Annals of Hepatology 27 (2022) 100773

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Editorial

The importance of bile Acids in NAFLD: current evidence and future directions

Non-alcoholic fatty liver disease (NAFLD) is the most rapidly increasing form of chronic liver disease in the world, with an estimated prevalence of 32.4% [1]. Although frequently asymptomatic, NAFLD can be a progressive disorder that results in fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). In addition, NAFLD is associated with insulin resistance, obesity, and type 2 diabetes [1]. Given the rising prevalence and relevant clinical implications, more focus has been given to understanding its risk factors as well as potential therapeutic targets that may treat or prevent the progression of the disease.

Exploring the relationship of NAFLD to bile acids (BA) has garnered a lot of interest, as BA not only plays key roles in lipid and fat-soluble vitamin absorption but also serves as hormone-like signaling molecules that activate nuclear receptors such as FXR and TGR5 to regulate the metabolic homeostasis of BA, cholesterol, lipids, and glucose [2]. In fact, disruption in BA homeostasis has been shown to lead to altered glucose and lipid metabolism, both of which are common features of NAFLD [3]. The relationship to NAFLD could be related to several mechanisms, including increased synthesis in hepatocytes, decreased conversion to secondary BA in the intestine, and decreased enterohepatic circulation, as well as other mechanisms that have been proposed and remain under investigation [4].

A general pattern in the literature is the finding of one or more conjugated primary BA to be related to NAFLD. For instance, a population-based study conducted in Guatemala reported that persons with NAFLD had significantly higher adjusted levels of the primary BA, GCA, TCA and TCDCA [5]. Examining primary BA in previous studies of NAFLD, increased total primary BA, GCA, TCA, GCDCA, and TCDCA levels have each been reported [6–8]. In contrast, other studies have found inverse associations or no total primary BA associations [9]. Significant findings concerning secondary BA have been fewer across studies, but increased DCA levels and increased total secondary BA levels have also been reported in the literature [9,10].

Some of the inconsistencies when assessing this relationship may be due to methodological aspects. For instance, sample size, variable definitions, limited matching or statistical adjustment for covariates, and differences between clinical populations and general populations are contributing factors. Furthermore, studies conducted among children and/or participants with the most advanced form of NAFLD, non-alcoholic steatohepatitis (NASH), may not produce generalizable results as both age and severity of NAFLD have been reported to affect bile acid levels [8].

Future directions

To date, most of the literature assessing the relationship between serum BA levels and NAFLD has come mainly from case-control or cross-sectional studies, as summarized by Mantovani & Thanger [11]. An important limitation of this type of study design is that it prohibits a determination of the temporal relationship. Thus, longitudinal studies are necessary to disentangle directionality in the relationship between BA and NAFLD. Furthermore, to prevent miss-classification, NAFLD measured by transient elastography at a population level is warranted.

The gut-liver axis refers to the bidirectional interaction that takes place between the gut and its microbiota on the one hand and the liver on the other [12]. Existing evidence suggests that gut-liver axis disruption leads to the progression of most forms of chronic liver disease, including NAFLD and NASH. A disrupted gut-liver axis includes the following features: altered intestinal microbiota, gut barrier damage with increased permeability and changes in luminal levels of bile acids. Furthermore, the evidence also suggests that alterations in bile acid levels reduce intestinal FXR-signaling, affecting intestinal mucous and antimicrobial peptide synthesis as well as gut-vascular barrier (GVB) integrity [12]. Therefore, more research towards understanding the gut-liver axis is needed to drive the development of diagnostic and therapeutic measures based on microbiota for the management of chronic liver disease [12]. The use of microbiome approaches such as profiling, shotgun metagenomics and specific antibodies is also warranted to understand the contribution of changes in gut microbiota to develop bile acid disruptions and NAFLD.

A promising therapeutic approach is the modification of bile acid signaling to strengthen intestinal barrier function and modulate the gut-liver axis. Employing this approach, FXR agonists could reduce intestinal FXR signaling and improve antibacterial protein synthesis, reversing GVB damage. Modifying intestinal contents with targeted fecal microbial transplantation or specific probiotics isolated from human feces could be another therapeutic modality worth exploring [12]. In addition, the translation of the expanding knowledge on BA signaling should also allow the targeting of BA-related pathways therapeutically and represents a broad and rapidly developing field for the therapy of liver disease as well as gastrointestinal disorders along the gut-liver axis [12,13].

In conclusion, BA seem to play an important role in the development of NAFLD. However, more research needs to be conducted to better assess this relationship as well as to understand the underlying

https://doi.org/10.1016/j.aohep.2022.100773

mechanisms, which may lead to the development of effective therapeutic targets to prevent or manage the progression of the disease.

Declaration of interest

None

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