

Insights in non-alcoholic fatty liver disease pathophysiology with lipidomic analyses

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Article commented:

Anjani K, Lhomme M, Sokolovska N, Poitou C, Aron-Wisnewsky J, Bouillot JL, Lesnik P, *et al.* Circulating phospholipid profiling identifies portal contribution to NASH signature in obesity. *J Hepatol* 2015; 62: 905-12.

Comment:

Non-alcoholic fatty liver disease (NAFLD) has a worldwide prevalence of around 20 to 30% and has been associated to increased liver-related mortality and risk for cardiovascular disease.¹ NAFLD comprises a spectrum including simple steatosis, steatohepatitis (NASH), and in some cases development of fibrosis or cirrhosis,² it has been recognized as a major cause of liver disease and a high proportion of cases of cryptogenic cirrhosis are due to NAFLD progression.³

NAFLD has been associated with diabetes, insulin resistance and obesity, more specifically with central obesity characterized by accumulation of visceral fat. In addition, other factors such alterations in lipid metabolism may be contributors to its development. Some of the described abnormalities in lipid metabolism include an increased delivery of free fatty acids to the liver, augmented very low-density lipoprotein synthesis, decreased triglyceride export, and reduced free fatty acids beta-oxidation.⁴

There are some studies that demonstrate alterations in the hepatic lipid profile in patients with NASH including accumulation of triacylglycerols, diacylglycerols, free cholesterol, elevation of lysoglycerophosphocholines, and an increase in saturated fatty acids.⁵ In a recent review by Beyoğlu and Idle on the metabolomichepatobiliary disease,⁶ the authors point out the dysregulation of the bile acid and phospholipid homeostasis in the liver. The dysregulation starts with the transition between the healthy liver (Phase 0) and NAFLD/NASH, or other insult (Phase 1). This phase is maintained in the presence or absence of cirrhosis (Phase 2) and whether or not either hepatocellular carcinoma or cholangiocarcinoma (Phase 3) develops. Inflammatory signalling in the liver triggers the appearance of the dysregulation.⁶

On the other hand, Garcia-Ruiz, *et al.*,⁷ have proposed that the acid sphingomyelinase (ASMase), a specific mechanism of ceramide generation, is required for the activation of key pathways that regulate steatosis, fibrosis and lipotoxicity, including endoplasmic reticulum stress, autophagy and lysosomal membrane permeabilization. Also the investigators suggested that ASMase modulates alterations of the methionine cycle and phosphatidylcholine homeostasis, two crucial events involved in NASH that regulate methylation reactions, antioxidant defence and membrane integrity.⁷

In the article entitled "Circulating phospholipid profiling identifies portal contribution to NASH signature in obesity"; the authors conducted an elegant study with lipidomic analysis using mass spectrometry in order to explore the contribution of the circulating lipid species to NASH. They concentrated on phospholipids and sphingolipids species in peripheral and portal circulation of morbid obese women with and without NASH. In addition, they examined the changes in lipid species in systemic blood one year after bypass surgery. They also implemented an integration of clinical variables and

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Manuscript received: May 17, 2015.
Manuscript accepted: May 17, 2015.

lipid species in peripheral and portal circulation to identify significant contributors to NASH (8).⁶

Previous reports have highlighted the role of different lipid species in NAFLD with diverse methodologies. From studies demonstrating the well-known accumulation of triglycerides within the liver (9)⁷ that makes hepatocytes susceptible to oxidative stress injury and damage induced by systemic inflammatory mediators (10)⁸ to studies identifying the role of specific lipid species involved in NAFLD to NASH progression, such the ratio of phosphatidylcholine to phosphatidylethanolamine regulating cell membrane integrity (11).⁹

Lipidomics consists in the identification and quantification of cellular lipids in biological systems. It has been used for the recognition of the role of lipids in many metabolic diseases. The lipidome describes the complete lipid profile within a tissue.

The results of the study indicate that the phospholipid composition in the portal and systemic circulation of morbid obese subjects with NASH differs from individuals without NASH. Increases in PC (glycerophosphatidylcholines), PE (glycerophosphatidic acids) and PG (glycerophosphatidylglycerols) were increased in the systemic circulation of individuals with NASH. After one year of the surgery the number of altered lipid species decreased, although some of them, mainly PG and Cer (ceramides) persisted elevated. By performing lipidomic analysis in biopsies from omental, mesenteric and subcutaneous adipose tissue, authors found few differences between NASH and non-NASH subjects, postulating that adipose tissue appears to have a small contribution to the systemic alterations in the circulating lipids. In comparison with systemic blood there were fewer alterations in portal circulation of NASH patients, including elevations of PE and PG. Finally, the integration of lipidomic and clinical variables identified 15 contributors including 7 lipid species (4 from portal and 3 from systemic circulation) and 8 clinical variables (8).⁶

Interestingly, the lipid species PE and PG that were altered in both systemic and portal blood of NASH subjects are mostly represented in bacterial membranes. The authors hypothesize that these alterations can be linked to disturbance of the gut microbiota. Changes in the microbiome in individuals with NASH have been previously reported (12).¹⁰ Therefore, the findings of this study might suggest a link between altered gut microbiota and NASH.

Limitations of the study should be recognized including the inclusion on women only, limiting the generalization of the results. In addition, the

inclusion of women with and without diabetes with diverse treatments may be a confounder factor modifying the presented results. Therefore, studies including men would be advisable in order to confirm the results.

The contribution of this study to the understanding of the physiopathology of NAFLD is significant. The findings of this study with assessment of 150 lipid species emphasize the contribution of specific lipid species to NASH development in women with obesity. The study also raises new hypotheses of novel factors involved in NAFLD development and progression. The contribution of the gut microbiota in the development and progression of NAFLD, as well as the impact of its modification, should be subject of future studies. Finally, it is known that the liver plays a central role in whole body lipid metabolism and responds rapidly to changes in dietary fat composition. Strategies for the development of therapeutic agents should involve lowering hepatic toxic saturated fatty acid and at the same time inhibiting key deleterious events occurring in NASH.

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