Significance of gut microbiota in alcoholic and non-alcoholic fatty liver diseases

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Abstract
Liver-gut communication is vital in fatty liver diseases, and gut microbes are the key regulators in maintaining liver homeostasis. Chronic alcohol abuse and persistent overnutrition create dysbiosis in gut ecology, which can contribute to fatty liver disease. In this review, we discuss the gut microbial compositional changes that occur in alcoholic and nonalcoholic fatty liver diseases and how this gut microbial dysbiosis and its metabolic products are involved in fatty liver disease pathophysiology. We also summarize the new approaches related to gut microbes that might help in the diagnosis and treatment of fatty liver disease.

Key Words: Fatty liver disease; Alcoholic fatty liver disease; Non-alcoholic fatty liver disease; Gut microbiome; Dysbiosis

Core Tip: In this review, we compare the gut microbial composition in two different fatty liver diseases: Alcoholic fatty liver and nonalcoholic fatty liver. This review enables readers to recognize the gut microbiota compositional differences that occur in these two histopathologically analogous conditions and to explore these gut microbial compositional variations in their research. Additionally, this review will also be helpful in the design of new experiments aiming to develop new diagnostic and/or therapeutic methodologies.

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INTRODUCTION

Significant increases in mortality and morbidity due to chronic fatty liver disease have raised great global health concerns. Alcoholic fatty liver disease (AFLD) and nonalcoholic fatty liver disease (NAFLD) are the most common chronic fatty liver illnesses in the Western world, with prevalences of 6% and 25%, respectively[1], and are the leading causes of liver transplantation[2,3]. Both AFLD and NAFLD start with fat accumulation in the liver, known as benign or simple steatosis, which leads to inflammation identified as steatohepatitis. Advanced disease includes fibrosis and cirrhosis, which can lead to a more severe state, including hepatocellular carcinoma and liver failure, and ultimately can cause death. Only 20% of patients with AFLD and NAFLD develop progressive liver disease[4,5]. In addition to fat accumulation, increased inflammation, and alcohol consumption, other causes, such as an altered gut microbial composition, gut microbial metabolites, or gut barrier function, are associated with the exacerbation of chronic liver disease[6,7].

The recent increase in the understanding of the microbiota and its metabolites has changed the perspectives of various chronic diseases[8]. The human gut microbiota represents a complex ecosystem with various species of microbes that are approximately 1-2 kg in weight in total[9,10]. The gut microbiota maintains homeostasis by interacting with the host and has important functions, including metabolism, digestion, vitamin production, mucosal immune reaction, and the translocation of microbial-associated molecular patterns[11-14]. Importantly, the gut microbiota is known to have a significant role in liver disease progression, but the associated mechanisms are still not fully established.

The liver is the first organ exposed to gut microbial metabolites through portal vein blood. Therefore, the gut microbial community has a vital role in liver homeostasis, and dysbiosis in gut microbial ecology can produce microbial metabolites and components that can have a direct impact on the liver[15-19]. Similarly, the liver also influences gut microbial ecology, particularly in the intestine, through primary bile acids[20-22]. In this way, the liver and gut share a close bidirectional relationship. Interestingly, fecal microbiota transplantation (FMT) studies showed a proof of concept in alcohol-associated and metabolic disease generation and establishment[19,23,24].

Although AFLD and NAFLD have similar histopathological characteristics, they have different etiologies[25]. Thus, gut microbial composition in AFLD and NAFLD could have some commonalities as well as dissimilarities at various classification levels[16,26]. These gut microbial compositional similarities in AFLD and NAFLD could help not only establish common pathophysiological pathways but also increase the chance of finding common treatments. Conversely, gut microbial compositional variations in AFLD and NAFLD could be helpful for the development of specific disease-based signatural gut microbiota profiles. Additionally, these disease-specific gut microbiota profiles could be valuable for the design of gut-microbiota-based therapies such as probiotics[27], synbiotics[28], postbiotics[29] and/or FMT[30] to ameliorate liver disease. These microbial therapeutics also could provide access for developing personalized patient-based treatments to restore liver functions in AFLD and/or NAFLD. AFLD and/or NAFLD-specific gut microbiota profiles could also be useful in the future as diagnostic biomarker tools for the early diagnosis of these diseases.

Considering the importance of the disease-specific gut microbial signature in AFLD and/or NAFLD, herein, we review the gut microbial compositions related to AFLD and/or NAFLD development, especially focusing on the relationship of these compositions with the progression of both diseases, particularly in humans. We also explicitly focus on the microbial signature pertaining to AFLD and/or NAFLD and common microbes in both fatty liver conditions. This review also helps in the understanding of the deep association between the gut microbiota and fatty liver diseases, which can also be considered microbiota-associated fatty liver diseases.

GUT MICROBIAL COMMUNITY EUBIOSIS

The gut microbiota is an endogenous ecosystem that coevolves with the host as a symbiotic organ and regulates the normal physiological functions of the gut, such as food digestion and nutrient absorption, and provides essential micronutrients to the host[31]. The gut microbial ecosystem maintains a balance between the microbial species living inside the gut known as “eubiosis” that is crucial for good health.
Microbial colonization in the gastrointestinal tract starts immediately after birth and is dominated by the Bifidobacterium genus, and a decline in this dominance is observed in the first year of life[32]. The infant gut microbiota is changeable, as this microbial colonization is affected by multiple external factors, such as the mode of delivery, medications, nourishment[33,34], age, genetic background, and cultural/geographic influence[32,35,36]. Similarly, breastfed infants have a less diverse gut microbiota than formula-fed infants, which is the best possible explanation for the difference in gut microbiomial composition between United States infants and non-United States infants, as United States infants have 28 operational taxonomic units dominated by the Prevotella genus[32]. As children start consuming solid foods, the gut microbiota becomes more diverse and starts stabilizing[32,35,37,38]. Fecal samples collected from different geographical regions showed that the gut microbiota composition took shape toward an adult-like configuration until 3 years of age[32], after which the gut composition became more persistent[39].

Primarily, the Firmicutes and Bacteroidetes phyla dominated the adult human gut microbial composition, and Actinobacteria, Proteobacteria and Verrucomicrobia were found in lesser abundance. Fecal metagenomic analysis from 4 different countries identified well-classified robust gut microbial communities, named enterotypes, represented through multiple numbers of 3 genera: Prevotella, Ruminococcus and Bacteroides[40], and this classification of enterotype was independent of nationality, age, body mass index (BMI), and sex. However, this enterotype-based classification remains a topic of debate because external factors such as diet are considered primary regulators of gut microbiota composition and functions[41,42] and fail to be identified in healthy and elderly individuals[43]. In addition to diet, aging is also a considerable factor that changes the gut microbiota composition. Bacteria belonging to the Bacteroidaceae, Lachnospiraceae and Ruminococcaceae families are negatively correlated with aging independent of geographical region, lifestyle, and dietary habits[44-46].

Moreover, healthy aging showed increased microbial richness and higher numbers of Bifidobacterium, Oscillospira, Akkermansia, and Christensenellaceae[15]. Emerging metagenomic empirical evidence suggests that a healthier gut always has a more diverse microbiota population and that a healthy gut is essential to maintain human health[47, 48].

GUT MICROBIAL COMMUNITY DYSBIOSIS

A change or alteration in gut microbial composition, which can be related to diseased conditions, is termed “dysbiosis”[49]. Gut microbiota composition varies from birth to death[50] and is influenced by various environmental factors[31-34]. Gut microbial dysbiosis also has a close connection with AFLD and NAFLD.

Gut microbiota alteration in AFLD

Persistent high intake of ethanol is the root cause of AFLD[55], as it disrupts the multilayered intestinal defense system involving physical, immunological, and humoral components[36]. Normally, the liver enzyme alcohol dehydrogenase and the ethanol-oxidizing system convert ethanol to acetaldehyde, which is toxic to hepatic cells. Acetaldehyde is immediately metabolized to acetate, released into the bloodstream, and used as a biological fuel by cells for energy production. In a persistently elevated ethanol consumption state, the accumulation of toxic acetaldehyde is increased in the liver, which leads to the production of highly reactive molecules that generate an oxidative stress milieu and contribute to liver injuries[16]. An increase in the flow of ethanol in the liver alters SIRT1 signaling and initiates fat accumulation in hepatocytes[57]. Ethanol reduces SIRT1 expression in the liver, which leads to the fat accumulation in liver cells by disrupting multiple SIRT1-dependent transcription factors and cofactors, such as peroxisome proliferator-activated receptor α, PPARγ coactivator-1α, AMP-activated kinase, lipin-1, β-catenin, forkhead transcription factor O1, sterol regulatory element-binding protein 1, nuclear factor activated T cells c4, and nuclear transcription factor-xB[57-59]. Ethanol facilitates the inhibition of SIRT1, which leads to various signaling network disruptions that increase the accumulation of fat in hepatocytes by decreasing β-oxidation and lipolysis, boosting lipogenesis and inflammation, and collectively leading to AFLD. Recently, human and animal models suggested that even a small intake of alcohol can harm intestinal barrier integrity and raise microbial byproduct levels in the circulation[60,61]. Moreover, there is adequate experimental evidence proving that the interrelationship between alterations in the intestinal microbiota and alcohol abuse and acute and
chronic alcohol exposure is primarily responsible for gut microbiota dysbiosis and can lead to AFLD through various pathways, as shown in Figure 1[62]. Animal model-based studies explain that alcohol-induced microbial dysbiosis in the intestine changes homeostasis in the gut-liver axis and that this altered intestinal microbiota plays a crucial role as a mediator in the production of the many negative effects of alcohol.

Animal studies have shown that 3 weeks of alcohol exposure causes a ‘leaky gut’, which increases the number of Bacteroidetes and Verrucomicrobia and decreases the growth of bacteria with anti-inflammatory activity, such as Firmicutes (genera such as Lactobacillus, Lactococcus, Leuconostoc and Pediococcus), in the cecum[63]. Another rodent alcohol-based model showed that changes in intestinal permeability associated with intestinal microbial alterations are related to the decreased expression of hypoxia-induced factor 1α. These studies showed a relative increase in Actinobacteria and Proteobacteria and a decline in the Firmicutes phylum. Moreover, these changes were restored by treatment with probiotic Lactobacillus rhamnosus (L. rhamnosus) GG therapy[64-67].

Interestingly, gnotobiotic animals have become an imperative alcoholic model to explore the relationship between the gut and the liver. A comparative study of gnotobiotic and wild-type rats showed less proinflammatory cytokine release and inflammation in gnotobiotic rats than in wild-type rats when treated with alcohol for one week. Moreover, fecal transplantation from alcohol-fed wild-type rats in gnotobiotic animals increased hepatic and intestinal inflammation, indicating the involvement of the intestinal microbiota in AFLD[68]. Chronic alcohol intake also changes the intestinal mucus composition, and mucin knockout animals have less bacterial overgrowth, minimal translocation of the bacteria and reduced intestinal inflammation when administered alcohol[69]. In other studies, the bacterial species Akkermansia muciniphila (A. muciniphila) from the Verrucomicrobia phylum showed potential anti-inflammatory properties in AFLD[70], and the depletion of A. muciniphila species was noticed in alcoholic animal models[71,72]. A. muciniphila improves intestinal markers such as gut barrier function and mucus thickness and diminishes the liver damage produced by alcohol[73]. Cumulatively, animal studies strongly indicate that alcohol intake considerably changes the intestinal microbial composition (as shown in Table 1), which can be responsible for producing early-onset AFLD by inducing proinflammatory changes, translocating the bacteria and bacterial material by reducing mucus thickness and increasing intestinal permeability.

Likewise, human studies also support the close association between alcohol intake and intestinal microbial dysbiosis in the onset of AFLD, similar to animal models. Prolonged alcohol intake markedly decreases the Bacteroidetes population and increases Proteobacteria, which leads to compromised intestinal permeability and an increase in the level of bacterial materials such as lipopolysaccharides (LPS) and endotoxins in the hepatic circulation and ultimately causes liver injuries[74]. The families Ruminococcaceae and Lachnospiraceae and their ratio are considered to be protective, whereas Enterobacteriaceae to Bacteroidaceae and their ratio are believed to be potential pathobionts in the intestine, especially in those with a liver disease with an alcoholic etiology. Therefore, the overgrowth of potentially pathogenic species in the gut in chronic alcohol abuse conditions is related to the initiation of liver injuries[74-76]. The effect of these microbial alterations in the gut is not yet completely understood. However, the administration of L. rhamnosus GG improves the Lachnospiraceae population and limits the growth of Enterobacteriaceae, which leads to a decline in proinflammatory cytokines[77]. A reduction in A. muciniphila was observed in patients with alcoholic steatohepatitis compared with healthy controls, and this decline in A. muciniphila seems to be related to the severity of liver injuries[73]. Additionally, A. muciniphila was considered a health-boosting bacterial species along with Bifidobacterium spp., Roseburia hominis, and Faecalibacterium prausnitzii[78]. However, human and animal empirical data hinted that alcohol-induced gut microbial dysbiosis, especially ethanol consumption, but that some alcoholic beverages, such as red wine, could exert a positive impact on gut microbial ecology. A human crossover study demonstrated that red wine consumption increased the number of Bacteroides, Enterococcus, and Bifidobacterium[79].

Alterations in the gut microbiota due to persistent alcoholic intake are not restricted to bacterial species; the fungal composition also changes. Remarkably, alcoholic liver disease (ALD) patients have a high risk of bacterial infection, and patients with advanced cirrhosis are more prone to fungal infections. Moreover, fungal infections increased the mortality rate in cirrhosis and alcoholic hepatitis patients[80-82]. In an alcoholic murine model, increased fungal growth, particularly Candida spp., was observed and was related to an increase in liver damage[83]. The study results showed that liver inflammation was induced by β-glucan, which is a fungal cell wall component. β-Glucan binds with Kupffer cell C-type lectin-like receptor and

| Table 1 |
|---------|
| Family  | Percentage | Effect |
| Ruminococcaceae | 5.2% | Protective |
| Lachnospiraceae | 12.3% | Protective |
| Enterobacteriaceae | 7.6% | Potential pathobionts |
| Bacteroidaceae | 48.7% | |
| Firmicutes | 17.4% | |
| Proteobacteria | 11.8% | |
| Actinobacteria | 2.5% | |
| Verrucomicrobia | 0.6% | |

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| Ref.             | Sequencing method | Overgrown microbes                          | Depleted microbes                          | Model   |
|------------------|-------------------|---------------------------------------------|--------------------------------------------|---------|
| Yan et al[63] (2011) | Pyrosequencing    | ↑Bacteroidales                              | ↓Lactococcus                               | Murine  |
|                  |                   | ↑Bacteroides                                | ↓Pediococcus                               |         |
|                  |                   | ↑Porphyromonadaceae                         | ↓Lactobacillus                             |         |
|                  |                   | ↓Leuconostoc                                |                                            |         |
| Otterson et al[64] (2013) | Pyrosequencing    | ↑Corinebacterium                            | ↓Bacteroides                               | Murine  |
|                  |                   | ↑Alcaligenes                                | ↓Tannarella                                |         |
|                  |                   | ↑Listeria                                   | ↓unclassified Lachnospiraceae              |         |
|                  |                   | ↑Acetivibrio                                | ↓undefined Ruminococcaceae                 |         |
|                  |                   | ↑Allobaculum                                |                                            |         |
| Lowe et al[71] (2017) | 16S rDNA         | ↑Actinobacteria                             | ↓Tenericutes                               | Murine  |
|                  |                   | ↑Eubacteriaceae                             | ↓Verrucomicrobiace                         |         |
|                  |                   | ↑Eubacteriace                               | ↓Lachnospiraceae                           |         |
|                  |                   | ↓Moraxellace                               | ↓Akkrermansia                              |         |
| Grander et al[73] (2018) | Illumina MiSeq   | ↑Olsenella                                 | ↓Acinetobacter                             | Murine  |
|                  |                   | ↑Eubacteriace                               | ↓Anaerotruncus                             |         |
|                  |                   | ↑Activibrio                                 | ↓Akkrermansia                              |         |
|                  |                   |                                            |                                            |         |
| Kakiyama et al[74] (2013) | Pyrosequencing   | ↑Enterobacteriace                           | ↓Blastia                                   | Human   |
|                  |                   | ↑Villonellace                               |                                            |         |
|                  |                   |                                            | ↓Ruminococcaceae                           |         |
|                  |                   |                                            | ↓Lachnospiraceae                           |         |
|                  |                   |                                            | ↓Rikenellace                               |         |
| Bajaj et al[75] (2014) | Pyrosequencing   | ↑Enterococcae                              | ↓Clostridiales XIV                         | Human   |
|                  |                   | ↑Staphylococcae                             |                                            |         |
|                  |                   | ↑Enterobacteriace                           |                                            |         |
|                  |                   |                                            | ↓Lachnospiraceae                           |         |
| Yang et al[83] (2017) | Illumina MiSeq   | ↑Candida spp.                              | ↓Epiconocum                                | Human   |
|                  |                   | ↑Candida albicans                           |                                            |         |
|                  |                   | ↑Candida dubliniensis                       |                                            |         |
| Ferrere et al[144] (2017) | Illumina MiSeq   | ↑Actinobacteria                             | ↓Bacteroidetes                             | Murine  |
|                  |                   | ↑Firmicutes                                 |                                            |         |
|                  |                   | ↑Coriobacteriace                            |                                            |         |
|                  |                   | ↑Omotrivibacteriace                         |                                            |         |
|                  |                   | ↑Clostridiales                              |                                            |         |
|                  |                   | ↑Dorea                                      |                                            |         |
| Wang et al[145] (2019) | Illumina MiSeq   | ↑Verrucomicrobiace                          | ↓Bacteroidetes                             | Monkey  |
|                  |                   | ↑Proteobacteria                             |                                            |         |
|                  |                   | ↑Optitutus                                  |                                            |         |
|                  |                   | ↑Biotryps                                   |                                            |         |
|                  |                   | ↑Sporothrix                                 |                                            |         |
|                  |                   |                                            |                                            |         |
|                  |                   |                                            |                                            |         |
|                  |                   |                                            |                                            |         |
Figure 1 Gut microbiota role in alcoholic fatty liver disease and non-alcoholic fatty liver disease pathogenesis. Intestinal microbes have the potential relationship with fatty liver disease progression. Regular intake of alcohol and overnutrition altered the gut microbial composition which influence the various pathways and induce the liver injuries and produce the alcoholic fatty liver disease (AFLD) and non-alcoholic fatty liver disease (NAFLD). There are some common pathways found in both AFLD and NAFLD diseases (in the purple box) and others are specifically related to a particular disease. AFLD: Alcoholic fatty liver disease; NAFLD: Non-alcoholic fatty liver disease; HDED: High dense energy diet; SCFA: Short chain fatty acids; IgA: Immunoglobulin A; IL22: Interleukin 22; Reg3g: Regenerating islet-derived protein 3 gamma; C4: Precursor 7a-hydroxy-4-cholesten-3-one; FGF19: Fibroblast growth factor 19; PAA: Phenylacetic acid; TMAO: Trimethylamine N-oxide.

upregulates IL-1β. Similarly, ALD patients also showed an increased immune response to intestinal fungi compared to healthy controls. These findings suggest that the composition of nonbacterial gut microbes, such fungi, can also affect AFLD generation, progression, and final outcomes in patients with AFLD.

**Gut microbiota alterations in NAFLD**

The gut microbiota exacerbates and/or alleviates NAFLD conditions through several pathways (Figure 1). Animal and human studies have presented a causal involvement of the gut microbiota in NAFLD establishment [84-86] and its severity [87-89]; however, a robust correlation between the gut microbiota and NAFLD advancement has not yet been established. Differences in gut microbial composition at various hierarchical
levels have been recorded in NAFLD patients compared with healthy controls[30,91]. In NAFLD, alterations in the gut microbial community have been shown to start at the phylum level, where increased Proteobacteria have been reported in many studies[90,92,93]. Likewise, altered composition has also been observed at the family level, where an overgrowth of Enterobacteriaceae[84,92] and suppression of Rikenellaceae[84,94] and Ruminococcaceae[91,92,95] have been reported. Moreover, genera such as Escherichia[84,90], Doreae[94,95], and Peptostreptococcus[84,94] were overpopulated, and Anaeroplasma[91], Coprococcus[84,90,91], Eubacterium[84,90], Faecalibacterium[84] and Prevotella[90,96] were less populated. In a comparative study, Wang et al.[91] showed a higher proportion of gram-negative bacteria, including Bacteroidetes, and decreased Firmicutes in NAFLD patients when the gut microbiota was compared with lean healthy subjects. The decline in Firmicutes is associated with short-chain fatty acid (SCFA)-producing bacteria such as Lactobacillaceae, Lachnospiraceae, and Ruminococcaceae. An overgrowth of gram-negative bacterial species was seen in children with NAFLD, with an increased ratio of Gammaproteobacteria and Epsilonproteobacteria compared to their obese and lean counterparts[97]. In contrast, bacteria from the Firmicutes phylum (such as Lactobacillus, Roseburia, Dorea, and Robinsonella) were found to be increased in the population of NAFLD patients in another study[95]. However, contradictory results were reported in other studies that showed increases in Dorea and Ruminococcus in NAFLD patients[94,98]. Variability in gut microbial composition was observed with different levels of NAFLD severity. Bacteria belonging to Firmicutes were more dominant in moderate NAFLD, while the prevalence of Proteobacteria was noted to be associated with the severity of disease, as in fibrosis[93]. The bacterial species that were dominant in mild NAFLD compared to severe NAFLD conditions were Eubacterium rectale and Ruminococcus obeum[95]. These human study results reflect the conflicting gut microbiota composition in NAFLD, which needs to be evaluated further by implementing a greater number of NAFLD patient-based gut microbial compositional studies.

The gut microbial composition was also assessed in severe NAFLD conditions such as fibrosis and/or in nonalcoholic steatohepatitis (NASH) to examine the functional role of gut microbial dysbiosis in fibrosis progression. The results of these comparative studies exhibited a decline in gram-negative bacterial abundance. Comparative analysis of the gut microbiota between individuals with severe NAFLD and healthy or less severe NAFLD conditions showed a decrease in the Fusobacteria phylum population and an increase in Enterobacteriaceae family bacteria such as the genera Shigella, Ruminococcus and Bacteroides[92,96]. Similarly, gram-positive bacteria from the Firmicutes phylum, the family Prevotellaceae and the genus Prevotella also showed increases in severe NAFLD conditions[93]. Recently, a study presented a significant alteration based on fibrosis severity in nonobese patients but not in obese patients, where Ruminococcaceae and Veillonellaceae were the leading microbes related to fibrosis severity in nonobese subjects[99]. Interestingly, oral microbes, including Streptococcus [76,100,101], Veillonellae[91,100], and Prevotella[100,102], are discriminatory microbes for advanced NAFLD conditions (especially cirrhosis). Additionally, some microbe representations were constant in NAFLD patients compared with healthy individuals, but some showed conflicting tendencies[103]. Conclusively, microbial composition in NAFLD patients presented a drastic shift in taxonomic group composition by showing an increased ratio of pathogenic microbes and a decline in microbes that are considered metabolically beneficial microbes. Subsequently, this compositional shift in microbial composition might be responsible for NAFLD pathogenesis and exacerbate the severity of the disease from simple steatosis to NASH and from NASH to cirrhosis. Summarized information on gut microbial dysbiosis in NAFLD is listed in Table 2, which provides details regarding the increased and decreased populations of bacteria in NAFLD.

The gut microbiota composition in NAFLD presented a considerable contradiction, where some microbial taxa showed variability in their occurrence, as shown in Table 2. The underlying reasoning behind these contradictory compositional variabilities might be related to study design, clinical study end points, result interpretation, etc. Moreover, these underlying reasons could be fundamental restraints in the process of establishing a robust relationship between the gut and NAFLD. Thus, to determine the pathophysiological association between the gut and liver, these fundamental limitations should be resolved.
Table 2 Representative studies presenting gut microbial dysbiosis in non-alcoholic fatty liver disease

| Ref.         | Sequencing method | Overgrown microbes | Depleted microbes | Model         |
|--------------|-------------------|--------------------|-------------------|---------------|
| Michail et al[97] (2015) | Ion torrent         | ↑Actinobacteria    | ↓Erysipelotrichia | Human         |
|              |                    | ↑Prevotella        | ↓Alphaproteobacteria |               |
|              |                    | ↑Clostridia        | ↓Verrucomicrobia  |               |
|              |                    | ↑Fusobacteria      |                   |               |
|              |                    | ↑Epsilonproteobacteria |              |               |
|              |                    | ↑Gammaproteobacteria |               |               |
| Wang et al[91] (2016) | Pyrosequencing   | ↑Bacteroidaceae  | ↓Lachnospiraceae | Human         |
|              |                    | ↑Prevotellaceae    | ↓Ruminococcaceae |               |
|              |                    | ↑Clostridia        | ↓Lactobacillaceae |               |
| Raman et al[95] (2013) | Pyrosequencing | ↑Alpha-proteobacteria | ↓Ruminococcaceae | Human         |
|              |                    | ↑Lactobacillaceae  | ↓Oscillibacter    |               |
|              |                    | ↑Lachnospiraceae   | ↓Porphyromonadaceae |           |
|              |                    | ↑Veillonellaceae   |                   |               |
| Chierico et al[94] (2017) | Pyrosequencing | ↑Actinobacteria   | ↓Bacteroidetes    | Human         |
|              |                    | ↑Bradyrhizobium    | ↓Oscillipira      |               |
|              |                    | ↑Anaerococcus      | ↓Rikenellaceae    |               |
|              |                    | ↑Peptostreptococcus |               |               |
|              |                    | ↑Propionibacterium acnes |           |               |
|              |                    | ↑Doros             |                   |               |
|              |                    | ↑Ruminococcus      |                   |               |
| Hoyles et al[90] (2018) | Shotgun       | ↑Proteobacteria   | ↓Firmicutes       | Human         |
|              |                    | ↑Actinobacteria    | ↓Euryarchaeota    |               |
|              |                    | ↑Verrucomicrobia   |                   |               |
| Shen et al[92] (2017) | 16S rDNA        | ↑Proteobacteria    | ↓Bacteroidetes    | Human         |
|              |                    | ↑Fusobacteria      | ↓Prevotellaceae   |               |
|              |                    | ↑Lachnospiraceae   | ↓Ruminococcaceae  |               |
|              |                    | ↑Enterobacteriaceae| ↓Prevotella       |               |
|              |                    | ↑Erysipelotrichaceae |               |               |
|              |                    | ↑Streptococcaceae  |                   |               |
|              |                    | ↑Escherichia Stieglitz |             |               |
| Zhu et al[84] (2013) | Pyrosequencing   | ↑Bacteroidetes     | ↓Actinobacteria   | Human         |
|              |                    | ↑Proteobacteria    | ↓Bifidobacteriaceae |            |
|              |                    | ↑Alcaligenace      | ↓Clostridales family XI |            |
|              |                    | ↑Campylobacteriaceae |               |               |
|              |                    | ↑Enterobacteriaceae |               |               |
| Chierico et al[94] (2017) | Pyrosequencing | ↑Coriobacteriaceae | ↓Porphyromonadaceae | Human         |
|              |                    | ↑Bacteroidiaceae   | ↓Rikenellaceae    |               |
| Minicis et al[147] (2014) | Pyrosequencing | ↑Firmicutes | ↓Bacteroidetes | Murine         |
|              |                    | ↑Actinobacteriaceae |               |               |
| Lee et al[148] (2020) | 16S rDNA        | ↑Firmicutes        | ↓Bacteroidetes    | Murine         |
|              |                    | ↑Deferribacteriaceae |               |               |
|              |                    | ↑Lactobacillus murinus |             |               |
GUT ROLE IN FATTY LIVER

Trillions of microorganisms reside in the gut, including bacteria, archaea, fungi, and viruses, but liver-disease-related research primarily targets the bacterial community, which includes more than 10 bacterial phyla[104,105]. The gut microbiota includes more than 3 million genes collectively, in comparison to the 23000 genes of the human genome; however, human cells and gut bacterial cells are roughly equal in number [106]. This gut microbial genetic material certainly has a defining role in human pathophysiology through multiple mechanisms, especially in liver disease, due to its close relationship with the gut[6,107,108].

Gut microbial dysbiosis
Generally, the gut microbiota starts to be shaped at birth and becomes stable in early childhood. This balanced and stable gut microbiota acquires a unique quotient for each microbial species in a healthy state[38]. As discussed above, gut microbial dysbiosis, defined by diminished microbial diversity and distorted gut microbial composition, is observed in both AFLD and NAFLD patients compared to healthy controls[18,103]. Alcohol abuse and overnutrition deplete several bacterial species and shift the microbial composition toward gram-negative bacteria. Microbial species depleted in liver diseases are considered beneficial microbes, and overgrown microbial species are associated with liver pathophysiology and known as pathobionts[109]. Alcohol consumption is linked with diminished fungal diversity generated by an increased number of Candida species[83,110,111]. Moreover, gut viruses are the most abundant gut microbes; nonetheless, they have not yet been characterized in liver disease.

This gut compositional proclivity toward gram-negative bacterial species influences multiple pathways directly or indirectly that contribute to AFLD and NAFLD establishment[16,91,92]. The distorted gut microbiota alters various metabolic processes, such as bile acids, short-chain fatty acids, and energy harvesting, which leads to the initiation of fatty liver disease[112]. The distorted gut microbiota also damages gut barrier function, through which microbes and their metabolites can translocate and activate the inflammasome in the liver and cause fatty liver[112]. The detailed role of the gut microbiota in fatty liver pathogenesis is presented in Figure 1.

Leaky gut syndrome
In the intestine, there are multiple layers of barriers, including physical, biochemical, and immunological barriers, that restrict the translocation of microbes and their products. Chronic alcohol abuse causes gut barrier dysfunction by altering the gut microbial composition[113]. Thus, pathogen-associated molecular patterns, such as LPS, are able to translocate from the lumen of the intestine to the liver via the portal vein and are recognized by inflammasomes such as Toll-like receptors in the liver to stimulate hepatic inflammation, which leads to hepatocyte injuries and liver fibrosis [112]. Likewise, similar pathophysiological pathways are involved in NAFLD progression, but gut disruption and inflammation are stimulated by dietary factors other than alcohol[112]. Other types of inflammasomes, including NOD-like receptor protein 3 (NLRP3), also respond to LPS and cause liver inflammation. The activation of NLRP3 triggers the caspase 1 pathway and produces interleukin-1β and several other inflammatory cytokines, which cause apoptosis and fibrosis. Higher levels of inflammasomes such NLRP3 and others were found in severe fatty liver conditions induced by both alcohol and overnutrition[114,115]. The translocation of the microbial metabolites from the intestine to the liver because of the dysfunction of intestinal barriers and increased intestinal permeability could be the contributing factor for AFLD and NAFLD, but more studies are required to establish robust associations.

Bile acid dysregulation
Bile acid synthesis and secretion are essential functions performed by liver cells. Importantly, bile acids not only are crucial for dietary fat emulsification but also act as ligands for nuclear and G-protein coupled receptors and regulate various metabolic functions, including glucose and fat metabolism[116]. Therefore, smooth regulation of bile acids is important for maintaining a healthy metabolic profile, but gut microbial
dysbiosis is associated with bile acid dysregulation and is associated with fatty liver pathogenesis through metabolites[117].

Normally, conjugated bile acids are released from hepatocytes, carried by the biliary duct, and secreted into the intestine. After lipid emulsification, the remaining bile acids (primary, hydrophilic, and conjugated) are reabsorbed in the terminal ileum. Bile acid secretion from hepatocytes is primarily regulated by the farnesoid X receptor (FXR) negative feedback mechanism[118]. The release of primary bile acids in the intestine activates intestinal FXR, which precedes the transcription of fibroblast growth factor 19 (FGF19). The ileal hormone FGF19 is carried to the liver via the portal vein, where FGF19 suppresses CYP7A1 expression and controls bile acid secretion[119]. The disruption of bile acid homeostasis is the leading cause of fatty liver[119-121].

The change in the gut microbial composition induced by alcohol abuse and a high intake of energy-dense food cause the dysregulation of the bile acid system and instigate fatty liver diseases (AFLD and NAFLD)[122,123]. In AFLD and NAFLD, pathobionts increased in number and were responsible for the conversion of secondary bile acids from primary bile acids and reduced FXR signaling. This downregulation of FXR expression increased insulin resistance and altered glucose and lipid metabolism, which are the key regulatory pathways in AFLD and NAFLD generation. Moreover, AFLD and NAFLD patients showed higher levels of secondary bile acids than primary bile acids in feces and blood. Similarly, the dysregulation of FXR signaling and FGF19 is increased with the severity of the disease in both AFLD and NAFLD[124-127]. These outcomes suggest that FXR and bile acid compositional dysregulation are the metabolic features of AFLD and NAFLD and that the dysregulation of both metabolic factors (FXR and bile acids) increases with the severity of AFLD and NAFLD.

Although gut bacteria control bile acid metabolism, the involvement of intestinal bacteria or other gut microbes (including archaea, fungi, and viruses) in bile acid dysregulation in fatty liver patients is not completely understood, and more experimental evidence is required to fill the fundamental gaps.

**Short-chain fatty acid dysregulation**

Nondigestible carbohydrates in food are fermented by gut bacteria, and SCFAs are produced. Butyrate, acetate, and propionate are the most abundant SCFAs found in the intestine. SCFAs have many beneficial effects, including being used as an energy source by colonocytes and enterocytes, maintaining gut barrier function, suppressing hepatic cell proliferation, reducing inflammation, and lowering food intake by increasing satiety[128]. Considering the beneficial function of SCFAs in regulating metabolic pathways, their level in the body is crucial to maintain good health.

Chronic alcohol abuse is related to reduced SCFA levels in the stool[129]. The SCFA concentration and SCFA-producing bacterial concentration are decreased in the feces of alcoholic hepatitis patients[109]. The low circulatory butyrate level is also associated with serum endotoxin, inflammation, and more advanced liver diseases[130]. In contrast, a higher level of SCFAs and an increased number of SCFA-producing bacteria were found in NASH patients; however, the study population was small[131]. Additionally, increasing levels of SCFAs are related to immune regulation and NAFLD progression[131]. Higher fecal concentrations of propionate and butyrate were observed in mild to severe NAFLD patients, whereas higher fecal concentrations of acetate and formate were found in advanced fibrosis patients[132,133]. There is an insufficient amount of empirical proof to establish a concrete relationship between SCFAs and fatty liver diseases, and more studies are required to determine the association between SCFAs and fatty liver diseases.

**Endogenous ethanol production**

Microbial fermentation of dietary sugar increases the endogenous alcohol level in pediatric NASH patients[84]. Recently, a Klebsiella pneumonia strain was identified in a NASH patient fecal sample and was responsible for producing endogenous ethanol and increasing the blood ethanol level without alcohol consumption[134]. FMT from NASH patients to animals results in liver damage, and the elimination of alcohol-producing Klebsiella pneumoniae strains reduces liver damage. Additionally, NASH patient weight reduction was also related to a reduced ability to produce ethanol in the gut microbiome[134]. Another study focusing on comparing the gut microbial profile in pediatric NAFLD patients showed higher circulatory ethanol levels in diseased patients, which was related to the higher number of Prevotella and Gammaproteobacteria[97]. The results from another study showed that a higher circulatory level of ethanol in NAFLD patients could be the end result of ethanol dehydrogenase activity in insulin-dependent impairment conditions[135]. Thus, gut
microbial dysbiosis, which can lead to an increasing level of endogenous ethanol in the body, could be an underlying cause of NAFLD and could be responsible for producing the same histopathological characteristics as AFLD. However, some inconsistencies in the results were observed, and establishing an association between this endogenous ethanol phenomenon and NAFLD generation needs more experimental proof[16,136,137].

**Gut microbial virulence factors**

Virulence factors are microbial proteins and peptides that help pathobionts colonize and are associated with disease generation. A recent study recognized that cytolysin, a protein secreted (exotoxin) by *E. faecalis*, damages hepatocytes and is highly associated with increased mortality in alcoholic hepatitis patients[18,138]. Unfortunately, few studies have shown any further toxins or other proteins related to gut microbiota that can be associated with liver disease.

**FUTURE PERSPECTIVES**

Fatty liver disease (both AFLD and NAFLD) is intricately linked with the gut microbiota and its dysbiosis. Recent advancements in gut microbiome-based metagenomics studies related to liver disease have shown that an increase in and/or depletion of the specific microbial content could contribute greatly to liver injuries and is possibly the key regulator in fatty liver disease establishment and progression[112]. Growing evidence regarding the role of the gut microbiota in fatty liver disease generation and progression turns this noncommunicable disease into a communicable disease[139]. Therefore, targeting the gut microbiota through various techniques may be an approach for the management of liver disease in the future.

**Prognostic and/or diagnostic biomarkers**

As discussed above, the microbial composition in fatty liver diseases is different from that in healthy individuals. Gut microbes themselves or their microbial metabolites might be useful as prognostic and/or diagnostic tools for the early detection of fatty liver conditions. Generally, constant alcohol intake of more than 60 g per day leads to alcoholic hepatic steatosis, which also presents with higher levels of liver enzymes, such aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and in NAFLD, daily alcohol intake is approximately 30 g per day. Typically, two to three times higher serum AST levels have been observed compared to serum ALT due to alcoholic liver injuries. Patients with AFLD also have higher serum gamma-glutamyl-transpeptidase levels[140]. Similarly, NAFLD also has noninvasive biomarker detection protocols, such as the NAFLD fibrosis score (including age, BMI, the AST-to-ALT ratio, impaired fasting glucose and diabetes, albumin and platelets), FIB-4 index (including age, ALT, AST, and platelets), and FibroTest (including total bilirubin, α2-macroglobulin, γ-glutamyl transferase, haptoglobin, and apolipoprotein A1 corrected for sex and age)[141]. These are the common diagnostic parameters used for AFLD and NAFLD diagnosis. However, there is a lack of conclusive biomarkers that can help in the early diagnosis of hepatic steatosis, and the repertoire of gut microbes and their metabolite profiles might help to fill this gap. Interestingly, a set of gut bacteria combined with age and BMI was used to identify liver disease, and a much more accurate diagnosis was able to be made with its use in patients with advanced fibrosis [93]. The gut microbes used as a marker in this study were first identified from NAFLD and advanced fibrosis patients via metagenomics analysis and then further used for diagnostic purposes[93]. In a separate study, the combination of metagenomic signature microbes with age and serum albumin levels precisely identified cirrhosis in patients with geographically different origins. Additionally, adding serum aspartate aminotransferase levels to these diagnostic tools increased diagnostic efficacy even in the early stage of fibrosis[142]. In other studies, gut-microbe-derived metabolites showed great potential as diagnostic markers for fatty liver diseases and other liver conditions[18,90,143].

Although gut microbes and their metabolites have the potential to be noninvasive prognostic and/or diagnostic tools for fatty liver and other liver diseases, larger population-based studies are still required to eliminate constraints related to geographical factors, ethnicity, and dietary factors. Further studies are also warranted to compare the diagnostic ability of gut microbes and their metabolites with contemporary in-use investigative practices such as biopsy and image-based approaches.
CONCLUSION

Gut microbiota is crucial in fatty liver diseases (in both AFLD and NAFLD), thus relevance of fatty liver disease specific gut microbial signatures should be further explored in longitudinal human studies. Where, a team of clinician and researchers can prospectively correlate the deterioration of liver with the alteration in the gut microbiota community. Merging fatty liver disease specific gut microbiota with microbial derived metabolites can be helpful in the future to diagnose and treat the AFLD and NAFLD patients.

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