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Gut Microbiota and Non-Alcoholic Fatty Liver Disease: Current Pathogenic Paradigm and Therapeutic Aspect

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ABSTRACT

Changes in the gut microbiota are essential factors that cause non-alcoholic fatty liver disease (NAFLD), obesity, and diabetes. Small intestine bacteria overgrowth is discovered in NAFLD patients. Disruptions in the gut-liver axis include environmental factors that induce microbiota dysbiosis and/or increased intestinal permeability that causes liver inflammation. The most recommended therapy for NAFLD patients is still limited to lifestyle changes. This review will describe the role of the gut microbiota in the pathogenesis and therapeutic intervention of NAFLD. Recent evidence reveals that the gut microbiota is one of the main factors in the pathogenesis and progression of NAFLD through several mechanisms, particularly dysbiosis. This significant role makes the gut microbiota a non-invasive biomarker for NAFLD examination and a more effective therapeutic target.

Keywords: *gut microbiota, NAFLD, current pathogenic, therapeutic aspect*

ABSTRAK

Perubahan pada mikrobiota usus merupakan faktor esensial yang dapat menyebabkan non-alcoholic fatty liver disease (NAFLD), obesitas, dan diabetes. Pertumbuhan bakteri usus kecil yang berlebih dilaporkan telah ditemukan pada pasien NAFLD. Gangguan pada gut-liver axis termasuk faktor lingkungan menginduksi dysbiosis mikrobiota dan/atau peningkatan permeabilitas usus yang menyebabkan peradangan hati. Terapi yang paling direkomendasikan untuk pasien NAFLD masih terbatas pada perubahan gaya hidup. Telaah ini menjelaskan peran mikrobiota usus dalam patogenesis dan intervensi terapeutik NAFLD. Bukti terbaru mengungkapkan bahwa mikrobiota usus adalah salah satu faktor utama dalam patogenesis dan perkembangan NAFLD melalui beberapa mekanisme, terutama dysbiosis. Peran penting ini membuat mikrobiota usus menjadi biomarker non-invasif untuk pemeriksaan NAFLD dan target terapi yang lebih efektif.

Kata kunci: *mikrobiota usus, NAFLD, patogen, aspek terapeutik*

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is excessive fat accumulation or steatosis and is not caused by significant alcohol consumption. *Liver steatosis* is fat accumulation in 5% of hepatocytes.[16] NAFLD has a broad spectrum from simple steatosis to nonalcoholic steatohepatitis (NASH), which is a progressive form characterized by steatosis, hepatocyte swelling, and inflammation. NASH can progress to fibrosis, cirrhosis, and hepatocellular carcinoma. NAFLD is closely related to metabolic syndrome, including obesity, insulin resistance, hyperlipidemia, and hypertension.[1] The global prevalence of NAFLD is rapidly increasing and is estimated at 25%, while in Indonesia, it is 30%.[1,2]

NAFLD has a highly complex pathogenesis and is not fully elucidated yet. The current theory, namely the multiple-hit hypothesis, states that NAFLD is caused by a complex interaction between diet, gut microbiota dysbiosis, genetic factors, insulin resistance, and environmental factors. Changes in the gut microbiota are essential factors that cause NAFLD, obesity, and diabetes. In addition, small intestine bacteria overgrowth is discovered in NAFLD patients.[3]

Several studies have revealed that changes in the gut microbiota interfere with hepatic carbohydrate and fat metabolism and affect the pro-and anti-inflammatory balance in the liver, which then triggers NAFLD and its development into NASH. However, the mechanism that explains this is still not apparent. This review will describe the role of the gut microbiota in the pathogenesis and therapeutic intervention of NAFLD.

GUT MICROBIOTA

Gut microbiota is a population of microbes in the gastrointestinal tract with the highest concentration in the terminal ileum and colon, reaching 1,011 microbes/gram. Anaerobic microbes dominate the gut microbiota population with a percentage of 99.9%. Some microbes typically found in the intestines are *Clostridium* spp., *Bacteroides* spp., *Prevotella* spp., and *Peptostreptoc*occus spp. Gut microbiota is closely involved in the physiology of the human body. These microbes are involved in digestive functions by forming and absorbing many metabolic products such as lipids, amino acids, vitamins, and bile acids. Gut microbiota can also prevent the colonization of potentially harmful foreign bacteria by producing antibacterial molecules and competing for food sources.[4] The gut microbiota also has a vital role in metabolic syndrome and is associated with weight gain and other metabolic disorders. The diversity of gut microbiota is influenced by various factors, such as demographical location, diet, lifestyle, age, host genetics, and mode of delivery.[5]

THE RELATIONSHIP BETWEEN MICROBIOTA GUT AND NAFLD

Gut-Liver Axis

The gut-liver axis is a bidirectional connection through the biliary tract, portal vein, and systemic circulation. This unique interaction between the liver and the gastrointestinal tract allows the transport of nutrients from the intestines directly to the liver, whereas the liver provides feedback via bile secretion into the digestive tract. The intestinal mucosa structure is anatomically and functionally allowing interaction between these two organs. Excellent and healthy interactions allow several physiological functions, such as absorption of nutrients by the liver, preventing the spread of microbial germs, and toxins to the systemic circulation.[6] Disruptions in the gut-liver axis include environmental factors that induce microbiota dysbiosis and/or increased intestinal permeability that causes liver inflammation. This triggers disease progression, including NAFLD.[1]

Intestinal Barrier Dysfunction (Gut Barrier)

The primary function of the gut barrier is to protect tissues and organs from parasites, microorganisms, microbes associated molecular patterns (MAMPs), microbiota metabolites, food antigens, or toxins when the intestines absorb nutrients. The gut barrier consists of several functional elements. The physical barrier consists of commensal bacteria, mucins secreted by goblet cells, and intestinal epithelium covered by tight junction proteins. In comparison, the immune barrier consists of cellular and humoral immune components. Humoral factors such as antimicrobial peptides and secretory immunoglobulin A (SIgA) secreted by plasma cells control the number and composition of microbiota in the lumen and protect against intestinal mucosal damage by binding to microbial antigens and toxins. There is no solid explanation regarding the main factors that cause increased intestinal permeability. However, some mentioned that environmental factors, i.e. low fiber and high fructose diet and some food additives, have a significant role. For example, consuming fructose in large amounts and for a long

time is associated with the breakdown of tight junction proteins, thereby increasing intestinal permeability and causing gut barrier dysfunction.[1]

Dysbiosis

NAFLD is associated with changes in the composition and function of the gut microbiota, known as dysbiosis. Dysbiosis includes two characteristics. The first is the decrease or disappearance of some commensal bacteria. The loss of specific microbial species causes a decrease in microbiota diversity associated with metabolic and immune disorders. The second is the overgrowth of commensal pathogenic bacteria (pathobionts). In healthy gut ecosystems, pathobionts show a low percentage. However, in some diseases, pathobionts outgrow other commensal bacteria. In NAFLD and metabolic syndrome, gram-negative bacteria such as *Enterobacteriaceae and phylum Proteobacteria* are often found. Dysbiosis may be caused by host factors such as genetic background, health status (infection, inflammation), lifestyle or environmental factors such as diet (high in sugar, low in fiber), or use of xenobiotics (antibiotics, drugs, food additives).[1]

Microbiota dysbiosis can affect host immunity, metabolic systems, and mucosal integrity through several different mechanisms. Dysbiosis affects the immune system by modulation of inflammasome signaling with microbial metabolites, Toll-like receptor (TLR) and NOD-like receptor (NLR) signaling, SIgA degradation, the altered balance between regulatory and pro-inflammatory T cell subsets, and direct mucolytic activity. These signaling changes increase the expression of IL-1 and TNF-cytokines that cause steatosis and inflammation through Kupffer cell activation. The mechanism of modulation of the metabolic system is through the production of short-chain fatty acids (SCFAs) and the conversion of choline to trimethylamine (TMA), which affect glucose and lipid metabolism. The integrity of the intestinal mucosa can be impaired due to the production of acetaldehyde by exogenous or endogenous ethanol microbes.[1] The control of the gut microbiota is also essential, particularly in maintaining the homeostasis of the gut-liver axis as previously described.[6]

Changes in the composition of the microbiota in NAFLD depend on the clinical degree of the disease.[7] The most common characteristic in NAFLD progression is an increase in gram-negative bacteria, especially Protoebacteria.[8] These changes also affect the development of a pro-inflammatory and metabolically toxic gut environment that results in dysfunction of the gut barrier, exposure of the liver to dietary and microbial factors and the progression of NAFLD.[7] Other changes in microbiota composition that occur in NAFLD patients are an increase in Proteobacteria, Enterobacteriaceae, *Escherichia, Bacteroides, Dorea*, and *Peptoniphilus* (genus), as well as a decrease in Rikenellaceae, Ruminococcaceae, *Faecalibacterium, Coprococcus, Anaerosporobacter*, and *Eubacterium*.[1]

Small Intestine Bacterial Overgrowth (SIBO)

SIBO was defined as bacterial culture > 105 colony forming units (CFU)/mL in the upper jejunum. SIBO directly relates to the severity of liver disease and is found in 39–85% of NAFLD/NASH patients. SIBO results from decreased intestinal motility and bile acid production. In the pathogenesis of NAFLD, SIBO plays a role in interfering with intestinal permeability and fat development in the liver. SIBO-induced release of Toll-like receptor 4 (TLR4) and IL-8 can trigger inflammation. In addition, SIBO also increases endogenous ethanol, increasing the secretion of lipopolysaccharide (LPS). Therefore, SIBO is considered as an independent risk factor for NAFLD severity and is vital in progressing to NASH and cirrhosis.[9]

Intestinal Factors

Intestinal factors involved in the pathogenesis of NAFLD may be food, products of the gut microbiota, or host factors. Several studies have shown that the factors described below have a significant role in NAFLD occurrence.

Components of Microbiota

In healthy conditions, exposure to the liver by microbiota and its components does not occur significantly. However, if the gut barrier is disrupted due to the direct influence of dietary factors, such as ethanol or fructose, or indirectly due to dysbiosis, the liver can be exposed to significant amounts of bacteria. Increased exposure to microorganisms and their products, such as LPS, peptidoglycan, viral or bacterial DNA, leads to pro-inflammatory changes. These components are collectively referred to as MAMPs and are then recognized by the innate immune cells of the liver (Kupffer cells, dendritic, natural killer, natural killer T, and hepatic stellate cells). Activation of these cells will trigger fibrosis, cirrhosis, and hepatocellular carcinoma.[1]

Fructose

Sugar consumption in general increases the potential for metabolic syndrome, which is one of the predisposing factors for NAFLD. Many pre-clinical and clinical studies have proven the primary role of fructose in the pathogenesis of NAFLD. Fructose induces dysbiosis of gut microbiota and increases intestinal permeability by damaging protein tight junctions. Histological changes in the intestinal wall induced by fructose are thinning of the mucosa, loss of crypts and glands and oedema of the lamina propriae. In addition, the translocation of bacterial antigens from the gut to the liver leads to activation of the innate immune system and hepatic inflammation. More significantly, fructose also has deleterious effects on the liver. The different metabolism of fructose with glucose causes a decrease in ATP synthesis, uric acid formation, mitochondrial dysfunction, de novo lipogenesis, and inhibits beta-fatty oxidation.[1] Therefore, a high sugar diet, including fructose, will cause high sugar levels in the blood, resulting from absorption from the lumen of the digestive tract. This absorption is mediated by glucose transporter 5 (GLUT 5), which is a glucose transporter. Then after entering the systemic circulation when it reaches the hepatic portal vein system, it will be stored in the liver. In the liver, fructose is metabolized to glucose and is a motor for lipid synthesis. This repeated condition can trigger a condition of steatosis, increased triglycerides and fat (adipose) tissue.[10]

Choline and Its Metabolites

Choline is an essential nutrient with many functions, including the synthesis of phosphatidylcholine, which is required to synthesize cell membranes, and very-low-density lipoprotein (VLDL), which is responsible for the transport of triglycerides out of the liver. Choline itself can be obtained both from the daily diet and endogenous synthesis. The liver is the primary organ that regulates choline metabolism. Choline deficiency in humans is associated with NAFLD and muscle damage. However, under some conditions, choline can have a negative effect on the pathogenesis of NAFLD. A specific subset of gut microbiota can convert choline into TMA, transported to the liver via the portal vein and then metabolized into trimethylamine-N-oxide (TMAO), a dangerous metabolite. Elevated serum TMAO levels are consistently associated with liver steatosis.[1] Differences in the composition of the gut microbiota in each individual can trigger differences in choline absorption. Besides that, the gut microbiota is also suspected to play a role in the metabolism of several components of the diet in the intestine, one of which is choline which can trigger changes in bioavailability and potentially cause choline deficiency.[11] The conversion of choline by these microbiota plays a role in the pathogenesis of NAFLD through two mechanisms. First, a decrease in choline's bioavailability causes a lack of export of VLDL particles from the liver, resulting in lipid accumulation and inflammation. Second, increased levels of TMAO in the liver increase insulin resistance and decrease glucose tolerance.[3] In addition, TMAO, which reduces the activity of CYP7A1 and CYP27A1 enzymes, can reduce the conversion of cholesterol to bile acids. Elevated TMAO levels are also associated with other metabolic syndromes, such as cardiovascular disease and type 2 diabetes.[1]

Short Chain Fatty Acids (SCFAs)

SCFAs are fatty acids with a structure of less than six carbon atoms, such as butyrate and acetate. The gut microbiota makes SCFAs from fibers in the colon. SCFAs play a role in physiological functions such as immunomodulation, maintaining intestinal barrier integrity and metabolism. Unfortunately, increased levels of SCFA in feces are associated with NAFLD and liver fibrosis.[12] SCFAs are produced by the gut microbiota, mainly from indigestible starch or dietary fiber and have an essential role in various physiological processes, including maintaining gut barrier function, immunomodulation, glucose and lipid metabolism, and appetite regulation. However, high levels of SCFA were found in the feces of patients with NAFLD and liver fibrosis.[8] The pathogenetic mechanism that might explain the role of SCFA is the activation of G-protein-coupled receptors (GGPR41 and GPR43), which trigger the release of the gut hormone, namely peptide YY (PYY), which can then slow down intestinal transit time and increase nutrient absorption which will ultimately lead to accumulation of lipids in the liver. In addition, SCFAs entering the liver via the portal vein triggers glucogenesis and triglyceride accumulation, both of which are associated with NAFLD.[1]

Ethanol and Its Metabolites

Dysbiosis can increase intestinal ethanol production. For example, one gram of *Escherichia coli* can produce about 0.8 grams of ethanol per hour under anaerobic conditions. In patients with NASH, Proteobacteria, especially *Escherichia coli* species, were substantially

increased. Elevated blood ethanol levels were also observed in patients with NASH. Ethanol produced by gut bacteria can cause liver damage by increasing intestinal permeability and causing activation of TLRs and other inflammatory mediators. In addition, ethanol directly affects liver tissue.[1,13]

Low blood ethanol levels were also found in individuals who did not even consume alcohol. Gut microbiota, such as Klebsiella pneumonia, can produce endogenous ethanol. NAFLD is associated with increased serum levels of ethanol and its metabolites, namely acetate and acetaldehyde. Increased levels of endogenous ethanol and its metabolites trigger disease progression through several mechanisms. In the gut, ethanol and its metabolites increase intestinal permeability by stimulating the production of pro-inflammatory cytokines, decreasing AMP production, and impairing tight junction proteins. This results in gut barrier dysfunction and microbiota translocation to the liver, leading to increased production of pro-inflammatory cytokines and induction of lipogenesis. In the liver, ethanol interferes with lipid metabolism by inducing fatty acid uptake and de novo lipogenesis leading to impaired fatty acid oxidation and inhibition of VLDL export. Continuous exposure to ethanol can increase the production of free radicals or reactive oxygen species (ROS), which, together with increased levels of acetaldehyde and acetate, can trigger liver damage.[1]

FACTORS DERIVED FROM THE LIVER

Bile Acids and Its Metabolites

Primary bile acids, namely cholic and chenodeoxycholic (CCA), are organic molecules synthesized by cholesterol and secreted into the duodenum in conjugated bile salts glycine/taurine along with other bile components such as bilirubin, phospholipids, cholesterol, amino acids, and xenobiotics. Bile acids have a significant function in the digestive system and absorption of lipids and lipid-soluble vitamins. Bile acids prevent SIBO and control the composition of the microbiota. Meanwhile, the microbiota can metabolize bile salts into bile acids again. Ninety-five percent of bile acids and their salts are actively absorbed in the ileum and transported back to the liver for recycling via the portal vein. Changes in bile acid secretion caused by dietary changes are responsible for changes in the microbiota community.[1] Several pre-clinical and clinical studies have shown that impaired bile acid metabolism is associated with NAFLD incidence. The mechanism that explains this is dysbiosis which alters the balance between primary and secondary bile acids, causing a decrease in farnesoid X receptor (FXR) signalling. This can lead to dysregulation of lipid and glucose metabolism. Decreased FXR also actively causes a decrease in levels of fibroblast growth factor 19 (FGF19) and inhibition of cholesterol 7-monooxygenase (CYP7A1), which is an essential enzyme in bile acid synthesis.[1]

Secretory Immunoglobulin A (SIgA)

SIgA plays a role in controlling the number and composition of microbiota in the lumen and protects against damage to the intestinal mucosa. The primary source of SIgA in the gut is plasma cells, but those capable of producing SIgA-specific microbiota are also present in the liver. Liver SIgA is transported to bile via biliary epithelial cells, expressed by the polymeric immunoglobulin receptor (pIgR).[1] In the mouse model, a low concentration of SIgA was found. Furthermore, the decrease in concentration was associated with an increase in the composition of *Proteobacteria*, which are typical microbiota in NAFLD.[14] However, the exact role of SIgA in the pathogenesis of NAFLD has not been fully elucidated.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS (PPARS)

PPARs is a nuclear receptor superfamily group that plays a role in various metabolic functions by regulating lipid and glucose metabolic pathways. In NAFLD, PPAR activation prevents triglyceride accumulation and inflammation in the liver and antagonizes the activity of inflammatory transcription factors, such as NF-B, thereby reducing the expression of pro-inflammatory cytokine genes. Meanwhile, PPARγ has a role in modulating immune responses by suppressing specific genes, including genes that express NF-kB and regulate Kupffer cells that play a role in the pathogenesis of NAFLD.[15]

The gut microbiota is associated with metabolic pathways, including the PPAR signalling pathway. Lactobacillus casei can increase PPARγ activity to suppress inflammation in the liver. Changes in the gut microbiota in NAFLD, such as a decrease in *Bacteroides*, *Bifidobacterium*, and *Lactobacillus*, increase SCFAs production, which can also upregulate PPARα and PPARγ expression.[15]

MICROBIOTA-BASED DIAGNOSTICS AND BIOMARKERS

Until now, liver biopsy has been the gold standard for diagnosing and monitoring NAFLD. A liver biopsy examination is intended to determine the spectrum of liver disease. The spectrum in question is NAFL and NASH. These two spectra can be distinguished from the histopathological appearance by the presence of intense inflammatory activity in NASH.[16] From the gut microbiota point of view, reliable non-invasive markers are needed to evaluate NAFLD. Studies on the gut microbiota suggest that several microbiota and metabolites can be potential diagnostic and prognostic markers. Research has demonstrated that a panel of gut microbiota consisting of 37 bacterial strains can be used to accurately diagnose fibrosis in NAFLD patients.[8]

Several metabolites derived from microbiota can be used as biomarkers of NAFLD, such as succinate and 3-(4-hydroxyphenyl). Succinate, produced by NAFLD-associated microbes (Bacteroidaceae and *Prevotella*), was elevated in stool, serum, and liver samples from NAFLD patients. Meanwhile, in NAFLD patients, it was found that there was a decrease in the diversity of microbial genes that caused changes in the metabolism of aromatic amino acids. Aromatic amino acids produce 3-(4-hydroxyphenyl) associated with fibrosis.[8]

NAFLD THERAPY STRATEGY TARGETTING GUT MICROBIOTA

The most recommended therapy for NAFLD patients is still limited to lifestyle changes that include exercise, diet, and weight loss to prevent worsening risk factors such as obesity and diabetes. Lifestyle interventions, according to some literature, have good effectiveness in NAFLD patients. The goal to be achieved is not only towards a good or healthy liver, but also health from cardiovascular and metabolic aspects. Lifestyle changes include primary management in addition to pharmacological therapy in NAFLD patients.[17] Pharmacological therapy to improve insulin resistance, reduce oxidative stress and inflammation, or slow the mechanism of fibrosis has been widely used in NAFLD patients but has not been fully demonstrated. Altering the gut microbiota is widely cited as having a potential role in treating NAFLD. Several approaches to changing the gut microbiota have been investigated in NAFLD patients, including antibiotics, probiotics, prebiotics, synbiotics, and fecal transplantation.

Prebiotics

Prebiotics are food products that cannot be digested but can trigger the growth and metabolism of bacteria that ferment prebiotics into SCFAs.[18] Prebiotics are potential candidates for NAFLD therapy because they are low in cost and safe, but their effectiveness has not been proven. Prebiotics are able to reduce the level of intestinal permeability through stimulation of the glucagon-peptide-2 hormone which then acts on bacterial translocation.[19] Oligofructose (OFS), fructooligosaccharides (FOS), and insulin are some types of prebiotics that are widely explored. Several studies have shown that prebiotic therapy can reduce pro-inflammatory cytokines, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), triglyceride levels, body weight, and improve gut microbiota composition.[20] A study showed that prolonged treatment with prebiotic (fructooligosaccharide) plus probiotic (*Bifidobacterium longum*) leads to reductions in serum AST, endotoxin, and hepatic steatosis in NASH patients. The efficacy of this medication in curing hepatic lipogenesis and blood triglyceride levels has been demonstrated. In addition, there has been an increase in SCFAs, especially acetate and propionate through the processing of intestinal flora.[21]

A double-blind, placebo-controlled study in obese women given OFS 16 g/day for three months improved gut microbiota composition. There was an increase in *Bifidobacterium* and *Faecalibacterium prausnitzii*, which was not associated with serum lipopolysaccharide levels and decreased some microbiota associated with weight loss.[22] A pilot study in NASH patients treated with OFS 16 g/day for eight weeks showed a decrease in serum aminotransferase, aspartate aminotransferase, and insulin levels.[23] Prebiotics have been found to reduce plasma cholesterol, triglycerides and increase HDL concentrations in diabetes trials.[24]

Various evidence has shown the beneficial effects of intestinal bacteria modulation by prebiotics in order to NAFLD inventions.[25] Prebiotics have revealed to contain potential in the obesity and NAFLD development prevention through the decreasing intestinal wall v, attenuating metabolic endotoxemia, and demolishing the fat accumulation.[26] An essential consideration in prebiotics is that different probiotics have different effects on the liver. Thus, the efficacy of prebiotics as a therapy for NAFLD has not been established.[27]

Probiotics

Probiotics are live bacteria that enhance intestinal mucosa integrity by modulating the gut microbiota to benefit the host.[27] Probiotics have the potency to decrease of endotoxemia in the intestine through the balance restoration of micro ecological in the gut, decreasing the "second hit" formation on hepatocytes.[28] The effectiveness of probiotics as NAFLD therapy was evaluated based on serum markers of enzyme dysregulation or biomarkers of liver injury. Research shows that giving probiotics can significantly reduce transaminases, TNF, and insulin resistance.[30] Probiotics are widely used in combination with *Lactobacillus* and *Bifidobacteria* species. In a study with an experimental model of NAFLD obtained on a high-fructose diet, administration of *Lactobacillus rhamnosus* GG (LGG) was shown to be a protective agent, preventing the development of NAFLD by reducing levels of duodenal inhibitor kappa B (IκB), reducing activation of TLR-4 signaling cascade, and increasing peroxisome proliferator-activated receptor gamma (PPAR-γ) activity. Treatment based on *Lactobacillus rhamnosus* GG has been shown to lead to reduction in endotoxemia, TNF-α, IL-8R, and IL-1b mRNA expression in the liver. In addition, LGG decreased cholesterol levels, mediated by suppression of FXR signals and fibroblast growth factor signaling. Consensual changes were also detected in the microbiota, in which the population of Enterobacteriaceae was reduced and the relative abundance of famili Clostridiales XIV increased.[19] A study in obese children treated with 12 billion CFU/day of *Lactobacillus rhamnosus* GG for eight weeks showed a significant reduction in ALT and slight changes in BMI and visceral fat scores.[30]

Meanwhile, research on high-fat diet mice showed that the administration of *Bifidobacterium* spp. can reduce body weight and serum levels of total cholesterol, HDL-C, LDL-C, glucose triglycerides, AST, ALT, and lipase.[31] Pre-clinical and clinical research on probiotics needs to be done to determine their potential effectiveness in NAFLD treatment.

Synbiotic

Synbiotics are a combination of the use of prebiotics and probiotics. Prebiotics can reduce lipid accumulation and bacterial overgrowth.[29] A pilot study with 52 NAFLD patients given synbiotic twice daily for eight weeks showed lower ALT, AST, CRP, TNF-, NFkB, and fibrosis scores compared to placebo.[32] Another study involving 80 NAFLD patients treated with synbiotic capsules of 500 mg per day for eight weeks showed that this therapy was beneficial in reducing the degree of fibrosis but had no effect on ALT and AST levels.[33] A 2018 systematic review study also showed that supplementing synbiotics had a good impact, significantly improving inflammatory parameters, liver function and patient anthropometry, lipid and sugar profiles in patients with NAFLD.[34] Symbiotic supplementation has also been shown to reduce plasma fasting insulin and triglyceride levels in patients with diabetes.[24]

Antibiotics

In a pre-clinical model, the administration of an antibiotic cocktail consisting of bacitracin, neomycin, and streptomycin significantly improved NAFLD.[29] Antibiotics can suppress local or systemic infection and may regulate inflammation caused by the gut microbiota. A study on the effects of polymyxin B and neomycin in an animal model of liver disease when combined with fructose supplements, showed a decrease in hepatic lipid accumulation. Whereas treatment with neomycin alone showed that the air exhaled by ob/ob mice contained higher concentrations of alcohol when compared to control mice, indicating that neomycin-induced changes in gut microbiota decreased systemic alcohol concentrations.[19] Treatment with cidomycin increases the rate of small bowel transit and decreases serum ALT, AST, and TNF- levels in NASH patients.

The use of non-absorbable antibiotics such as rifaximin has long been used in the treatment of hepatic encephalopathy (HE). This use is supported by underlying pathophysiological mechanisms as bacterial translocation and bacterial products play an important role in the development of HE. Treatment with rifaximin significantly reduced pro-inflammatory cytokines, ALT, and liver fat scores in NAFLD patients. Improvement by these antibiotics is associated with changes in gut microbiota populations, bile acid metabolism, decreased FXR signaling and decreased liver ceramide levels. A study with 42 NAFLD patients treated with rifaximin 1200 mg/day for 28 days was able to slightly reduce BMI and significantly reduce endotoxin and IL-10 levels. In addition, rifaximin also significantly reduced serum AST, ALT, LDL, ferritin and improved steatosis.[35] Despite the benefits of antibiotics in NAFLD, their use needs to be carefully monitored because antibiotics have the potential to reduce the normal bacterial flora and overgrowth of pathogenic bacteria such as *Clostridium difficile*.[36]

Fecal Microbiota Transplantation (FMT)

FMT is a new therapeutic approach to replenishing the gut microbiota of patients with healthy gut flora. The effects of FMT on obesity, IR, and NAFLD are consistent with various animal studies, some of which were previously mentioned as having a role in the pathogenesis of NAFLD. FMT from NAFLD-affected mice stimulated the development of NAFLD in a major group of different species recipient mice that eventually became major post-transplant colonizers.[37] FMT can inhibit HFD-induced NASH development in mice by decreasing lipid accumulation, insulin resistance, and serum levels of pro-inflammatory cytokines.[27] Another study in NAFLD animals showed that FMT decreased liver glucogenesis and intestinal permeability.[38] In a clinical trial, patients with metabolic syndrome who received gut microbiota from healthy individuals experienced increased insulin sensitivity and gut microbiota diversity six weeks after FMT.[39] In humans, FMT is most often used as a therapeutic tool for recurrent *Clostridium difficile* infections that do not respond to antimicrobial treatment. FMT has recently been recognized as a potential therapy for various other diseases in humans, such as colonization of antimicrobial-resistant pathogens, syndrome insulin resistance, irritable bowel syndrome, and metabolic syndrome insulin resistance.[40] This therapeutic option provides distortion to the intestinal flora. This procedure is also an invasive procedure that has the possibility of significant side effects, and most of them are contagious. Therefore studies in animal models are still needed to confirm its efficacy and safety in this setting.[41]

CONCLUSION

Pathogenicity is a complex mechanism involving many factors. Recent evidence reveals that the gut microbiota is one of the main factors in the pathogenesis and progression of NAFLD through several mechanisms, particularly dysbiosis. This significant role makes the gut microbiota a non-invasive biomarker for NAFLD examination and a more effective therapeutic target. However, further research is needed to evaluate the effectiveness of the gut microbiota as a biomarker or therapy.

REFRENCES

1. Hrncir T, Hrncirova L, Kverka M, Hromadka R, Machova V, Trckova E, et al. Gut microbiota and NAFLD: pathogenetic mechanisms, microbiota signatures, and therapeutic interventions. Microorganisms 2021;9:957.
2. Prasetya IB, Hasan I, Wisnu W, Rumende CM. Prevalence and profile of fibrosis in diabetic patients with non-alcoholic fatty liver disease and the associated factors. Acta Med Indones 2017;49:91–8.
3. Khan A, Ding Z, Ishaq M, Bacha AS, Khan I, Hanif A, et al. Understanding the effects of gut microbiota dysbiosis on nonalcoholic fatty liver disease and the possible probiotics role: recent updates. Int J Biol Sci 2021;17:818–33.
4. Giuffrè M, Campigotto M, Campisciano G, Comar M, Crocè LS. A story of liver and gut microbes: how does the intestinal flora affect liver disease? A review of the literature. Am J Physiol Gastrointest Liver Physiol 2020;318:G889–906.
5. Clarke G, Sandhu KV, Griffin BT, Dinan TG, Cryan JF, Hyland NP. Gut reactions: breaking down xenobiotic-microbiome interactions. Pharmacolo Rev 2019;71:198–224.
6. Albillos A, de Gottardi A, Rescigno M. The gut-liver axis in liver disease: pathophysiological basis for therapy. J Hepatol 2020;72:558–77.
7. Aron-Wisnewsky J, Vigliotti C, Witjes J, Le P, Holleboom AG, Verheij J, et al. Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. Nat Rev Gastroenterol Hepatol 2020;17:279–97.
8. Loomba R, Seguritan V, Li W, Long T, Klitgord N, Bhatt A, et al. Gut microbiome-based metagenomic signature for non-invasive detection of advanced fibrosis in human nonalcoholic fatty liver disease. Cell Metab 2017;25:1054–62.
9. Wang L, Wan YY. The role of gut microbiota in liver disease development and treatment. Liver Res 2019;3:3–18.
10. Roeb E, Weiskirchen R. Fructose and non-alcoholic steatohepatitis. Front Pharmacol 2021;12:634344.
11. Sherriff JL, O'Sullivan TA, Properzi C, Oddo JL, Adams LA. Choline, its potential role in nonalcoholic fatty liver disease, and the case for human and bacterial genes. Adv Nutr 2016;7:5–13.
12. Ghoshal UC, Goel A, Quigley EMM. Gut microbiota abnormalities, small intestinal bacterial overgrowth, and non-alcoholic fatty liver disease: an emerging paradigm. Indian J Gastroenterol 2020;39:9–21.
13. Leung C, Rivera L, Furness JB, Angus PW. The role of the gut microbiota in NAFLD. Nat Rev Gastroenterol Hepatol 2016;13:412–25.
14. Inamine T, Schnabl B. Immunoglobulin A and liver diseases. J Gastroenterol 2018;53:691–700.
15. Wu L, Li J, Feng J, Ji J, Yu Q, Li Y, et al. Crosstalk between PPARs and gut microbiota in NAFLD. Biomed Pharmacother 2021;136:111255.
16. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. Obesity facts 2016;9:65–90.
17. Hallsworth K, Adams LA. Lifestyle modification in NAFLD/NASH: facts and figures. JHEP Rep 2019;1:468–79.
18. Zhou J, Tripathi M, Sinha RA, Singh BK, Yen PM. Gut microbiota and their metabolites in the progression of non-alcoholic fatty liver disease. Hepatoma Res 2021;7:11.

19. Bugianesi E. Non-Alcoholic Fatty Liver Disease: A 360-degree Overview 2020. 1st ed. New York: Springer International Publishing 2020.p.1–362.
20. Chen J, Vitetta L, 2020. Gut microbiota metabolites in NAFLD pathogenesis and therapeutic implications. Int J Mol Sci 2020;21:5214.
21. Brandi G, De Lorenzo S, Candela M, Pantaleo MA, Bellentani S, Tovoli F, et al. Microbiota, NASH, HCC and the potential role of probiotics. Carcinogenesis 2017;38:231–40.
22. Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut 2013;62:1112–21.
23. Delzenne NM, Cani PD, Daubioul C, Neyrinck AM. Impact of inulin and oligofructose on gastrointestinal peptides. Br J Nutr 2005;93:S157–61.
24. Beserra BTS, Fernandes R, do Rosario VA, Mocellin MC, Kuntz MGF, Trindade EBSM. A systematic review and meta analysis of the prebiotics and synbiotics effects on glycaemia, insulin concentrations and lipid parameters in adult patients with overweight or obesity. Clin Nutr 2015;34:845–58.
25. Daubioul C, Horsmans Y, Lambert P, Danse E, Delzenne NM. Effects of oligofructose on glucose and lipid metabolism in patients with nonalcoholic steatohepatitis: results of a pilot study. Eur J Clin Nutr 2005;59:723.
26. Cani PD, Delzenne NM. The gut microbiome as therapeutic target. Pharmacol Ther 2011;130:202–12.
27. Zhou J, Tripathi M, Sinha RA, Singh BK, Yen PM. Gut microbiota and their metabolites in the progression of non-alcoholic fatty liver disease. Hepatoma Res 2021;7:11.
28. Borrelli A, Bonelli P, Tuccillo FM, Goldfine ID, Evans JL, Buonaguro FM, et al. Role of gut microbiota and oxidative stress in the progression of non-alcoholic fatty liver disease to hepatocarcinoma: current and innovative therapeutic approaches. Redox Biol 2018;15:467–79.
29. Chen J, Vitetta L. Gut microbiota metabolites in NAFLD pathogenesis and therapeutic implications. Int J Mol Sci 2020;21:5214.
30. Vajro P, Mandato C, Licenziati MR, Franzese A, Vitale DF, Lenta S, et al. Effects of lactobacillus rhamnosus strain GG in pediatric obesity-related liver disease. J Pediatr Gastroenterol Nutr 2011;52:740–3.
31. An HM, Park SY, Lee DK, Kim JR, Cha MK, Lee SW. Antiobesity and lipid-lowering effects of *Bifidobacterium* spp. in high fat diet-induced obese rats. Lipids Health Dis 2011;10:116.
32. Eslamparast T, Poustchi H, Zamani F, Sharafkhah M, Malekzadeh R, Hekmatdoost A. Synbiotic supplementation in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. Am J Clin Nutr 2014;99:535–42.
33. Asgharian A, Askari G, Esmailzade A, Feizi A, Mohammadi V. The effect of symbiotic supplementation on liver enzymes, c-reactive protein and ultrasound findings in patients with non-alcoholic fatty liver disease: a clinical trial. Int J Prev Med 2016;7:59.
34. Hadi A, Mohammadi H, Miraghajani M, Ghaedi E. Efficacy of synbiotic supplementation in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis of clinical trials: synbiotic supplementation and NAFLD. Crit Rev Food Sci Nutr 2019;59:2494–505.
35. Gangarapu V, Ince AT, Baysal B, Kayar Y, Kılıç U, Gök Ö. Efficacy of rifaximin on circulating endotoxins and cytokines in patients with nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2015;27:840–5.
36. Zhou J, Tripathi M, Sinha RA, Singh BK, Yen PM. Gut microbiota and their metabolites in the progression of non-alcoholic fatty liver disease. Hepatoma Res 2021;7:11.
37. Ebrahimzadeh Leylabadlo H, Ghotaslou R, Samadi Kafil H, Feizabadi MM, Moaddab SY, Farajnia S, et al. Non-alcoholic fatty liver diseases: from role of gut microbiota to microbial-based therapies. Eur J Clin Microbiol Infect Dis. 2020;39:613–27.
38. Porras D, Nistal E, Martinez-Florez S, Gonzalez-Gallego J, Garcia-Mediavilla MV, Sanchez-Campos S. Intestinal microbiota modulation in obesity-related non-alcoholic fatty liver disease. Front Physiol 2018;9:1813.
39. Vrieze A, Nood EV, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 2012;143:913–6.
40. Cammarota G, Laniro G, Tilg H, Rajilić-Stojanović M, Kump P, Satokari R, Sokol H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut 2017;66:569–80.
41. Chu H, Williams B, Schnabl B. Gut microbiota, fatty liver disease, and hepatocellular carci noma. Liver Res 2018;2:43–51.

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