Sports Science, Human Performance, and Health Journal
ISSN 3064-7533
Volume 12 Issue 1
January – March 2024
Impact Factor: 7.71
Enquiry: contact@continentalpub.online
Published by Continental Publication | http:// https://continentalpub.online/index.php/sshphj

DECIPHERING THE GUT-LIVER CONNECTION: UNDERSTANDING MECHANISMS OF LIVER DISEASE

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Abstract: *The human gastrointestinal tract houses a complex ecosystem of microorganisms known as gut flora, crucial for maintaining symbiotic host-microbe relationships. Disruption of this balance can lead to intestinal permeability and bacterial translocation, contributing to various diseases. The liver's intimate connection with the gut is described by the "gut-liver axis." Dysregulation of gut microbiota can trigger immune responses, resulting in inflammatory reactions and various liver diseases. This paper explores the intricate relationship between gut microbiota and liver diseases, offering insights into diagnosis and treatment.*

Keywords: *gut flora, gut-liver axis, intestinal permeability, bacterial translocation, liver diseases*

Introduction

The human gastrointestinal tract is inhabited by a range of bacteria and microorganisms that have a symbiotic relationship with the host, including bacteria, fungi, viruses, and archaea, and is known as the gut flora. More than 99% of the gut microbiota are specialized anaerobes, with the remainder including aerobic bacteria, parthenogenetic anaerobes, and other species of microorganisms [1]. The remaining include aerobes, parthenogenic anaerobes, and other microbial species. Under normal conditions, these gut microbiota can maintain a dynamic balance. When the intestinal barrier is compromised, intestinal permeability increases, causing bacterial translocation, which can lead to a range of diseases. From an anatomical and physiological point of view, the liver has a close relationship with the intestine. The theory of the "gut-liver axis" was proposed by Marshall in 1998, and in recent years, the research on liver diseases and gut microbiota has received increasing attention. The gut-liver axis is a bidirectional relationship between the gut and the liver through the gut microbiota, and when the gut microbiota is dysregulated or dysfunctional due to various reasons, it will activate the body's immune system to produce a series of inflammatory reactions, which will lead to a variety of liver diseases. In this paper, the correlation between gut microbiota and liver diseases is elaborated to provide ideas for the diagnosis and treatment of liver diseases.

1. Gut microbiota

The intestinal microenvironment is the largest and most complex microecosystem in the human body, accounting for up to 80% of the body's microbial library [2]. The majority of the gut microbiota are anaerobic, with the remainder being parthenogenetic anaerobes and aerobes. Among the most common flora, there are five phyla of dominant bacteria: Thick-walled phylum, Actinobacteria, Actinobacteria, Ascomycetes, Ascomycetes, and Micrococcus wartyi, with Thick-walled phylum accounting for 60%-80%, followed by Ascomycetes, accounting for 20%-40% of the flora [3]. Gut microorganisms play an important role in digestion, nutrient absorption, and immunomodulation [4]. Gut flora plays a crucial role in the regulation of Toll-like receptor (TLR), NF-κB signaling, janus kinase/signal transduction

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DOI: https//doi.org/10.5281/zenodo.14178853

and transcription (JAK/STAT) pathways, and $CD4^+$T cell activation [5]. Normally, the gut microbiota can maintain a certain balance, which is disrupted when influenced by internal or external environmental factors, such as smoking, alcohol consumption, drugs, diet, obesity, genetics, and gastrointestinal diseases, leading to a series of pathological changes in the organism [5].

2. Intestine-liver axis

The enterohepatic axis consists of the lymphatic system, the portal vein, and the biliary circulatory system [6]. The intestine and the liver have a bidirectional connection through the enterohepatic axis; on the one hand, the liver excretes bile acids and other substances that are transported to the intestine through the bile ducts, and on the other hand, nutrients, inflammatory mediators, and bacterial metabolites absorbed by the intestinal tract are transported to the liver through the portal venous system [7]. The gut-liver axis theory explains the interaction between the gut microbiota and the liver from an anatomical and physiological perspective.

3. Gut microbiota and liver disease

The liver is the first organ to come into contact with the intestinal blood, about 70% of the blood comes from the intestines, which digests and absorbs nutrients such as glucose, proteins, and vitamins, while toxins and bacterial metabolites produced in the intestines enter the liver through the gut-liver axis, and therefore the liver is exposed to the toxic substances and harmful bacteria from the intestines [5, 8]. Therefore, the liver is exposed to toxic substances and harmful bacteria from the intestinal tract. When the intestinal microbial system is stimulated to lose its dynamic balance, the intestinal mucosal barrier is damaged, and bacterial metabolites are transported to the liver through the portal circulation, leading to liver injury [9]. The liver is not only affected by the intestinal microbial system but also by the liver. The liver is not only affected by the intestinal microflora, but it in turn affects the intestinal microflora by secreting bile acids, IgA antibodies and other metabolites.

3.1 Gut microbiota and viral hepatitis

Hepatitis B virus (HBV) infection is a global public health problem. The gut microbiota is associated with the pathogenesis of liver disease caused by chronic HBV infection. Yang et al. [10] showed that the onset and progression of viral hepatitis are associated with gut microbial diversity. The present study also found decreased gut alpha diversity and increased abundance of genera including Aeromonas spp., butyric acidophilus, Shigella spp., Legionella spp. and Lactobacillus spp. may serve as potent biomarkers for predicting the risk of viral hepatitis infection. Sun et al. [11] found that intestinal dysbiosis may be involved in the abnormal accumulation of serum metabolites, disruption of the intestinal barrier, and induction of inflammatory responses in the Toll-like receptor/NOD-like receptor (TLR/NLR) pathway, and may also affect the progression of chronic hepatitis B and even cirrhosis.Wang et al. [12] reported that circadian rhythms have the potential ability to regulate changes in gut microbiota involved in the diagnosis, progression and prognosis of HBV-related diseases. A study found that when the gut microbiota composition of recombinant adeno-associated virus serotype 8 (rAAV8)-mediated persistent HBV-infected mice and entecavir (ETV)-treated mice was compared with that of healthy controls, the α-diversity of the gut microbiota was reduced in the rAAV8 HBV-infected mice, and was significantly reversed after ETV treatment. Suggesting that hepatitis B-associated liver disease is associated with gut flora dysbiosis [13]. A prospective cohort study showed [14] that hepatitis C virus (HCV)-infected patients had an altered gut microbiota compared with uninfected controls, and that the overall microbial composition did not change significantly after eradication of the virus with direct antiviral agent (DAA) therapy. In a study that included 40 non-cirrhotic chronic hepatitis C virus-infected patients and 10 healthy individuals as controls, total lactate as well as Lactobacillus acidophilus counts were significantly higher in fecal samples from the healthy group compared to chronically infected HCV patients. In addition, there was a statistically significant difference in microbial composition (Lactobacillus acidophilus and Bifidobacterium bifidum) between the healthy and chronically infected groups, and both were reduced in HCV [15].

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3.2 *Gut microbiota and alcoholic liver disease*

Alcohol is the most common substance that can cause liver injury. Alcohol and its metabolites cause oxidative stress in liver cells and increase their sensitivity to inflammatory stimuli. Alcoholic Liver Disease (ALD) is one of the most common causes of liver disease. In addition to the toxic effects of alcohol and its metabolites on intestinal epithelial cells, intestinal inflammation due to microecological dysregulation also affects intestinal barrier dysfunction and microbial product translocation in ALD [16]. Gut microbiota is closely associated with alcoholic liver disease and is involved in pathological processes such as hepatocellular steatosis, steatohepatitis, hepatic fibrosis, cirrhosis, and hepatocellular carcinoma. The gut microbiota and the liver act as a material basis for each other and jointly contribute to the disease process [17]. The gut microbiota and the liver serve as the material basis for each other and jointly promote the process of disease development.

Alcohol can increase the door deformation bacteria and enterobacteriaceae and the relative abundance of streptococcus pneumonia, and reduce the bacteroidetes, Mr. Ackman's bacteria and fecal bacteria of the genus abundance [18]. It may be related to alcohol-induced oxidative stress (poorly tolerated by specialized anaerobes such as Anabaena spp.) and alcohol down-regulation of antimicrobial peptides such as α-defensins [19]. Seo et al. [20] demonstrated that the use of Rhodobacter sphaeroides in a murine model of ALD ameliorated hepatic steatosis and inflammation, improved the intestinal ecosystem, and prevented leaky gut. The possible mechanism is the recognition of TLR5, which restores intestinal barrier integrity due to upregulation of tight junction protein (TJ) expression, increased IL-22 (interleukin-22) expression, and restoration of islet-derived protein 3-γ. Liu et al. [21]found that the serum AST, ALT, TC, and TG levels were significantly higher in the alcoholic fatty liver disease (AFLD) mouse model group compared with the sea buckthorn polysaccharide (HRP) and astragalus polysaccharide (APS) administration group, suggesting that the combination of HRP and APS can effectively regulate liver function impairment and lipid accumulation in AFLD mice. It was also found that Observed species, Chao1, Shannon, and Faith's PD indices of the intestinal tract of mice in the model group were significantly reduced, suggesting that alcohol consumption had a certain inhibitory effect on the abundance and diversity of the gut microbiota of the mice. HRP and APS helped to restore the diversity of the intestinal mucosal bacteria to a certain extent, relative abundance, and community structure. A study found that the expression of Fmo5 and PPARα was significantly downregulated in liver tissues of AFLD patients, which was closely related to the gut microbiota and alcohol consumption.AFLD induces an imbalance in the gut microbiota and reduces the expression of intestinal hepatoprotective factor α (Fmo5 and PPARα), which activates the NF-κB signaling pathway and thus promotes cell apoptosis and inflammation. [22]. Co-expression of Fmo5 and PPARα reduces AFLD-mediated apoptosis, inflammation, and liver injury by inhibiting NF-κB signaling pathway activation [22]. Fmo5 and PPARα co-expression reduces AFLD-mediated apoptosis, inflammation, and liver injury by inhibiting NFκB signaling pathway activation.

3.3 *Gut microbiota and nonalcoholic fatty liver disease*

Non-alcoholic fatty liver disease (NAFLD) is a global disease with an increasing incidence year by year. NAFLD starts as hepatic steatosis and can evolve into non-alcoholic steatohepatitis (NASH), and if liver fibrosis is present, it can progress to cirrhosis or even hepatocellular carcinoma (HCC). The development of NAFLD is related to obesity, type 2 diabetes, metabolic syndrome, hyperlipidemia, genetics, and environment. Based on this, the international consensus recommends replacing NAFLD with Metabolic-Associated Fatty Liver Disease (MAFLD) [23]. Studies have shown that gut microbiota plays an important role in metabolism and immunity, and may be associated with dysregulated intestinal ecology, impaired intestinal barriers leading to increased absorption of free fatty acids, bacterial migration, and release of toxic bacterial products, lipopolysaccharides (LPS), and pro-inflammatory cytokines [24]. Dysregulated gut ecology leads to NAFLD through different mechanisms, categorized as inflammatory and metabolic. Inflammatory mechanisms include decreased expression of tight junction proteins and increased ethanol. Metabolic mechanisms include altered short-chain

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DOI: https//doi.org/10.5281/zenodo.14178853

fatty acids (SCFA), decreased fasting-induced adipokines, altered bile acid profiles, and increased conversion of choline to methylamine [25]. It has been suggested that disorders of the gut-liver axis, such as intestinal barrier dysfunction, bacterial translocation, inflammatory responses, and activation of the Toll-like receptor signaling pathway, play a key role in the pathogenesis of NAFLD [26-28]. The pathophysiology of NAFLD is associated with insufficient microbial diversity and deterioration of the intestinal barrier, revealing the bacterial composition of the host and potential pathways related to inflammation through TLR signaling and immune defense [29].

3.4 Gut microbiota and liver cirrhosis

Cirrhosis is the terminal stage in the development of various chronic liver diseases, and patients with cirrhosis tend to have varying degrees of imbalance in the gut microbiota, which is mainly manifested in the proportions, types, quantities, and metabolic activities of the gut microbiota, as well as changes in the local distribution of the gut microbiota. Compared with healthy individuals, patients with cirrhosis have slower intestinal transit times, overgrowth of intestinal bacteria, and altered fecal microbial profiles, with an enrichment of the phylum Aspergillus and Clostridium and a decrease in the phylum Anabaena [30, 31]. The imbalance in the gut microbiome leads to intestinal mucosal barrier damage and excess enteric endotoxins circulating through the portal vein into the liver and systemically. Elevated levels of endotoxin and proinflammatory cytokines stimulate the activation and proliferation of hepatic stellate cells (HSCs), which secrete large quantities of extracellular matrix and promote the proliferation and deposition of fibrous connective tissue in the liver, contributing to the development of cirrhosis [6]. TLR4 is expressed by a variety of cells in the liver, such as kupffer cells (KCs) and hepatic stellate cells. It has been found that TLR-4 activation then initiates an intracellular signaling cascade in hepatocytes, causing activation of nuclear factor NF-κB, P38MAPK, and JNK, which triggers immunoinflammation and sustained inflammatory stimulation, leading to regenerative repair of hepatocytes after repeated injury and promoting progression of cirrhosis [32]. In addition to the physical damage to the intestinal barrier, the intestines of cirrhotic patients are infiltrated by potent immune cells, as evidenced by an increase in lymphocytes expressing TNF-α and IFN-γ and a decrease in Th17 cells.

3.5 Gut microbiota and hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors of the digestive system. A vicious cycle of liver injury, inflammation, and regeneration exists in patients with chronic liver disease, resulting in liver fibrosis and cirrhosis, which may ultimately lead to HCC. Statistically, about 80%-90% of patients with HCC have advanced liver fibrosis or cirrhosis. In addition, about 5%-25% of patients with cirrhosis will eventually develop HCC [5]. In recent years, studies have shown that gut microbiota is closely related to liver cancer. The main reason for the imbalance of the flora is the pathological conditions of advanced liver disease, such as decreased bile secretion, changes in antimicrobial peptides, and intestinal secretion of IgA [5]. KCs, HSCs, and hepatocytes in the liver express TLR4, which recognizes LPS in the gut microbiota. Activation of TLR4 by LPS regulates the expression levels of other immune molecules through a series of reactions. Activation of TLR4 in HSCs leads to NF-κB-mediated upregulation of hepatic mitogen-activated proteins and promotes hepatocyte mitosis. On the other hand, activation of the LPS-TLR4 axis leads to the blockage of NF-κB-mediated apoptosis in hepatocytes, which ultimately promotes the formation of hepatocellular carcinomas [34, 35]. LPS also induces the differentiation of hepatic progenitor cells (HPCs) into myofibroblasts. It further induces the activation of the tumor-related signaling pathway Ras and the inactivation of the tumor suppressor signaling pathway p53 in HPCs through the secretion of IL-6 and TNF-α (tumor necrosis factor), which ultimately promotes the aberrant proliferation and transformation of HPCs as well as hepatocellular carcinogenesis.

4. Conclusion

Gut microbiota plays a crucial role in the pathogenesis of liver disease, and the current western medical treatment of gut microbiota dysbiosis mainly includes oral antibiotics, probiotics, prebiotics, immune

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DOI: https//doi.org/10.5281/zenodo.14178853
checkpoint inhibitors, and fecal bacteria transplantation. Probiotics have a positive effect on the treatment of liver inflammation and cirrhosis, and can effectively prevent the occurrence of hepatocellular carcinoma. It can be used as a key research direction for subsequent clinical work, but the current research focuses on animal experiments and relatively few clinical experiments. Fecal bacteria transplantation is a new treatment method, which lacks effective clinical research data to support its safety and efficacy due to problems such as unknown composition and pathogenicity of fecal bacteria. Several studies have shown that Chinese medicine is unique in the treatment of liver diseases, and the oral dosage form of Chinese medicine has a greater advantage in regulating gut microbiota therapy. On the one hand, Chinese medicines and their compositions are complex and can act on the intestinal-hepatic axis in a multi-targeted manner; on the other hand, the gut microbiota can be transformed and metabolized to enhance the active ingredients of Chinese medicines and their compositions to enhance the therapeutic effect. However, the study on the effect of TCM on the intestinal microecology of liver disease patients is still limited. Therefore, it is necessary to explore the specific biomarkers involved in various liver diseases, and the targeted regulation of gut microbiota may become a new way to prevent or treat the development of liver diseases. A large number of randomized clinical trials targeting the microbiome are still needed in the future to provide feasible options for the clinical treatment of liver disease and thus improve the prognosis of liver disease.

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