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Short Communication

Probiotics Role in Liver Diseases - A Magic Bullet?

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End-stage liver cirrhosis is associated with progressive decompensation and manifestations of portal hypertension and complications of liver dysfunction. There is increasing evidence suggests that the intestinal microbial community plays important role in complications of cirrhosis. By modulating gut microbiota, it has expanded the horizon for newer therapeutic strategies for limiting these complications of portal hypertension. Encouraging data on use of probiotics in these patients has further exemplified the importance of identifying these unique gut microbiome signatures and develop personalized medicine for improved patient outcomes.

There is strong evidence emerging that there is an unfavorable gut microbiota in patients with end-stage liver disease, and this dysbiosis is significantly associated with poor outcomes. It has also been shown that the intestinal microbiota play an important role in the natural history of progression in liver disease [1].

Microbiota composition, bile acid profiles, endotoxin levels and lipidomic changes approximate the healthy population values [2]. An additional aspect observed in gut microbial function is the conversion of dietary amino acids and proteins into ammonia, which is involved in the development of hepatic encephalopathy [3]. Dysbiosis is also associated with reduced bacterial conversion of primary to secondary bile acids (via bacterial 7α-dehydroxylase) leading to an overall reduction in the circulating bile acid pool [4]. In our preliminary study [5] looking into gut microbiome signatures in cirrhotics and their healthy donors undergoing living donor liver transplantation, we noted that the phyla distribution was different in donors, they had more Bacteroidetes compared to recipients (48.3% vs. 31.9%, $p = 0.007$), and less Proteobacteria (7.71% vs. 26.57%, $p = 0.001$); at the genera level, recipients compared to donors, showed less Prevotella (8.9% vs 29.4%), Lachnospira (4.16% vs 10.1%), and more abundant Enterobacteriaceae (20.1% vs 3.5%), and Lactobacillaceae (7.71% vs 0.64%) ($p < 0.05$). Based on MELD score, recipients were categorized into three groups (score < 15,15-25, >25) and compared with donors. Proteobacteria (phyla), Enterobacteriaceae (family) positively correlated and Prevotella, Lachnospira negatively correlated as the MELD score increased ($p < 0.05$). Interestingly, as the number of events of portal hypertension (SBP, bleed, hepatic encephalopathy, sepsis) increased, there was significantly reduced Firmicutes and Proteobacteria ($p < 0.05$) and more abundant Actinobacteria and Bacteroidetes/Firmicutes ratio ($p < 0.05$).

Bacterial translocation from the gut in cirrhotics leads to endotoxemia, which results in worsening of portal hypertension [6]. Probiotic therapy is aimed at changing the make-up of the indigenous gut microbiota through administration of specific strains of non-pathogenic and potentially beneficial micro flora. The probiotic VSL#3 has been shown in a study to reduce endothelial dysfunction in portal hypertension [7]. Consequently, probiotics have been shown to reduce portal pressure and improve systemic

hemodynamics resulting in improvement in serum sodium levels [8]. In a randomized controlled trial, the addition of VSL#3 to propranolol has been shown to significantly reduce portal pressure in patient with large varices compared to propranolol alone [9].

In conclusion, gut microbiome alterations in patients with advanced liver disease are likely multifactorial ranging from etiology of liver disease, co-morbidities, drugs like proton pump inhibitors, and the severity of liver disease. Emerging data on the role of fecal microbiota transplant in steroid non-responsive severe alcohol associated hepatitis [10] and engineering gut microbiome in order to reduce hyperammonemia [11] has opened new vistas for treating the complications of portal hypertension and improving survival in these patients. Probiotics may also help in restoring the cirrhosis-dysbiosis balance, and a targeted approach by studying the gut microbiome signatures should help to specifically correct the cirrhosis dysbiosis ratio in these patients.

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