Nonalcoholic Fatty Liver Disease and the Gut Microbiome

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KEYWORDS

• Nonalcoholic fatty liver disease • Fatty liver • Steatohepatitis • Fibrosis
• Liver cirrhosis • Hepatocellular carcinoma • Gut microbiota

KEY POINTS

- As observed in other chronic metabolic diseases, nonalcoholic fatty liver disease (NAFLD) is associated with gut dysbiosis.
- At the interface between diet and the liver, gut microbiota can induce liver steatosis through its metabolic functions and endotoxemia.
- Gut microbiota can also drive the severity of NAFLD through increased endogenous production of alcohol, activation of liver inflammation, or altering the bile acid profile.
- Modulation of the gut microbiota, such as pre/probiotic use, for the treatment of NAFLD needs to be evaluated further.

INTRODUCTION

The human gastrointestinal tract hosts about one hundred trillion commensal organisms that represent 10 times more cells than the whole body cell count.[1] Approximately 800 to 1000 different bacterial species and more than 7000 different strains inhabit the gut.[2] These commensal bacteria are grouped into phyla, which are dominated by the Gram-negative Bacterioidetes and Proteobacteria, and the Gram-positive Firmicutes and Actinobacteria. The taxonomic composition of gut microbial community varies between individuals, even between those who are closely related.[3] Consequently, all genes of microbes that make up the gut microbiome has recently been referred as our "second genome" that outnumbers human genes by more

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than 100-fold. Gut microbiota participates in health maintenance and helps to balance vital functions for the host, including immunity, nutritional status, and metabolic functions.[4–6]

It is now well-established that gut flora and chronic liver diseases are closely interrelated. This association is the most evident at late stages of the disease: cirrhosis and impaired liver function are associated with intestinal bacterial overgrowth, small bowel dysmotility, increased gut permeability, and decreased immunologic defenses, all promoting bacterial translocation from the gut to the systemic circulation and leading to infections that in turn aggravate liver dysfunction in a vicious circle.[7] For a long time, the implication of gut flora in the pathophysiology of less-advanced chronic liver diseases has been underestimated because technical limitations allow only for the culture of a small fraction of gut bacteria. Recent technological progress and next-generation DNA sequencing has allowed for more sophisticated analysis and sampling of the gut microbiota by culture-independent methods.[8] Thanks to these recent technological advances, the knowledge about the role of gut microbiota disruption (dysbiosis) in gut diseases such as colon cancer, inflammatory bowel diseases, or irritable bowel syndrome has greatly increased with possible new therapeutic strategies. More surprisingly, gut dysbiosis has been implicated in chronic metabolic disorders, such as obesity, metabolic syndrome, diabetes, and cardiovascular diseases.[5] Nonalcoholic fatty liver disease (NAFLD) is the liver manifestation of the metabolic syndrome and thus evolves in the same context as these metabolic diseases.[9] It is thus not surprising that recent literature emphasizes a potential role for gut dysbiosis in the pathophysiology of NAFLD.

NAFLD encompasses a spectrum of hepatic pathology (ie, liver phenotypes). Accumulation of triglycerides in hepatocytes (hepatic steatosis) is the most common liver phenotype in NAFLD. Some individuals with hepatic steatosis develop nonalcoholic steatohepatitis (NASH), a more severe type of liver damage characterized by hepatic inflammation and liver cell death. In some individuals with the NASH phenotype, liver regeneration cannot keep pace with the increased rate of hepatocyte death, and liver scarring (fibrosis) ensues. Over time, some of these individuals accumulate sufficient fibrosis to develop cirrhosis. Liver cirrhosis is the NAFLD phenotype that has the worst prognosis because cirrhosis dramatically increases the risk for both primary liver cancer and overall liver-related mortality.[10,11] Epidemiologic studies indicate that NAFLD is now the most common cause of liver disease in many countries, including the United States.[12] It is estimated that at least 25% of American adults have some form of NAFLD, with about 6% of the general adult population having NASH and 2% to 3% having NAFLD-related cirrhosis.

GUT MICROBIOTA PROMOTES THE ONSET OF NONALCOHOLIC FATTY LIVER DISEASE

By using fecal transplantation, recent animal studies have demonstrated that gut microbiota can itself directly induce NAFLD. Conventional C57BL/6J mice fed 16 weeks with a high-fat diet (HFD) generally display liver steatosis, hyperglycemia, and systemic inflammation (responders), but some mice are nonresponders, developing no metabolic disorder with this dietary manipulation.[13] To explore the potential role of gut microbiota in these discrepant responses, gut microbiota from a responder or from a nonresponder mouse were transplanted into germ-free mice (ie, responder or nonresponder receivers) that were then fed HFD for another 16 weeks. Despite similar weight gain, food consumption, and epididymal fat, responder–receiver mice developed a higher level of liver steatosis, glycemia, and insulin resistance than nonresponder receivers. Level of the transcription factors SREBP and ChREBP