NASH IN FOCUS

Current Developments in the Management of Nonalcoholic Steatohepatitis

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The Gut Microbiome and Nonalcoholic Steatohepatitis

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G&H What makes up a healthy microbiome?

JS A healthy microbiome is not completely identical in every person. It is influenced by the type of diet, as well as the genetic background, of a person. Overall, its composition is the sum of interactions, both internal (determined by the host) and external (determined by outside factors, such as diet and activity).

Having said this, there are certain strains of bacteria or signatures in the gut microbiome that have been associated with disease severity. It is likely that unhealthy signatures in the gut microbiome could help diagnose nonalcoholic steatohepatitis (NASH), including advanced fibrosis in NASH.

G&H How much does diet drive bacterial colonization of the gut?

JS Diet is one of the most important factors that determines different liver disease phenotypes. For example, a diet rich in red meat and ultra-processed foods promotes obesity, affects the diversity of the gut microbiome, and promotes advanced fibrosis from NASH. Beyond the individual bacterial genera that are in the gut, diversity is a very important aspect. A diet that is very restrictive in terms of dietary patterns leads to low diversity of the gut microbiome. This is more frequently seen in unhealthy patients with metabolic syndrome.

G&H What is the role of the gut microbiome in the pathogenesis of NASH?

JS This is a complex issue, but there are several important aspects that should be discussed. The gut microbiome interacts with the mucosal immune system and modulates immune activation in the gut. This individual immune phenotype depends on the composition of the gut microbiota. The activation of the immune system in the gut directly affects liver-residing cells, including hepatocytes, Kupffer cells, and endothelial cells, and thus is an important aspect of hepatic immune modulation.

Another aspect that is very important, and sometimes overlooked, is bile acid metabolism. Much has been learned about bile acid metabolism, which involves enterocytes, hepatocytes, and stellate cells, and is influenced by the gut microbiota. Bile acids are produced in the liver, secreted and modified in the gut, and then reabsorbed. Well-defined receptors in the intestine and the liver (eg, farnesoid X receptors [FXR] and fibroblast growth factor [FGF] receptors) are involved in this gut-liver cross talk and regulate inflammation and fibrogenesis. The activation of these receptors has been linked to the pathogenesis of NASH, and their potential to act as treatments is being explored in clinical trials targeting patients with fibrotic NASH.

The third aspect is that the gut microbiota produces molecules and metabolites (eg, short-chain fatty acids) that are capable of modulating the liver and the NASH phenotype. These microbial metabolites act at multiple levels. Gut barrier integrity and intestinal motility can be affected. When absorbed, microbial metabolites are recognized through pattern recognition receptors, triggering inflammatory pathways and affecting liver cell metabolism.

G&H Could you further discuss how the gut microbiome has been shown to affect NASH, especially its severity?

JS Certain genera have been linked to a more severe NASH phenotype. For example, certain signatures can be seen in the gut microbiome in patients with advanced fibrosis and NASH. As mentioned, the overall richness of the gut microbiome decreases with advanced disease states, especially cirrhosis and more severe inflammation.

Very early studies have looked at endotoxemia, for example bacterial-derived lipopolysaccharide, which transitions through the intestinal barrier in an unhealthy patient and activates inflammation and promotes scarring of the liver. It has become very clear that metabolites coming from the gut can act as signals that affect NASH disease severity.

G&H Has there been any research specifically on bacteriophages, fungi, and viruses and their relationship with NASH?

JS This area is clearly understudied. We know that the gut microbiome is very diverse and includes bacteriophages, viruses, and fungi. This rich mixture of organisms regulates itself. For example, bacteriophages are able to lyse bacteria, and this could, in theory, be exploited therapeutically. In preclinical studies of alcoholic liver disease, bacteriophage therapy was able to modulate disease severity by reducing the number of harmful bacteria that have contributed negatively to outcomes in patients. This proof-of-concept research has laid down a foundation that will allow for personalized approaches based on a gut microbiome signature linked to unfavorable outcomes that is potentially susceptible to modulation using bacteriophages. With advances in technology, this will be easier and hopefully will become available to patients in the future.

G&H How does the gut microbiome in NASH patients who are lean compare with the gut microbiome in NASH patients who are obese?

JS There have been a number of studies exploring the microbiome in lean patients with NASH. This is of particular interest, as the lean patient group lacks the classical risk factors of NASH. In cohort studies, different metagenomic signatures have been observed between lean and obese NASH patients. This suggests that the gut microbiome could be one factor explaining the lean NASH phenotype. On the other hand, it is difficult to prove this and rule out that the risk factor of obesity, rather than the gut microbiome, is the underlying cause for this difference.

G&H What data are currently available on modulating the gut microbiome for the treatment of patients with NASH?

JS In the beginning, most of the data on modulating the gut microbiome involved nutrition. Nutritional intervention, or changing dietary habits, is a clear first-line recommendation for every patient I see in clinic. Switching from a protein-rich, meat-based diet to, for example, a fiber-rich diet clearly leads to changes in the gut microbiome. There has been research exploring probiotics or antibiotics to modulate the gut microbiome in mice, as well as in humans. The data on this approach are much stronger in mice. Several years ago, a study found that mice without NASH developed the condition when they were placed in the same housing cage with mice who had NASH and, importantly, developed the same gut microbiome signature. These experiments generated proof that NASH can be transmitted by cohousing. The effects were explained by coprophagia.

There have been many studies looking at probiotics in humans but not all are well conducted. Thus, the data are a little conflicting. Only a few studies are exploring fecal microbiota transplantation in patients with NASH, and those studies are ongoing.

G&H What other effects might the gut microbiome have in this area?

JS The gut microbiome might be one of the factors that adds to the variability of the placebo response seen in clinical drug trials for NASH. Depending on the mechanism of action, the effects of a drug could be altered based on the microbiome signature. This is likely most relevant for drugs that modulate FXR or FGF signaling, as their effects are directly linked to the gut-liver axis. In a small interventional exercise study in patients with nonalcoholic fatty liver disease, my colleagues and I were able to demonstrate that even a short phase of increasing physical activity led to a significant increase in the richness of the gut microbiota. This shows the complexity of the gut microbiome, and changes during clinical trials are currently not being captured as far as I am aware.

G&H What further research is needed?

JS From my perspective, further research is needed to determine whether the gut microbiome can help to diagnose patients with NASH. Advanced disease stages, particularly cirrhosis, are associated with an unhealthy gut microbiome signature, and the gut microbiome is pathophysiologically linked with NASH. For these reasons, it is plausible to me to explore the gut microbiome as a diagnostic tool. The challenge is to account for confounders such as diet, but also sample handling. Another area that we are just beginning to understand is the role of bacteriophages and viruses in the gut.

Additional research is needed in the therapeutic arena as well. There is much evidence, particularly preclinically, that the composition of the gut microbiome affects disease severity, and, therefore, its modulation is appealing. This could be done in addition to pharmacotherapy and, as mentioned previously, could be synergistic for certain classes of drugs. This is an interesting but challenging area of research.

I would also like to see research on the role of the gut microbiota as a tumor biomarker for the detection of early-stage hepatocellular carcinoma (HCC). HCC is a detrimental event in this patient population and can occur even in the absence of cirrhosis. Because ultrasound-based surveillance is challenging and not rigorously performed, microbiome testing to select patients for further diagnostic workup would be a very impactful development.

Finally, to have reproducible results in this field, it is important to conduct standardized trials with stringent measures, well-defined sampling, and technologies for assessment. Much of the data that have been generated thus far do not have the same quality, which is why there are some conflicting findings. In the future, I would like to see increased rigorousness of clinical trials and research questions to help propel this field.

Disclosures

Dr Schattenberg has served as a consultant to BMS, Boehringer Ingelheim, Echosens, Genfit, Gilead Sciences, Intercept Pharmaceuticals, Madrigal, Merck, Nordic Bioscience, Novartis, Pfizer, Roche, Sanofi, and Siemens Healthcare GmbH; has received research funding from Boehringer Ingelheim, Gilead Sciences, and Siemens Healthcare GmbH; and has received speaker honoraria from Falk Foundation, Madrigal, and MSD.

Suggested Reading

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