JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2025.70288
J Inonu Liver Transpl Inst 2025;3(Suppl. 1): S134-S142

Review

Current Clinical Importance of Fecal Microbiota Transplantation Treatment (FMT) in Liver Diseases and Liver Transplant (LT) Recipients

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Abstract

The gut microbiota (GM) constitutes a complex, metabolically active "organ" weighing 1–2 kg and comprising more than 100 trillion microorganisms whose collective genome far exceeds that of the human host. Culture-independent sequencing techniques have clarified its taxonomic structure and functional roles in host metabolism, immunity, and inflammation, and have established the bidirectional "gut–liver axis" as a key pathway in liver homeostasis and disease. Dysbiosis, increased intestinal permeability, and altered bile acid and microbial metabolite profiles contribute to the pathogenesis and progression of a broad spectrum of liver diseases, including viral hepatitis (HBV, HCV, HEV, HAV, HDV), alcoholic liver disease, metabolic dysfunction-associated steatotic liver disease, autoimmune hepatitis, primary sclerosing cholangitis, cirrhosis, drug-induced liver injury, and hepatocellular carcinoma. Characteristic disease-specific shifts in bacterial composition and diversity have been described and may serve as potential diagnostic or prognostic biomarkers. Fecal microbiota transplantation (FMT) has emerged as an effective strategy to restore intestinal microecological balance, with robust evidence for antibiotic-refractory *Clostridioides difficile* infection and encouraging early data in chronic hepatitis B, severe alcoholic hepatitis, and PSC. In liver transplantation (LT) recipients, who are highly susceptible to infections and profound post-transplant changes in GM, FMT appears to be a safe and potentially valuable adjunct, particularly for recurrent *C. difficile* infection. Overall, modulation of the gut microbiota through FMT, probiotics, prebiotics, bacteriophages, and targeted antibiotics represents a promising avenue for prevention and treatment of liver diseases and for improving outcomes after LT, although large, well-designed prospective studies are still needed to define indications, protocols, and long-term safety.

Keywords: Gut microbiota; gut–liver axis; fecal microbiota transplantation; liver transplantation

Please cite this article as "Uygun A. Current Clinical Importance of Fecal Microbiota Transplantation Treatment (FMT) in Liver Diseases and Liver Transplant (LT) Recipients. J Inonu Liver Transpl Inst 2025;3(Suppl. 1): S134-S142".

As a novel approach to reconstruct the intestinal microecological balance, fecal microbiota transplantation (FMT) has been gradually and widely practiced in the treatment of a variety of diseases in recent decade. This method transfers processed fecal materials from healthy donors to patients to rebuild the balance of their gut microbiota. Under normal conditions, the human gastrointestinal (GI) tract, which is colonized with numerous bacterial species, individually differs and is relatively stable over time , while several genetic backgrounds and environmental factors, such as diet, viruses, and use of drugs can alter the balance and further cause a variety of diseases.[1] The gut microbi-

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ota (GM) is a diverse ecosystem that consists of bacteria, protozoa, archaea, fungi, and viruses, which exist in a specific symbiosis between each other and the human body as well.

Currently, it is well known that GM plays relevant roles in physiological and pathological conditions of human health, taking part in digestion, vitamin B synthesis, immunomodulation, and promotion of angiogenesis and nerve function. In addition, it is unavoidable that the GM has an impact on pathogenesis of gastrointestinal, hepatic, respiratory, cardiovascular, endocrine, and many other disorders, arising as "a new virtual metabolic organ". The GM colonizes human intestinal tract, which accounts for more than 100 trillion bacteria, and has a complex genome of 150-fold more genes than the human genome. The majority of gut microorganisms cannot be cultured using standard techniques, so the development of culture independent molecular methods based on sequencing of the phylogenetic marker—16S/18S ribosomal RNA offer better insight in the GM structure. The GM is essentially ecomposed of the five phyla-Firmicutes (79.4%) (Ruminococcus, Clostridium, and Eubacteria), Bacteroidetes (16.9%) (Porphyromonas, Prevotella), Actinobacteria (2.5%) (Bifidobacterium), Proteobacteria (1%), and Verrumicrobia (0.1%). Lactobacilli, Streptococci, and Escherichia coli are found in small numbers in the gut. Different genetic and environmental factors influence the GM composition. For example, children born by natural childbirth inherit about 40% of the mother's intestinal flora, while GM composition is very different after the caesarean section. During the first two years of life, the diet is the most prominent factor that determines GM. Later in life, GM composition depends on age, diet, medications, and the environment.

Studies published in the last decade confirmed that the GM is implicated in the pathogenesis of various diseases, such as cancer and autism, depression, Clostridium difficile infection, inflammatory bowel disease, irritably bowel syndrome, colorectal carcinoma, infectious and non-infectious chronic liver diseases, obesity, diabetes mellitus type 2, atherosclerosis, and chronic kidney diseases.

On the other hand, some diseases (such as chronic liver diseases) can also break the balance of gut microbiota. In 2013, Els et al. performed the first randomized controlled trial and demonstrated that duodenal.

infusion of donor feces into patients with Clostridium difficile infection (CDI) had a significant efficacy in resolving symptoms than use of antibiotics alone.[2]

To date, FMT has earned endorsement of professional societies in the treatment of antibiotic-refractory CDI. In addition, FMT has been applied to treat other diseases, such as autoimmune diseases, behavioral diseases, metabolic disorders, and organic diseases.[3]

In fact, a great number of studies demonstrated that gut microbiota is associated with liver diseases. In 1987, it was first found that the relationship between the gut and liver was bidirectional and a cyclic process, and this physiological process was described as the gut–liver axis.[1]

İn recent two decades, the gut microbiota plays a pivotal role in the pathogenesis and progression of various liver diseases, including viral hepatitis, alcoholic fatty liver disease, metabolic dysfunction-associated steatotic liver disease, drug-induced hepatitis, liver cirrhosis, hepatocellular carcinoma, and other hepatic disorders. Research indicates that dysbiosis of the gut microbiota can disrupt the integrity of the intestinal barrier and interfere with the immune functions of the gut-liver axis, thereby mediating the progression of liver diseases. Analysis of microbial composition and metabolites in fecal samples can assess the diversity of gut microbiota and the abundance of specific microbial populations, providing auxiliary diagnostic information for liver diseases. Furthermore, interventions such as fecal microbiota transplantation, probiotics, prebiotics, bacteriophages, and necessary antibiotic treatments offer multiple approaches to modulate the gut microbiota, presenting promising new strategies for the prevention and treatment of liver diseases.[4-6]

The gut-liver axis has an impact on pathogenesis of numerous chronic liver diseases such as chronic hepatitis B (CHB), chronic hepatitis C (CHC), alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), development of liver cirrhosis, and hepatocellular carcinoma (HCC). In recent years, the clinical value and place of FMT in liver transplant (LT) recipients has begun to be discussed. To fully understand the subject, it is necessary to briefly mention the Gut Microbiota, the Gut–Liver Axis and FMT.

The Gut Microbiota and the Gut – Liver Axis

The gut microbiota consists of millions of species, with weight of approximately 1–2 kg.[6] The gut microbiota has been considered as an indispensable "organ". In recent twenty years, the advent of genetic tools and the metagenomics assisted scholars to realize the composition and function of gut microbiota and their association with several potential diseases. The gut microbiota has important functions in hormonal responses, inflammatory pathways, immune reactions, and metabolites.[7]

Generally, the gut–liver axis refers to the bidirectional communication between GI tract and liver by biliary tract, portal vein, and systemic circulation. Through portal vein, liver mainly receives almost two-thirds of its blood and nutritional supply from the gut, as well as gut-derived toxic factors, such as metabolites, damage/pathogen-associated molecular patterns, and detrimental microbiota.[8] On the one hand, probiotics and beneficial compositions from the gut can protect liver through the gut–liver axis. On the other hand, liver regulates the intestinal function and balance of gut microbiota through circulation of bile acid. Therefore, the close interaction between gut and liver may be a very important factor in the pathogenesis of liver diseases.

The gut–liver axis refers to the bidirectional communication between the gastrointestinal tract and the liver by the biliary tract, the portal vein, and systemic circulation. Through portal vein, liver mainly receives blood and nutritional supply, as well as gut-derived toxic factors. Probiotics and beneficial compositions from the gut can also protect liver through the gut–liver axis. Liver regulates the intestinal function and balance of gut microbiota through the bile acid.[9]

Fecal Microbiota Transplantation

FMT is also known as stool transplantation. FMT is the process of placing the stool obtained from an individual who is determined to be healthy by all laboratory tests, through various processes, and then placing this material into the patient's gastrointestinal system by endoscopic means. The components of the fecal transplants contain about 55% of microbiota and 24% of soluble components, including mucus, fat, proteins, small molecules, short chain fatty acids, etc.[10]

To date, FMT has been widely used in the treatment of recurrent CDI. In addition, with the fast development of high-throughput sequencing technologies, a variety of diseases, such as diabetes, various types of cancer, and organ diseases were found to be associated with the gut microbiota.[11]

Fecal Microbiota Transplantation (FMT) in the Treatment of Liver Diseases

As mentioned earlier, it was confirmed that the gut–liver axis plays an important and critical role in progression of liver diseases. Disturbances in the intestinal barrier may increase the portal influx of bacteria and their products into the liver, and further worsen a range of hepatic diseases. Recently, a growing body of evidence demonstrated that dysfunction of gut microbiota plays a key role in the pathogenesis of ALD and NAFLD. Furthermore, other liver-associated infections, autoimmune hepatitis (AIH), and HCC have been demonstrated to be caused by dysfunction of gut microbiota.[12]

Alteration of gut microbiota in Chronic Hepatitis B Virus (CHB) Infection

HBV infection is one of the most common public health challenges in the world, and about 15–40% of HBV-infected patients may finally develop chronic liver diseases, including cirrhosis, liver failure, and even HCC. The ideal endpoint of HBV-infected patients is hepatitis B surface antigen (HBsAg) loss. For HBV e-antigen (HBeAg)- positive chronic hepatitis B (CHB) patients, HBeAg seroconversion is mainly the first step for treatment. With the significant advances in the treatment of HBV infection, several approved therapies, including oral nucleos(t)ide analogue(s)—entecavir (ETV), tenofovir disoproxil fumarate (TDF)/tenofovir, alafenamide (TAF), and peg-interferon can be used. Despite using these methods, only few patients could obtain HBeAg clearance or seroconversion, even after multiple years of antiviral therapy. The specific reason has not been clearly expounded.[13] İn recent years, some studies demonstrated that recent therapies neglected the role of gut microbiota and it may play a key role in immune clearance of HBV. Several pilot trials with the small sample size have been conducted to explore the therapeutic effects of FMTonCHB patients.[14]

In 2017, Ren et al. first carried out a case-controlled, open-label pilot study on the application of FMT in 18 CHB patients who remained HBeAg-positive, following >3 years of ongoing ETV- or TDF-based antiviral therapy. Among them, 5 patients were included in the FMT arm who received 1–7 cycles of FMT, and 40% (2/5) of patients achieved HBeAg clearance after 1–2 cycles of FMT.[15]

In 2021, Chauhan et al. performed another similar pilot study, and their results showed that in the FMT arm, 16.7% (2/12) of patients had HBeAg clearance. While in the AVT arm, no patient achieved HBeAg clearance. These clinical studies confirmed the significant effects of FMT on stubborn CHB patients. However, more evidence from large-scale prospective studies is required.[14] Several studies attempted to explain the mechanism underlying whether the gut microbiota composition could affect the HBV infection.

The CHB infection has been found to be associated with the dysfunction of HBV-specific immune responses, causing failure in the treatment of infected hepatocytes. Furthermore, it has been reported that HBV infection could alter the intestinal microbiota. For instance, compared with healthy controls, the levels of Bifidobacteria and Lactobacillus were higher, and the levels of Enterococcus and Enterobacteriaceae were lower in CHB patients. Moreover, compared with healthy controls, Enterobacteriaceae, Faecalibacterium prausnitzii, and Enterococcus faecalis showed a noticeable increase in asymptomatic HBV carriers, and the increased range was significantly greater in HBV patients. These changes caused an increase in bacterial translocation and endotoxin load, in which activation of Toll-like receptor (TLR) facilitated immune-mediated liver injury. Most concerningly, HBV-related liver disease patients exhibit a pro-inflammatory microbiome signature characterized by opportunistic pathogens (Proteus, Klebsiella e.g) enrichment and butyrate-producing bacteria (Ruminococcus e.g) depletion.[16]

Recent studies on HBV have shown that there are significant changes in the intestinal microbiota of those with HBV infection. In the study conducted by Lin et al. in patients with CHB, changes in the intestinal microbiota were seen. İncreased; Firmicutes, Verrucomicrobia, Fusobacteria, Streptococcus, Blautia, Veillonella, Fusobacteria, Akkermansia. Decreased; Bacteroidetes, Bacteroides, Megamonas, Bacteroides, Sutterella, Lachnoclostridium.[17] Another study found that the dominant strains of Bacteroides affected the treatment.[18]

How Does Intestinal Microbiota Affect Viral Hepatitis?

The gut microbiota plays a crucial role in metabolic processes, not only facilitating the digestion and absorption of food but also producing various metabolites that influence host metabolic functions. During HBV infection, bacteria from the Leptospiraceae family may exert a positive role in managing HBV infection by reducing bacterial translocation and lowering lipopolysaccharide (LPS) levels. Multi-omics analysis has demonstrated that electroacupuncture combined with tenofovir disoproxil fumarate can increase the abundance of gut microbiota such as Bacteroides and Blautia by modulating the PPAR signaling pathway, while enhancing the expression of tight junction proteins (ZO-1, Occludin, Claudin-4), thereby improving intestinal barrier integrity. Additionally, Enterocloster bolteae isolated from chronic HBV patients can produce ethanol, potentially promoting the progression of liver disease. Ruminococcus gnavus promotes cholic acid production by secreting bile salt hydrolase, which activates the farnesoid X receptor alpha (FXRα) signaling pathway. This process enhances the transcription of HBV core antigen (HBcAg), thereby prolonging the HBV immune tolerance phase. Conversely, Akkermansia muciniphila suppresses Ruminococcus gnavus growth and its bile acid-converting function through metabolite secretion, reduces CA levels, blocks the FXRα-HBcAg axis, and facilitates HBV clearance. The reduction of BA in viral hepatitis is associated with increased intestinal permeability, leading to elevated levels of LPS and other endotoxins, which promote the progression of liver disease.[19]

HCV infection drives disease progression by inducing alterations in the intestinal bile acid profile and gut microbiota dysbiosis, which downregulate CYP8B1 expression (a key enzyme in cholic acid biosynthesis), thereby perpetuating pathogenesis through the gut-microbiome-liver axis . Increased circulating LPS levels in CHC patients indicate that microbial translocation is closely linked to hepatic inflammation and injury, thereby driving disease progression. Additionally, impaired intestinal barrier function in HCV patients is evidenced by elevated levels of zonulin-1, LPS, and calprotectin, suggesting that intestinal inflammation, microbial imbalance, and increased barrier permeability play significant roles in the pathophysiology of HCV infection. These studies demonstrate that the pathogenesis of viral hepatitis is closely related to intestinal barrier function, microbiota-derived metabolites, and BA metabolism. Viral infections can alter the diversity and composition of gut microbiota, leading to gut-liver axis dysregulation and exacerbating hepatic inflammation and injury. Therefore, modulating gut microbiota may emerge as a novel strategy to improve intestinal barrier function and mitigate liver disease progression. Metabolites and microbiota signatures may serve as potential biomarkers for disease diagnosis, though their clinical application requires further validation. Future research should focus on elucidating the specific mechanisms of gut microbiota in liver diseases to enhance clinical diagnosis and treatment efficacy.[20]

Alteration of Gut microbiota in Chronic Hepatitis C Virus (CHC) Infection

In 86 patients with HCV infection, the abundance of 10 taxa, including Desulfovibrio, Eubacterium eligens, and Prevotella, was significantly higher than that in the HC group, while the abundance of 11 genera, such as Barnesiella, Colidextribacter, and Dorea, was significantly reduced. Additionally, treatment-naïve HCV patients exhibited increased gut microbiota diversity, with elevated abundances of Prevotella, Megasphaera, and Ruminococcaceae and decreased abundances of Bacteroides, Streptococcus, and Enterobacteriaceae. 16S RNA sequencing analysis also revealed lower bacterial diversity in 166 Japanese patients with chronic hepatitis C (CHC), characterized by a reduction in the order Clostridiales and an increase in Streptococcus and Lactobacillus. Compared to the HC group, the total abundance of Lactobacillus and Lactobacillus acidophilus was significantly lower in patients with chronic HCV infection.[21, 22]

Alteration of Gut microbiota in HEV, HAV and HDV

In 33 patients with acute hepatitis E (AHE), the abundance of Proteobacteria, Gammaproteobacteria, and Enterobacteriaceae was significantly higher in the gut compared to the HC group. Furthermore, compared to the AHE group, the HEV-associated acute liver failure (ALF) group showed increased abundances of Gammaproteobacteria, Proteobacteria, Xanthomonadaceae, and Stenotrophomonas, and decreased abundances of Firmicutes, Streptococcus, Subdoligranulum, and Lactobacillus. HAV, an acute and self-limiting disease, has limited research on gut microbiota changes during infection. 16S rRNA analysis revealed gut microbiota dysbiosis in HIV patients co-infected with HAV, characterized by reduced Proteobacteria abundance and enrichment of Bifidobacterium and Bacteroides, with this dysbiosis persisting long after clinical recovery.. As for HDV infection, no relevant studies on gut microbiota have been identified, likely because HDV is an incomplete virus requiring HBV for replication, making it challenging to obtain relevant data. These findings suggest that regional, dietary, and ethnic differences may contribute to the variability in gut microbiota expression in viral hepatitis-related liver diseases. Therefore, long-term, multicenter studies are still needed to further explore the relationship between gut microbiota and viral hepatitis.[21, 23]

How can Intestinal Microbiota be Treated in Viral Hepatitis?

Currently, targeting the gut microbiota has emerged as a novel therapeutic approach for viral hepatitis infections and their complications. FMT as a method to restore and reconstruct the balance and diversity of gut microecology, has demonstrated promising outcomes. In a study involving 20 patients with liver disease related to CHB progression, FMT treatment significantly improved the Shannon and Simpson indices of gut microbiota, repaired the impaired abundance of gut microbiota, and subsequently promoted the improvement of amino acid metabolism. In a preliminary study in China, FMT induced HBeAg clearance in 18 HBeAg-positive patients who had undergone long-term antiviral therapy. Similarly, in a non-randomized pilot clinical trial involving 14 CHB patients in India, the potential safety and efficacy of FMT in achieving viral suppression and HBeAg clearance in HBeAg-positive CHB patients were observed.[24]

Alteration of Gut microbiota in Alcoholic Liver Disease (ALD)

ALD, driven by chronic excessive alcohol intake, progresses from hepatic steatosis to fibrosis and cirrhosis via gut microbiota dysbiosis. ALD is a spectrum of diseases, ranging from asymptomatic liver steatosis to the development of fibrosis, cirrhosis, and alcoholic hepatitis. Over the past few years, studies demonstrated that gut microbiota played a key role in the progression of ALD.[25]

In 2017, Philips et al. first reported a patient with severe alcohol hepatitis who was a steroid non-responder and underwent FMT. In this case, the patient's clinical, biochemical, and liver disease severity scores were significantly improved after FMT, which demonstrated that a distinct bacterial population changed before and after FMT.[26] Subsequently, another open-label study was performed with follow-up of 3 months to compare the outcomes in patients with severe alcoholic hepatitis using different methods, including nutritional therapy (n=17), corticosteroid therapy (n=8), pentoxifylline therapy (n=10), and FMT (n=16) from healthy donors. This clinical trial finally indicated that FMT for severe alcoholic hepatitis could improve survival beyond what is suggested by other therapies. After 1–2 years, the relative abundance of Porphyromonas was significantly lower and that of Bifidobacterium was higher in patients who underwent FMT than in patients who underwent corticosteroid therapy. Furthermore, FMT could function as a cost-effective bridge to LT or to improve survival without transplantation. FMT was also demonstrated as a safe therapeutic approach to reduce the incidence of ALD. Based on the clinical evidence, FMT is suggested as a safe and efficient therapy for ALD, especially for noncorticosteroid- responsive patients and without history of undergoing LT.[27]

Alteration of Gut Microbiota in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

MASLD, formerly known as non-alcoholic fatty liver disease, is a chronic liver condition affecting approximately 30% of the global population. Characterized by abnormal lipid accumulation in hepatocytes, MASLD can progress from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), and ultimately lead to hepatic fibrosis, cirrhosis, and even hepatocellular carcinoma.[28]

Studies have shown that the diversity and abundance of gut microbiota are significantly reduced in MASLD patients compared to HC.[29]

However, findings vary across regions and ethnicities. For example, a study in Indonesia involving 37 MASLD patients reported a predominance of Firmicutes and an elevated F/B ratio.[30]

In contrast, a study in Taiwan involving 50 biopsy-confirmed MASLD patients demonstrated a higher abundance of Bacteroidetes, a lower abundance ofFirmicutes, a reduced F/B ratio, and decreased levels of Ruminococcaceae, Clostridiales, and Clostridium compared to healthy individuals.[31] A study in Korea involving 23 MASLD patients with elevated liver enzymes found an enrichment of Firmicutes, an increased F/B ratio and a significant rise in the abundance of Veillonella, Dialister, Collinsella, Latilactobacillus, and Bifidobacterium. In MASLD patients, the abundance of beneficial bacteria such as Akkermansia muciniphila, Faecalibacterium prausnitzii and Bifidobacterium is significantly reduced. A study involving 100 adolescent MASLD patients found a notable decrease in the abundance of Lactobacillus and Escherichia coli and a significant increase in Prevotella.[32,33]

These findings indicate that the gut microbiota of MASLD patients exhibits significant diversity, which may be closely related to factors such as ethnicity, dietary habits and geographic environment.

Alteration of Gut Microbiota in Autoimmune Hepatitis (AIH)

AIH is an entity of chronic and immune-mediated hepatitis characterized by hepatocyte injury, with the presence of circulating autoantibodies and elevated level of serum immunoglobulin G (IgG). At present, the main pathogenetic mechanism of AIH is considered as a loss of tolerance against the patient's own liver antigens, which is potentially triggered by both genetic and environmental risk factors, such as xenobiotics and pathogens. AIH may develop to liver cirrhosis and HCC, and it may even lead to fulminant hepatic failure.[34]

In fact, triggers of AIH are very complex and have not yet been identified. For treatment, AIH patients favorably respond to corticosteroids, while some patients who are irresponsive to standard treatment may quickly develop to fibrosis and cirrhosis. Therefore, development of effective therapies for patients who are irresponsive to corticosteroids is essential. In recent years, evidence from murine models exhibited that the gut microbiota is an important environmental risk factor, participating in the pathogenesis of AIH. Wei et al. performed a cross-sectional study on 91 patients with AIH and 98 healthy controls by 16S rRNA gene sequencing, and the results showed that compared with healthy controls, the gut microbiome of patients with AIH before steroid treatment was accompanied by a lower alpha-diversity and a distinct microbial composition.[35, 36] However, to our knowledge, no clinical study has yet assessed the therapeutic value of FMT for AIH.

Alteration of Gut Microbiota in Primary Sclerosing Cholangitis (PSC)

PSC is a chronic immune-related cholestatic liver disease, which can lead to cholestasis, bile duct stenosis, and hepatic fibrosis. A previous study demonstrated that PSC is closely associated with inflammatory bowel disease (IBD) suggesting that gut microbiota plays a key role in the PSC. Compared with healthy controls, PSC and PSC-IBD patients have significantly distinct gut microbial profiles with decreasing expression of Prevotella copri (P. copri). Several studies demonstrated that P. copri could improve glucose homeostasis with GI resection by enhancing the bile acid metabolism and signaling and promote immune tolerance.

For the treatment of PSC, there is no effective therapy. LT seems to be the only therapeutic option. However, there is still a risk of recurrent PSC after LT. According to the protective role of gut microbiota in PSC. Over the past few years, additional studies have concentrated on the therapeutic effects of gut microbiota on PSC. In 2019, Allegretti et al. performed an open-label pilot study on 10 patients with PSC-IBD. These patients underwent FMT and 30% of them experienced a more than 50% decrease in alkaline phosphatase (ALP) levels. Moreover, no relevant adverse event occurred. Following FMT, the patient's liver biochemistry, bile acid, and bacterial community were significantly improved, suggesting the applicability of FMT in the treatment of PSC. However, further evidence is required to verify the above-mentioned findings.[37] Following FMT, the patient's liver biochemistry, bile acid, and bacterial community were significantly improved, suggesting the applicability of FMT in the treatment of PSC. However, further evidence is required to verify the above-mentioned findings.

Gut microbiota dysbiosis plays a crucial role in the development and progression of autoimmune and genetic liver diseases (such as Wilson's disease). These diseases are closely associated with gut microbiota dysbiosis. Modulating the gut microbiota may provide new insights for the diagnosis and treatment of these diseases. Future research should further explore the specific mechanisms of gut microbiota in these liver diseases and develop gut microbiota-based early diagnostic and therapeutic approaches, thereby offering more precise and personalized treatment strategies for patients.

Alteration of gut microbiota in Liver Cirrhosis (LC)

LC represents a severe stage of chronic liver disease characterized by extensive hepatocyte degeneration, fibrosis, and nodular regeneration, leading to significant morbidity and mortality.

In hepatitis B-related cirrhosis, a common subtype of LC, progressive liver damage is further aggravated by gut microbiota dysbiosis and associated metabolic dysfunction. Studies consistently demonstrate that LC patients exhibit markedly reduced gut microbial diversity compared to healthy individuals, with notable depletion of beneficial bacteria such as Agathobacter and Prevotella, with Chinese LC patients showing elevated Bacteroidota/Firmicutes ratios and Proteobacteria abundance correlated with inflammatory responses, while North American cohorts demonstrate distinct associations between Enterobacteriaceae / Streptococcaceae dominance and clinical outcomes including extrahepatic organ failure.

The clinical relevance of these microbial alterations is underscored by their correlations with disease complications, including the association between Akkermansia muciniphila depletion and sarcopenia development, as well as the close relationship between pathogenic bacterial overgrowth and systemic inflammatory markers like TNF-α and IL-6. These findings collectively establish gut microbiota dysbiosis as a key contributor to LC progression through multiple interconnected pathways.

The gut microbiota plays a critical role in the pathogenesis of LC. In LC patients, gut microbiota dysbiosis, bacterial overgrowth and increased intestinal permeability disrupt the protective mechanisms of the gut, leading to pathological bacterial translocation and increased endotoxin uptake. These endotoxins subsequently reach the liver and mesenteric lymph nodes, activating immune cells and triggering the release of pro-inflammatory cytokines such as TNF-α and IL-8.

Meta-analysis results indicate that endotoxin-producing Enterobacteriaceae and Enterococcus are significantly increased in LC patients, which may be related to the impaired intestinal mucosal barrier function caused by LC.

The impaired intestinal barrier and gut microbiota dysbiosis not only lead to bacterial translocation and endotoxemia but also exacerbate liver injury and fibrosis through abnormal related metabolites. In LC patients, dysbiosis of the ascending colon mucosa-associated microbiota, particularly the reduction of SCFA-producing bacteria, compromises intestinal barrier integrity and BA metabolism, thereby exacerbating liver fibrosis progression via the gut-liver axis.[38, 39, 40]

The gut microbiota plays a pivotal role in the development of cirrhosis, with its dysbiosis not only directly affecting liver inflammation and fibrosis but also influencing systemic metabolism and immune responses through the gut-liver axis.

Alteration of Gut Microbiota in Drug-İnduced Liver Injury (DILI)

Drug-induced liver injury (DILI), a leading cause of ALF and acute hepatitis globally,[1] is a severe adverse drug reaction associated with medications such as anti-infectives, herbal products, and non-steroidal anti-inflammatory drugs. Emerging evidence highlights the critical role of gut microbiota in DILI pathogenesis. Patients with DILI exhibit significant gut microbial dysbiosis, characterized by reduced richness and diversity (99), with distinct patterns across drug types. In acetaminophen (APAP)-induced models, APAP exposure increases Cyanobacteria and Deferribacteres while decreasing Firmicutes at the phylum level, and elevates Bacteroides/Enterococcus but depletes Bifidobacterium/Lactobacillus at the genus level. These findings collectively underscore gut microbiota as a pivotal mediator in DILI progression.[41]

Alteration of Gut Microbiota in Hepatocellular Carcinoma (HCC)

HCC is the fourth leading cause of cancer-related deaths globally, with its incidence primarily associated with hepatitis B (40%), hepatitis C (40%), alcohol (11%) and MASH. Recent studies have shown that alterations in the gut microbiota are closely related to the occurrence and progression of HCC.[42] By 2025, over one million cases will be globally affected by HCC. LT has become a standard treatment for patients with early stage HCC in several countries. However, for those patients with advanced HCC whose number and size of tumor beyond Milan criteria, the 5-year survival rate after LT remains poor. Over 80% of HCC cases are associated with liver cirrhosis, representing inflammation and hepatocellular proliferation. A study demonstrated that bacteria derived from gut might play a role in the recurrence of cirrhosis and HCC.

In early-stage HCC patients, the species richness of fecal microbiota is increased compared to the LC group. Analysis of published fecal datasets from four different regions in China revealed that the relative abundance of Firmicutes was significantly lower in HCC patients compared to HC and further decreased with disease progression, while the relative abundance of Bacteroidetes and Proteobacteria significantly increased.

However, Yan et al. reported inconsistent findings in a study conducted in Beijing, showing that the abundance of both Bacteroidetes and Firmicutes gradually decreased in HCC patients. Additionally, the abundance of Proteobacteria, Streptococcus, and Ruminococcus was significantly higher in the HCC group compared to controls, while the abundance of Subdoligranulum was significantly reduced.[43]

In early-stage HCC patients, the abundance of Actinobacteria increased, and 13 genera, including Gemmiger and Parabacteroides, were enriched in early HCC. The relative abundance of potentially beneficial bacteria, such as Lactobacillus, Bifidobacterium, and Bacteroides, was significantly reduced in HCC patients, while the relative abundance of potentially pathogenic bacteria, such as Escherichia-Shigella and Enterococcus, was significantly increased. Furthermore, Akkermansia was most enriched in LC patients, while its abundance was relatively lower in the HC group, CHB patients and HCC patients.[44]

When the literature is examined, Some clinical trials related to gut microbiota in HCC have been performed or are ongoing. However, to our knowledge, no clinical study has assessed the applicability of FMT for HCC. Only Baruch et al. Reported the first human clinical trial where they found how treatment with FMT was associated with favorable changes in gene expression profiles and immune cell infiltrates in the tumor microenvironment. These data indicated the benefits of FMT for the treatment of HCC.[45]

Clinical Value of Fecal Microbiota Transplantation for Liver Transplantation (LT) Recipients

It is widely accepted that LT is still the only therapeutic option for patients with end-stage liver disease, acute liver failure, and HCC. Over the recent decades, LT has been used as a mature and conventional surgical method for liver diseases. However, patients receiving LT are at a particularly higher risk of infection, such as CDI, cytomegalovirus (CMV) infection, fungi infection, recurrent HBV infection, etc. A previous cohort study demonstrated that about 19% of deaths occurred at five years after LT were related to various sources of infection.[46]

That is mainly due to administration of immunosuppressive agents after LT attenuates immune surveillance, enabling pathogens to evade natural immunity and facilitate infection. Furthermore, pre- transplant infection and some other risk factors are also associated with post-LT infection. In addition, several studies demonstrated that the types of gut microbiota may significantly change after LT.[47]

Hence, restoring the gut microbiota balance by FMT may be particularly critical for LT recipients. For instance, Schneider et al. reported a case of successful FMT in a LT recipient with severe CDI that was complicated with acute kidney injury.[48] Furthermore, the safety of FMT in immunocompromised patients has been demonstrated in a meta-analysis of 44 studies.[49] Therefore, FMT may be a potential therapeutic method for CDI after LT. However, to our knowledge, no clinical study has yet assessed the applicability of FMT for infectious diseases.

The gut–liver axis has shown a mutual association between the intestine and liver. Hence, the close interaction between gut and liver may be a very important factor in the pathogenesis of liver diseases. In addition, a growing body of evidence demonstrated that FMT is a novel approach to reconstruct the intestinal microecological balance, therefore, FMT has been gradually and widely utilized in the treatment of several liver diseases. Moreover, restoring the gut microbiota balance by FMT may be particularly critical for LT recipients.[50]

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