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Nonalcoholic steatohepatitis and gut microbiota: Future perspectives on probiotics in metabolic liver diseases

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See: "Determination of certain bacterial groups in gut microbiota and endotoxin levels in patients with nonalcoholic steatohepatitis" on page 361-9.

Nonalcoholic fatty liver disease (NAFLD), a clinical spectrum that encompasses simple steatosis and nonalcoholic steatohepatitis (NASH), is a leading cause of chronic liver disease in the industrialized world (1). The increasing prevalence rates of obesity, metabolic syndrome, and diabetes mellitus increase the risk for developing NAFLD (2). While only a small proportion of patients with simple steatosis, the earliest form of NAFLD, eventually progress to NASH with hepatic inflammation and fibrosis, the recent increase in NAFLD rates is such that even a small proportion of patients who develop NASH-related complications (cardiovascular disease, advanced fibrosis, cirrhosis, and hepatocellular carcinoma) will lead to a significant burden to the healthcare system (3,4). These epidemiological trends are particularly concerning given the increasing effect of NAFLD on the rates of hepatocellular carcinoma and end-stage liver disease, thus leading to the need for liver transplantation (1). While new therapeutic agents that target NASH are under investigation, widely available therapies are not expected in the near future. Thus, lifestyle interventions (diet and physical activity/exercise) continue to remain the cornerstone for clinically managing patients in the spectrum of NAFLD (5). Although several mechanisms are expected to underlie the preventive and therapeutic effects of lifestyle interventions in NAFLD, it has been recently hypothesized that a regular healthy balanced diet can also have a positive effect on the composition and function of the gut microbiota (6).

The gut microbiota, the term used to indicate the bacterial composition of the human digestive tract, has been most extensively studied in the distal colon. Fecal bacterial populations in adults have been estimated to comprise 10^{13}-10^{14} microorganisms, with approximately 1100 prevalent species; notably, the gene content in gut microbiota is at least 150-fold higher than the human genome (7). Disruption of a stable and diverse microbial community, termed "dysbiosis," has been shown to have a profound impact on different disease conditions. Owing to the close association among diet, gut, and the liver, it is not surprising that all NAFLD stages have been linked to dysbiosis of the gut microbiota, both in animal models and clinical studies (8-10). Via a quantitative polymerase chain reaction (qPCR) approach, the study published in the current issue of the Turkish Journal of Gastroenterology investigated the differences in the gut microbiota between patients with biopsy-proven NASH and healthy controls. After thoroughly analyzing the data, numerous relevant findings were found. First, the gut microbiota of patients with NASH was characterized by significantly decreased *Akkermansia muciniphila* and increased Enterobacteriaceae proportions compared with that of healthy controls (even after statistical adjustment for age and body mass index). Second, patients with significant fibrosis (≥F2) had significantly higher Enterobacteriaceae proportions compared with patients with no/mild fibrosis (F0/F1). Third, serum endotoxin and high-sensitivity C-reactive protein levels were significantly higher in patients with NASH

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than in healthy controls. Fourth, *Lactobacillus reuteri* was identified as a dominant *Lactobacillus* species in the patient group, whereas it was undetectable in the healthy control group. Finally, *Bifidobacterium infantis* was found in the feces of patients with NASH but not in those of healthy controls.

The depletion of *A. muciniphila*, the sole intestinal representative of the verrucomicrobia in human feces, is associated with a reduction in the protective inner mucus layer, ultimately reducing the intestinal barrier integrity and promoting bacterial component and endotoxin leakage from the gastrointestinal tract to the liver. Increased colonization by Enterobacteriaceae can also promote gut permeability via increased ethanol production, ultimately synergistically acting with *A. muciniphila* depletion. The observed association between higher Enterobacteriaceae proportions and hepatic fibrosis is also noteworthy and may be explained by an increased binding of Enterobacteriaceae-derived endotoxin to toll-like receptor 4 expressed by hepatic stellate cells (11-13). In contrast, the potential pathogenetic role played by *L. reuteri* and *B. infantis* in NASH is unexpected because both species are among the most commonly used probiotics for gastrointestinal complaints or diseases (14). Unfortunately, current clinical applications of probiotics frequently lack an adequate knowledge of the principle mechanisms by which orally administered bacteria establish themselves as residents in the gastrointestinal tract through their interactions with the host environment. In this context, future studies should aim to acquire a deeper understanding of the metabolic activity and diversity of the gut flora within the complexity of the host genotype and intestinal immune response. Hopefully, a more in-depth knowledge of the gut microbiota in patients with NASH could ultimately lead to new, targeted preventive approaches. For example, the gut delivery of non-digestible carbohydrates that selectively induce the proliferation of favorable bacterial strains (e.g., *A. muciniphila*) will positively modulate the microbiota through the production of antiinflammatory molecules with potential hepatoprotective properties.

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