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EDITORIAL

Gut-microbiome composition and function in progression of alcohol-associated liver disease: going beyond western experiences

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Alcohol-associated liver disease (ALD) is a major worldwide burden with the spectrum of diseases ranging from asymptomatic liver steatosis to the development of fibrosis, cirrhosis, and alcohol-associated hepatitis. Occurrence and progression of ALD is variable among different individuals based on gender, alcohol consumption, and ethnicity. An important aspect is the role of the gut microbiome, which is reactive to internal and external influences, including alcohol [1]. Alcohol directly affects the gut microbiota and intestinal barrier leading to increased permeability and can also indirectly impact the microbiome through ALD progression. Cirrhosis itself leads to alterations in gut microbiota which has been observed in patients with not only alcohol-associated liver disease but also nonalcoholic liver disease. At the same time, dysbiosis of the gut microbiome secondary to direct toxic effects have been shown to occur even before fibrosis develops. Therefore, alcohol itself and the different disease entities on the way to progression to alcohol-related cirrhosis likely play a role in the gut microbiome dysbiosis observed in this study as it had been described previously by Dubinkina et al. This can potentiate bile-acid production and systemic inflammation and could give us insight into the pathophysiology of ALD development [2]. However, in addition to the structural and compositional aspects of gut microbiome, the functional aspects are critical to fully understand the interaction between alcohol, liver disease and gut microbiome. Alcohol-associated liver disease has been observed to not only cause changes in the bacterial microbiota of the gut but also virome and mycobiota. Studies have shown an increase of Candida spp. and decreased fungal diversity in these patients. At the same time patients with alcohol-associated hepatitis have been noted to have increased *Escherichia-, Enterobacteria-*, and *Enterococcus* phages.2].

In this issue of Hepatology International, Ganesan et al. report on a large cohort of individual with and without ALD from South Korea [3]. The team evaluated the composition and functional aspects of the gut microbiome using the MiSeq sequencer and liquid chromatography with spectrometry rRNA sequencing and metabolomics. Metagenomics showed increases in Proteobacteria and reduction in Bacteriodes abundance with worsening ALD severity. The team identified through untargeted metabolomics an imbalance in the metabolism of linoleic acid, indole compounds, histidine, fatty acid, and glutamate metabolism in patients with ALD with disease progression. Moreover, bile acid and short-chain fatty acid metabolism was even further disrupted in patients with alcohol-related cirrhosis compared to the other groups.

However, the drawbacks of being a cross-sectional study without major details on diet and amount of alcohol intake, relatively low number in patient subgroups, and using one center limit the generalizability of results. These details are critical since interactions between diet, etiology, and ethnicity can impact not only the underlying microbiome but also could influence the progression of liver disease [4, 5].

Although it is one of the first Asian studies compared to the mostly Western studies previously performed, it only included South Korean patients, this limits the generalizability and application of the findings to the Western population. It is unclear if factors which are specific to the South Korean population played a role as confounding factors. For example, their specific diet, genetics, disease comorbidities and lifestyle could play a role in gut microbiome dysbiosis which are not attributed to alcohol-related liver disease. 16S rRNA sequencing has been used widely to identify and characterize microorganisms. It is less expensive than other methods and has a large database of bacteria used. Limitations of this method include limited resolution, inability to assess function of the microbiomes and finding other microbiomes

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such as fungi. Untargeted metabolomics allows to assess for a wide range of metabolites but is limited by uninformative fragments included and difficulty to interpret false positives. However, both together could give a good overall view of the structure and function of the microbiomes.

Therefore, findings in this study of different species compared to previous Western studies could be attributed to the different analytical techniques, processing, and method of collection among different laboratories. To avoid these a standardization among different laboratories is needed. Despite these limitations, several findings complement prior studies from Western countries as well as some limited Asian experiences [6].

Prior human studies on ALD predominantly come from Western countries using stool, saliva, blood, colonic mucosa, and duodenal mucosa for gut microbiome and stool, blood, and urine for targeted and untargeted metabolomics [7]. Most studies show worsening dysbiosis (higher pathobionts and lower commensals) with advancing ALD, alcohol-associated hepatitis, and cirrhosis. Some studies have focused on gut luminal and circulating bile-acid profiles, while others have published on untargeted metabolomics and lipidomics. Underlying most of these studies is a recognition that microbiome composition and function are important modulators of ALD that could amplify the negative impact of alcohol but could be a target to alleviate ALD progression regardless of the population studied. Bajaj et al. performed an analysis of stool, duodenal, ileal, and colonic microbiota, and stool metabolomics on cirrhotic patients in a US population of actively drinking, abstinent, and healthy controls. Similar to other studies, dysbiosis was noted in all actively drinking patients with cirrhosis on 16SrRNA sequencing and gas chromatography/mass spectrometry of stool metabolomics. Alferink et al. published a cross-sectional prospective study in Hepatology which aimed to assess the composition and diversity of the gut microbiome in hepatic steatosis. Similar to this study, they used 16S ribosomal RNA gene sequencing, 1355 patients were included. Association of hepatic steatosis with aromatic and branched chain amino acids and glycoprotein and R. Gnavus were found [4].

This cross-sectional experience further underlines the importance of carefully phenotyping subjects according to alcohol intake and the consequences on the liver-disease severity.

An unanswered question is whether microbial dynamics can predict which individual will develop advanced ALD, alcohol-associated hepatitis, or cirrhosis in the setting of alcohol intake.

Other questions that are unanswered with this study include if the dysbiosis of the gut microbiome is only attributed to alcohol-related liver disease and its progression or are there other confounding factors such as diet, alcohol use, individual patient factors or ethnicity of the study population compared to previous studies for it to be used for targeted therapy. Also, can we base on the composition of the gut dysbiosis conclude which patient will have progression of ALD for it to be used as a disease prevention tool.

Given the long duration of ALD development and unpredictable transition to alcohol-associated hepatitis and cirrhosis, these studies are difficult to perform as cohorts. However, studies have shown that abstinence improves gut-microbial composition and function, while modulation of the microbiome using treatments such as fecal microbiota transplant could in turn reduce alcohol intake [8, 9]. This bidirectional gut-brain axis in ALD could have major implications in the development of ALD and alcohol-associated hepatitis and is likely mediated through microbial function studied using metabolomics. With the growing twin epidemics of obesity and alcohol use across the world, it is important for studies that represent a worldwide population to be presented as done by Ganesan et al. [10]. These findings could be of importance in prevention, early detection and targeted treatment options in patients with ALD if findings are externally validated in the Korean context and provide a useful addition to the growing global literature on alcohol-related liver disease and microbiota.

Nonetheless, while previous studies have shown the association of a disrupted gut-liver axis in alcohol-associated liver disease, this study has shown a potential dysbiosis of the gut flora in patients with alcohol-associated liver disease at different stages of liver disease in an Asian population. This could be an important step in early detection of alcohol-associated liver disease and also plays a role for targeted therapy.

Nevertheless, further prospective studies are needed including larger number of patients with external validation to apply these findings to a more generalized patient population in order to apply these findings into clinical practice.

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Declarations

Conflict of interest Neither GK nor JSB have any conflicts regarding this publication.

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