

The Gut–Liver Axis in Metabolic Dysfunction-Associated Steatotic Liver Disease

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) or non-alcoholic fatty liver disease (NAFLD) is now regarded as a leading global cause of chronic liver disease associated with metabolic syndrome. The key element here is the gut-liver axis, which, through dysbiosis, leads to the appearance and development of NAFLD. Metabolic damage reduces the number of intestinal bacteria that affect liver function, tight junction protein expression, and intestinal permeability; this results in lipopolysaccharides and other bacterial metabolites entering the liver through the portal vein. At the same time, short-chain fatty acids are suppressed, as well as the FXR nuclear receptor, which regulates the synthesis of bile acids in the liver. This spiral leads to increased levels of triglycerides in hepatocytes and their accumulation in the liver (over 5% of liver volume). Translocation of endotoxins activates Toll-like receptors (TLR4) and NF- κ B transcription factor in Kupffer cells and hepatocytes; this triggers the secretion of pro-inflammatory cytokines (TNF α , IL-6). Inflammatory factors activate hepatic stellate cells, which leads to fibrosis and extracellular matrix deposition. Thus, MASLD progresses to fibrosis and cirrhosis of the liver. The term MASLD is used to describe patients with a wide range of phenotypes, from healthy people with fatty infiltration to severe liver failure with complications such as ascites, jaundice, and hepatic encephalopathy. Measures to regulate the gut-liver axis, such as prebiotics, probiotics, synbiotics, and postbiotics, have shown good results in reducing intestinal permeability and inflammation in patients with NAFLD. However, the results of histological changes were not consistent enough to recommend these drugs for therapeutic use. Therefore, it is necessary to consolidate the data obtained using multi-omics technologies and to conduct clinical trials in order to develop methods for personalized medicine that would be applicable in the clinic.

KEYWORDS

MASLD, Liver, Gut, Microbiota, Axis

INTRODUCTION

In recent years, Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a leading cause of chronic liver illness worldwide (Thielemann et al., 2025). To outline MASLD, it is latest term for steatotic liver disease associated with metabolic syndrome previously known as Non-Alcoholic Fatty Liver Disease (NAFLD). It refers to the

excessive buildup of fat in the liver that is not caused by heavy alcohol use, but rather by metabolic conditions like obesity, type 2 diabetes, or high blood pressure. The complex progression of MASLD extends beyond the liver, driven by “gut-liver axis” which describes the complex, bidirectional communication between the gastrointestinal tract and the liver, primarily mediated by the portal vein. (Joon et al., 2024) The liver acts as a filtering unit for the microbial by products present in the gut. (Ortiz-López et al., 2024) Under normal body conditions, a strong gut lining and a variety of microbes keep the body balanced. However, in MASLD, an imbalance in the gut microbes weakens this barrier, causing ongoing inflammation throughout the body and liver. This paper provides a detailed account of the gut-microbiota mechanisms underlying MASLD pathogenesis, alongside emerging therapeutics aimed at modulating the gut-liver axis.

PATHOGENESIS

A core mechanism of MASLD is an unhealthy shift in the gut microbiome, marked by a surge in pro-inflammatory, gram-negative bacteria alongside a decline in protective species that maintain the gut lining. (Bahitham et al., 2025). The pathogenesis of this disease can be divided into three distinct phases.

Microbiome Dysbiosis & Gut Barrier Breakdown: The Trigger.

High-fat or high-sugar diets and metabolic stress disturb the microbial balance, increasing harmful bacteria at the expense of beneficial ones. (Ma et al., 2025; Scarpellini et al., 2024) This imbalance, called dysbiosis, reduces the strength of tight junction proteins that maintain the integrity of the intestinal wall. As a result, it leads to a "leaky gut" condition, where increased intestinal permeability allows bacterial fragments such as lipopolysaccharides (LPS), also known as endotoxins, to enter the bloodstream. (Li & He, 2026; Scarpellini et al., 2024).

Microbial Translocation via the Portal Vein: The Axis in Action.

Through the portal vein, translocated endotoxins (LPS), unabsorbed metabolites, and bacterial byproducts bypass the intestinal barrier and drain directly into the liver. (Schnabl et al.), 2025 Concurrently, shifts in gut microbial metabolism lead to a depletion of protective Short-Chain Fatty Acids (SCFAs) and an imbalance in bile acid pools, ultimately blunting hepatic metabolic signaling pathways like the Farnesoid X Receptor (FXR). (Ma et al., 2025). Think of FXR as a master light switch inside your cells. When bile acids flip this switch on, it tells your body to balance fat, control sugar, and stop making too much bile.

Hepatic Steatosis Development: Fat Accumulation.

An influx of free fatty acids, combined with altered microbial signals, disrupts normal liver fat metabolism. This triggers accelerated *de novo* lipogenesis (fat synthesis) while reducing fatty acid oxidation. As a result, triglycerides accumulate inside hepatocytes, crossing the diagnostic threshold of >5% liver weight to establish steatosis. (Ma et al., 2025; Rodríguez-Rojas et al., 2025).

Inflammatory Cascade & Progression to MASH: Damage & Scarring.

Translocated LPS binds to Toll-Like Receptor 4 (TLR4) on hepatocytes and Kupffer cells (resident liver macrophages). This activates pro-inflammatory signaling pathways via Nuclear Factor kappa B (NF-κB), triggering the release of

inflammatory cytokines such as Tumor Necrosis Factor Alpha (TNF α) and Interleukin-6 (IL-6) (Dua et al., 2025; Ma et al., 2025). Chronic inflammation activates hepatic stellate cells (HSCs), which synthesize and deposit extracellular collagen, driving progression from simple steatosis to Metabolic Dysfunction-Associated Steatohepatitis (MASH) and eventual liver fibrosis (Ma et al., 2025; Schnabl et al., 2025).

SYMPTOMS

The progression of the disease can be presented in 3 stages:

1) Early/Simple Steatosis Stage — Often Asymptomatic

Most patients are diagnosed incidentally, since early MASLD is very asymptomatic. (Allen et al., 2024; Rinella et al., 2023). When symptoms do appear, they're vague and non-specific:

- Fatigue and generalized malaise (a feeling of being slightly unhappy)
- Right upper quadrant abdominal discomfort or dull ache (due to hepatomegaly stretching the liver capsule)
- Mild hepatomegaly (enlargement of liver) on examination

2) As Disease Progresses to MASH (Steatohepatitis) — Inflammatory Stage

This is where your gut-liver axis mechanisms (NF- κ B, NLRP3, TLR signaling) become clinically relevant (Yan et al., 2025):

- Persistent fatigue (more pronounced)
- Malaise and weakness
- Right upper quadrant pain (more consistent)
- Mild jaundice in some cases as hepatocyte injury increases

3) Advanced Fibrosis - Cirrhosis Stage

Disruption of Farnesoid X Receptor NF- κ B (FXR) and TGR5 signaling along the gut-liver axis impairs bile acid synthesis and enterohepatic clearance (Targher et al., 2024; Yan et al., 2025). The accumulation of toxic bile acids in the liver contributes directly to symptoms such as:

- Ascites (fluid accumulation — reflects portal hypertension)
- Peripheral edema (fluid build-up in extremities of the body like feet, ankles, legs etc.)
- Jaundice (more pronounced)
- Pruritus (itching from bile acid accumulation)
- Easy bruising/bleeding (impaired clotting factor synthesis)
- Muscle wasting
- Hepatic encephalopathy (confusion, altered consciousness) in decompensated cases
- Splenomegaly (Enlargement of spleen)

DIAGNOSIS

Sequencing of the 16S rRNA is a targeted molecular approach to assess and compare bacterial communities in the gut based on highly conserved 16S rRNA gene. It provides information on composition and relative abundance of bacteria but has limited resolution at the species level and does not directly provide functional capabilities of the microbiome. Gut

dysbiosis with reduced microbial diversity, loss of beneficial microbes and enrichment of potentially pathogenic tax has been consistently demonstrated by 16S rRNA sequencing in MASLD studies. These changes are associated with increased intestinal permeability, endotoxin, translocation, chronic inflammation, and hepatic steatosis. (Qin J, et al 2012, Tilg H, et al 2021). Shotgun metagenomic sequencing is an untargeted method for sequencing all the microbial DNA in a sample. It offers the species or strain level identification of microorganisms. Unlike 16S rRNA sequencing and describes their functional genes and metabolic pathways. Shotgun metagenomic has identified alterations in the microbiome associated with impaired by acid metabolism, decreased short chain fatty acid production and choline metabolism in MASLD. These functional changes result in gut barrier dysfunction, systematic inflammation, insulin resistance, and liver injury via gut liver axis. (Loomba R, et al 2019, Fan Y, et al 2021).

Table 1: Gut microbiota alterations in MASLD

Reference	Diagnostic Tool	Alterations	Analysis method
Leung et al 2016	Ultrasonography	Decreased Methanobrevibacter and Phascolarctobacterium, increased Slackia and <i>Dorea formicigenerans</i>	Shotgun metagenomic sequencing
Rau et al 2018	Liver biopsy	Fusobacteria and Fusobacteriaceae abundance	16S rRNA
Astbury et al 2020	Liver biopsy	Increased Collinsella	16S rRNA
Iino et al 2019	Ultrasonography	Ruminococcaceae and Faecalibacterium were significantly decreased	16S rRNA
Boursier et al 2016	Liver biopsy	Increased abundance of Bacteroides	16S rRNA
Alferink et al 2021	Ultrasonography	Coprococcus decrease and <i>Ruminococcus gnavus</i> increased	16S rRNA
Loomba et al 2017	Liver biopsy	Proteobacteria phylum increased while the Firmicutes phylum decreased.	Metagenomic sequencing
Oh et al 2020	Liver biopsy MRI-PDFF MRE	<i>Veillonella parvula</i> , <i>Veillonella atypica</i> , <i>Ruminococcus gnavus</i> , <i>Clostridium bolteae</i> and <i>Acidaminococcus</i> sp. D21 was increased and <i>Eubacterium eligens</i> , <i>Eubacterium rectale</i> , and <i>Faecalibacterium prausnitzii</i> were decreased	Shotgun metagenomic sequencing
Da Silva et al 2018	Liver biopsy	<i>Ruminococcus</i> , <i>Faecalibacterium prausnitzii</i> and <i>Coprococcus</i> were decreased	16S rRNA

Lanthier et al 2021	Fibroscan	<i>Clostridium sensustricto</i> was decreased and an enrichment of <i>Escherichia/Shigella</i>	16S rRNA
Hoyles et al. 2018	Liver biopsy	Proteobacteria, Actinobacteria and Verrucomicrobia were significantly correlated with liver steatosis, while Firmicutes and Euryarchaeota were significantly anticorrelated.	Shotgun metagenomic sequencing
Behary et al 2021	Transient elastography scores	<i>B. caecimuris</i> and <i>V. parvula</i> are increased	Shotgun metagenomic sequencing
Caussy et al 2019	MRI-PDFF MRE Fibroscan	Megasphaera was only enriched and more Gram-negative microbes were observed	16S rRNA
Ponziani et al. 2019	—	Bacteroides and Ruminococcaceae were higher	16S rRNA

PREVENTION

Prebiotics, including inulin, fructo-oligosaccharides, galacto-oligosaccharides and resistance starch, selectively stimulate beneficial bacteria, such as *Bifidobacterium*, and lactobacillus species. Several experimental and clinical studies demonstrate improvements in gut barrier function, inflammatory markers and metabolic parameters. However, human studies show variable responses depending on baseline microbiome composition. (Carlo Acierno, et al 2025).

Multiple randomised control trials have investigated probiotic supplementation in MASLD. Most studies report reduction in serum alanine aminotransferase, aspartate aminotransferase, inflammatory cytokines and insulin resistance. Nevertheless, improvement in liver histology remain inconsistent because of differences in probiotic strains, treatment duration, and study design. Current evidence, therefore, supports probiotics as an adjacent rather than a standalone preventive therapy. (Yadav MK, et al)

Synbiotics, which combine probiotics and prebiotics may provide greater benefits than intervention alone by improving microbial, colonisation and enhancing SCFA (short chain fatty acid) production. Postbiotics, including microbial metabolites, such as butyrate have emerged as potential therapeutic agents because they directly reduce inflammation and maintain intestinal epithelial integrity. However, clinical evidence remains limited and further randomise trials are required. (Al-Habsi N, et al.)

FUTURE DIRECTIONS

Future research will mostly focus on developing personalise medicines because gut microbial composition varies among individuals with MASLD. There is also a need for large long-term clinical trials to determine the safety efficacy, optimal dosage, and duration of microbiome targeted therapy before they can be adopted in routine, clinical

practice. (Mak LY, et al 2026). Future studies should standardise microbe sequencing methods and integrate multi omics approaches to better understand the gut, liver axis, and identify reliable bio markers for early diagnosis and disease progression. (Lau HC, et al 2025)

CONCLUSION

Gut microbial devices play a crucial role in development and progression of MASLD by increasing intestinal permeability, promoting inflammation and altering microbial metabolites through gut liver axis. Although therapy like prebiotics, probiotics, synbiotics and post biotics show, promising result the evidence right now is not sufficient for routine. Clinical use because the studies are very small and rely on surrogate outcomes. A better understanding of host microbiome interactions and high-quality clinical studies will be essential for translating these findings into effective preventive and therapeutic strategies for MASLD.

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