Viral Liver Disease and Intestinal Gut–Liver Axis

Subjects: Gastroenterology & Hepatology

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The intestinal microbiota is closely related to liver diseases via the intestinal barrier and bile secretion to the gut. Impairment of the barrier can translocate microbes or their components to the liver where they can contribute to liver damage and fibrosis.

gut–liver axis intestinal barrier chronic viral hepatitis microbiota dysbiosis

1. Introduction

A connection between the intestine and the liver was already postulated approximately two thousand years ago when the Greek-Roman doctor Galen suggested a connection between the gut and the liver [1].

In modern medicine, the clustering of microorganisms living in the same environment has been defined as microbiota, while the term microbiome applies to the collective genomes of the microbes [2][3].Microbiota are composed of bacteria, archaea, protozoans, fungi, and viruses [4]. Interestingly, every human being has their unique composition of gut microbiota properly defined as the “microbial fingerprint” [5].

The bacterial component of the microbiota is classified into 12 different phyla and 93.5% of the total belongs to *Proteobacteria*, the Gram positive *Firmicutes*, *Actinobacteria*, and the Gram negative *Bacteroidetes*. *Bacteroides* and *Prevotella* are the main genera of *Bacteriodetes*. *Clostridium*, *Blautia*, *Enterococcus*, *Faecalibacterium*, *Eubacterium*, *Roseburium*, *Ruminococcus*, *Streptococcus*, and *Lactobacillus* are the most prevalent genera of *Firmicutes*. *Actinobacteria* include *Bifidobacteria*, *Atopobium,* and *Collinsella*, while *Proteobacteria* are mainly composed of *Enterobacteriaceae* such as *Escherichia* and *Klebsiella. Akkermansia muciniphila* is the only species of *Verrucomicrobia* found in the human gut [6][7][8]. *Archaea* are predominated by *Methanobrevibacter* species. Viruses and bacteriophages are also colonizing the gut in considerable quantities [9].

Firmicutes and *Actinobacteria* predominate among luminal bacteria populations, while *Proteobacteria* are abundant among mucosal populations [10]. Early in the life of humans, there is a restricted diversity of the microbiota which is mostly composed of *Actinobacteria* and *Proteobacteria*. Diversity and variability are increasing with age and the species of *Bacteroides*, *Clostridium*, and *Escherichia coli* predominate in the intestinal flora in individuals over 65 years of age [11][12][13]. The gut microbiome is also variable among different ethnic groups [14][15][16] and between rural and urbanized populations of the same ethnicity [15][16][17][18]. Microbiota also differ between countries and continents [14][15][19].

Fungal species are also found in the gut including *Candida*, *Saccharomyces*, *Aspergillus*, *Penicillium*, *Rhodotorula*, *Trametes*, *Pleospora*, *Sclerotinia*, *Bullera*, and *Galactomyces* [20].

The human intestinal microbiota is now considered as a significant superorganism [21], colonized by approximately one-hundred trillion bacteria comprising nearly 40,000 types of microbes [22][23][24][25] most of which cannot be cultured, and 200–300 fungal species [26][27][28]. Microbial cells in the body are 10- to 100-fold higher than human cells [29][30]. In all, the microbiota weights approximately 1–2 kg in the adult, while the genetic material exceeds that of the human by about 100 times indicating its significance in human homeostasis [31][32].

There are several pathways of communication between microbes and the human host. This is achieved through different microbial components and products such as lipopolysaccharides (LPS), bacterial DNA, flagellin, short-chain fatty acids (SCFAs), tryptophan (Trp), and secondary bile acids (BAs) [33]. All these are recognized by pattern recognition receptors, mainly the Toll-like receptors (TLRs) family.

2. HBV Infection and Intestinal Microbiota

There are approximately 296 million people with chronic HBV infection worldwide, while 887,000 people die each year from complications of chronic HBV infection [34][35].

2.1. HBV and Intestinal Dysbiosis

HBV infection may be associated with intestinal dysbiosis [36] as demonstrated from animal experiments and clinical data. Thus, the ratio of *Bacteroidetes* and *Firmicutes* was stable in control mice, but it was significantly different in mice with HBV infection. Interestingly, differences were observed in *Lactobacillus* and *Bifidobacterium* between acute or chronic HBV infection [37]. In another experiment, decreased *Blautia* and *Clostridium* in HBV-infected mice were negatively correlated and increased *Butyricicoccus,* and *Prevotellaceae* were positively correlated with HBsAg and HBeAg levels. On the contrary, *Akkermansia*, which is considered a gut barrier protector, was reduced in HBV mice and was negatively correlated with HBV DNA in both serum and the liver [38].

Extensive changes in the gut microbiota composition have been reported in patients with chronic HBV infection [39][40]. Decreased genera of bacteria that metabolize bile acids have been described in association with changes in serum and fecal bile acids in chronic hepatitis B (CHB) patients with moderate/advanced fibrosis. *Bacteroides* and *Ruminococcus* were significantly lower in CHB patients compared to healthy controls. It was proposed that CHB fibrosis was in fact a modifier of the intestinal microbiota. Fibrosis limited the conversion of primary to secondary bile acids, activating the FXR and subsequently the FGF19 [41][42].

Microbiota changes already occur in early stage CHB patients. Operational taxonomic units (OTUs) belonging to *Actinomyces*, *Clostridium*, *Lachnospiraceae*, and *Megamonas* increased, while several OTUs decreased, including those belonging to *Alistipes*, *Asaccharobacter*, *Bacteroides*, and *Butyricimonas* [39]. The gut microbiota is also variable according to viral load. HBV patients with a low viral load have high diversity and taxa associated with fatty

acid and lipid metabolism predominate [43]. LPS produced by Gram-negative intestinal bacteria was related to liver inflammation and cirrhosis. LPS levels were an independent predictor towards end-stage liver disease in patients with HBV infection [44]. Controversial results on the composition of microbiota have been reported. There was no difference in the intestinal microbiome between chronic HBV patients with normal ALT and normal volunteers. *Megasphaera* showed positive correlations, and *Acidaminococcus* exhibited a negative correlation with high ALT levels [45]. However, in another report, abundance of *Lactobacillus*, *Clostridium*, and *Bifidobacterium* were reduced in CHB patients with normal ALT compared to healthy controls [42]. In acute on chronic liver failure associated with HBV infection, the microbiota was enriched with *Moraxellaceae*, *Sulfurovum*, *Comamonas,* and *Burkholderiaceae,* but *Actinobacteria*, *Deinococcus-Thermus*, *Alphaproteobacteria*, *Xanthomonadaceae,* and *Enterobacteriaceae* were significantly reduced. Moreover, an increase of *Prevotellaceae* was a predictor of mortality [46].

In recent extensive studies, patients with all stages of HBV–related liver disease were examined and compared to healthy people. *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Actinobacteria*, *Verrucomicrobia*, *Cyanobacteria*, and *Fusobacteria* accounted for almost 100% of the total sequences. Decreased *Firmicutes* and increased *Bacteroidetes* were found in all disease groups (Chronic Hepatitis, cirrhosis, Hepatocellular carcinoma) compared to healthy controls. *Bifidobacterium* and butyrate-producing bacteria families such as *Clostridia* and *Ruminococcus* were also decreased in all disease groups [47], but no difference was observed among patients with resolved HBV infection [47][48]. These findings may have pathogenetic implications as *Bacteroidetes* are Gram-negative bacteria which produce LPS, while *Firmicutes* are Gram-positive bacteria without LPS synthesis. Therefore, the higher *Bacteroidetes/Firmicutes* ratio means increased burden of LPS to the liver cells and increased liver damage [49]. On the other hand, the *Enterobacteriaceae* family bacteria comprising many pathogenic bacteria such as *Klebsiella*, *Escherichia coli*, *Proteus*, and *Enterobacter* were increased in all HBV groups [47][50]. The *Enterobacteriaceae* family were also increased in liver cirrhosis and were positively correlated to Child–Pugh (CP) score [51][52]. In detail, a negative correlation was found between the CP score and *Bacteroidetes*, while a positive correlation was demonstrated between CP score and *Enterobacteriaceae* or *Veillonella* [53]. Apart from increased LPS secretion, the *Enterobacteriaceae* produce endogenous ethanol that may be detrimental to the liver [54]. In addition, high *Enterobacteriaceae* release endotoxin that may cause inhibition of enterocyte protein synthesis leading to increased intestinal barrier permeability with further bacterial translocation to the liver [55]. In fact, two studies reported on barrier permeability in CHB patients. In the first, serum zonulin and copeptin were reduced in CHB patients and were negatively correlated with serum HBV DNA [56]. This was in disagreement with another study where serum zonulin was higher in HBV-related HCC, but no difference was observed in patients with CHB, cirrhosis or healthy controls [57].

A repeatedly confirmed finding of gut dysbiosis during progression of chronic HBV is the decrease of SCFAs-producing bacteria, such as *Lachnospiraceae* and *Ruminococcaceae* and their replacement by LPS-producing bacteria such as *Enterobacteriaceae*, *Haemophilus*, and *Enterococcus* [36][58]. The microbiota of HBV carriers contains more SCFA producers and less pro-inflammatory bacteria than patients with CHB, cirrhosis, and acute-on-chronic liver failure or hepatocellular carcinoma [59][60]. Another consistent finding of dysbiosis in HBV patients is that *Bifidobacteria* decrease with the increase of *Enterobacteriaceae* as the disease progresses. The ratio of

Bifidobacteria/Enterobacteriaceae is reduced as disease severity progresses from CHB to cirrhosis and HCC [39][47][55][61].

Microbiota changes are difficult to be studied in human acute HBV. Results from animal studies have shown that the ratio of *Firmicutes/Bacteroides* increased early in the disease at day 14, and decreased in late disease at day 49 [37].

The above controversial reports indicate that interpretation and comparisons of results should be done with great caution as many studies are performed in populations with particular diet habits which influence the composition of the intestinal microbiome. Moreover, most studies are cross-sectional with samples representing an individual time point, and only a few were performed at different periods of HBV infection [36][59][62].

Detailed descriptions of the microbiome in the different stages of HBV infection have been recently published [63][64][65][66].

2.2. Microbiota and Immune Responses in HBV

Microbiota affects the immune response in HBV. Apart from the effects that LPS has on the immunological response through the activation of TLR4, an additional pathway is implicated in the immune response of patients with HBV. The unmethylated CpG DNA-TLR9 pathway can activate TLR9 that produces protective cytokines, such as Interferons. Unmethylated CpG DNAs is mainly produced by *Lactobacilli*, *Bifidobacteria*, *Proteobacteria*, and *Bacteroidetes* [67]. As mentioned above, *Lactobacillus* and *Bifidobacteria* are reduced in the gut microbiota of chronic HBV patients. Therefore, beneficial cytokines are reduced and the immune effects are defective in HBV [68][69].

Gut microbiota is implicated in the clearance of the HBV infection. When the gut microbiota is deregulated by antibiotics, the intestinal barrier function is probably impaired and the ability of immunity to clear HBV may be compromised [70]. Thus, adult mice with an intact intestinal microbiota clear HBV after 6 weeks of infection, while infection is not cleared in young mice or after antibiotic use [71][72]. Young mice with a TLR4 mutation achieved prompt HBV clearance. It therefore seems that a TLR4-dependent pathway of tolerance is operative in young animals and prevents HBV clearance. Development of intestinal microbiota stimulated the immune mechanisms and HBV clearance was feasible [73]. Additionally, impairment of intestinal microbiota was shown to affect the systemic adaptive immunity leading to delayed HBV antigen clearance. Gene analysis of Peyer's patches (PPs) demonstrated that adaptive immunity was downregulated in intestinal microbiota-deficient mice, while the depletion of PPs led to higher HBsAg levels in serum [74]. Dysbiosis in mice and the resulting endotoxemia induced IL-10 production by the Kupffer cells and increased Kupffer cell-mediated T cell suppression. The immediate result was the protracted persistence of HBV infection [75]. However, in a mouse model of CHB, intestinal bacteria reduction by antibiotics had no effect on HBV replication in immune tolerant mice [76].

The immune response in HBV infection is also regulated by metabolic products produced by intestinal microbes, such as tryptophan, which interferes with the immune response of HBV through its metabolic product kynurenine

[77]. Indoleamine-2,3-dioxygenase (IDO) is an enzyme induced by interferon that catalyzes tryptophan into kynurenine [78] acting as a suppressor of intracellular pathogens and as an immune regulator [79]. Inducible IDO was shown to suppress HBV replication in HepG2 cells with the HBV genome [80]. The effect of IDO in HBV clearance was investigated in HBV infected patients. In acute hepatitis patients who finally cleared the virus, IDO activity was high at the peak of ALT. In patients with hepatic flare, on the other hand, IDO activity remained low irrespective of ALT levels indicating that IDO is an anti-HBV factor only during the early phase of HBV infection [81].

Integrated studies of microbiome and metabolome showed an extensive shift of intestinal microbiota and metabolites in chronic HBV patients attributed to either disease evolution and/or antiviral treatment. Peripheral mononuclear cells incubated with bacterial extracts (BE) from non-cirrhotic patients promoted the expansion of Th17 lymphocytes, while BE from cirrhotics reduced Th1 cell count [82]. This is a particularly important findings that may explain some of the findings during liver fibrogenesis. Th17 immunity is an important factor in all stages of fibrogenesis in chronic HBV patients [83] including hepatic stellate cell activation [84][85], increased TGF-β production [86], the secretion of matrix metalloproteases (MMPs), and collagen synthesis [84][86].

2.3. Microbiota and HBV Treatment

Based on the above findings, it was only logical to suggest that manipulation of the microbiome might be beneficial for the evolution of HBV. Fecal microbiota transplantation (FMT) was tested, but the data are still restricted [87][88]. In an interesting experiment, the gut microbiome in BALB/c mice was abolished by antibiotics and replaced with FMT from naïve mice to investigate the effect of FMT on the immune response to HBV infection. HBV clearance differed considerably depending on the origin of FMT. The fecal microbiota from C57BL/6 but not from BALB/c mice induced tolerance and prolonged HBV infection [89].

Gut microbiota changes, induced via FMT, resulted in promising results in HBeAg-positive patients. A study on HBeAg-positive CHB patients under treatment with oral antivirals showed that FMT induces HBeAg clearance in some cases who had failed to clear HBeAg despite long-term antiviral treatment. The problem with this study is that only five patients were studied in the FMT group [90]. In a similarly designed recent larger study of 14 patients in the FMT arm, 16.7% of patients cleared and none in the antiviral only arm. It should be noted, however, that all patients retained the HBsAg in either arm. However, after six months, serum HBV DNA was reduced in the FMT arm but not in the controls [91].

An informative review on all aspects of FMT has been recently published [87].

The effects of oral antiviral treatment on gut microbiota have also been examined in HBV. In a persistent HBV mouse model, *Akkermansia* was significantly reduced in HBV-infected mice, while Entecavir therapy restored levels back to those of the normal controls. *Akkermansia* levels showed a negative correlation with HBV DNA levels in serum and liver [38]. On the contrary, *Akkermansia* was increased in patients with CHB and liver cirrhosis [47]. Therefore, additional studies are required on the actual role of *Akkermansia* in HBV. In the treatment of naïve

patients, *E. hallii* group and *Blautia* were greatly reduced and were restored to normal levels after 5 years of entecavir treatment. *Turicibacter* with 4-hydroxyretinoic acid were negatively associated with AST [82][92].

The manipulation of intestinal microbiota with probiotics (Clostridium and Bifidobacterium) was tested in the treatment of minimal hepatic encephalopathy (MHE) in patients with HBV cirrhosis. Probiotics improved serum ALT and AST and albumin levels. Absolute fecal bacterial load of genera *Fecal Clostridia* and *Bifidobacteria* were increased, and *Enterobacteriaceae* were decreased. More importantly probiotics improved psychometric tests and cognition. Ammonia levels were reduced possibly due to the observed improvement of the intestinal microflora [93]. A recent study administered a mixture of lactulose, *Clostridium butyricum*, and *Bifidobacterium longum infantis* in a population of patients with HBV-related cirrhosis. The clinical response was insignificant, but intestinal dysbiosis and the metabolome of the patients improved compared to patients treated with placebo [94]. Obviously, more extensive studies are required, particularly when the above expressed reservations are considered.

3. HCV Infection and Intestinal Microbiota

Globally, approximately 58.5 million people are infected with HCV worldwide, while 1.75 million new cases are identified each year. Hepatocellular carcinoma (HCV-related) causes approximately 150,000 deaths and more than 350,000 deaths are HCV-related other complications. These figures are probably an underestimation of the real problem [95].

Gut microbiota has been connected to the various stages of HCV infection. A common finding of all studies performed so far is the lower bacterial diversity in HCV patients compared to healthy controls [51][96][97][98]. Diversity abnormalities are proportional to the stage of the disease [97]. Two hypotheses have been proposed that can explain how HCV infection can interfere with the gut–liver axis and the progression to fibrosis and cirrhosis. The first is that the gut microbiota is indirectly affected as a result of the liver damage. This is not compatible with changes in microbiota observed in early disease. The second hypothesis proposes a direct effect of HCV infection on B-lymphocytes and the consequent reduction of IgA production [96][99]. Reduced IgA secretion favors the abundance of *Prevotella*. *Prevotella* contains enzymes that may degrade mucin and increases the intestinal permeability leading to higher bacterial translocation [8]. A further indication of an impaired intestinal barrier in HCV-infected patients is also the finding of increased serum LPS levels [97][100].

Impairment of BAs metabolism is an additional explanation for the reduced microbial diversity in HCV. BAs profiles are different in chronic HCV compared with normal people. Fecal deoxycholic acid (DCA) was decreased and lithocholic or ursodeoxycholic acid predominated. The decrease in fecal DCA reduction was associated with *Clostridiales* reduction, while impaired synthesis of cholic acid (CA) was associated with a reduction in the transcription of CYP8B1, a key enzyme in CA synthesis [101]. This BAs disturbance results from overgrowth of pro-inflammatory bacteria, such as *Porphyromonadaceae*, *Enterobacteriaceae*, and reduction of *Firmicutes* the main producers of secondary bile acids [51][102][103][104].

The lower bacterial diversity is also associated with a reduction of the SCFAs producing *Clostridiales*, *Lachnospiraceae*, *Ruminococcaceae*, and an increase in *Streptococcus* and *Lactobacillus*, *Prevotella* and *Faecaliberium* [99][102]. SCFAs are critical for the differentiation of bowel regulatory T (Treg) cells that are the main suppressors of inflammation [105][106] as mentioned before. Apart from *Clostridiales*, the phylum of *Firmicutes* is also decreased in patients with chronic CHC. By contrast, the phylum of *Bacterioidetes,* the family of *Enterobacteriaceae*, *Viridans streptococci*, and the genera *Bacteroides*, *Blautia*, and *Collinsella*, are increased [88] [107]. A recent study also demonstrated a decreased diversity and found that *Lactic acid bacteria*, and *Lactobacillus acidophilus* were higher in early stage of fibrosis compared to patients with advanced fibrosis [108].

Low diversity is already evident even in patients with normal transaminases and minimal disease with a transient increase in *Bacteroides* and *Enterobacteriaceae.* Metagenomics have shown an increase in the urease gene encoded by *viridans streptococci* that may account for the hyperammonemia present in the later stages of the disease [104]. Similarly, bacterial translocation due to intestinal barrier dysfunction was reported in the absence of fibrosis, indicating that impairment of the gut barrier occurs even at the early stages of chronic HCV [44][109].

In contrast to all other reports, a recent study showed an increased microbiota diversity in patients with HCV infection compared to healthy individuals. A higher abundance of *Prevotella*, *Collinsella*, *Faecalibacterium*, *Megasphera*, *Mitsuokella multacida*, and *Ruminococcaceae*, and a lower abundance of *Bacteroides*, *Alistipes*, *Streptococcus*, and *Enterobacteriaceae* was observed. Possible explanations for the discrepancy may be the stages of disease analyzed, the effect of HCV genotypes, and, most importantly, the demographic characteristics of the study groups [110].

An important finding was recently reported. The use of Proton pump inhibitors (PPIs) was related to significant alterations of the microbiota in patients with chronic HCV infection which were more pronounced in patients with liver cirrhosis. *Streptococcus* species, *Enterobacter* species, and *Haemophilus* species were significantly increased in patients with PPI use irrespective of the stage of liver disease [111].

Detailed descriptions of microbiota alterations in the different stages of progressive severity have been recently published [112][113].

Effect of HCV Treatment on Intestinal Microbiota

The initial treatment of HCV infection with interferon showed that the microbes before and after treatment were not different [114].

The use of effective direct acting antivirals (DAAS) in the HCV elimination prompted a series of studies of the potential effects of treatment on intestinal bacteria. The use of DAAs in patients with chronic HCV infection could only rectify the intestinal bacterial abnormalities only in with initial degrees of fibrosis [115]. A later study verified these results. Bacterial diversity was restored in patients without cirrhosis after sustained viral response (SVR) within 24 weeks after the end of treatment. No diversity improvement was found in SVR patients with cirrhosis. The abundances of *Collinsella* and *Bifidobacter* genera were increased between baseline and SVR only in non-cirrhotic

patients [116]. However, in patients with genotypes 1,2,3 4 treated with glecaprevir/pibrentasvir, no significant differences in microbiota diversity, or microbial pattern were found before and after treatment at week 12 [117]. The same negative results were also very recently reported [118]. Two further reports also produced negative results. No significant alterations in the overall composition of gut microbiome or alpha diversity were observed after viral eradication. Some differences in abundance of certain bacteria, such as *Coriobacteriaceae*, *Peptostreptococcaceae*, *Staphylococcaceae*, and *Morganellaceae*, were identified but the overall compositions was not different after HCV eradication [119]. The diversity of the gut microbiota did not significantly alter before and after DAAs, even though the relative abundances of *Faecalibacterium* and *Bacillus* increased after eradication [120]. The reason for this discrepancy is not clear but the question is open to more detailed and larger studies.

The impact of DAAs on intestinal microbiota when cirrhosis is present also remains controversial as both favorable and negative studies have appeared and will be presented in the relevant section below [102][114].

Sustained viral response (SVR) seems to be a decisive factor, as alleviation of intestinal dysbiosis and microbial translocation were observed in responders but not in non-responders. Viral elimination increased the abundance of SCFAs-producing bacteria such as *Blautia* and *Bifidobacterium* [121]. However, successful response to DAAs eradication did not affect the intestinal barrier function. It is therefore likely that bacterial translocation is connected to abnormal composition of gut microbiota rather than to gut barrier dysfunction after DAAs therapy [102][121]. These reports are not consistent with findings demonstrating that microbial translocation markers, such as the lipopolysaccharide binding protein (LBP), were reduced after HCV elimination [122].

An interesting approach for restoration of gut dysbiosis is the use of Bacteriophages. In reality, phages are viruses that attack and eliminate bacteria [123]. The gut dysbiosis observed in HCV could potentially be corrected by using bacteriophages that target the chronic HCV associated bacteria [124], but this remains to be tested.

The current evidence on the effects of the gut microbiota in the evolution of HCV infection and the impact of DAAs elimination has been recently reviewed [31].

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