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Role of Gut-Liver Axis in Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Non-alcoholic fatty liver disease has emerged as a significant global health problem, mainly due to the increasing prevalence of obesity and metabolic syndrome. The gut microbiota plays an essential role in the development of NAFLD through the gut-liver axis. Dysbiosis of the GM is associated with the pathogenesis of NAFLD. Dietary choices and other lifestyle factors influence the composition of the GM and contribute to the development of NAFLD. At the phylum level, individuals with NAFLD show an increased level in *Actinobacteria* and *Firmicutes*, while Verrucomicrobia, Thermus, Proteobacteria, Lentiphaerae, and Fusobacteria are found to be decreased. Several genera, including *Faecalibacterium* and *Akkermansia*, exhibit alterations in NAFLD and are linked to disease progression. Modulating the GM through prebiotics, probiotics, or fecal microbiota transplantation represents a promising therapeutic strategy for NAFLD. This review summarizes the current understanding of GM changes in NAFLD, focusing on findings from both human and animal studies.
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Keywords: Dysbiosis, Gastrointestinal microbiome, Microbiota, Non-alcoholic fatty liver disease

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INTRODUCTION

Non-alcoholic fatty liver disease is a highly prevalent hepatic disorder globally[1]. While the manifestations of NAFLD closely resemble those of alcoholic fatty liver disease, hepatic steatosis in NAFLD is not attributed to excessive alcohol consumption[2]. NAFLD is characterized by at least 5% liver steatosis without evidence of liver damage, such as ballooning hepatocytes. In contrast, non-alcoholic steatohepatitis is defined by at least 5% hepatic steatosis accompanied by inflammation and hepatic injury (ballooning hepatocytes), which may include fibrosis. The pathophysiology of NAFLD involves both micro- and macrovascular fat accumulation with varying degrees of inflammation. Chronic inflammation can disrupt hepatic homeostasis and activate restoration processes.

HSCs secrete extracellular matrices, such as collagen-1, to support the damaged regions. This process results in the formation of scaffold structures that facilitate cellular proliferation, contributing to liver fibrosis,

List of Abbreviations:
A. muciniphila: *Akkermansia muciniphila*; ***E. coli***: *Escherichia coli*; ***F. prausnitzii***: *Faecalibacterium prausnitzii*; **FMT:** fecal microbiota transplantation; **GM:** gut microbiota; **HFD:** high-fat diet; **HSC:** hepatic stellate cell; **NAFLD:** non-alcoholic fatty liver disease; **NASH:** non-alcoholic steatohepatitis; **SCFA:** short-chain fatty acid

whereas necrotic tissue is cleared through leukocyte infiltration[3]. This 'wound-healing' process typically ends once HSCs become inactive and the extracellular matrix is degraded, allowing normal liver architecture to be restored. This behavior makes the harmful effects of fibrosis temporary if liver is not ongoing[4]. As a result, the harmful effects of fibrosis are temporary, provided that liver injury does not persist. Hence, hepatic fibrosis is considered a beneficial, coordinated response to liver injury; however, chronic and persistent liver injury is the primary driver of disease progression to advanced stages like fibrosis and cirrhosis, as it triggers sustained inflammation, activates HSCs, and drives excessive extracellular matrix accumulation[5]. Thus, accurate fibrosis assessment is crucial for managing patients with NAFLD because fibrosis is the key determinant of cirrhosis and hepatocellular carcinoma[6].

The prevalence of NAFLD is estimated to be 25% to 30% in the adult population of Western societies[7]. It is estimated that a total of 3% to 10% of all children, of which 34% are in developed countries, have NAFLD[8]. Although the prevalence of this disease is lower in Eastern societies, its incidence is rising due to changes in dietary patterns that contribute to diabetes mellitus, obesity, and metabolic syndrome. In Eastern communities, the prevalence of NAFLD ranges from approximately 15% to 20% and appears to be influenced by factors such as geographical location, gender, ethnicity, and age[9].

To date, the US Food and Drug Administration has not approved any medications for NAFLD treatment[10]. Nevertheless, lifestyle modifications to achieve weight loss—such as adhering to a healthy diet, engaging in regular physical activity, and maintaining a sustainable lifestyle—remain a cornerstone of NAFLD management. However, implementing exercise and nutritional changes in daily life can be challenging, potentially owing to factors such as lack of motivation, genetic background, adaptation to basal metabolism, insufficient weight loss, and hormonal disorders[11]. In general, less than 50% of individuals achieve a weight loss of 5% to 10%, which is necessary for reducing inflammation and fibrosis and may even regain weight[12]. Nonetheless, the positive effects of exercise depend mainly on weight loss[13]. Hence, there is a strong desire to deepen our understanding of the pathogenic mechanisms underlying NAFLD and its associated extrahepatic diseases. Despite the significant economic burden and healthcare costs, effective clinical management remains a major challenge.

Bacterial changes associated with NAFLD at different taxonomic levels

Studies have yielded similar results regarding the taxonomic differences in GM between healthy individuals and patients with NAFLD[14]. Typically, these differences can enhance the resilience of the GM; however, persistent external stimuli can be stressful and detrimental, leading to GM dysbiosis that contributes to the progression of NAFLD[14]. In the following, we summarize the results of various studies examining changes in GM across different taxonomic levels, conducted in both human and animal clinical conditions. Table 1 briefly illustrates the changes in intestinal and fecal microbiota observed in patients with NAFLD and NASH. Notably, the most significant alterations occur at the genus level.

In a study in which the GM alterations between obese and lean individuals had been evaluated , it was found that obese individuals exhibit an increase in the level of *Firmicutes* and a decrease in the level of *Bacteroidetes*[15]. Adverse outcomes, such as enhanced energy intake from the diet, weakened intestinal epithelial barrier integrity, and elevated systemic inflammation, are associated with an increase in the*Firmicutes* to *Bacteroidetes* ratio and an elevation in *Proteobacteria* population[16]. An HFD in mice increased both *Firmicutes* and *Proteobacteria*, along with an elevated *Firmicutes* to *Bacteroidetes* ratio[17]. The abundance of *Firmicutes* was more significant in obese mice, while *Bacteroidetes* levels decreased, further contributing to the increased *Firmicutes* to *Bacteroidetes* ratio[18]. Another study found that an HFD in mice increased the abundance of *Barnesiella* and *Roseburia* while decreasing the genus *Allobaculum* compared to the control group[19]. In contrast, an HFD in humans has increased *Bacteroidetes* and decreased *Firmicutes* and *Proteobacteria* populations[15]. The *Prevotellaceae* family and the genus *Prevotella* have increased in obese children with NAFLD[20]. An earlier investigation revealed that children with NAFLD exhibited a decrease in Bacteroidetes, *Rikenellaceae*, and *Oscillibacter* level, while levels of *Actinobacteria*, *Anaerococcus*, *Bradyrhizobium*, *Dorea*, *Propionibacterium acnes*, *Ruminoccocus*, and *Peptoniphilus* increased[21]. Significant differences in environmental diversity, diet patterns, age, and patient demographics could explain these results[21]. Several studies have reported inconsistent results regarding the prevalence of *Ruminococcaceae* in the fecal samples of obese individuals with NAFLD and NASH[22-24].

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Table 1. Microbiota alterations in individuals with NAFLD and NASH

Scientific classification					
Phylum	**Class**	**Order**	**Family**	**Genus**	**Species**
Bacteroidetes ↑ [31,32] ↓ [21,30]	*Gammaproteobacteria* ↑ [37]	*Clostridiales* ↓ [34]	*Prevotellaceae* ↑ [20]	*Prevotella* ↑ [20,22,27] ↓ [24,28]	*Propionibacterium acnes* ↑ [21,37]
Actinobacteria ↑ [21]			*Rikenellaceae* ↓ [21,37]	*Anaerococcus* ↑ [21,37]	*F. prausnitzii* ↓ [17,30,34]
Firmicutes ↑ [37] ↓ [17,22,30-32,34]			*Ruminococcaceae* ↓ [22-24,37]	*Bradyrhizobium* ↑ [21,37]	*Escherichia coli* ↑ [17,22,36]
Proteobacteria ↑ [22,36] ↓ [37]			*Porphyromonadaceae* ↑ [34] ↓ [23]	*Dorea* ↑ [21,23,37]	*Lactobacillus mucosae* ↑ [37]
Fusobacteria ↑ [23,37]			*Succinivibrionaceae* ↑ [34]	*Ruminococcus* ↑ [21,28,37] ↓ [30]	*Bacteroides vulgatus* ↑ [17]
Actinomycetes ↑ [37]			*Lactobacillaceae* ↑ [23,30,37]	*Peptoniphilus* ↑ [21,37]	*Ruminoccocus obeum* ↓ [17]
Lentisphaerae ↓ [24,37]			*Lachnospiraceae* ↑ [23]	*Bacteroides* ↑ [27,28]	*Enterobacterium rectale* ↓ [17]
Verrucomicrobia ↑ [37] *Thermus* ↑[37]			*Enterobacteriaceae* ↑ [22,36,54]	*Lactobacillus* ↑ [23,24,30,37]	*A. muciniphila* ↓ [54]
			Bifidobacteriaceae ↓ [37]	*Coprococcus* ↓ [30]	
			Bacteriodaceae ↑ [37]	*Escherichia* ↑ [22,24,37]	
				Streptococcus ↑ [24,37]	
				Anaerobacter ↑ [24]	
				Faecalibacterium ↓ [34,37]	
				Anaerosporobacter ↓ [34]	
				Parabacteroides ↑ [34]	
				Allisonella ↑ [34,37]	
				Aeromondales ↑ [34]	
				Robinsoniella ↑ [23,37]	
				Roseburia ↑ [23]	
				Oscillibacter ↑ [37] ↓ [21,23,37]	
				Alistipes ↓ [37]	
				Bifidobacterium ↓ [37]	
				Odoribacter ↓ [37]	
				Flavonifractor ↓ [37]	
				Akkermansia ↑ [37]	
				Clostridium XI ↑ [37]	
				Enterococcus ↑ [37]	
				Oribacterium ↑ [37]	
				Lactonifactor ↑ [37]	

↑ (up arrow) indicates an increase, ↓ (down arrow) indicates a decrease

Research has indicated that the level of SCFA, particularly propionate, is elevated in obese individuals, suggesting that SCFAs may be involving in obesity[25]. In children who are fed an HFS, there is an increase in the abundance of *Firmicutes* and *Proteobacteria* in their feces. However, these children exhibit a decrease in the levels of *Actinobacteria* and *Bacteroidetes*, along with a reduction in SCFA content, compared to children who are on a healthier diet that is high in fiber and low in fat[26]. One clinical study observed an elevation in the genus *Bacteroides* in patients with NASH, whereas an increase in the genus *Prevotella* was detected in those with NAFLD[27]. It appears that a Western diet favors the genus *Bacteroides*, while a high-fiber diet is more suitable for the genus *Prevotella*[28].

In the study conducted by Turnbaugh and colleagues, FMT from humans consuming an unhealthy diet— characterized by high sugar and high fat— was administered to germ-free mice. This research demonstrated that an unhealthy diet can alter the GM profile and its associated metabolic pathways. The recipient mice exhibited increased fat levels, an elevation in *Erysipelotrichi* and *Enterococcus*, and a decrease in *Bacteroidetes* populations[29]. Similarly, in another study, FMT was performed on germ-free mice exposed to excessive glucose and insulin levels, resulting in the development of NAFLD in the recipient mice[19]. Furthermore, the bacterial species *Lachnosiraceae bacterium 690* and *Barnesiella intestinihominis* were identified in the fecal samples of the recipient mice; these species are known to induce NAFLD. However, the level of *Bacteroides vulgatus* was also found to be reduced[19].

A decrease in the abundance of *Firmicutes* has been reported in NAFLD[30] and NASH[22,30]. A comparison of microbiota changes between individuals with NASH and non-NASH, showed that *Bacteroides* and *Ruminoccocus* increased in patients with NASH. At the same time, the level of *Prevotella* decreased[28]. Studies comparing lean individuals to those with NAFLD indicated that *Bacteroidetes* increased by 20%, whereas *Firmicutes* decreased by 24%. This finding supports the elevation in Gram-negative bacteria population associated with NAFLD[31,32]. A cross-sectional study observed that the phyla *Bacteroidetes* and *Firmicutes* decreased in NAFLD, while *Lactobacillus* increased. However, a decrease in *F. prausnitzii*, *Ruminoccocus*, and *Coprococcus* has been demonstrated in NASH, independent of body mass index[30]. Among obese individuals and patients with NASH, the abundance of *Firmicutes* and *Bacteroidetes* in human studies was similar. However, the level of *Proteobacteria* increased in NASH[22], indicating a correlation between high liver fibrosis and increased systemic inflammation, which may contribute to disease progression and hepatic dysfunction[33]. *Lentisphaerae phylum* decreased in individuals with NAFLD, while *Fusobacteria* increased by about 2.76% in NAFLD cases[23]. Moreover, one study reported a raise in the genera *Escherichia*, *Lactobacillus*, *Anaerobacter*, and *Streptococcus* in NAFLD[24]. In NASH, the abundance of *Faecalibacterium*, *Anaerosporobacter*, and *Clostridiales* decreased, whereas the levels of *Porphyromonadaceae*, *Parabacteroides*, *Allisonella*, *Aeromondales*, and *Succinivibrionaceae* augmented[34].

In cases of NAFLD and NASH, the abundance of *F. prausnitzii* was reduced[30]. A comparative clinical study of 30 patients with NAFLD and 30 healthy individuals found that NAFLD was associated with increased level of the *Lactobacillaceae* and *Lachnospiraceae* families. Notable changes was also observed at the genus level including increased *Lactobacillus*, *Dorea*, *Robinsoniella*, *and Roseburia*. In contrast, *Oscillibacter* levels decreased, suggesting a potential shift in GM composition that may contribute to the altered metabolic and inflammatory pathways in NAFLD progression[23]. A prospective cross-sectional study involving 39 patients with NAFLD confirmed by biopsy, demonstrated that the *Lactobacillaceae* family and the genus *Lactobacillus* were significantly enriched in these individuals. Additionally, in the same patients, the genera *Coprococcus* and *Ruminococcus* were found to be diminished[30]. The results of a large cohort study on NAFLD patients indicated that hepatic steatosis was linked to reduced GM diversity, with *Coprococcus* and *Rominococcus gnavus* also being present[35]. In small-scale studies, *Proteobacteria*, *Enterobacteriaceae*, and *E. coli* have increased in NAFLD patients[22,36]. A meta-analysis conducted by Pan and co-workers reported variations in GM composition in NAFLD at different taxonomic levels. At the phylum level, an increase in *Actinomycetota* and *Firmicutes* was observed, while *Verrucomicrobia*, *Thermus*, *Proteobacteria*, *Lentiphaerae*, and *Fusobacteria* showed a decreased level. The abundance of *Actinobacteria* and *Bacteroidetes* varied between patient and healthy individuals. At the family level, a lower abundance of *Rikenellaceae*, *Bifidobacteriaceae*, and *Ruminococcaceae* as well as a higher abundance of *Bacteroidaceae*, *Gammaproteobacteria*, and *Lactobacillaceae* were were observed. Additionally, the abundance of *Lachnospiraceae* and *Prevotellaceae* showed inconsistencies among the NAFLD patients. Significant differences were also noted at the genus level; for instance, *Alistipes*, *Bifidobacterium*, *Oscillibacter*, *Odoribacter*, *Faecalibacterium*, and *Flavonifractor* decreased in the GM population, while certain bacterial species, such as *Akkermansia*,

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Allisonella, *Anaerococcus*, *Bradyrhizobium*, *Dorea*, *Enterococcus*, *Clostridium XI*, *E. coli*, *Lactobacillus mucosae*, *Lactobacillus*, *Lactonifactor*, *Oribacterium*, *Oscillibacter*, *Peptoniphilus*, *Robinsoniella*, *Propionibacterium acnes*, *Ruminoccocus*, and *Streptococcus*, increased. However, the changes in the abundance of the genera *Blautia*, *Bacteroides*, *Oscillibacter*, and *Prevotella* remained inconsistent in the literature[37].

Studies have reported contradictory and variable results regarding changes in the fecal microbiome[22,25,38-40]. In some investigations, the ratio of *Firmicutes* to *Bacteroidetes* reduced in the fecal samples of obese individuals, while an increase in *Proteobacteria* was observed[22,40]. In patients with NAFLD, an elevation in *Lactobacillus*, *Roseburia*, *Robinsoniella*, *Dorea*, and *Lachnospiraceae* populations was identified, whereas *Porphyromondaceae*, *Ruminococcaceae*, and *Oscillibacter* showed decreased fecal abundance[23]. Two studies showed that *Prevotella* levels decreased in the fecal samples of individuals with NAFLD[23,24]. In contrast, other studies documented an increase in *Prevotella* abundance among obese children and those with NASH[22,41]. Additionally, *Enterobacteriaceae*, *Proteobacteria*, and *Escherichia* were enriched in the fecal microbiome of young individuals compared to obese children[22].

A study by Loomba and colleagues involving 86 biopsy-proven patients—72 with mild fibrosis and the remaining with severe fibrosis—identified 37 bacterial species, including *E. coli* and *Bacteroides vulgatus*, that exhibited differences across various disease phenotypes[17]. Moreover, the *Firmicutes* and *F. prausnitzii* levels were significantly reduced, while the *Ruminoccocus obeum* and *Enterobacterium rectale* levels were lower in patients with severe fibrosis[17]. The authors observed that as fibrosis advanced, *E. coli* levels increased, suggesting that GM disturbances facilitated the early proliferation of *E. coli*, which may contribute to the premature onset of portal hypertension[17]. Furthermore, it was noted that in the progressive stages of fibrosis, the abundance of *Ruminococcus* genus increased. It is also important to highlight that some species within this genus are capable of producing ethanol, which may adversely affect intestinal permeability and induce hepatic inflammation[28]. Level of Bacteroides was significantly higher in individuals with NAFLD who had severe fibrosis compared to those with mild fibrosis[28]. These findings suggest that microbial dysbiosis may contribute to the progression of NAFLD in humans and animals. However, further research is necessary to substantiate this claim. It seems that microbial dysbiosis can significantly influence the incidence and progression of liver disease; therefore, it is essential to identify the microorganisms involved in the pathogenesis of liver conditions. Additional investigation into the effects of GM dysbiosis on liver disease could enhance our understanding of their roles and the mechanisms involved in pathogenesis.

Specific bacterial changes associated with the NAFLD

The following section highlights studies on specific GM bacteria linked to the development of NAFLD.

Faecalibacterium prausnitzii

F. prausnitzii is a butyrate-producing bacterium constituting more than 5% of the total GM in healthy humans[42]. A decrease in *F. prausnitzii* has been observed in both NASH and NAFLD[30]. In individuals with NAFLD, a reduction in the abundance of this bacterium is associated with more than 5% of liver content and increased inflammation, which may worsen the progression from NAFLD to NASH[43]. In an animal study, mice fed an HFD were simultaneously administered *F. prausnitzii* as a probiotic. The results showed that hepatic lipid levels reduced, and aspartate aminotransferase and alanine aminotransferase levels improved, suggesting that the treated mice with probiotics had healthier liver than those on an HFD[44]. Likewise, this bacterium can increase the expression of cyclin-dependent kinase inhibitor 1A, which encodes the P21 protein; the level of this protein is inversely related to the progression of NAFLD and fibrosis[45]. *F. prausnitzii* is negatively correlated with $CD54^+$ and $CD163^+$ cells in the portal ducts. In contrast, *Prevotella* is negatively associated with $CD20^+$ cells in the hepatic lobule[46], indicating a correlation between GM and immune function in NAFLD.

Akkermansia muciniphila

One of the most abundant intestinal bacteria, accounting for 3% to 5% of the GM population, is a Gram-negative bacterium belonging to the phylum *Verrucomicrobia*, known as *A. muciniphila*[47]. This bacterium is considered beneficial and may have therapeutic potential as a probiotic for improving health[48]. *A. muciniphila* can decompose mucin and is found in the intestinal mucosa[49]. It obtains the nutrients from mucin and then releases free sulfate during mucin fermentation[49]. Without dietary fiber, this bacterium can overgrow, leading to thickening mucosa[50]. The colonization of this bacterium occurs during the first months of life[51]. Increased level of *A. muciniphila* is inversely related to metabolic disorders, indicating that higher concentrations of this influential bacterium can improve metabolic disorders, cholesterol level, and

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hepatic steatosis[48]. Research has shown that in obese and NAFLD animal models, the level of *A. muciniphila* decreases, which may be associated with metabolic disorders[48]. The intestinal barrier is compromised by increased fat, likely due to increased levels of blood endocannabinoids and intestinal peptides. However, *A. muciniphila* enhances the intestinal barrier, regulates the thickness of the mucosal layer, and promotes the production of immune and antimicrobial peptides[48]. The production of lipid bioactive compounds known as "gatekeepers" such as 2-oleoylglycerol, 2-palmitoylglycerol, 2-arachidonoylglycerol, N-palmitoylethanolamine, and the glycerol ester of prostaglandin D2 by *A. muciniphila* can strengthen the intestinal barrier[52]. A protein synthesized by *A. muciniphila*, called Amuc_100, plays an important role in regulating immunity. Daily gavage feeding of a supplement containing *A. muciniphila* to specific-pathogen-free grade mice improves metabolic profiles, glucose tolerance, and insulin sensitivity in the liver, while also reducing the expression of genes involved in glucose metabolism, such as phosphoenolpyruvate carboxykinase, and Glucose-6-phosphatase[51]. In addition, increasing the frequency of *A. muciniphila* reduces lipopolysaccharide-binding protein level, metabolic endotoxemia, and downstream signaling in the systemic circulation[51]. Individuals with moderate fibrosis exhibited higher *Enterobacteriaceae* level compared to those with mild fibrosis. Additionally, in patients with NASH, the level of *Enterobacteriaceae* increases while *A. muciniphila* level decreases[53]. Overall, *A. muciniphila* offers great therapeutic potential as a probiotic bacterium for preventing or improving metabolic disorders.

CONCLUSION

The GM is a complex, dynamic, and adaptable community in which both bacterial and potentially non-bacterial species contribute to the development of NAFLD. Therefore, it is crucial to study both individual bacterial species and the diverse bacterial communities such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* that play a role in health and disease. Moreover, changes in the profiles of non-bacterial species associated with NAFLD should be taken into account. While animal studies have provided valuable insights into the impact of GM on health and disease, further research is necessary to understand this intricate relationship. Comprehensive studies involving large human cohorts, considering both environmental and genetic factors, can yield significant data. Overall, additional research with diverse objectives in both humans and animals can enhance our understanding of the gut-liver axis, its disorders, and the influence of GM dysbiosis on the development of liver diseases.

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Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

All authors reviewed the results and approved the final version of the manuscript.

Authors' contributions

HY: investigation, conceptualization, supervision, writing–original draft preparation, writing–review, and editing; AMT: investigation, writing–original draft preparation, writing–review, SAN: investigation, conceptualization, validation, writing–review, and Editing; MS: investigation, writing–original draft preparation, writing–review, and editing; SS, MR, SMM, and SMH: investigation and writing–original draft preparation; SDS: investigation, conceptualization, project administration, supervision, writing–review, and editing.

Data availability

All relevant data can be found within the manuscript.

Competing interests

The authors declare that they have no competing interests.

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