNL-4 by itself was not associated with HBV clearance or progression to chronic liver disease.

Confirming the work of others, Fan, *et al.* have demonstrated the importance of HLA-DQ rs9275319 and its interaction with IFNL-4 in determining which patients when exposed to HBV, will clear the infection or develop chronic liver disease. Unfortunately, the protective rs9275319 C allele was found in only 17% of the study population, which may limit widespread clinical importance. The mechanism driving the complex interaction between HLA-DQ rs9275319 and IFNL-4 remains unknown and future investigation to confirm the authors' speculation on the role of ethnicity, environmental factors and virus seems warranted.

Thomas-Dupont P, *et al.*
Elevated circulating levels of IL-21 and IL-22 define a cytokine signature profile in type 2 autoimmune hepatitis patients

In this issue of the *Annals of Hepatology,* Thomas-Dupont, *et al.* aimed to compare circulating levels of pro- and anti-inflammatory cytokines in direct comparison of type 2 autoimmune hepatitis (AIH) to type 1 AIH and also to healthy unmatched controls.

Despite recent advances, the pathogenesis of AIH is still incompletely understood. Conceptually, AIH is caused by an environmental agent that triggers a cascade of T-cell mediated events directed at liver antigens in a host that is genetically predisposed, ultimately leading to necroinflammatory and fibrotic changes in the liver.[8] As type 1 AIH is the most common phenotype of AIH occurring in >80% of adults, the majority of research has focused on this subtype including the investigation of pro- and anti-inflammatory cytokines. Tumor necrosis factor alpha (TNFα), Interleukin-(IL) 6 and IL-8 are the best described cytokines in this population.[9]

Type 2 AIH is found in <5% of all adults, the hallmark of which is a positive anti-liver kidney microsomal antibody (anti-LKM). Unfortunately, type 2 AIH patients have poorer outcomes and are less likely to respond to conventional treatment with immunosuppression. Regardless of the type of AIH, there remains controversy as to the specificity of cytokine pattern as it has been suggested that cytokine patterns are a feature of chronic liver disease itself and are stage dependent and marginally effected by the type of underlying liver disease.[10]

Thomas-Dupont, *et al.* enrolled 46 Mexican subjects from a single center with biopsy-proven AIH, 41 of which had type 1 and five type 2. 80% were female. 10 patients had overlap syndrome with primary biliary cirrhosis. Contrary to the published literature, patients with advanced liver disease (fibrosis stage 3 or 4) were more likely to be in the type 1 group and no cases of cirrhosis were found in type 2 AIH. Type 1 AIH patients had higher antinuclear antibody (mean 1:1091 *vs.* 1:396) and higher anti-smooth muscle antibody titers (mean 1:488 *vs.* 1:160) when compared to type 2 AIH. Only one patient was not on treatment at the time of enrollment, however, only 52%

met criteria for remission as defined by serum aminotransferase normalization. Treatment with corticosteroids alone when compared to both corticosteroids plus thiopurines and to other treatment regimens including ursodeoxycholic acid did not impact circulating levels of cytokines. While multiple cytokines were significantly elevated in patients with elevated aminotransferases, only IL-17F was correlated with the degree of aminotransferase elevation. Type 2 AIH patients had significantly higher levels of IL-21 and IL-22 when compared to type 1 or healthy controls.

These findings are novel and shed more light on the pathophysiology of AIH as IL-17F is known to interact with both TNFα and IL-6, and may accelerate hepatic fibrosis. Taken as a whole, the available literature seems to be unclear as to the exact implications of particular cytokine profiles, however, this study suggests that future investigation into the complex interaction between IL-17F, TNFα and IL-6 would be of interest. It is our hope that this may offer a more upstream therapeutic target in those patients with refractory disease rather than the more downstream, less specific agents currently available including mycophenolate, tacrolimus and even TNFα antagonists.

CONFLICTS OF INTEREST/DISCLOSURES

The authors of this manuscript have no relevant conflicts of interest to disclose.

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