Gut-Liver Axis, Malnutrition, and Non-alcoholic Fatty Liver Disease: Exploring the Association

Reviewed by:

Dr. Umesh Jalihal
MD, DM,DNB
Director & Chief Gastroenterologist
Karnataka Gastro Center, Bangalore

Non-alcoholic fatty liver disease: Overview

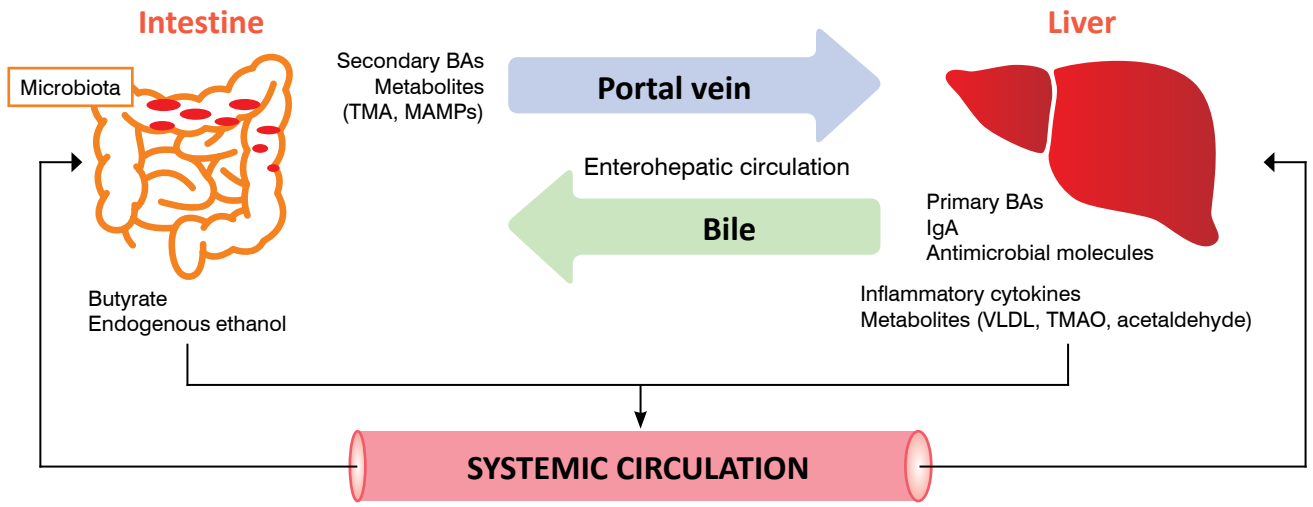
Non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of metabolic syndrome, is one of the most frequent forms of chronic liver disorder, with steadily increasing incidence rates worldwide.[1-3] Ranging from hepatic steatosis and steatohepatitis to fibrosis and cirrhosis, NAFLD refers to the significant fat accumulation of hepatocytes (≥5% of the weight of liver) in the absence of excessive alcohol consumption or other causes of liver disease.[4-7] When individuals present with the features of metabolic syndrome, such as overweight/obesity, hypertension, insulin resistance, and dyslipidemia, it is reasonable to envisage the possibility of NAFLD.[7,8]

NAFLD affects approximately one-quarter of the global adult population and the global prevalence is expected to considerably increase in both adult and pediatric populations.[5] While recent data estimate that NAFLD affects 3% to 12% of the pediatric population,[9] the global prevalence of NAFLD among individuals > 15 years of age is estimated to be 33.5% in 2030.[4]

Gut-liver axis: A gateway between microbes and liver

The gut-liver axis refers to the anatomical and functional interaction between the gastrointestinal tract, along with its microbiota, and the liver.[3,10] The communication between the liver and the gut is bidirectional, mediated through the biliary tract, the portal vein, and systemic circulation (Figure 1).[1,11] The liver secretes primary bile acids and other bioactive mediators into the biliary tract, which reach the intestinal lumen, and contribute to maintenance of gut eubiosis. The intestine signals back to the liver secreting enterokines from the terminal ileum; gut products include host and/or microbial metabolites and microbial-associated molecular patterns (MAMPs). In the distal gut, microbiota, which is mainly composed of bacteria and other microbial components, has many functional roles in health

Figure 1: Bidirectional communication of the gut-liver axis



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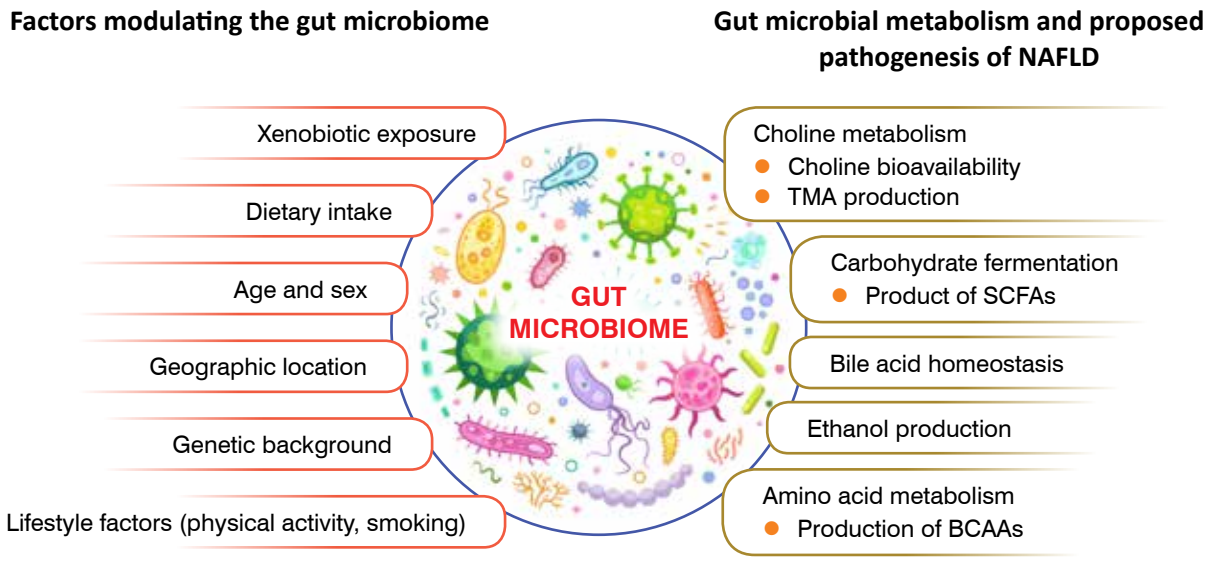
Abbreviations: BAs, bile acids; MAMPs, microbial-associated molecular patterns; TMA, trimethylamine; TMAO, trimethylamine N-oxide; VLDL, very-low density lipoprotein.

Figure 2: Potential mechanistic links between the gut microbiome and NAFLD



Abbreviations: TMA, trimethylamine; SCFAs, short chain fatty acids, BCAAs, branched-chain amino acids.

Adapted from: Sharpton SR, Yong GJM, Terrault NA, et al. Gut Microbial Metabolism and Nonalcoholic Fatty Liver Disease. *Hepatol Commun.* 2018;3(1):29-43.

and disease (such as digestion, vitamins production, resistance to colonization by pathogenic bacteria, and stimulation of the immune system). Gut microbiota metabolizes bile acids and amino acids, which are transported through the systemic circulation to reach the liver; its composition is modified by diet, alcohol consumption, and medications.[1,11]

Link between gut microbiome and the pathogenesis of NAFLD

The gut-liver axis plays critical roles in the pathogenesis and progression of NAFLD, likely mediated through two of its main components – intestinal barrier and gut microbiome.[3,11] The presence of the dysbiotic microbiome and an altered intestinal barrier influenced by bacterial ethanol, possibly associated with disruption of tight-junctions (TJs), promotes the translocation of several bacterial metabolites and pro-inflammatory components into the portal circulation. Ultimately, it may induce an acceleration in occurrence and development of NAFLD.[3,4]

Several potential mechanistic links between the gut microbiome and NAFLD have emerged; postulated mechanisms include dysregulation of methylamine metabolism, carbohydrate fermentation and generation of short chain fatty acids (SCFAs), bile acid metabolism, endogenous ethanol production, and amino acid metabolism (Figure 2).[12]

NAFLD and nutrition

Considering the hepatic expression of metabolic syndrome, NAFLD is significantly affected by malnutrition. Malnutrition, although mostly linked to dietary inadequacies, is an umbrella term encompassing both overnutrition and undernutrition.[5] Overnutrition has so far been considered the key problem of NAFLD; therefore, after a diagnosis of NAFLD, the primary focus is usually given to controlling overfeeding and body weight.[13]

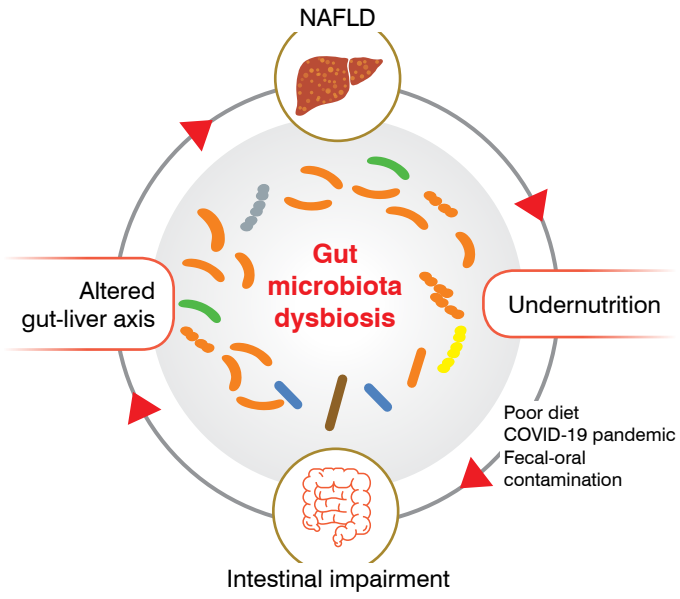
It has been reported that different diet components affect the progression and development of NAFLD. Among macronutrients, fat and carbohydrate rich diets support the pathogenesis of NAFLD. Fiber and low glycemic index diets from carbohydrates, as well as MUFAs and ω-3 fatty acids from fats, prevent NAFLD pathogenesis. Among micronutrients, vitamin C, vitamin E, vitamin D and polyphenols prevent NAFLD pathogenesis.[13]

Undernutrition-induced NAFLD

Although NAFLD etiology and treatment have been extensively examined in the context of overnutrition and obesity, recent data suggest that NAFLD also manifests in undernourished populations.[5,9]

Undernutrition affects more than 10% of the world's population and remains a serious public health concern, especially for children in low- to middle-income nations. Nearly half of all fatalities in children under the age of five are caused by malnutrition. Undernutrition is primarily caused by nutritional deficiencies; however, there are a number of interrelated factors that also contribute to malnutrition, such as poverty, poor sanitation, climate change, and most recently, the COVID-19 pandemic. Childhood undernutrition markedly increases the risks of the metabolic syndrome, visceral adiposity, and fatty liver disease.[5,9]

Figure 3: The vicious loop of undernutrition-induced NAFLD



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The vicious cycle of undernutrition-induced NAFLD

Fecal-oral contamination is a significant environmental burden that contributes to the persistence of early-life malnutrition. Recurrent exposure to fecal-oral contamination alters the gut microbiota, promotes intestinal inflammation, and disrupts barrier integrity.[5,9] Fecal-oral contamination and consequent gut dysbiosis in pediatric populations are associated with growth stunting and long-term effects of malnutrition.[9] Although undernutrition alone appears to be sufficient to promote hepatic steatosis and fecal microbiome shifts, the combination of poor diet and fecal-oral contamination seems to exacerbate hepatic triglyceride levels; this suggests a link between bacterial-induced gut barrier disruption and the progression of NAFLD.[5]

In fact, malnutrition-induced NAFLD is supposed to be facilitated by a vicious loop of gut-liver dysfunction. External factors, such as poor diet and gastrointestinal insult, alter gut metabolism and barrier function, which contribute to gut microbiota dysbiosis. In turn, the dysbiotic gut promotes malabsorption and modifies the gut-liver axis through microbial-dependent pathways, thus contributing to undernutrition and hepatic pathologies (Figure 3).[5]

Clinical and experimental model studies investigating gut-liver pathologies from a multiomic perspective indicate that dietary excesses and deficits cause similar pathologic features during NAFLD pathology (Table 1).[5]

Dietary intervention and gut microbiome-targeted-therapy in the management of NAFLD

Breaking the vicious cycle of undernutrition-induced NAFLD entails a multifaceted approach, including the use of microbiome-targeted therapies and established therapeutic dietary interventions.[5] In fact, the potential for addressing the gut microbiome provides a unique approach to the management of NAFLD.[12] Dietary interventions, probiotics, prebiotics, synbiotics, functional oligosaccharides, dietary fibres, ω-3 polyunsaturated fatty acids (ω-3 PUFAs), functional amino acids (L-tryptophan and L-glutamine), carotenoids, and polyphenols are just a few of the methods used to manipulate the gut microbiome.[4,12]

Table 1: Undernutrition and overnutrition-induced NAFLD pathophysiology

Undernutrition	Overnutrition
Pathophysiologic features	
• ↓ Protein, fat, and/or ↑ carbohydrate diets • Altered micronutrients (MND, iron deficiency) • Increased oxidative stress • Impaired hepatic metabolism (↓ PUFA, ↑ triglyceride) • Metabolic syndrome (increased risk) • Hepatic steatosis • Gut microbiota dysbiosis (↑LPS, EED: increased pathogenic microbes) • Altered bile acid profile (Kwashiorkor: ↑ secondary bile acids)	• ↑ Fat, carbohydrate diets • Altered micronutrients (↑ ferritin, MND) • Increased oxidative stress • Impaired hepatic metabolism (↓ PUFA, ↑ triglyceride) • Metabolic syndrome (increased risk) • Hepatic steatosis • Gut microbiota dysbiosis (↑ LPS, reduced Bacteroidetes) • Altered bile acid profile (↓ secondary: primary bile acid ratio)
Treatment approaches	
• ↑ Protein and/or caloric consumption, ↑ Body weight ↓ Gut dysbiosis (Kwashiorkor: MDCF intervention)	• ↓ Carbohydrate and/or caloric consumption, ↓ body weight ↓ Gut dysbiosis (probiotic + dietary intervention)

Abbreviations: MND, micronutrient deficiency; PUFA, polyunsaturated fatty acid; LPS, lipopolysaccharide; EED, environmental enteric dysfunction; MDCF, microbiota-directed complementary food.

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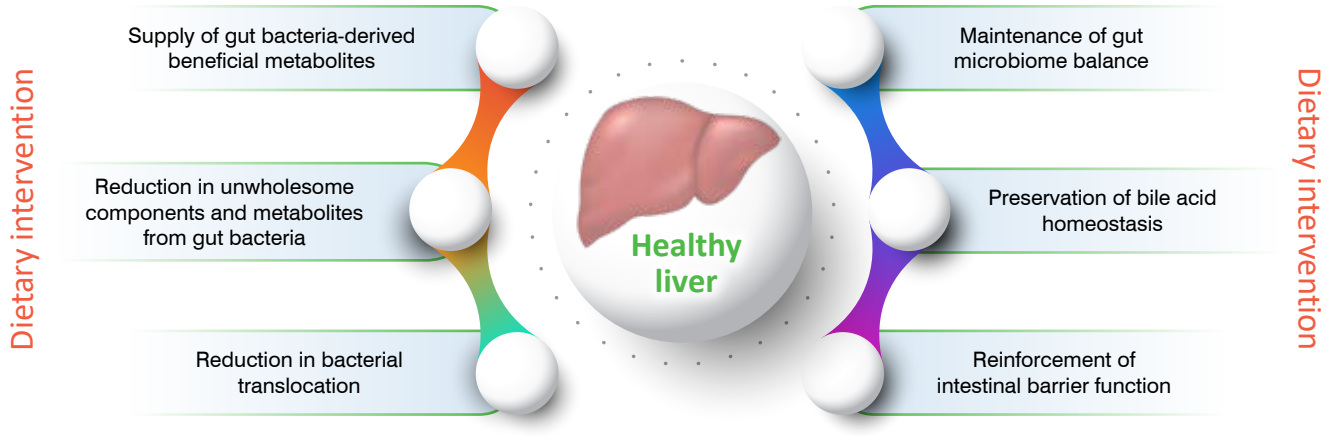
Figure 4: Role of dietary intervention in protecting and ameliorating NAFLD based on gut-liver axis



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Nutritional supplements aid in the prevention of NAFLD by facilitating the maintenance of homeostasis in the gut microbiome, improving intestinal barrier function and bile acid profiles, and decreasing the migration of bacteria and harmful factors into the liver.[4] These dietary interventions have been shown to protect and improve NAFLD by targeting the gut-liver axis, including maintenance of gut microbiome balance; preservation of bile acid homeostasis; reinforcement of intestinal barrier function; reduction in bacterial translocation; reduction in unwholesome components and metabolites from gut bacteria; and supply of gut bacteria-derived beneficial metabolites (Figure 4).[4,5,12]

Conclusion

The term "gut-liver axis" refers to the mutual interaction between the gut, along with its microbiota, and the liver. The gut-liver axis is now widely acknowledged to have a significant role in the onset and progression of liver disease. Gut barrier integrity, disturbed bile acid balance, and altered intestinal flora have all been identified as important regulators of metabolic dysfunction, which accelerates the progression of NAFLD. Although NAFLD etiology and treatment have been extensively examined in the context of overnutrition and obesity, recent data suggest that NAFLD also manifests in undernourished populations. External factors, such as poor diet and gastrointestinal insult, alter gut metabolism and barrier function, which contribute to gut microbiota dysbiosis. In turn, the dysbiotic gut promotes malabsorption and modifies the gut-liver axis through microbial-dependent pathways, thus contributing to undernutrition and hepatic pathologies. Nutritional supplements help prevent NAFLD likely by targeting the gut-liver axis and facilitating the maintenance of gut microbiome balance, ameliorating the intestinal barrier function and bile acid homeostasis, and reducing the bacterial translocation and migration of toxic substances into the liver.

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