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OPINION

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The Presence and Severity of Nonalcoholic Steatohepatitis Is Associated with Specific Changes in Circulating Bile Acids

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease nowadays with currently no approved therapies for the disease. The liver plays a pivotal role in lipid and glucose metabolism. The interactions of molecular mechanisms on the gut for example influences the development still needs to be understood. Bile acids (BA) have been shown to impact metabolic homeostasis and insulin sensitivity. Here, we comment on a study analyzing BA profiles in NAFLD patients addressing novel pathways involved in NAFLD progression.

Key words. NAFLD. NASH. Bile acids. Steatosis. Microbiome.

OPINION

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in industrial countries worldwide.[1,2] NAFLD is therefore known as the hepatic manifestation of the metabolic syndrome.[3] NAFLD can progress from a fatty liver to non-alcoholic steatohepatitis (NASH), 15-20% of NASH- patients will develop a cirrhosis.[4] By 2020, NAFLD/NASH is estimated to be the leading cause of liver transplantation.[5] The pathogenesis of NAFLD/NASH however, remains incompletely understood and there are currently no approved therapies for NASH. In recent years, more attention has been payed towards the interaction of the intestine-liver- axis for the development of NAFLD/NASH. Bile acids (BA) for example have been shown to play an important role in metabolic homeostasis as well as insulin sensitivity.[6,7] We have previously described a free fatty acid induced dysregulation of BA signaling in NASH as well as a correlation of BA levels with NASH severity in obese individuals.[8] Alterations in serum and fecal BA levels in NASH were later confirmed by others.[9,10]

Puri, *et al.* characterized plasma BA profiles in NAFLD and NASH, compared to controls with no known liver disease.[11] Further, plasma BA was related to liver histology (steatosis, inflammation, hepatocellular ballooning, fibrosis) as well as disease activity and stage. In this prospective cross- sectional study patients were recruited from a single-center. NAFLD was proven via liver biopsy. Eighty-six patients were included in this study (24 controls, 25 NAFLD and 37 NASH). Puri, *et al.* showed that NAFLD/NASH is associated with a significantly altered circulating BA profile, which correlated with histological features of NASH. The study showed that especially primary BAs are significantly increased in NASH patients, while secondary BA were decreased in NASH compared to controls. Secondary BAs are significantly lower in NASH patients, except for Ursodeoxycholate (UDCA) and Deoxycholate. Primary as well as Secondary BA are both related to hepatocyte ballooning. In addition to that, an increase in Primary BAs is directly related to the NALFD Activity Score (NAS).

This study reveals specific BA profiles in NAFLD, NASH and control patients, proving alterations in NAFLD/NASH. The shifting towards more primary BAs could be explained either because of an increased synthesis, decreased conversion to secondary BAs or decreased bile excretion of primary BAs. Since the decrease of intes-

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tinal dehydroxylation of primary BAs as well as a reduced formation of secondary BA has been known for decades as intestinal-microbiota-dependent,[6,7] at that point of the study the question if the imbalance of BA actually is a metabolic expression for NAFLD/NASH development or a result of dysbiosis, remains uncertain. Interestingly, the authors identified increased levels of UDCA in NAFLD/NASH. Hydrophilic forms might therefore be synthetized to attenuate BA-mediated hepatotoxicity. While Legry, *et al.* recently found that BA dysregulation in NAFLD is mostly associated with insulin resistance and not with histological features of NASH in obese individuals,[12] Puri, *et al.* showed alterations of BA profiles in NAFLD patients regardless of the presence of type 2 diabetes. These diverging results undermine the need for further characterization of BA signaling and metabolism in bigger cohorts and potentially also in "lean" NASH individuals.

This study is yet another piece of the puzzle, trying to understand and solve the complex interactions between the intestine and the liver. Over the last years more and more studies have been conducted to understand the meaning of the gut metabolome in hepatic and extraintestinal diseases. Specific understanding of BA-metabolizing microbiota is needed. As other authors, Puri, *et al*. demonstrate that an imbalance of primary and secondary BA may be associated with disease progression in NASH. These studies offer the opportunity to a more differentiated approach in analyzing mechanistic hypotheses, which may help find possible treatment leverages in the therapy of NAFLD/NASH. Finally, in complex diseases like NAFLD/NASH, alterations in individual pathways must always be seen in the context of accompanying diseases and preconditions like obesity and insulin resistance. Further studies on bigger cohorts are needed to identify mechanisms relevant for treatment and understanding of NAFLD/NASH. Piece by piece, these studies will help to understand and treat metabolic diseases with tremendous impact on society, the health system and the economy worldwide.

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