

The fate of fatty liver disease: of bile and fatty acids

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Article commented:

Bechmann LP, Kocabayoglu P, Sowa JP, Sydor S, Best J, Schlattjan M, Beilfuss A, et al. Free fatty acids repress small heterodimer partner (SHP) activation and adiponectin counteracts bile acid-induced liver injury in superobese patients with nonalcoholic steatohepatitis. *Hepatology* 2013; 57: 1394-406.

Comment:

Non-alcoholic fatty liver disease (NAFLD) is a modern plague that affects more and more populations with increasing prevalence.¹⁻³ NAFLD is often considered to be primarily a hepatic manifestation of the metabolic syndrome with an *a priori* increased risk for morbidity and mortality in particular from cardiovascular events.⁴ Non-alcoholic fatty liver (NAFL), or bland steatosis, can progress to non-alcoholic steatohepatitis (NASH), which is characterized by the presence of hepatocellular ballooning and chronic inflammation in addition to steatosis. Patients with NASH are threatened by the additional risk of liver fibrosis, cirrhosis and the development of hepatocellular carcinoma. Although the exact molecular mechanisms contributing to disease progression are yet to be fully defined, there is emerging evidence that intrahepatic lipid homeostasis and liver-adipose tissue cross talk are two key factors for the development and progression of NAFLD. In particular the adipocytokine adiponectin has been shown to exert hepatoprotective properties and to be reduced in patients with NAFLD.^{5,6}

At the genetic level a number of host risk factors for steatosis and NASH have been identified, the strongest and most consistently replicated being the p.I148M variant of the lipid droplet-associated enzyme adiponutrin, or *PNPLA3*.⁷ Interestingly, increased bile acid levels have also been reported in livers of patients with steatohepatitis⁸ and have been shown to activate adipocytes to produce adiponectin,⁹ consistent with critical crosstalk between adipose tissue and liver in NAFLD.

The recent paper by Bechmann, Geier, Canbay and coworkers published in *Hepatology* aimed at elucidating the multiple (and complex) interactions of bile acids, free fatty acids and adiponectin in patients with NASH undergoing bariatric surgery in comparison to patients with NAFL and healthy controls.¹⁰ The investigators studied serum bile acid levels in relation to serum free fatty acid (FFA) and adiponectin levels in morbidly obese (BMI > 40 kg/m²) and moderately obese (BMI ~ 30 kg/m²) patients with NAFLD. Because bile acid biosynthesis is determined by the rate-limiting enzyme CYP7A1 and hepatic bile acid transporters are controlled by the central bile acid sensor FXR (nuclear receptor *NR1H4*), they also studied the hepatic expression of *CYP7A1*, *NR1H4*, and the sinusoidal bile acid transporter NTCP (solute carrier *SLC10A1*) as well as the canalicular bile salt export pump *ABCB11* at the mRNA and, at least in part, protein levels as well as by immunohistochemistry.

In this study, hepatic *CYP7A1* expression was strongly induced in all NAFLD patients, although with high interindividual variability at the protein level, and *SLC10A1* (and *ABCB11*) expression levels were induced particularly in patients with lower NAFLD activity scores (NAS). Whereas expression of both critical genes (*CYP7A1*, *SLC10A1*) is normally repressed by bile acids via FXR and subsequent induction of the small heterodimer partner (SHP, or *NROB2*), this effect was absent in the obese NAFLD patients, and the hepatic mRNA expression of both nuclear receptors was unchanged in comparison to healthy controls.

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Complementary experimental data from cell culture experiments indicated the independent induction of *CYP7A1* and *SLC10A1* by FFA, leading to increased bile acid synthesis and uptake with potentially detrimental effects *in vivo* (although the authors did not observe any effect on the viability *in vitro*). In fact, the grade of ballooning as marker for NAFLD severity was associated with higher serum bile acid levels. As expected, serum FFA concentrations were significantly increased in NASH patients, and FFA-induced lipolysis led to higher levels of serum markers of cell death (M30 and M65), which discriminated NASH patients from NALFD and normal controls.

As shown previously¹¹ adiponectin levels were inversely correlated with serum FFA (and bile acid) concentrations as well as NAS, being lowest in patients with NASH. In contrast to Kaser, *et al.*¹² an increase of the hepatic adiponectin receptor *APOR2* expression was noted in NASH (as compared to patients with NAS < 5), which was interpreted as a potential counteracting mechanism. Interestingly, the cell culture experiments indicated transcriptional repression of *CYP7A1* by adiponectin independent of FXR.

The authors finally aimed at defining a cut-off level for adiponectin as serum marker for the presence of NASH in contrast to simple NAFLD. In this study, they identified the optimal cut-off to predict NASH to be 29.16 ng/mL, with patients below being at risk to present with NASH.

In summary, this comprehensive clinical study suggests that increased FFA and diminished adiponectin levels in NAFLD lead to increased intracellular bile acid concentrations levels due to induction of bile acid uptake and synthesis. The consecutive bile acid-mediated hepatocellular toxicity potentially contributes to increased cell death, fibrosis, and malignant transformation. These effects are suggested to be due to insufficient repression via SHP in the presence of excess FFA and the loss of the protective effect of adiponectin on bile acid homeostasis, which this study is the first to report.

The conceptual findings extend our knowledge about the interaction between adipose tissue and liver in NAFLD and render –together with the clinically useful adiponectin cut-off for NASH– this paper an important cornerstone for the understanding of the clinical manifestations of NALFD. However since the study cannot differentiate between cause and effect for many observations, additional work is

needed to further dissect the exact functional mechanisms of bile and fatty acids. This should help to define what differentiates ‘superobese’ from lean NASH patients at the molecular level - with the aim to design more ‘precisely’ stratified strategies for the prevention and treatment of fatty liver disease and its sequelae.

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