The Significance of Dysbiosis in the Gut Microbiome to HCV Infection and Disease Progression

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Abstract

With the development of science and technology, the amazing function of gut microbiota is being understood more and more each day. A person's physiological, metabolic, and even mental health are all touched by a tiny imbalance in the intestinal microbial community. It has been suggested that such microbiome dysbiosis contributes to the development of a variety of microbial infections, including bacterial, fungal, parasitic, and even viral infections. Throughout time, quite a few connections between gut microbiota and other parameters were found. The significance of the gut microbiome in hepatitis C virus (HCV) infection and disease development is the main topic of this review study. Millions of individuals are affected by HCV worldwide, which is a serious public health issue. Recent research has demonstrated that the pathophysiology of HCV infection and its associated illnesses, such as liver fibrosis, cirrhosis, and hepatocellular carcinoma, heavily depends on the status of the gut microbiome. The current state of knowledge regarding the gut microbiome and its interactions with HCV is summarized in this review, along with information on the effects of HCV on gut microbial diversity, potential mechanisms by which gut microbes affect HCV pathogenesis and the therapeutic potential of focusing on the gut microbiome in HCV-infected patients. On the contrary, it also covered how the gut microbiome can be modulated. We also talked about the shortcomings and difficulties of the current knowledge of the gut microbiota in HCV infection and proposed future research options in this area. Overall, this work highlights the significance of the gut microbiome in HCV infection and suggests that it may be a therapeutic target for HCV-related liver diseases.

Keywords: Gut microbiome, Hepatitis C, HCV Infection, Disease, Human

Significance | Impact of Gut microbiome dysbiosis in HCV infection and disease progression

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Editor Fazlul Huq, Editor-in-Chief at Journal of Angiotherapy. And accepted by the Editorial Board August 3, 2023 (received for review May 11, 2023)

Introduction

Around 71 million people are infected with the hepatitis C virus (HCV) globally, and an estimated 400,000 people die each year from liver illnesses linked to the virus (WHO, 2023; Dore et al., 2020). Although improvements in antiviral medication have altered the way that HCV infection is treated, more knowledge of the etiology must be gained to find novel therapeutic targets for HCV-related liver disorders. The development of certain liver illnesses, such as non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), and viral hepatitis, has recently been linked to the gut microbiota (Tilg and Moschen, 2014; Ma et al., 2018; Chen et al., 2022). Again, certain latest research demonstrated that gut microbiota plays an important role in HCV infection and disease development (Lavezzo et al., 2019; Yamashiro et al., 2017). These investigations revealed that HCV infection is linked to changes in the variety of gut microbes, inclu-

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Please cite this article:
Khan, S.H. (2023). The Significance of Dysbiosis in the Gut Microbiome to HCV Infection and Disease Progression. Microbial Bioactives, 6(1),

-ding a decline in helpful commensal bacteria and an increase in harmful bacteria (Zhang et al., 2013). Moreover, the gut microbiome has been implicated in HCV-associated liver fibrosis, cirrhosis, and hepatocellular carcinoma (Lavezzo et al., 2019; Yamashiro et al., 2017).

The gut microbiome is a diverse community of microorganisms in the digestive tract, crucial for maintaining health and overall well-being (Cresci & Izzo, 2019). It plays a symbiotic role in digestion, nutrient absorption, and vitamin and fatty acid synthesis. The gut microbiome also plays a critical role in immune function, metabolism, and the brain-gut axis, influencing the body's fat storage and energy extraction. Dysbiosis, or imbalances in the gut microbiome, can lead to various health conditions, such as gastrointestinal disorders, autoimmune diseases, obesity, diabetes, and mental health issues (Round and Mazmanian, 2009). Gut microbiome dysbiosis (GMD), characterized by an imbalance in the composition and function of gut microbial communities, is increasingly recognized as a significant factor in hepatitis C virus (HCV) infection and its progression to liver disease (Inoue et al., 2018). GMD in HCV patients has been associated with altered immune responses, increased liver inflammation, and enhanced fibrogenesis, highlighting the importance of the gut-liver axis in HCV pathogenesis (Jiang et al., 2019). Understanding the role of GMD in HCV infection and disease progression can provide valuable insights for the development of novel therapeutic strategies targeting the gut microbiome to improve HCV outcomes.

The goal of the current study is to present a summary of the state of knowledge on the gut microbiome's contribution to HCV infection and disease development. We will talk about how HCV infection affects the variety of gut microorganisms, the mechanisms by which gut microbes affect HCV pathogenesis and the therapeutic potential of focusing on the gut microbiome in HCV-infected patients. Additionally, the limitations and difficulties of the current knowledge of the gut microbiota in HCV infection will be emphasized, and recommendations for future research directions in this area will be made.

HCV infection and disease progression

Hepatitis C is a viral infection caused by the hepatitis C virus (HCV), primarily affecting the liver and causing both acute and chronic liver diseases. It is transmitted through contact with infected blood, sharing needles, receiving contaminated blood products, organ transplants, sexual contact, or from an infected mother to her child during childbirth (Prati et al., 2006). Acute hepatitis C is the initial phase, with most people experiencing no symptoms. However, 75% to 85% of infected individuals progress to chronic infection. Chronic hepatitis C is characterized by a long-term infection lasting over six months, causing inflammation and potential liver damage. If left untreated, chronic hepatitis C can progress to severe liver conditions like cirrhosis, liver failure, or liver cancer. Symptoms include fatigue, fever, nausea, vomiting, abdominal pain, and jaundice (Shivakrishnan and Pharm, 2019). Hepatocytes are the primary target of the single-stranded RNA virus HCV, which can cause cirrhosis of the liver, hepatocellular cancer, and chronic hepatitis (Pawlotsky, 2013).

The natural history of HCV infection is variable, with some individuals developing chronic infection, while spontaneous clearing of the virus occurs for others. Chronic HCV infection can progress over several decades and lead to cirrhosis and hepatocellular carcinoma (Hajarizadeh et al., 2013). The mechanisms underlying HCV pathogenesis are not fully understood, but they involve interactions between viral and host factors that lead to chronic inflammation, fibrosis, and liver damage (Liang and Ghany, 2013).

HCV infection is linked to severe morbidity and mortality, with an estimated 71 million people worldwide afflicted and over 400,000 deaths annually from HCV-related liver disorders (Pawlotsky, 2013). The etiology of HCV infection needs to be better understood, and there is a need to find new therapeutic targets for HCV-related liver disorders, even though DAAs are successful.

Gut microbiome: Composition and function

A complex ecosystem of bacteria in the gastrointestinal tract is called the human gut microbiome, which is essential for preserving immunological function, food metabolism, and gut homeostasis. The gut microbiome is made up of a wide variety of microbes, including bacteria, viruses, fungi, and archaea, which engage in intricate interactions with the host and one another (Cresci & Izzo, 2019). A wide variety of microbes make up the gut microbiome, with bacterial species accounting for the majority of it. Firmicutes and Bacteroidetes are the most prevalent bacterial phyla in the gut microbiome, with Actinobacteria and Proteobacteria being present in smaller numbers (Ley et al., 2006). The gut microbiome also contains a diverse array of viral, fungal, and archaeal species, although their contribution to gut microbial communities is not well understood (Minot et al., 2013).

To maintain food metabolism and gut homeostasis, gut microbiota is essential. Complex carbohydrates, such as dietary fiber, are broken down into short-chain fatty acids (SCFAs) by the gut bacteria, which serve as an important energy source for the host (Flint et al., 2012). The gut microbiome is also involved in the metabolism of amino acids and vitamins, such as B12 and K, which are important for host health (Rowland et al., 2018).

The gut microbiome is crucial in influencing the host immune system in addition to its metabolic roles. Through several processes, including the generation of immunomodulatory chemicals like lipopolysaccharides and SCFAs, which can affect immune cell activity and differentiation, the gut microbiome interacts with the host immune system (Siddiqui and Cresci,

2021). The gut microbiome is also involved in the development of immune tolerance, particularly during early life when the gut microbiome is rapidly developing (Dogra et al., 2021).

Dysbiosis of the gut microbiome, characterized by alterations in the composition and diversity of gut microbial communities, has been implicated in the pathogenesis of several diseases, including obesity, diabetes, inflammatory bowel disease, and cancer. This can also lead to chronic inflammation, which is thought to contribute to the development of these diseases (DeGruttola et al., 2016). The factors that can contribute to dysbiosis of the gut microbiome include diet, antibiotics, and lifestyle factors, such as stress and physical inactivity (Thaiss et al., 2014).

Gut Microbiome's Role in Maintaining Healthy Liver

The gut microbiota is essential for immune system regulation and maintaining general health. The synthesis of metabolites like short-chain fatty acids (SCFAs), which can affect immune cell function and control inflammatory responses, is one way that the gut microbiome regulates hepatocyte function. Inflammation and illness of the liver can result from immune cell dysregulation (Yao et al., 2022). The intestinal barrier's integrity is maintained by healthy gut flora, preventing dangerous compounds from entering the bloodstream. Hepatocyte function is also influenced by bile acid metabolism, and variations in bile acid composition affect both liver health and hepatocyte function (Liu et al., 2020).

When Toll-like receptors (TLRs) are activated in the stomach, pro-inflammatory cytokines are produced, which can have an impact on liver inflammation and hepatocyte function. Endotoxins, which are made by unfavorable gut bacteria, can cause immunological reactions and inflammation that may impair liver function (Zhang et al., 2023). Maintaining ideal hepatocyte function and general health depends on knowing these pathways.

Gut microbiome dysbiosis (GMD) in HCV infected person

It's crucial to remember that the gut microbiota is complicated, and the alterations seen in people with HCV infection may differ based on factors like the disease stage, past medical history, and other personal factors (Honda et al., 2021). In individuals with cirrhosis brought on by HCV, there is a decrease in beneficial bacteria and an increase in harmful bacteria. HCV infection has been shown to change the gut microbiome's capacity for metabolism (Hsu et al., 2022). For example, HCV-infected individuals have been found to have altered bile acid metabolism, which can affect the composition of the gut microbiome (Honda et al., 2021; Hsu et al., 2022). HCV infection has been associated with decreased microbial diversity in the gut. This means that there are fewer different types of bacteria in the gut of HCV-infected individuals compared to healthy individuals (Heidrich et al., 2018). HCV infection has been linked to an increase in the abundance of certain bacteria, such as *Enterococcus*, *Streptococcus*, and *Veillonella*. HCV infection has also been associated with a decrease in the abundance of other bacteria, such as *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium* (Milosevic et al., 2021; Sehgal et al., 2020).

During a hepatitis C virus (HCV) infection, the body produces several biochemical compounds as well as cytokines, such as interferons, in response to the viral infection (Paracha et al., 2013). These cytokines can alter the composition of the gut microbiome by promoting the growth of pathogenic bacteria and suppressing the growth of beneficial bacteria.

By changing the synthesis of antimicrobial peptides and the permeability of the gut epithelium, chemokines generated during HCV infection can also have an impact on the gut flora. Immune cells create reactive oxygen species (ROS) as a result of HCV infection. Although ROS are crucial in the fight against infections, they can also cause tissue damage and inflammation. By changing the redox balance of the gut environment, ROS can harm the development of beneficial bacteria. The release of these and other biochemical compounds during HCV infection can contribute to changes in the gut microbiome (Vernocchi et al., 2016).

Interaction between HCV and the gut microbiome

Complex and intricate interactions exist between HCV and the gut microbiota. Dysbiosis of the gut microbiome can impact HCV infection through its impact on various host functions, including the immune response and antiviral therapy efficacy. Recent years have seen a significant amount of research on the interactions between HCV and gut flora. Numerous studies have demonstrated that HCV infection can change the gut microbiome's makeup, resulting in dysbiosis and affecting a variety of host processes.

One study found that HCV-infected individuals had decreased microbial diversity and an altered microbial composition compared to healthy controls, with a decrease in Firmicutes and an increase in Proteobacteria (Ren et al., 2017). Another study showed that HCV-infected patients had higher levels of bacterial endotoxin in their blood, suggesting that HCV infection could disrupt the gut barrier and promote bacterial translocation (Compare et al., 2012).

The host's immunological response is one way in which the gut microbiota might affect HCV infection. According to studies, the host's immune response to HCV infection can be modified by the gut microbiome by fostering the growth of regulatory T cells and creating anti-inflammatory substances such as SCFAs (Szabo and Bala, 2018).

Furthermore, the gut microbiome can affect the efficacy of HCV antiviral therapy too. The ability of the gut microbiome to metabolize HCV antiviral drugs, leading to decreased drug efficacy and potential treatment failure, was reported in my studies (Wilson and Nicholson, 2009). A better understanding of the interactions between HCV and the gut microbiome will guide the adoption of novel therapeutics and alternative administration methods for improved treatment.

Influence of gut microbiome on the treatment of HCV patients

According to studies, changes in the makeup and operation of the gut microbiome may play a role in the onset and progression of liver disease linked to HCV. In patients with HCV-related liver disease, for instance, dysbiosis, or an imbalance in the gut microbiota, has been linked to increased inflammation, oxidative stress, and fibrosis (Rashid et al., 2013).

The gut microbiome may also affect the response to HCV treatment. According to a study, people who had certain gut bacteria at higher levels responded better to antiviral therapy than those with lower levels (Baktash et al., 2017). Additionally, it has been discovered that some gut bacteria create compounds that can directly stop HCV replication (Moriishi et al., 2018).

Furthermore, HCV-related liver disease itself may lead to further alterations in the gut microbiome. According to a study, people with cirrhosis brought on by HCV had less diverse gut microbes and higher concentrations of potentially harmful bacteria than healthy controls (Chen et al., 2011). Another study discovered that certain good gut flora were less prevalent in individuals with HCV-related cirrhosis (Bajaj et al., 2014).

In general, there are complicated and potentially reciprocal interactions between the gut microbiome and liver illness caused by HCV. More research is needed to fully understand the mechanisms at work and to develop potential therapies that target the gut microbiota to improve outcomes in individuals with HCV-related liver disease.

Modulation of the gut microbiome in HCV infection

Recent research has revealed that modulating the gut microbiota may offer a possible therapeutic option for the treatment of hepatitis C virus (HCV) infection.

One approach to modulating the gut microbiome in HCV infection is the use of probiotics, which are live microorganisms that can confer health benefits on the host. Several studies have shown that probiotics can improve liver function and reduce liver inflammation in patients with HCV infection (Nanis et al., 2019; Fakruddin et al., 2022). Additionally, probiotics have been demonstrated to alter the gut microbiome in people with HCV infection by boosting the population of helpful bacteria while decreasing the number of potentially dangerous bacteria (Sultan et al., 2020).

Another approach to modulating the gut microbiome in HCV infection is the use of prebiotics, which are dietary fibers that are not digested and can specifically promote the development and activity of good bacteria in the gut. Studies have shown that prebiotics can improve liver function and reduce liver inflammation in patients with HCV infection (Chauhan et al., 2021). Prebiotics are non-digestible food components that stimulate the growth and activity of beneficial bacteria in the gut microbiome. The modulation mechanism involves selective fermentation, increased beneficial bacteria, short-chain fatty acid production, pH reduction, cross-feeding effects, and enhanced gut barrier function. Prebiotics help maintain gut health by promoting the growth of beneficial bacteria and reducing inflammation. The pH reduction helps inhibit harmful bacterial growth, while cross-feeding effects support the growth of beneficial bacteria (Saeed et al., 2022). A diverse and balanced diet with prebiotic-rich foods is recommended to promote a healthy gut microbiome. Consulting a healthcare professional or registered dietitian for personalized advice is essential for optimal gut microbiome health.

Another method of modifying the gut microbiome in HCV infection is fecal microbiota transplantation (FMT). Fecal microbiota transplantation (FMT) is a medical procedure that involves implanting the gastrointestinal tract of a recipient with a fecal microbiome from a healthy donor that contains a diverse community of microorganisms. This procedure should be carried out under controlled circumstances by medical professionals (Quaranta et al., 2019; Kelly et al., 2015). Modulation of the gut microbiome and the restoration of a balanced and healthy microbial community are the main objectives. FMT entails many crucial phases, including microbial diversity restoration, the transfer of advantageous bacteria, an increase in metabolic capacity, the production of short-chain fatty acids (SCFAs), the encouragement of competition and colonization resistance, and immune system modulation. To completely comprehend its long-term effects and potential hazards, more research is required. FMT is still not a standard of care for maintaining good gut health and is largely utilized for certain medical causes, such as recurrent Clostridium difficile infections. Although there is limited research on the use of FMT in HCV-infected people, a recent case report revealed that FMT may be useful in treating patients with cirrhosis due to HCV by enhancing liver function.

As a whole, the findings point to modification of the gut microbiome as a potentially effective therapeutic approach to treating HCV infection. However, further research is required to better understand how the gut microbiota affects HCV infection and to identify the most effective strategies for doing so.

Influence of microbiome therapy on the HCV infected Persons

Microbiome therapy, which involves the use of probiotics, prebiotics, or fecal microbiota transplantation (FMT), has been studied for its potential to impact HCV infection (Preveden et al., 2017; Aly et al., 2016; Sadiq et al., 2021). Probiotics are live bacteria that are intended to have a beneficial effect on the gut microbiome. Several studies have investigated the potential of probiotics to reduce inflammation, improve liver function, and impact HCV viral load. While some studies have reported a potential benefit, others have found no significant effect (Lopez-Santamarina et al., 2021; Nanis et al., 2019). The gut microbiome may impact the outcome and progression of HCV infection, including liver inflammation, bile acid metabolism, immune response modulation, and treatment response. A well-balanced gut microbiome can help regulate the immune response,

potentially affecting the course of HCV infection and the outcome of antiviral therapy. However, the field of microbiome therapy, particularly in HCV, is still evolving, and more research is needed to establish the safety, effectiveness, and mechanisms of action of these therapies. Patients should follow their healthcare provider's guidance regarding appropriate treatments and management strategies until more data is available (Kelly et al., 2015; Ma et al., 2017). Overall, more research is needed to fully understand the potential benefits of microbiome therapy for HCV infection. However, given the important role of the gut microbiome in immune function and overall health, it is an area of interest for further study. It is important to note that microbiome therapy should only be considered under the supervision of a healthcare provider, as there can be risks associated with these interventions.

Future approaches for using the gut microbiota to treat HCV infections

Despite the expanding volume of evidence on the involvement of the gut microbiota in HCV infection and disease development, there are numerous gaps in our understanding. One of the major limitations is the lack of standardized and comprehensive methodologies for microbiome investigation, which makes comparing results across studies challenging (Schulze et al., 2020). Furthermore, more large-scale, long-term research is needed to show causal links between the gut microbiome and HCV-related outcomes (Iebba et al., 2019). Moreover, the precise pathways by which the gut microbiota influences HCV infection and disease progression remain largely unknown and require further investigation (Rizzetto et al., 2021). Finally, more research is needed to determine the optimal strategies for manipulating the gut microbiome to improve HCV treatment outcomes (Ferrere and Loomba, 2020).

Future research on the importance of gut microbiota in HCV infection and disease progression may focus on several areas. First, there is a need for more studies investigating the causality and mechanisms underlying the associations between gut microbiome dysbiosis and HCV-related liver disease, including cirrhosis and hepatocellular carcinoma (Sharpton, 2020; Ponziani et al., 2017). Second, further research is needed to investigate the effects of antiviral therapy on the gut microbiota and whether modulating the gut microbiome can improve antiviral therapy efficacy and tolerability (Malaguarnera et al., 2014). Third, the role of probiotics and prebiotics in HCV treatment should be investigated further in larger-scale randomized controlled studies with a longer follow-up time (Lozupone et al., 2012). Fourth, future research might look into the impact of diet and lifestyle factors on altering the gut microbiota in HCV infection, as well as how tailored nutrition and lifestyle interventions can improve the gut microbiome and HCV-related outcomes (Li et al., 2020). Finally, more studies should be conducted on the gut-brain-liver axis, the potential involvement of the gut microbiota in modulating central nervous system function, and the etiology of HCV-related neurocognitive problems.

Conclusions

Finally, the gut microbiota is important for HCV infection and disease progression. Changes in gut microbiota composition and function have been linked to HCV replication, liver inflammation, fibrosis, cirrhosis, and potentially HCC formation. Modification of the gut microbiota via diverse techniques such as antiviral medication, probiotics, prebiotics, and dietary and lifestyle changes may provide new therapeutic targets for controlling HCV infection and its associated liver disorders. Despite tremendous advances in understanding the relationships between gut microbiota and HCV, many gaps in knowledge and study remain, emphasizing the need for additional research in this area. Future research into the underlying processes of these interactions, as well as the development of tailored microbiome-based therapeutics, has the potential to alter the treatment of HCV infection and its consequences.

Author Contributions

Khan wrote, drafted, reviewed & edited the manuscript.

Acknowledgment

None

Competing financial interests

The author has no conflict of interest.

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