GUT MICROBIOTA AND VIRAL HEPATITIS (A NARRATIVE REVIEW)

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Small intestinal bacterial overgrowth (SIBO) is a distinct but interconnected form of gut dysbiosis and often coexists with broader alterations in gut microbiota diversity, particularly in patients with chronic liver disease. Excessive colonization of the small intestine with pathogenic or opportunistic bacteria contributes to increased intestinal permeability, endotoxemia, and systemic inflammation, which exacerbates liver damage. The intestine and liver are closely interconnected, and disturbances in the composition of the gut microbiota can significantly impact liver health (the gut-liver axis). In this review, the authors highlight the main mechanisms of liver damage in SIBO and the risk factors associated with this condition, which influence the clinical severity of viral hepatitis.

Keywords: small intestinal bacterial overgrowth syndrome, chronic liver disease, viral hepatitis, liver fibrosis, diagnostic methods

Introduction. In recent years, a close link between the gut microbiota and a wide range of liver diseases (viral hepatitis, autoimmune liver diseases, alcoholic liver disease, metabolic-associated fatty liver disease (MAFLD), metabolic steatohepatitis, liver cirrhosis, and hepatocellular carcinoma) has been clearly demonstrated.

The gut and liver are closely interconnected, and disturbances in the gut microbiota can have a significant impact on liver health. This bidirectional relationship is widely known as the gut-liver axis. Numerous studies have identified a link between gut dysbiosis and viral hepatitis, primarily hepatitis B and C. According to recent research, the gut microbiota produces various compounds that translocate to the liver and interact with liver immune cells, exerting pathogenic effects. These bioactive molecules (e.g., peptides, lipopolysaccharides, bacterial DNA, lipoteichoic acid, indole derivatives, bile acids, and trimethylamine) play a crucial role in mediating the interaction between the gut microbiota and the liver. Consequently, this complex interaction has become a key factor determining both the development of liver disease and the development of therapeutic strategies aimed at maintaining host health and managing pathological processes.

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The overall genetic content of the vast and varied population of microbes that reside the intestinal tract is significantly more than that of the human genome. About 100 trillion intestinal bacteria comprising about 1,000 species coexist together with humans in the gastrointestinal tract. The stomach and small intestine harbor only limited varieties of intestinal bacteria, whereas the colon contains the predominant proportion of the microbial population [1]. Only 15 to 20% of the bacteria in various intestinal parts are harmful, while the majority of the gut microbiota (80 to 85%) is made up of beneficial bacteria [2]. The immune system's regulation, food energy extraction, and fat accumulation are all significantly influenced by the gut flora. It contributes to metabolic functions and facilitates the development of an intricate immune response.

Gut Microbiota and the Liver: General Concepts. Since over 99 percent of the gut microbiota belongs to one of four phylums; Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria one may argue that it is an organ unto itself [3]. While those who regularly consume large amounts of meat are likely to have bacteria in their intestines that promote inflammation, those who regularly consume large amounts of vegetables, fish, and fibre are likely to have bacteria that help reduce inflammation [4]. As people age, their gut microbiota's makeup significantly shifts. Several distinct trends have been identified regarding how the composition of the gut microbiota evolves throughout the lifespan. For

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instance, Firmicutes are predominantly observed in the adult population, whereas Proteobacteria tend to be more prevalent both in early infancy and in older individuals. In addition, the relative abundance of Actinobacteria has been shown to decline progressively with advancing age, while Bacteroidetes demonstrate a tendency to increase as ageing occurs [5].

Dysbiosis and the Gut-Liver Axis. A qualitative and quantitative abnormality of the gut microbiota that has garnered a lot of interest is called dysbiosis. An elevated synthesis of pro-inflammatory cytokines, sensed by specific receptors within the portal venous circulation, can trigger a targeted inflammatory reaction in individuals experiencing gut dysbiosis. The innate immune system's reaction to microbial compounds is a major factor in the production of these pro-inflammatory cytokines. The activity of gut bacteria extends beyond the mere production of short-chain fatty acids (SCFAs), encompassing a variety of additional metabolic and immunological functions. Butyrate, which is also produced by the pentose phosphate pathway and glycolysis, encourages the growth of Bifidobacteria and Lactobacilli bacteria in the colon. Numerous studies have demonstrated the critical role microbiota-derived nutrients play in the hepatic system's regular functioning [6].

The physical and physiological relationship between the gut and the liver is termed to as the gut-liver axis. Because of the tight anatomical link between these organs, the gut-liver axis is predicated on the idea that the portal vein circulation carries enzymes, metabolites, and immunological signals to the liver [7]. The gut microbiota represents a principal factor within the gut-liver axis, and their role in modulating hepatic function has recently become the focus of considerable scientific interest [8]. It has been shown that the GM profile of individuals with chronic hepatitis is significantly different from that of healthy individuals. Furthermore, the severity of gut dysbiosis is directly correlated with the degree of liver insufficiency [9]. The portal blood flow of intestinal origin reaches the liver first, and a number of intestinally derived elements, including intestinal bacteria, bacterial components, and intestinal bacterial metabolites, are thought to have a significant impact on liver disease.

Mechanistic Insights into Microbiota-Driven Hepatic Inflammation and Fibrosis. Many elements have drawn special attention, and their importance has been thoroughly examined. Pathogen-associated molecular patterns (PAMPs) constitute one of the relevant components that reach the liver via the portal vein. During the progression of chronic hepatic disorders, both hepatic stellate cells and hepatic macrophages play pivotal roles as primary targets of microbial compounds originating from the intestine. Firstly, hepatic stellate cells (HScs) become activated in response to chronic liver injury, adopting a myofibroblast-like morphology characterized by elevated expression of α-smooth muscle actin (α-SMA) [10, 11]. This activation contributes to liver fibrosis through the production of significant amounts of extracellular matrix components, including collagen. Moreover, hepatic stellate cells are susceptible to activation by multiple factors, including reactive oxygen species, damage-associated molecular patterns, and a diverse array of cytokines and chemokines that collectively contribute to hepatic injury and fibrosis. Consequently, it is well recognised that they are crucial in the development of the cancer microenvironment, which promotes the growth and expansion of cancer cells by triggering fibrosis and angiogenesis [12].

The second one, monocyte-derived macrophages and Kupffer cells are examples of liver macrophages. In order to induce liver fibrosis during inflammation, activated liver macrophages produce several secretory substances, attract neutrophils and monocytes originating from bone marrow, and activate HScs. Furthermore, active liver macrophages express tumour necrosis factor-related apoptosis inducing ligand (TRAIL), which causes liver parenchymal cells to undergo apoptosis, and secrete matrix metalloprotease, an enzyme that breaks down extracellular matrix. As a result of these insights, this mechanism is now being progressively acknowledged as a viable target for therapeutic intervention aimed at mitigating liver fibrosis [13].

Microbiota Changes in Viral Hepatitis (HBV & HCV Specific). Primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), viral hepatitis (hepatitis B and C), autoimmune hepatitis (AIH), and alcoholic liver disease are all more significantly impacted by gut flora. Saccharomyces boulardii, Bifidobacterium, Lactobacillus, and Lactobacillus plantarum has become more important in the medical management of hepatitis and other metabolic diseases [14].

Viruses and intestinal microbes are among the many pathogens that employ mucous membranes as their entry point. Hepatic viruses emit pro-inflammatory cytokines that contribute to the development of liver cirrhosis and HCC, as well as breach intesti-

nal permeability, resulting in gut dysbiosis. Gut dysbiosis promotes Proteobacteria, Enterobacteriaceae, and Veillonellaceae while decreasing Bacteroidetes and Lachnospiraceae in the majority of liver diseases, including cirrhosis. The cirrhosis dysbiosis ratio (CDR) was recently developed to characterise the alterations in the gut microbiome of cirrhosis patients with detrimental Enterobacteriaceae bacteria and beneficial Lachnospiraceae and Ruminococcaceae bacteria [15].

The association between gut microbiota alterations, especially small intestinal bacterial overgrowth and liver illnesses, particularly those linked to the hepatitis viruses, was described in this review.

The hepatitis C virus (HCV) was responsible for 399,000 deaths and an estimated 71 million chronic infection diagnoses in 2016. 10% of HBV and over 30% of HCV generate persistent infections that result in cirrhosis and hepatocellular cancer. Research has demonstrated that patients affected by chronic HCV infection commonly display diminished microbial diversity within their gut microflora, which may have implications for disease progression and immune function [16]. Among patients with chronic hepatitis C residing in Egypt a country with the world`s highest rates of HCV infection-the intestinal microbial communities are characterized by increased representation of genera such as Prevotella, Faecalibacterium, Acinebacter, Veillonella and Phascolarctobacterium.

Additionally, Inoue et al. examined hepatitis C patients' gut microbiome according to the progression of their fibrosis and reported that not only in chronic hepatitis C, liver cirrhosis, HCC patients, also in HCV carriers with normal liver function (persistent normalized alanine aminotransferase, (PNALT)) as liver fibrosis advances, it becomes easier for dysbiosis to develop at a high rate because the pH of the stool rises, the number of bacterial species that make up the gut flora declines, and the occupancy rate of native bacteria in the intestinal flora falls. Streptococcus salivarius, which may break down urea in the intestinal tract to produce ammonia and raise stool pH, is abnormally increased in the intestinal flora as hepatitis C worsens [17]. LPS is significantly elevated during HCV infection, which may indicate microbial translocation and inflammation as the illness progresses.

Nevertheless, evidence indicates that treatment of HCV using ribavirin (RBV) in combination with the immune modulator pegylated interferon (PEG-IFN) does not exert a direct impact on gut dysbiosis. Actually, these medicines boost bile acid production, which is crucial for gut microbiota [18]. In patients with HCV-infected cirrhosis, several pathogenic bacteria, including Enterobacteriaceae, Staphylococcus, and Enterococcus, diminished bile acid, which restored to normal following a course of direct-acting antiviral therapy. Additionally, it was shown that oral direct-acting antivirals (DAAs) improved gut health, particularly in the Lachnospira and Dorea genera, and raised TNFα levels. Following therapy with direct-acting antivirals, patients with cirrhotic chronic HCV infection exhibited increased expression of biomarkers such as calprotectin, zonula occludens-1 (ZO1), and lipopolysaccharide (LPS). Moreover, researchers have proposed that Bifidobacterium strains alongside Lactobacillus acidophilus could function as beneficial adjunctive therapies, offering both antiviral and antibacterial effects during the management of hepatitis C virus infection. Probiotic use proved to be extremely helpful for cirrhosis patients with HCV infection [19].

Mechanisms of Interaction: Immune and Molecular Pathways. The main element of gram-negative bacteria is LPS. The CD14/TLR4/MD2 receptor complex is the functional receptor for LPS during activation. To cause liver damage it secretes a variety of pro-inflammatory cytokines, such as chemokines, IL-1, IL-6, and tumour necrosis factor-α via NF-κB signalling. Through enhancing the permeability of the intestinal mucosa, LPS diminishes the levels of critical tight junction components, including ZO-1 and occludin proteins, which in turn enables its passage into the bloodstream through the portal venous pathway. The LPS-TLR4 pathway in the liver promotes Kupffer cells, which are specialised macrophages, to release immunosuppressive mediators like IL-10, which in turn prevent Kupffer cells from releasing inflammatory mediators [20]. During viral hepatitis, this inhibits immunological responses specific to the infection, hence impeding the efficient elimination of viruses and germs. Furthermore, TLRs in the liver or colon identify hepatitis viruses and start subsequent signalling cascades. Bifidobacteria and Lactobacillus are lower in chronic HBV patients. Both have high quantities of unmethylated CpG DNA, which eventually influences the immune response to HBV and the CpG DNA-TLR9 pathway [21]. Patients with various HCV genotypes have diverse GMs. Variations in the microbial composition in genotype 1 are linked to the chronic HCV infection and not the stage of fibrosis. Therefore, further

exploration of different pathological conditions and their progression is warranted to uncover possible correlations, as existing research designs that contrast liver disease patients with healthy controls may fail to capture how the underlying illness affects the intestinal microbial community.

Only 5–10% of individuals who have an acute hepatitis B virus (HBV) infection go on to develop chronic HBV infection, whereas 90% of newborns and 30–50% of children between the ages of 1 and 5 do not completely rid their systems of HBV [22]. According to the World Health Organisation (WHO), 4.5 million people (16.7%) were diagnosed with chronic hepatitis B virus (HBV) infections in 2016, while 887,000 people died from HBV infections in 2015 [23]. Age-related differences in the ability to eliminate the HBV virus have also been linked to the gut microbiota in addition to immune system maturation. Antibiotic-induced dysbiosis makes it impossible for adult mice to eradicate the HBV virus within six weeks of infection unlike with stable gut microbiota, indicating the significance of anti-HBV action through immune system modulation via gut microbiota. Studies have documented a reduction in Bifidobacteria and other lactic acid-producing microorganisms, accompanied by an increased abundance of Enterococcus and members of the Enterobacteriaceae family, within the gut microbiota of patients suffering from chronic hepatitis B infection and HBV-associated liver cirrhosis. Wei et al. compared the gut microbiota of patients with HBV-related liver cirrhosis with healthy people and found that the former had more Proteobacteria (43 vs. 4%) and fewer Bacteroidetes (4 vs. 53%) [24].

A recent investigation assessed the composition of the gut microbiota among healthy individuals and patients with HBV-associated chronic liver disease across three clinical stages: chronic hepatitis B, liver cirrhosis (LC), and hepatocellular carcinoma (HCC). Compared to healthy people, patients with chronic hepatitis B, LC, and HCC had increased Bacteroidetes abundance and decreased Firmicutes abundance. Increase in glycan biosynthesis and metabolism-related genes were shown to be more prevalent in HBV-chronic liver disease compared to healthy persons, according to metagenomic investigation of microbial communities. According to their findings, HBV-chronic liver disease can be linked to gut dysbiosis, which manifests as a decrease in potentially beneficial bacteria (Firmicutes) or related genes and an increase in potentially dangerous bacteria (Bacteroidetes) or related genes [25]. Gram-negative bacteria's outer membrane contains lipopolysaccharides (LPS), which recognise TLRs, particularly TLR2 and 4, and promote in the activation of the innate immune response. Butyrate-producing bacteria gradually drop as a result of HBV infection. However, there is an enrichment of LPS-producing species in HBV infection. Several studied have highlighted the potential anti-inflammatory effects mediated by SCFAs produced by bacterial genera including Faecalibacterium, Pseudobutyrivibrio, Lachnoclostiridium, Ruminoclostiridium, Prevotella, Alloprevotella and Phascolarctobacterium. These microbes are associated with elevated butyrate concentrations relative to those found in healthy controls [26].

In patients with HBV-related cirrhosis, notable alterations have been observed in the abundance of Faecalibacterium prausnitzii, Enterococcus faecalis, members of the Enterobacteriaceae family, Bifidobacteria, as well as various lactic acid bacteria, including Lactobacillus, Pediococcus, Leuconostoc, and Weissella.

Furthermore, the studies highlighted the involvement of bacterial genera including Faecalibacterium, Pseudobutyrivibrio, Lachnoclostridium, Ruminoclostridium, Prevotella, Alloprevotella and Phascolarctobacterium in mediating anti-inflammatory effects through SCFA synthesis, resulting in an increased proportion of butyrate when compared with the microbiota composition observed in normal controls. A decrease in Bacteroidetes and an increase in Proteobacteria are suggested by the yellow tongue coating and dysbiosis in the oral microbiota that was seen during HBV infection [27]. Moreover, Zhao et al. (2018) reported a positive correlation between serum HBV-DNA levels and the abundance of Neisseriaceae. In contrast, Yun et al. observed no significant variation in the B/E ratio among HBsAg-positive individuals, regardless of whether their ALT levels were normal or elevated, as well as among non-cirrhotic HBV carriers. However, a pronounced decrease in the B/E ratio was detected in cirrhotic patients with chronic HBV infection [28].

Other research, however, found that the HBsAg + high ALT group had a higher abundance of the Megasphaera genus from the Firmicutes phylum than the normal ALT group. According to another study, cirrhosis patients with chronic hepatitis B infection have significantly higher levels of Enterococcus and Enterobacteriaceae and significantly lower levels of Bifidobacteria and Lactobacillus when compared to healthy people. Additionally, bacterial transloca-

tion is seen when hepatocellular carcinoma (HCC) develops [29]. Wang et al. have recently reported that, in the context of HBV-associated cirrhosis and hepatocellular carcinoma, serum zonulin serves as a biomarker reflecting intestinal barrier dysfunction and is positively correlated with serum AFP levels. They are useful in connecting it to more advanced disease stages. Patients with cirrhosis linked to hepatitis B also commonly have Candida [30].

Therapeutic Approaches. The primary goal of FMT is to introduce beneficial bacteria into the affected gut. In summary, the patient's intestinal system receives processed and injected faecal matter from a healthy family member who is fed the same food as the patient. These have few negative effects and helped the patient's gut flora return to normal [31]. FMT is linked to better survival and less severe disease than steroids in cases of severe alcoholic hepatitis (SAH).

Within the framework of the PROFIT clinical study, Woodhouse and colleagues reported that faecal microbiota transplantation conferred notable benefits on the small intestine of individuals diagnosed with liver cirrhosis. [32]. Additionally, Meiglani et al. (2020) noted that FMT treatment had a positive effect on cirrhotic individuals with antibiotic-resistant Clostridium difficile infection (CDI). Notably, the transfer of fecal microbiota from alcohol-resistant mice to alcohol-sensitive counterparts resulted in a reduction of Bacteroidetes and an increase in Actinobacteria and Firmicutes, effectively preventing the onset of steatosis [33].

Conclusion. The development of chronic viral hepatitis seen in animal-based studies and the possible involvement of intestinal overgrowth of pathogenic bacteria appear to be supported by the data in people. Viral, alcoholic, and metabolic liver disorders are all significantly influenced by gut flora. The janus kinase/signal transducer and transcription (JAK/STAT) pathway, NF-κB signalling, toll-like receptors, and CD4 + T cell activation are all significantly influenced by gut microbiota. Many beneficial microbiotas, including Ruminoclostridium, Faecalibacterium, Lachnoclostridium, Prevotella, Alloprevotella, Pseudobutyrivibrio, and Phascolarctobacterium, are important because they increase the abundance of butyrate and stimulate the anti-inflammatory short chain fatty acid (SCFA) activity, both of which are important in the treatment of different viral infections related to hepatitis. Furthermore, recent clinical trials using various therapeutic approaches have advanced our understanding of the gut-liver axis and produced promising outcomes for managing viral hepatitis.

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XÜLASƏ

BAĞIRSAQ MİKROBİOTASI VƏ VİRAL HEPATİT (İCMAL)

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Nazik bağırsaq bakteriyalarının çoxalması (SIBO) bağırsaq disbiozunun fərqli, lakin bir-biri ilə əlaqəli formasıdır və tez-tez bağırsaq mikrobiotasının müxtəlifliyində, xüsusən də xroniki qaraciyər xəstəliyi olan şəxslərdə daha geniş dəyişikliklərlə birlikdə olur. Nazik bağırsağın patogen və ya "fürsətçi" bakteriyalarla həddindən artıq kolonizasiyası bağırsaq keçiriciliyinin artmasına, endotoksemiyaya və qaraciyərin zədələnməsini gücləndirən sistemli iltihaba kömək edir. Bağırsaq və qaraciyər bir-biri ilə sıx bağlıdır və bağırsaq mikrobiotasının tərkibindəki pozuntular qaraciyərin sağlamlığına ("bağırsaq-qaraciyər oxu") əhəmiyyətli dərəcədə təsir göstərə bilər. Bu araşdırmada müəlliflər SIBO-da qaraciyərin zədələnməsinin əsas mexanizmlərini və viral hepatitin klinik şiddətinə təsir edən bu vəziyyətlə əlaqəli risk faktorlarını vurğulayırlar.

Açar sözlər: nazik bağırsaq bakteriyalarının çoxalması sindromu, xroniki qaraciyər xəstəliyi, viral hepatit, qaraciyər fibrozu, diaqnostik üsullar

РЕЗЮМЕ

МИКРОБИОТА КИШЕЧНИКА И ВИРУСНЫЙ ГЕПАТИТ (ОБЗОР)

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Избыточный бактериальный рост в тонком кишечнике (SIBO) представляет собой отдельную, но взаимосвязанную форму дисбиоза кишечника и часто сосуществует с более широкими изменениями в разнообразии кишечной микробиоты, особенно у пациентов с хроническими заболеваниями печени. Чрезмерная колонизация тонкого кишечника патогенными или условно-патогенными бактериями, способствует повышению кишечной проницаемости, эндотоксемии и системному воспалению, что усугубляет поражение печени. Кишечник и печень тесно взаимосвязаны и нарушения в составе кишечной микробиоты могут оказывать существенное влияние на здоровье печени (ось «кишечник–печень»). В данном обзоре авторы осветили все основные механизмы повреждения печени при SİBO и факторы риска, связанные с данным состоянием, влияющие на тяжесть клинического течения вирусных гепатитов.

Ключевые слова: синдром избыточноо бактериального роста, хронические заболевания печени, вирусные гепатиты, фиброз печения, методы диагностики

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