ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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The Relationship Between the Gut Microbiota and Liver Disease

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G&H What are the typical function and composition of the gut microbiota in a healthy adult?

JB The gut microbiota are comprised of countless millions of microorganisms that live inside the human digestive tract, all the way from the mouth to the anus. These microorganisms are essential for human survival and have many nutritive and nonnutritive functions. For example, the gut microbiota synthesize nutrients into forms that the body can absorb; produce short-chain fatty acids, which are nutritive to the gut epithelium; and stimulate the local gut immunity. Humans and the gut microbiota have co-evolved over several centuries to the point that each benefits from the other.

The gut microbiota can be comprised of various phyla, namely Bacteroidetes, Firmicutes, Proteobacteria, and Fusobacteria, among others. However, most of a healthy adult's stool has mainly Firmicutes and Bacteroidetes. Proteobacteria typically make up 2% to 3% of a healthy microbiota, and the other phyla are even less.

G&H How does this composition compare with that of patients with obesity-related liver diseases, such as nonalcoholic fatty liver disease and nonalcoholic steatohepatitis?

JB Several studies have examined the gut microbiota of patients with precirrhotic or cirrhotic nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH), and all have found that these patients have a different microbiota composition than that of healthy controls. Interestingly, this difference also extends to the function of the stool microbiota.

In one study, Raman and colleagues showed that not only is there a composition change in the gut microbiota of NAFLD patients, but there is also a change in function. The researchers found that patients with NAFLD have significant increases in butyric acid and propyl ether in addition to a reduction in microbiota-associated functionality through these metabolites.

In another study, Zhu and colleagues compared healthy children, obese children with NASH, and obese children without NASH, and found that the production of endogenous ethanol was much higher in children with NASH. The researchers hypothesized that the production of internal alcohol, which could potentially cause liver disease, was caused by the gut microbiota of the patients and not by alcohol (the usual cause).

A study by my colleagues and I found that the impact of NASH continues even when patients are cirrhotic. When the gut microbiota of cirrhotic patients with NASH were compared with the gut microbiota of cirrhotic patients without NASH, the compositions were very different. In addition, the compositions were different between alcoholic cirrhotics and nonalcoholic cirrhotics.

The ultimate hope is that modification of the gut microbiota can manage and perhaps even prevent liver diseases such as NASH.

G&H Which agents have been found thus far to modify the gut microbiota of patients with NAFLD or NASH?

JB Probiotics have been examined in these patients, although only 1 meta-analysis of these agents has been conducted to date. Ma and colleagues studied 4 different probiotic and synbiotic preparations. Unfortunately, since the preparations were all different from each other, it is not possible to draw much from this study, except for a general statement that probiotics help the liver enzymes in NAFLD patients.

Both vitamin E and coffee have been found to change the gut microbiota in patients with NASH. In the PIVENS (Pioglitazone Vs Vitamin E Vs Placebo for Treatment of Non-Diabetic Patients With Nonalcoholic Steatohepatitis) trial, Cheng and colleagues measured the metabolites of the patients who responded to vitamin E, and found at least 2 microbiota-derived metabolites: indole propionate and hydrocinnamate. This means that part of the impact of vitamin E could be due to the gut microbiota's functional changes.

Provocatively, several studies have shown that coffee can reduce liver fat. Both Cowan and colleagues and Jaquet and colleagues have shown that coffee intake increases *Bifidobacterium*, which are beneficial bacteria that have been used in several probiotic formulations. This may be one of the reasons that coffee improves NASH.

In addition, Kong and colleagues have shown that gastric bypass can very favorably affect the gut microbiota. While gastric bypass itself is not recommended as a treatment for NASH, most patients with NASH who undergo gastric bypass show improvement in histology. This could be due to caloric restriction, malabsorption, and changes in the gut microbiota as a result of this bypass.

G&H Would you recommend the use of probiotics in these patients?

JB The data on this issue are still evolving, as seen from the aforementioned meta-analysis, which included 4 different groups of probiotic and synbiotic preparations and, thus, could not draw many conclusions. There has not been any evidence against using probiotics, but the challenge is that, in the United States, probiotics do not require approval from the US Food and Drug Administration. Therefore, most probiotics that can be found over-the-counter may or may not have the desired dose and advertised constituents. Even if the data clearly supported the use of probiotics, pharmaceutical-grade probiotics, which are not currently available, would be necessary. All of these challenges apply not just for NASH patients, but for all patients with liver disease.

G&H What is the role of the gut microbiota in cirrhosis and its complications, such as hepatic encephalopathy?

JB Many studies have been conducted on the gut microbiota in the setting of cirrhosis. It is quite apparent that many of the treatment options, without knowing about specific gut microbiotic action, depend upon changing the gut milieu, if not the gut microbiota themselves. For example, the mainstays of treatment for hepatic encephalopathy are lactulose and rifaximin (Xifaxan, Salix), which act on the gut. Another complication of cirrhosis, spontaneous bacterial peritonitis, is treated with antibacterial agents, such as norfloxacin and ciprofloxacin, which are also used for prophylaxis and can affect the gut microbiota, as well as cause systemic effects, as some of these treatments can be absorbed systemically.

The studies in this area can be divided into those from the culture-based era and those from the non–culture-based era. In the past, very few of the microbiota in the gut could be cultured successfully without much pain, so our view of the microorganisms that were present in the bowel was very skewed. Our understanding of the gut microbiota was centered toward the microorganisms that could be cultured easily; thus, we did not have much insight into the entire spectrum of microorganisms present. Now, with recent advances in DNA techniques, there have been many changes in our understanding of the gut microbiota, as many more microorganisms can be identified and evaluated.

For example, in the culture-based studies, it was found that the medications commonly used, such as lactulose, improve beneficial gut bacteria, such as *Lactobacillus* and *Bifidobacterium.* In recent studies in cirrhotic and noncirrhotic subjects, lactulose has not been shown to have a major change in the composition of the gut microbiota. This could mean that it works via changes in function or through its laxative effect.

Therefore, the important question is whether the gut microbiota change as cirrhosis progresses. It is well known that cirrhosis has 2 main stages. The first is the compensated stage, in which patients do not have any complications of cirrhosis (ie, no hepatic encephalopathy, variceal bleeding, ascites, or spontaneous bacterial peritonitis). In this stage, patients do very well and have a very good survival rate. However, when the cirrhosis becomes decompensated (ie, when patients develop hepatic encephalopathy, variceal bleeding, ascites, or spontaneous bacterial peritonitis), the survival rate of patients is very dramatically reduced.

Multiple studies from our group, as well as from other groups such as Chen and colleagues, have been conducted across several countries. These studies have shown that as cirrhosis progresses from being compensated to decompen-

sated, the gut microbiota of patients change from eubiosis (ie, good bacterial balance) to dysbiosis (ie, an increase in harmful bacteria, such as those belonging to the Enterobacteriaceae family, and a decrease in beneficial or commensal bacteria, which are autochthonous). This may be the reason that these patients have a permissive environment for the development of decompensation, or the decompensation may be the reason that these patients have this environment. It is unknown which of these—the environment or the decompensation—comes first, but it is quite clear at this point that patients who have decompensated cirrhosis have a much worse gut microbiota (ie, dysbiosis).

G&H Is the change in the composition of the gut microbiota reflected in microbiota elsewhere?

JB Interestingly, it is not just the composition of the stool microbiota that is different. Studies by our group have shown that the colonic mucosal microbiota are also very different in patients with cirrhosis compared with those without cirrhosis as well as those with and without hepatic encephalopathy. This difference in the microbiota may even be more important because stool contains bacteria that the body does not interact with anymore, whereas the colonic mucosal microbiota contain bacteria that still directly impact the body.

Even more interestingly, our group also found that the salivary microbiota are very different in patients with cirrhosis compared with those without cirrhosis, independent of any oral infections or periodontitis. This finding suggests that the salivary microbiota may be an issue to consider when managing patients with liver disease and its progression.

G&H Does the modification of the gut microbiota via antibiotics or probiotics impact these diseases?

JB Several antibiotics, some of which are absorbable and some of which are nonabsorbable, have been examined in this area. The absorbable antibiotics, which can have an impact beyond the gut, include ciprofloxacin and norfloxacin. These agents are currently used for prophylaxis of spontaneous bacterial peritonitis and have a beneficial impact on overall survival. They can, however, radically change the gut microbiota.

The nonabsorbable antibiotics, which involve only the gut, include rifaximin, paromomycin, and oral vancomycin. These agents have been used sparingly in this area, with rifaximin having the highest evidence base of this group. Rifaximin has been shown to change the natural history of patients with cirrhosis and to reduce rehospitalizations due to hepatic encephalopathy through functional changes in the gut microbiota. There is also some research suggesting that rifaximin could help prevent other complications of cirrhosis, but this theory is not completely evidence-based at this point.

In addition, there is emerging and very good evidence that certain probiotics, such as VSL#3, can improve outcomes in patients with cirrhosis. The most recent study, by Dhiman and colleagues, showed that VSL#3 can improve outcomes in patients with hepatic encephalopathy. Another study by our group used *Lactobacillus GG* and showed that gut microbial function and composition can be improved after this therapy in cirrhotic subjects. However, when considering the use of probiotics, it is important to keep in mind the challenges discussed above.

G&H Is there a role for fecal microbiota transplantation in the management of liver disease?

JB There is no current evidence on this issue. There is animal evidence not of fecal microbiota transplantation, but of just changing large groups of bacteria, which was shown to reduce hepatic encephalopathy. However, unlike *Clostridium difficile* infection, in which fecal microbiota transplantation has been shown to be effective, decompensated cirrhosis is a riskier setting, as the potential infectious and immunologic impacts need to be considered. Any treatment must be performed in a rigorous and controlled environment.

Dr Bajaj has no relevant conflicts of interest to disclose.

Suggested Reading

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