

Microbiota liver crosstalk in diabetic liver injury: Mechanistic insights and therapeutic promise of faecal microbiota transplantation

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ABSTRACT

Dysbiosis primarily causes diabetic liver damage, and studies show that people with type 2 diabetes mellitus (T2DM) exhibit considerable changes in their gut microbiome. *Escherichia coli*, *Clostridium symbiosum*, and *Clostridium hathewayi* are among the harmful microorganisms known to increase in diabetes and adversely affect the liver. Importantly, plasma triglycerides, fasting glucose, and glycosylated haemoglobin (HbA1c) showed a negative correlation with *Clostridium* species, while fasting glucose, HbA1c, and plasma triglycerides showed a positive correlation with *Lactobacillus* species. These findings suggest that specific bacterial taxa may contribute to the development of T2DM and, in turn, promote liver-related complications. Faecal microbiota transplantation (FMT) may help restore a healthy gut microbiota, which may enhance insulin sensitivity, reduce hepatic fat accumulation, and alleviate metabolic dysfunction associated with the liver. Furthermore, diabetic liver damage has been linked to dysbiosis-related changes in bile acid metabolism. FMT can restore the diversity and function of bile acid-metabolizing bacteria, leading to a more balanced bile acid profile and enhanced bile acid signalling in the liver. This might reduce liver fibrosis and inflammation. Overall, by focusing on dysbiosis and its related pathways, FMT shows potential as a therapeutic intervention for diabetic liver disease. However, further investigation is required to clarify the ideal procedures, long-term security, and effectiveness of FMT in this particular situation. Furthermore, innovations are shifting FMT toward personalized precision therapies that address the complex relationship between gut bacteria, metabolism, and liver health in Type-2 diabetes. This study highlights a novel mechanistic framework linking dysbiosis, liver injury, and FMT restoration, emphasising donor–host microbiome compatibility, duration of effect, and the promise of precision microbiome and next-generation FMT therapies as future directions.

1. INTRODUCTION

The fact that the formation of the liver commences from the fetal foregut, readily establishes a close relationship between the gastrointestinal tract (GIT) and the liver. The liver regulates various metabolic pathways in a manner that can influence the entire body and also highlights its potential to regulate gut function. This relationship is bi-directional,

as various metabolites, inflammatory and immune mediators, hormones, and by-products of digestion, significantly impact liver function. The involvement of gut microbiota in the GIT and liver connection can be traced back more than 80 years. Evidences suggest that alterations in the gut microbiota, known as dysbiosis, are one of the major etiological factors responsible for the development and progression of diabetic liver injury (DLI), which is a significant global health burden. It demonstrates that gut microbiota exert metabolic influence pertinent to obesity, insulin resistance, and thereby liver injury.

Patients with type 2 diabetes mellitus (T2DM) demonstrate only a rise in several harmful microorganisms, including *Escherichia coli*, *Clostridium symbiosum*, and

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Clostridium hathewayi. Notably, fasting glucose and glycosylated haemoglobin (HbA1c) showed a positive correlation with *Lactobacillus* species; in contrast, fasting glucose, HbA1c, and plasma triglycerides showed a negative correlation with *Clostridium* species, raising the possibility that these bacterial taxa may be connected to the onset of T2DM. In newly diagnosed T2DM patients, Chen *et al.* [1] recently showed that levels of *Lactobacillus* were significantly higher, while levels of *Clostridium coccoides* and *Clostridium leptum* were significantly lower. The intestinal microbiota of patients with refractory T2DM (RT2D), whose HbA1c increased by at least 8% despite treatment, was studied in a notable study [2]. Refractory diabetic (RT2D) patients had higher concentrations of *Bacteroides vulgatus* and *Veillonella denticariosi* and lower concentrations of *Akkermansia muciniphila* and *Fusobacterium* compared with T2DM controls. Among these, the relative abundance of *A. muciniphila* showed a negative correlation with HbA1c.

Specific bacterial genera, including *Clostridium* and *Bacteroides*, have been found to modulate the expression and activity of tight junction proteins such as occludin, claudins, and zonula occludens-1. Pathogenic strains of *Clostridium* produce toxins and metabolites capable of degrading or dephosphorylating occludin, resulting in weakened epithelial barriers and enhanced intestinal permeability. Likewise, *Bacteroides* species can impair tight junction stability through their lipopolysaccharides (LPS) and proteolytic enzymes, which trigger inflammatory signalling cascades such as nuclear factor κ B (NF- κ B) and MAPK, leading to reduced occluding expression. This microbial regulation of tight junctions disrupts gut barrier integrity, promoting microbial translocation and endotoxemia that intensify hepatic inflammation and aggravate DLI [33,34].

The driving factor in the pathogenesis of T2DM is insulin resistance, which is also crucial in the development of hepatic insulin resistance, consequently hepatocyte injury and inflammation. Development of insulin resistance can be attributed to the endotoxins, i.e., LPS, which are produced by the gram-negative bacteria. Generally, the mucosal membrane of the intestinal walls acts as a barrier for these endotoxins. However, under certain conditions, if the barrier fails, bacterial translocation occurs, causing endotoxemia in portal circulation as well as systemic organs. Prolonged exposure of the liver to these toxins, also termed hepatotoxins, initiates a cascade of acute inflammatory response. The central system responsible for the development of insulin resistance is the LPS-Toll-like receptor 4 (TLR4)-monocyte differentiation antigen CD14 system. TLR4 expressed on the hepatocytes is highly responsive to LPS. The interaction between LPS and TLR4 causes the production of IL-8 and chemokine-2, which further activate NF- κ B and c-Jun, promoting liver inflammation. Overgrowth of small intestinal bacteria has been linked to the pathogenesis of liver disorders, mainly cirrhosis. *et al.*, showed that a significant reduction in small intestine bacteria count led to reduced levels of proinflammatory cytokines and leading to reduced insulin resistance.

The intestinal microbiota shows a strong association with obesity and diabetes-related fatty-liver disorders [3–5].

Researchers indicate that pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), NF- κ B, interleukin-6 (IL-6), and IL-1 β , released during T2DM, can modify the gut microbiome composition. Elevated levels of TNF- α are linked to reduced population of Proteobacteria and *Clostridiaceae*. This rise in TNF- α disrupts insulin secretion in the pancreatic β -cells, contributing to insulin resistance in adipose tissue, the heart, skeletal muscles, and other organs. Based on these findings, the gut microbiota appears to play a crucial role in the coexistence of diabetes-induced liver injury. This short communication explores the intricate relationship between microbiota and DLI, and further focuses on the emerging therapeutic approach of fecal microbiota transplantation (FMT) as a potential management strategy.

Despite notable progress in understanding the gut–liver axis in metabolic disease, many questions remain unsolved. Current findings highlight links between gut dysbiosis, insulin resistance, and DLI, yet molecular pathways connecting specific microbes to hepatic inflammation and cell damage are still unclear. Most studies emphasise associations rather than causation, leaving uncertainty about which microbial shifts directly trigger hepatic insulin resistance in T2DM. Moreover, longitudinal evidence on how microbial dynamics influence the progression of reversal of DLI following treatment is scarce. Although FMT appears promising in rebalancing gut flora, its safety, efficacy, and long-term impact in DLI require further study.

This research integrates microbial, immunologic, and metabolic insights to clarify gut–liver communication in diabetes and explores FMT as a potential precision-based therapy targeting microbiota-driven hepatic injury.

2. MECHANISMS LINKING DYSBIOSIS TO THE PATHOGENESIS OF DLI

Mounting evidence suggests that dysbiosis (imbalance in the gut microbiota composition as depicted in Table 2) plays a significant role in the progression of DLI. Several mechanisms have been identified to elucidate the intricate interplay between dysbiosis and the pathogenesis of DLI.

2.1. Intestinal barrier dysfunction

DLI is a complex complication of diabetes mellitus, with emerging evidence highlighting the pivotal role of intestinal barrier dysfunction in its pathogenesis. Dysbiosis disrupts the delicate balance between beneficial and pathogenic microbes, resulting in the development of an environment conducive to the progression of DLI. A fundamental mechanism linking dysbiosis to DLI is increased gut permeability, also known as Leaky gut. Altered gut permeability disrupts tight junction proteins between intestinal epithelial cells, causing translocation of microbial metabolic by-products, such as LPS, into the bloodstream [6,7]. Gut microbiota also produces compounds such as ammonia, phenol, acetaldehyde, ethanol, and benzodiazepines, which are metabolized in the liver and are hepatotoxic. Systemic circulation of LPS, a component of the outer membrane of gram-negative bacteria, initiates the inflammatory cascade by activating immune cells, mainly kupffer cells [8]. Activated Kupffer cells, which are also the

macrophages of the liver, produce nitric oxide and other cytokines. Among the various by-products produced by microbial metabolism, endogenous ethanol production and LPS-induced activation of the inflammatory cascade are the most critical mechanisms leading to the progression of liver disorders [9].

2.2. Endotoxemia and inflammation

Increased levels of systemic LPS due to intestinal barrier dysfunction can activate the inflammatory cascade by binding to the lipopolysaccharide binding protein, and the resulting complex further binds to CD14 on Kupffer cells. TLR4 then associates with CD14 on the cell surface, thereby initiating signaling pathways in hepatic cells and triggering the production of pro-inflammatory cytokines and chemokines by the activation of NF κ B. This process leads to hepatic inflammation and recruitment of immune cells such as macrophages and neutrophils, exacerbating liver injury. Inflammatory mediators, such as TNF- α , cyclooxygenase 2, and interleukin-6 (IL-6), contributing to hepatocellular damage and fibro genesis [10,11].

Studies suggest that in a healthy state, the gut microbiome is predominated by the *Firmicutes*, comprising mainly Gram-positive obligate aerobic or facultative anaerobic bacteria, and the *Bacteroides*, comprising mainly Gram-negative anaerobic pathogenic bacteria. Bacteria belonging to the *Firmicutes* phylum are involved in the conversion of complex carbohydrates into short-chain fatty acids, which act as growth factors for the gut epithelium. *Bacteroides*, on the other hand, are a significant source of LPS in the intestine. Studies suggest that an imbalance in the ratio of *Firmicutes* to *Bacteroides* due to a high-fat diet, iron overload, obesity, and so on, causes leaky gut. The majority of bacteria like *Lactobacillus*, Enterococci within Firmicutes are beneficial; however, certain strains, such as *clostridial* species are pathogenic and lead to intestinal barrier damage. Similarly, particular species of *Bacteroides* provide nutrient sources for other gut bacteria. Bacteria of the phylum Proteobacteria (Pseudomonadota), also include gram-negative bacteria, and their overgrowth causes intestinal barrier dysfunction. Thus, it is evident that microbiota dysbiosis plays a significant role in the nexus of DLI.

2.3. Influence of FMT on LPS-TLR4 pathway

Faecal Microbiota Transplantation provides a promising approach to counteract LPS-induced liver injury arising from gut barrier dysfunction and microbial imbalance. By restoring a balanced gut microbiota, FMT helps strengthen intestinal barrier integrity, decreasing permeability and limiting the entry of LPS and other bacterial components into the bloodstream. Reintroducing beneficial microbes enhances short-chain fatty acid production and supports the mucin layer and tight junction proteins, all of which are essential for maintaining barrier stability. Improved gut integrity reduces circulating LPS levels, thereby lowering activation of Kupffer cells and hepatic TLR4/CD14 pathways that drive NF- κ B-mediated inflammation and immune infiltration in the liver [12].

Table 1. Clinical evidence.

Sr.no.	Clinical trial title	Observations	Reference
1.	Effect of FMT on NAFLD: a randomized clinical trial	FMT had better effects on the gut microbiota reconstruction in lean NAFLD than in obese NAFLD patients	[38]
2.	Microbiota transplantation in individuals with type 2 diabetes and a high degree of insulin resistance.	FMT from healthy and lean donor nor a probiotic were effective in improving insulin sensitivity and HbA1c in patients with T2D.	[39]
3.	Allogenic FMT in patients with NAFLD improves abnormal small intestinal permeability.	No significant change in insulin resistance or hepatic fat fraction overall, but in subgroup with elevated small intestine permeability baseline, there was significant reduction after allogenic FMT.	[40]

2.4. Metabolic derangements

There is a reciprocal relationship between metabolic disorders such as T2DM, cardiovascular diseases like atherosclerosis, liver disorders such as nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis, and the gut microbiota. Next-generation sequencing has provided a clearer picture of the types of microbes that colonize the gut in these diseases [35]. High-fat diet-induced obesity has a prominent role in the gut dysbiosis, leading to the impairment of glucose metabolism and enhancing the accumulation of macrophages in white adipose tissue [13]. The breakdown of indigestible dietary components, primarily plant-derived polysaccharides, by the microbiota is one of the primary mechanisms through which the host extracts energy from the diet. The microbiota breaks complex polysaccharides into short-chain fatty acids such as butyric acid and propionic acid, which are further metabolized to provide energy. Short-chain fatty acids also modify gut peptide production [glucagon-like peptide (GLP-1)] and gastric inhibitory peptides and act as a primary energy source for enterocytes [14]. Therefore, these short-chain fatty acids regulate the cell proliferation and differentiation and induce GLP-2 production, reduce oxidative damage and inflammation by inhibiting histone deacetylases and the activation of the transcription factor NF κ B and the associated cytokine production. Reduced SCFA levels due to dysbiosis can impair glucose and lipid metabolism in the liver, contributing to insulin resistance and hepatic steatosis [13–15].

2.5. Bile acid dysregulation

Recent evidence strongly points to the involvement of bile acid dysregulation and gut microbiota dysfunction in numerous inflammatory processes. Serum bile acid levels serve as biomarkers for liver diseases, obesity, and diabetes and play a role in regulating hepatic de novo lipogenesis, TG export, hepatic gluconeogenesis, and insulin sensitivity through the actions of FXR and TGR5. Bile acid dysregulation also leads

Table 2. A table comparing microbiota composition changes across healthy, T2DM, and DLI conditions.

Sr.no.	Condition	Key microbiota finding	Gut–liver axis	References
1.	Healthy	Diverse microbiota, higher α -diversity SCFA- producing genera (butyrate, propionate) abundant.	Intact gut barrier (tight junctions, mucin layer), minimal translocation of LPS/endotoxin to liver.	[41]
2.	T2DM	Reduced diversity compared to healthy. Increased genera; eg- <i>E. coli</i> / <i>Escherichia shigella</i> group positively associated with T2DM.	Reduced SCFA production- impaired GLP-1 signaling, worse insulin sensitivity. Microbiota influence on bile acids less well defined here but increasingly studied	[42]
3.	DLI	Reduced diversity; gut bacteria dysfunction prominent; bile acid dysregulation; small intestinal bacterial overgrowth seen in some.	Altered bile acid metabolism; accumulation of secondary bile acid, impaired FXR/TGR5 signaling; inflammation, fibrosis.	[43]

to increased bacterial translocation through the disruption of the intestinal barrier, contributing to systemic infection. The gut microbiota plays a pivotal role in bile acid metabolism by regulating their synthesis, transport, and metabolism [16]. Dysbiosis can result in altered bile acid profiles, leading to impaired bile acid signalling and dysregulated lipid metabolism in the liver. Accumulation of toxic bile acids and disturbed bile acid homeostasis contribute to liver injury and fibrogenesis [17].

2.6. Gut–liver axis and immune dysregulation

The gut–liver axis describes the bidirectional communication between the gut and the liver. Dysbiosis-induced changes in gut microbial composition and metabolites can affect immune cell populations and their function in the liver. An imbalance in gut microbial communities triggers an aberrant immune response, promoting inflammation, oxidative stress, and fibrosis in the liver [18].

3. RATIONALE FOR USING FMT FOR TREATING DLI

The expanding body of research demonstrates a strong connection between dysbiosis and liver pathology in individuals with diabetes mellitus [19]. Intestinal bacteria and their metabolites travel through the portal vein to the liver, leading to various pathological conditions. Thus, the gut microbiota and its metabolites act as molecular vehicles between intestine and liver, contributing to metabolic disorders such as obesity and T2DM. Considering the role of gut microbiota dysbiosis in the same, FMT serves as a reliable and noninvasive route for the treatment of diabetic liver impairment. This mechanism is based on the concept of bacterial interference, which involves the use of nonpathogenic or harmless bacteria to displace pathogenic bacteria by creating a competitive niche exclusion. A minimally manipulated microbiome from a healthy donor is introduced into the patient's intestinal tract, leading to the establishment of a normal and healthy microbial community. Two mutually inclusive mechanisms underlie the therapeutic action of FMT direct interaction or competition between the gut microbiota of healthy donors and pathogenic bacteria and the immune system, which affects the survival of pathogenic bacteria. Khoruts and Sadowsky [10] reported the use of FMT for the treatment of *Clostridium difficile* infection, a condition that is difficult to control by antibiotics alone. The procedure resulted

in engraftment and restoration of the structure and function of the normal gut microbial community [10]. The administered gut microbiota competes with *C. difficile* for nutrition and colony-forming resources, disrupts its virulence factors, and activates the host's immune system. The potential advantages of FMT in this situation are supported by several crucial aspects. First and foremost, dysbiosis has been linked to increased intestinal permeability and endotoxemia, both of which exacerbate liver inflammation and injury [11]. FMT can improve gut barrier performance and reduce the translocation of bacterial products into the liver while restoring the gut microbiota balance [20,21]. This restoration may mitigate inflammation and subsequent liver damage. Second, metabolic abnormalities such as insulin resistance and hepatic steatosis, commonly coexist with dysbiosis in diabetes (Fig. 1). FMT can modify the gut microbiota composition and metabolic activity, thereby influencing glucose and lipid metabolism. Through FMT, a healthy gut microbiota can be restored, which may enhance insulin sensitivity, lessen the buildup of hepatic fat, and lessen metabolic dysfunction in the liver. Furthermore, diabetic liver damage is associated to dysbiosis-related alterations in bile acid metabolism. A more balanced bile acid profile and enhanced bile acid signaling in the liver can result from FMT, which can restore the diversity and function of bile acid-metabolizing bacteria. This might lessen liver fibrosis and inflammation [22]. Microbiota transferred from a healthy donor to the patient rapidly re-establishes the beneficial gut microbiota. The gut microbiota comprises more than a trillion bacteria, that are physically separated from intestinal epithelial cells by gut mucosa. The gut mucosal barriers act as first line of defense, protecting from exaggerated inflammation. The tight junctions holding the epithelium cells together prevent the bacteria from entering the portal circulation. The presence of immune cells in mucosa provides additional protection from infectious diseases. The gut vascular barrier acts as an additional barrier, preventing the bacteria from entering the circulation in cases where the intestinal epithelium is breached. FMT containing microbiota derived from the distal gut of a healthy donor is administered to the patient in the form of an odorless and tasteless preparation. It repairs and rebuilds the physiological barriers, blocking the uncontrolled entry of bacterial metabolites to the liver. Overall, there is improvement of the intestinal structure and function leading to improved lipid metabolism, decreased insulin resistance, and suppression of the inflammatory cascade [23–24].

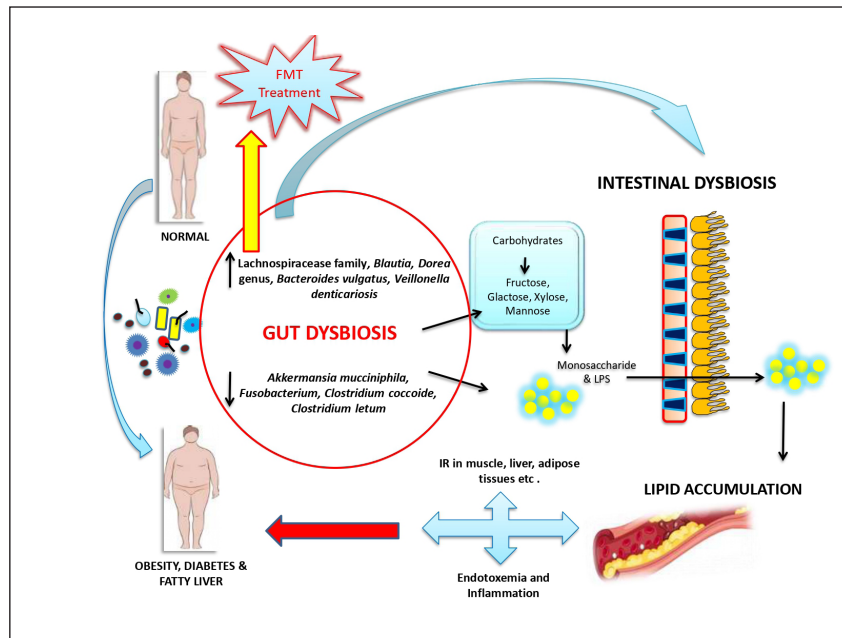


Figure 1. Illustration of intestinal dysbiosis link with insulin resistance (IR), endotoxemia, inflammation for the progression of diabetic associated liver complications. Gut dysbiosis leads to the imbalance of certain microbes which further alter the metabolic process for the synthesis of LPS that leads to the lipid accumulation in different vital organs of the body. The lipid accumulation leads to formation of fatty liver related complications; insulin resistance and the respective conditions lead to the development of dual disease model of DLI. However, the FMT treatment help in the management of both the condition of insulin resistance and fatty liver related complications.

4. INTERACTION BETWEEN ANTI-DIABETIC DRUGS (E.G., METFORMIN, GLP-1 AGONISTS) AND MICROBIOTA

The widely prescribed anti-diabetic medications, including metformin and GLP-1 receptor agonist, achieve part of their efficacy by modulating the gut microbiome. Metformin has been observed to enrich populations of beneficial bacteria such as *A. muciniphila* and *Bifidobacterium*, while it decreases the abundance of potentially pathogenic *Clostridium* species. This shift in microbiota composition strengthens the intestinal barrier and decreases systemic endotoxemia. Enhanced short-chain fatty acid production resulting from these changes also supports improved insulin sensitivity and more favourable hepatic lipid metabolism. In parallel, GLP-1 receptor agonists not only improve glycemic regulation but also reshape gut microbial communities and influence bile acid pathways, thereby fostering a less inflammatory state within the gut–liver axis. These microbiota-dependent mechanisms of anti-diabetic drugs may work in tandem with FMT, underscoring the complex interplay between pharmacological therapy and microbial modulation in mitigating DLI [37].

FMT represents a comprehensive microbiome restoration strategy that transfers an entire healthy microbial community into the patient's gut. This approach restores microbial diversity and balance, strengthens the intestinal barrier, and reduce gut permeability. By limiting lipopolysaccharide translocation and downregulating the TLR4-NF κ B pathway,

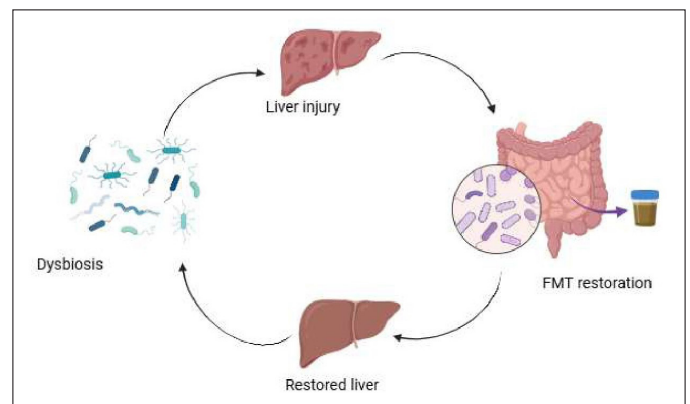


Figure 2. The schematic diagram depicts the gut–liver axis interaction in dysbiosis-induced liver injury and its restoration by the FMT. Dysbiosis disrupts intestinal microbial balance, leading to the increased gut permeability and translocation of microbial metabolites and endotoxins into the portal circulation. These activate hepatic inflammatory pathways (TLR4/NF- κ B), resulting in liver injury. FMT restores healthy microbiota composition, enhances intestinal barrier integrity, modulates bile acid FXR and GLP-1 signaling, and reduces inflammatory cytokines, thereby promoting hepatic recovery and homeostasis.

FMT decreases hepatic inflammation, oxidative stress, and fibrosis [36]. It also normalizes bile acid metabolism and FXR/TGR5 signaling, thereby improving lipid and glucose regulation. In contrast, probiotics and synbiotics work through

targeted modulation. Probiotics introduce specific beneficial bacteria, while symbiotics pair them with prebiotics that promote their growth. These therapies increase short-chain fatty acid production, support mucosal immunity, and modestly improve gut barrier function and metabolic parameters. However, their benefits are strain specific, mild, and temporary, and they do not fully restore microbial diversity. In essence, FMT provides deep and durable microbiota reconstruction, whereas probiotics offer limited, transient modulation [25].

5. FUTURE PERSPECTIVES AND RESEARCH GAPS

Future research should aim to establish a detailed mechanistic framework linking gut dysbiosis, liver injury, and FMT-driven recovery within the gut–liver axis (Fig. 2). This framework should incorporate key regulatory elements, including microbial translocation, bile acid FXR/TGR5 signalling, SCFA-GPCR pathways, and GLP-1-dependent metabolic regulation, which collectively mediate hepatic and systemic metabolic restoration after FMT. Although progress has been made, key mechanistic uncertainties persist, including the influence of donor-recipient microbiome compatibility, stability of microbial engraftment, and duration of FMT-induced improvements in hepatic insulin sensitivity and inflammation. Moreover, discrepancies in donor selection, microbial diversity, and host genetic and metabolic variability continue to challenge reproducibility and therapeutic consistency.

Recent research from 2023 to 2025 on the gut–liver axis and FMT in metabolic disorders remains limited, though growing evidence identifies bile acid FXR/TGR5 signaling, microbial metabolites, and GLP-1 pathways as promising therapeutic targets [26–28]. Investigations by Stadlbauer [26] and Wei *et al.* [27] highlight that the application of microbiome transplantation in metabolic disease management is still in the early development stage. Likewise, emerging findings associate microbiota bile acid interplay and FXR-FGF-19 signaling with lipid regulation and progression of NAFLD [29]. Advances in multiomics technologies and longitudinal metagenomic analyses have begun to uncover FMT-related modulation [30] of phage populations and restoration of bile acid profile [31]; however, such studies remain rare in the context of DLI. Additionally, accumulating evidence correlates microbial metabolites with NAFLD and metabolic dysfunction-associated steatotic liver disease, underscoring the need to integrate precision microbiome-based interventions and next-generation FMT strategies such as synthetic microbial consortia, phage therapy, and post biotic or metabolite-centered treatments [32].

Future studies should utilize integrated multiomics methodologies, including metagenomics, metabolomics, and immuno phenotyping to monitor microbiota recovery, uncover biomarkers predictive of donor-recipient compatibility, and elucidate long-term mechanistic effects in DLI. Bridging these knowledge gaps will facilitate the transition from empirical FMT use to precision-oriented, mechanistically informed microbiome therapies. The innovation of this work lies in the presenting a unified mechanistic framework connecting dysbiosis, DLI, and FMT-mediated repair, with a focus on donor-host compatibility, the sustainability of the therapeutic benefits, and the potential of next generation microbiome interventions in metabolic liver disorders.

6. CONCLUSION

The mechanisms linking dysbiosis to the pathogenesis of DLI involve multiple interconnected processes, including intestinal barrier dysfunction, endotoxemia-induced inflammation, metabolic derangements, bile acid dysregulation, and immune dysregulation within the gut–liver axis. Understanding these mechanisms is essential for developing targeted therapeutic strategies to restore gut microbial balance, ameliorate liver injury, and improve the management of diabetic liver complications. Further research is warranted to unravel the intricate interactions between dysbiosis and liver pathogenesis, leading to novel treatment approaches for DLI. Overall, FMT holds promise as a therapeutic intervention for DLI by targeting dysbiosis and its associated mechanisms. Moreover, further research is needed to elucidate the optimal protocols, long-term safety, and efficacy of FMT in this specific context. However, while FMT offers promise in managing DLI by restoring gut microbial balance, several challenges and safety concerns persist. Variability in donor selection, stool processing, dosage, and delivery methods limits standardisation and complicates cross-study comparisons. The long-term persistence of transplanted microbiota is still unclear due to limited follow-up in clinical trials and some of are cited in Table 1. Hence, standardised and comprehensive research is essential to optimise FMT protocols, confirm long-term safety, and define the patient groups most likely to benefit from this evolving microbiome-targeted therapy.

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12. AVAILABILITY OF DATA AND MATERIALS

All the data is available with the authors and shall be provided upon request.

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The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

REFERENCES

- Chen PC, Chien YW, Yang SC. The alteration of gut microbiota in newly diagnosed type 2 diabetic patients. *Nutrition*. 2018;63–64:51–6. doi: <https://doi.org/10.1016/j.nut.2018.11.019>
- Candido TL, Alfenas RD, Bressan J. Dysbiosis and metabolic endotoxemia induced by high-fat diet. *Nutr Hosp*. 2018;35:1432–40. doi: <https://doi.org/10.20960/nh.1792>
- Arora A, Behl T, Sehgal A, Singh S, Sharma N, Bhatia S, *et al.* Unravelling the involvement of gut microbiota in type 2 diabetes mellitus. *Life Sci*. 2021;15:119311. doi: <https://doi.org/10.1016/j.lfs.2021.119311>
- Corb Aron RA, Abid A, Vesa CM, Nechifor AC, Behl T, Ghitea TC, *et al.* Recognizing the benefits of pre-/probiotics in metabolic syndrome and type 2 diabetes mellitus considering the influence of *Akkermansia muciniphila* as a key gut bacterium. *Microorganisms*. 2021;9:618. doi: <https://doi.org/10.3390/microorganisms9030618>
- Deng J, Zeng L, Lai X, Li J, Liu L, Lin Q, *et al.* Metformin protects against intestinal barrier dysfunction via AMPK α -dependent inhibition of JNK signaling activation. *J Cell Mol Med*. 2018;22:546. doi: <https://doi.org/10.1111/jcmm.13423>
- Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, *et al.* Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. *Nature*. 2015;528:262. doi: <https://doi.org/10.1038/nature15766>
- Guo X, Okpara ES, Hu W, Yan C, Wang Y, Liang Q, *et al.* Interactive relationships between intestinal flora and bile acids. *Int J Mol Sci*. 2022;23:8343. doi: <https://doi.org/10.3390/ijms23158343>
- Gupta M, Krishan P, Kaur A, Arora S, Trehanpati N, Singh TG, *et al.* Mechanistic and physiological approaches of fecal microbiota transplantation in NAFLD. *Inflamm Res*. 2021;70:765–76. doi: <https://doi.org/10.1007/s00011-021-01485-w>
- Chancharoentana W, Kamolratanakul S, Schultz MJ, Leelahavanichkul A. The leaky gut and the gut microbiome in sepsis-targets in research and treatment. *Clin Sci*. 2023;137(8):645–62. doi: <https://doi.org/10.1042/CS20220798>
- Khoruts A, Sadowsky MJ. Understanding the mechanisms of faecal microbiota transplantation. *Nature Rev Gastroenterol Hepatol*. 2016;13(9):508–16. doi: <https://doi.org/10.1038/nrgastro.2016.104>
- Lee JY, Bae E, Kim HY, Lee KM, Yoon SS, Lee DC. High-fat-diet-induced oxidative stress linked to the increased colonization of *Lactobacillus sakei* in an obese population. *MicrobiolSpectr*. 2021;9:e000742. doi: <https://doi.org/10.1128/spectrum.0007421>
- An L, Wirth U, Koch D, Schirren M, Drefs M, Koliogiannis D, *et al.* The role of gut-derived lipopolysaccharides and the intestinal barrier in fatty liver diseases. *J Gastrointestinal Surg*. 2022;26(3):671–83. doi: <https://doi.org/10.1007/s11605-021-05212-y>
- Li T, Chiang JYL. Bile acid signaling in metabolic disease and drug therapy. *Pharmacol Rev*. 2014;66:948–83. doi: <https://doi.org/10.1124/pr.113.008201>
- Li YJ, Chen X, Kwan TK, Loh YW, Singer J, Liu Y, *et al.* Dietary fiber protects against diabetic nephropathy through short-chain fatty acid-mediated activation of G protein-coupled receptors GPR43 and GPR109A. *J Am Soc Nephrol*. 2020;31:1267–86. doi: <https://doi.org/10.1681/ASN.2019080860>
- Morris G, Berk M, Carvalho A, Caso JR, Sanz Y, Walder K, *et al.* The role of the microbial metabolites including tryptophan catabolites and short chain fatty acids in the pathophysiology of immune-inflammatory and neuroimmune disease. *Mol Neurobiol*. 2017;54:4432–51. doi: <https://doi.org/10.1007/s12035-016-0267-0>
- Mouries J, Brescia P, Silvestri A, Spadoni I, Sorribas M, Wies R, *et al.* Microbiota-driven gut vascular barrier disruption is a prerequisite for non-alcoholic steatohepatitis development. *J Hepatol*. 2019;71:1216–28. doi: <https://doi.org/10.1016/j.jhep.2019.07.023>
- Pomié C, Blasco-Baque V, Klopp P, Nicolas S, Waget A, Loubières P, *et al.* Triggering the adaptive immune system with commensal gut bacteria protects against insulin resistance and dysglycemia. *Mol Metab*. 2016;5:392–403. doi: <https://doi.org/10.1016/j.molmet.2016.04.004>
- Qiu XX, Cheng SL, Liu YH, Li Y, Zhang R, Li NN, *et al.* Fecal microbiota transplantation for treatment of non-alcoholic fatty liver disease: mechanism, clinical evidence, and prospect. *World J Gastroenterol*. 2024;30(8):833–42. doi: <https://doi.org/10.3748/wjg.v30.i8.833>
- Ramirez-Perez O, Cruz-Ramon V, Chinchilla-Lopez P, Mendez-Sanchez N. The role of the gut microbiota in bile acid metabolism. *Ann Hepatol*. 2018;16:s15–s20. doi: [https://doi.org/10.1016/S1665-2681\(18\)30005-6](https://doi.org/10.1016/S1665-2681(18)30005-6)
- Saad MJA, Santos A, Prada PO. Linking gut microbiota and inflammation to obesity and insulin resistance. *Physiology*. 2016;31:283–93. doi: <https://doi.org/10.1152/physiol.00036.2015>
- Sehgal R, Bedi O, Trehanpati N. Role of microbiota in pathogenesis and management of viral hepatitis. *Front Cell Infect*. 2020;11:341. doi: <https://doi.org/10.3389/fcimb.2021.00341>
- Shih CT, Yeh YT, Lin CC, Yang LY, Chiang CP. *Akkermansia muciniphila* is negatively correlated with hemoglobin A1c in refractory diabetes. *Microorganisms*. 2020;8(9):1360. doi: <https://doi.org/10.3390/microorganisms8091360>
- Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. *Front Endocrinol*. 2020;11:11. doi: <https://doi.org/10.3389/fendo.2020.00011>
- Yuan JH, Xie QS, Chen GC, Huang CL, Yu T, Chen QK, *et al.* Impaired intestinal barrier function in type 2 diabetic patients measured by serum LPS, Zonulin, and IFABP. *JDC*. 2021;35:107766. doi: <https://doi.org/10.1016/j.jdiacomp.2021.107766>
- Han TR, Yang WJ, Tan QH, Bai S, Zhong H, Tai Y, *et al.* Gut microbiota therapy for nonalcoholic fatty liver disease: evidence from randomized clinical trials. *Front Microbiol*. 2023;13:1004911. doi: <https://doi.org/10.3389/fmicb.2022.1004911>
- Stadlbauer V. Liver-gut interaction: role of microbiome transplantation in the future treatment of metabolic disease. *J Pers Med*. 2023;13(2):220. doi: <https://doi.org/10.3390/jpm13020220>
- Wei M, Tu W, Huang G. Regulating bile acid signalling for NAFLD: molecular insights and novel therapeutic interventions. *Front Microbiol*. 2024;15:1341938. doi: <https://doi.org/10.3389/fmicb.2024.1341938>
- Guo GJ, Yao F, Lu WP, Xu HM. Gut microbiome and metabolic-associated fatty liver disease: current status and potential applications. *World J Hepatol* 2023;15(7):867–86. doi: <https://doi.org/10.4291/wjhep.v15.i7.867>
- Xu H, Fang F, Wu K, Song J, Li Y, Lu X, *et al.* Gut microbiota-bile acid crosstalk regulates murine lipid metabolism via the intestinal FXR-FGF19 axis in diet-induced humanized dyslipidemia. *Microbiome*. 2023;11:262. doi: <https://doi.org/10.1186/s40168-023-01679-1>
- Zuppi M, Vatanen T, Wilson BC, Golovina E, Portlock T, Cutfield WS, *et al.* Fecal microbiota transplantation alters gut phage communities in a clinical trial for obesity. *Microbiome*. 2024;12:122. doi: <https://doi.org/10.1186/s40168-024-01421-9>

31. Lu G, Zhang S, Wang R, Wu X, Chen Y, Wen Q, *et al.* Fecal microbiota transplantation improves bile acid malabsorption in patients with inflammatory bowel disease: results of microbiota and metabolites from two cohort studies. *BMC Med.* 2025;23:511. doi: <https://doi.org/10.1186/s12916-025-04353-y>
32. Ouyang C, Liu P, Liu Y, Lan J, Liu Q. Metabolites mediate the causal associations between gut microbiota and NAFLD: a Mendelian randomization study. *BMC Gastroenterol.* 2024;24:244. doi: <https://doi.org/10.1186/s12876-024-03277-w>
33. Eichner M, Protze J, Piontek A, Krause G, Piontek J. Targeting and alteration of tight junctions by bacteria and their virulence factors such as *Clostridium perfringens* enterotoxin. *Pflügers Archiv-European J Physiol.* 2017;469(1):77–90. doi: <https://doi.org/10.1007/s00424-017-2003-y>
34. Pruteanu M, Shanahan F. Digestion of epithelial tight junction proteins by the commensal *Clostridium perfringens*. *Am J Physiol-Gastrointestinal Liver Physiol.* 2013;305(10):G740–8. doi: <https://doi.org/10.1152/ajpgi.00193.2013>
35. Hauser G, Benjak Horvat I, Rajilić-Stojanović M, Krznarić-Zrnić I, Kukla M, Aljinović-Vučić V, *et al.* Intestinal microbiota modulation by fecal microbiota transplantation in nonalcoholic fatty liver disease. *Biomedicines.* 2025;13(4):779. doi: <https://doi.org/10.3390/biomedicines13040779>
36. Ma L, Zhang MH, Xu YF, Hao YX, Niu XX, Li Y, *et al.* Fecal microbiota transplantation: a promising treatment strategy for chronic liver disease. *World J Gastroenterol.* 2025;31(28):105089. doi: <https://doi.org/10.3748/wjg.v31.i28.105089> (verified from journal index)
37. Pavlo Petakh, Kamyshna I, Kamyshnyi A. Effects of metformin on the gut microbiota: a systematic review. *Mol Metab.* 2023;77:101805. doi: <https://doi.org/10.1016/j.molmet.2023.101805>
38. Xue L, Deng Z, Luo W, He X, Chen Y. Effect of fecal microbiota transplantation on non-alcoholic fatty liver disease: a randomized clinical trial. *Front Cellular Infect Microbiol.* 2022;12:759306. doi: <https://doi.org/10.3389/fcimb.2022.1056394>
39. Gómez-Pérez AM, Muñoz-Garach A, Lasserrot-Cuadrado A, Moreno-Indias I, Tinahones FJ. Microbiota transplantation in individuals with type 2 diabetes and a high degree of insulin resistance. *Nutrients.* 2024;16(20):3491.
40. Craven L, Rahman A, Nair Parvathy S, Beaton M, Silverman J, Qumosani K, *et al.* Allogenic fecal microbiota transplantation in patients with nonalcoholic fatty liver disease improves abnormal small intestinal permeability: a randomized control trial. *Off J Am Coll Gastroenterol| ACG.* 2020;115(7):1055–65.
41. Motta BM, Grander C, Gögele M, Foco L, Vukovic V, Melotti R, *et al.* Microbiota, type 2 diabetes and non-alcoholic fatty liver disease: protocol of an observational study. *J Translational Med.* 2019;17:408. doi: <https://doi.org/10.1186/s12967-019-02130-z>
42. Razavi S, Amirmozafari N, Zahedi Bialvaei A, Navab-Moghadam F, Khamseh ME, Alaei-Shahmiri F, *et al.* Gut microbiota composition and type 2 diabetes: are these subjects linked together?. *Heliyon.* 2024;10:e39464. doi: <https://doi.org/10.1016/j.heliyon.2024.e39464>
43. Yang C, Xu J, Xu X, Xu W, Tong B, Wang S, *et al.* Characteristics of gut microbiota in patients with metabolic associated fatty liver disease. *Sci Rep.* 2023;13:9988. doi: <https://doi.org/10.1038/s41598-023-40503-8>

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