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MINIREVIEWS

# Influence of gut bacteria on development and progression of non-alcoholic fatty liver disease

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## Abstract

The intestine of the human contains a dynamic population of microbes that have a symbiotic relationship with the host. In addition, there is an effect of the intestinal microbiota on metabolism and digestion. Non-alcoholic fatty liver disease (NAFLD) is a common cause worldwide of hepatic pathology and is thought to be the hepatic manifestation of the metabolic syndrome. In this review we examine the effect of the human microbiome on the components and pathogenesis of the metabolic syndrome. We are now on the threshold of therapeutic interventions on the human microbiome in order to effect human disease including NAFLD.

**Key words:** Microbiome; Metabolic syndrome; Stool transplantation; Non-alcoholic fatty liver disease



**Core tip:** The human intestine contains more bacterial cells than mammalian cells. These have a symbiotic relationship with the host. Non-alcoholic fatty liver disease is the hepatic manifestation of the metabolic syndrome and a major cause of hepatic morbidity as a consequence of the obesity epidemic. We examine the effect of the human microbiome on the components of the metabolic syndrome and fatty liver and mention the possibility of therapeutic interventions in humans.

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of the metabolic syndrome. The metabolic syndrome is defined by clear clinical and laboratory criteria (Table 1). NAFLD encompasses a range of liver damage ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and its complications. NAFLD is present in approximately

**Table 1 The definitions of the metabolic syndrome**

| | NCEP ATP Ⅲ | IDF |
|---|---|---|
| Absolutely required | None | Central obesity (waist circumference) ⩾ 94 cm in males or ⩾ 80 cm in females European origin<br>⩾ 90 cm in males or ⩾ 80 cm in females |
| Criteria | Any three of the five criteria below | Central obesity plus two of the four criteria below |
| Obesity | (1) waist circumference > 40 inches in males, or > 35 inches in females | |
| Hyperglycemia | (2) fasting glucose ⩾ 100 mg/dL or treated for DM | (1) fasting glucose ⩾ 100 mg/dL |
| Dyslipidemia | (3) TG ⩾ 150 mg/dL or treated for dyslipidemia<br>Or<br>(4) HDL cholesterol < 40 mg/dL in males, or < 50 mg/dL in females or under treatment | (2) TG ⩾ 150 mg/dL or treated for dyslipidemia<br>Or<br>(3) HDL cholesterol < 40 mg/dL in males, or < 50 mg/dL in females or under treatment |
| Hypertension | (5) > 130 mmHg systolic or > 85 mmHg diastolic or treated for HTN | (4) > 130 mmHg systolic or > 85 mmHg diastolic or treated for HTN |

NCEP ATP Ⅲ: National Cholesterol and Education Program - Adult Treatment Panel Ⅲ; IDF: International diabetes federation; DM: Diabetes mellitus; TG: TG: Triglycerides; HTN: Hypertension.

1/3 of the United States population, who have isolated steatosis of the liver[1]. Of the patients with NAFLD, approximately 30% have NASH[2]. NASH refers to those patients who have developed liver inflammation and fibrosis. It is those patients with NASH who may develop stage 3 or 4 fibrosis (cirrhosis)[3].

Many factors including diet, sedentary lifestyle and genetics have been shown to influence the progression from steatosis through NASH to cirrhosis. However, not all people who are obese develop NAFLD and neither are all patients with NAFLD obese.

## GUT MICROBIOTA

The intestinal microbiome is attracting an increasing amount of attention[4]. It is becoming apparent that there is a symbiotic relationship between the intestine and its microbiota and that disturbance in this relationship can be associated with the pathogenesis of many disorders. The most striking example of such an association is *Clostridium difficile* infection, for which fecal transplantation from healthy donors is now an accepted treatment[5].

Distinct gut microbiota profiles are linked with specific metabolomes. Ninety-five percent of the gut microbiota of humans consists of the *Firmicutes*, *Bacteroidetes* and *Actinobacteria* phyla. The species level of the human microbiota, however, has higher diversity, with approximately 200 highly prevalent and up to 1000 less common bacterial species[6]. In humans as in mice, each individual has an unique bacterial species profile[7]. The gut bacteria may alter in response to a high fat diet (HFD), which could be responsible for some of the responses to an HFD.

Bacteria from human stools can be transferred to germ free (GF) mice and result in a similar microbiome in the host mice[8]. This can result in the appearance of human gut enzymatic activities in GF rodents after human fecal transplantation[9,10].

Recently, the transfer of human gut microbiome from obesity discordant twins to GF mice was shown to result in the transfer of the adiposity phenotype of the donor twin[11]. Thus, the transfer of human fecal microbiota to GF mice may result in the development of human diseases and provide an experimental study system.

## INTESTINAL MICROBIOTA ARE RELATED TO OBESITY AND INSULIN RESISTANCE

The gut microbiota is now recognized as contributing to obesity and NAFLD[12]. GF mice have been found to gain less weight than conventional mice after being fed a high sugar and fat diet in spite of a higher amount of food consumption[13,14]. Furthermore, GF mice on an HFD develop an increase in insulin sensitivity[15] and GF mice colonized with conventional mouse intestinal microbiota develop an increase in body fat content[13]. There are, however, wide variations in the development of HFD-associated features[16,17], but the responsible factors are still undefined.

The insulin resistance index can be transferred by gut microbiota transplantation[18]. Gut microbiota affects both macrophage fat accumulation and systemic glucose metabolism by different mechanisms[19]. In a diet-induced obesity mouse model, administration of antibiotics improved fasting glycemia and insulin resistance independently of both food intake or adiposity[20]. Furthermore the improved insulin sensitivity correlated with less hepatic lipogenesis and steatosis in the antibiotic-treated mice[21]. Taken together, these findings suggest that the gut microbiota influences both host glucose metabolism and liver function.

A study in humans showed that transfer of intestinal microbiota from lean donors to males with the metabolic syndrome resulted in increased insulin sensitivity[21]. Dietary factors and changes in diet influence the composition of the microbiome. The intestinal microbiota of obese individuals has a different microbial diversity compared to lean persons. They have less *Bacteroides* and more *Firmicutes*[22]. Furthermore, an HFD increases the proportion of Gram-negative to

Gram-positive microbes, resulting in the production of lipopolysaccharide (LPS) which is responsible for inflammation[23]. Gram-positive microbes are increased following the administration of prebiotics[24]. A prebiotic is a nondigestible food substrate which increases the growth of intestinal bacteria that can result in health benefits for the host.

The intestinal microbiome in obesity has an increased capacity to extract energy from the host diet. Bacterial enzymes extract calories from otherwise indigestible dietary polysaccharides[25]. Enteric bacteria suppress the synthesis and secretion of small intestinal fasting-induced adipocyte factor, resulting in an increased activity of lipoprotein lipase and increased liver triglyceride[13,14].

GF lean mice that were resistant to becoming obese on a fat-enriched diet had an increase of phosphorylated adenosine monophosphate-activated protein kinase (AMPK) in both the skeletal muscle and liver. AMPK phosphorylates acetyl coenzyme A (CoA) carboxylase, resulting in decreased malonyl CoA levels. Malonyl CoA controls the rate-limiting step of long-chain fatty acyl CoA entry to the mitochondria by blocking carnitine palmitoyltransferase which promotes the oxidation of fatty acid and results in a lower storage of fat[14,26].

Thus, the intestinal microbiome has an effect on both obesity and insulin resistance, as well as hepatic fat content.

## GUT MICROBIOTA AND NAFLD

In view of the intimate connection between the metabolic syndrome with its concomitant insulin resistance and NAFLD, it is expected that there is an effect of the intestinal microbiome on NAFLD.

The fecal microbiota in NAFLD and NASH patients has been examined using quantitative polymerase chain reaction (PCR) and deep sequencing of a conserved region in the bacterial 16S ribosomal RNA gene[27-30]. A recent review provides a summary of the changes in the intestinal microbiota associated with NAFLD and NASH[12]. Many of these studies have variable and often contradictory findings. This may be due to differences in patient mix, methodology and documentation of liver disease.

In addition to the mixture of bacteria in the colon, patients with obesity or NAFLD have more small intestinal bacterial overgrowth[31,32]. Small intestinal bacterial overgrowth was found in 50% of patients with NASH, significantly more than that in a control population[33]. The intestinal permeability and bacterial overgrowth were shown to be related to the degree of hepatic steatosis but not inflammation or fibrosis[31].

However, it is not clear if the assessment of small bowel bacterial overgrowth by breath tests is accurate since an estimate of total fecal bacterial count by real-time PCR did not detect any difference between healthy controls and patients with NAFLD and NASH[28].

Possible mediators of the link between the enteric microbiome and the host include alcohol, choline and endotoxins. Obese animals have been shown to have higher levels of alcohol in breath tests than thin animals[34]. Alcohol reaches the liver *via* the portal blood and can cause triglyceride accumulation in hepatocytes[35]. In addition, alcohol may provide the "second hit" to the liver for making the transformation from steatosis to steatohepatitis[36].

Choline may also be involved in the development of NAFLD and NASH. It is well known that choline deficiency may result in chronic liver disease[37]. In animal models choline-deficient diets were utilized, but it is now known that choline deficiency can exist while there is a diet that is not deficient. HFDs produce intestinal microbiota that converts dietary choline into methylamines. This results in a reduction of serum level of phosphatidylcholine which can cause NASH[26]. Phosphatidylcholine is important for the production of very low-density lipoprotein (VLDL)[38] and thus choline deficiency secondary to the intestinal microbiome will result in lower hepatic secretion of VLDL and result in triglyceride accumulation in hepatocytes.

The products of the intestinal microbiota are also implicated in the development of NAFLD and NASH. Endotoxemia has been found in patients with NASH[39]. Toll-like receptor 4, a receptor for LPS, in hematopoietic-derived cells is necessary for the development of hepatic steatosis but not for obesity in mice[40]. Mice that are deficient in sensing pathogen-associated molecular patterns (PAMPs) or downstream signaling are resistant to NASH[41,42].

The microbial products reach the liver *via* the portal vein and cause inflammation. Mice that are genetically obese are more sensitive to endotoxin-induced hepatotoxicity and develop steatohepatitis after being exposed to low doses of LPS[43]. NAFLD patients have an increased intestinal permeability and changes in the intestinal tight junctions, as compared to healthy individuals[31]. The increased permeability, in combination with bacterial overgrowth, increases the hepatic exposure to endotoxins.

Alteration of the fecal microbiome by administration of probiotics has been shown to decrease the amount of intrahepatic triglyceride content in addition to a decrease in *Firmicutes* and an increase in *Bacteroidetes*[30]. A meta-analysis of the published trials of probiotics in patients with NAFLD, showed a reduction in serum transaminases, total cholesterol, tumor necrosis factor-$\alpha$ and an improvement in insulin resistance[44].

Dysbiosis can induce intestinal inflammation. Indeed GF mice are protected from inflammation of the small intestine[45]. Mice deficient in Nlrp3 and Nlrp6 are unable to form cytoplasmic multiprotein complexes composed of nucleotide-binding domain and leucine-rich repeat-containing proteins (NLR) family, inflammasomes. Inflammasomes are sensors of exogenous PAMPs that regulate cleavage of precursors of inflammatory cytokines including pro-interleukin 1 beta (pro-IL1$\beta$) and pro-IL18. In mice, loss of Nlrp3 and Nlrp6 inflammasomes is associated with intestinal dysbiosis and colonic inflammation *via* CCL5. Dysbiosis is linked to an increase in *Prevotella*[46]. The consequent translocation of bacteria

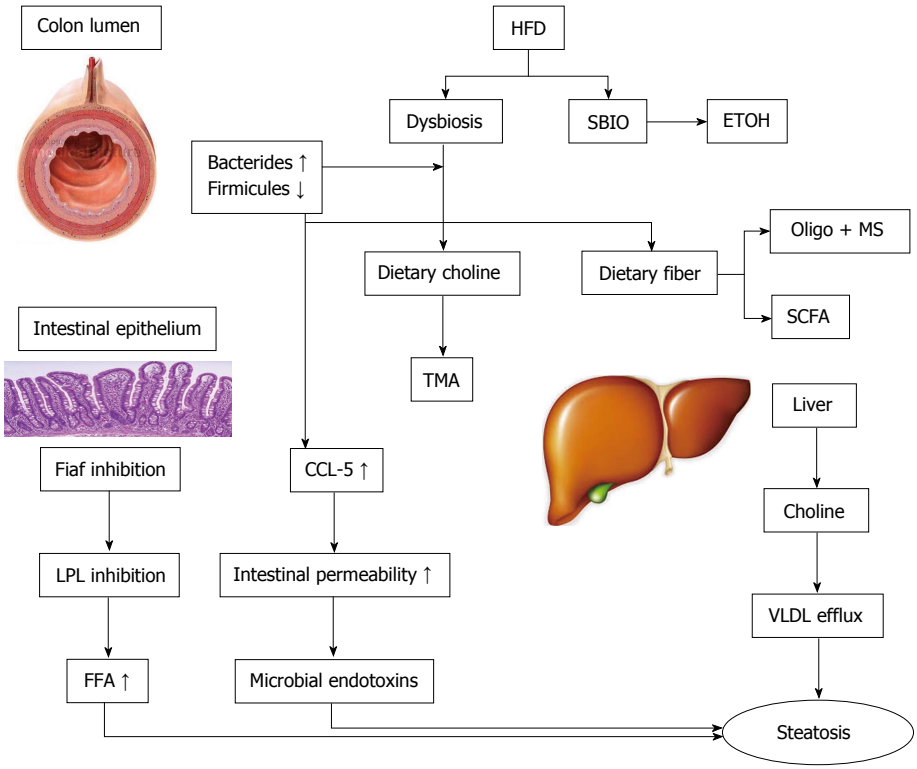


**Figure 1 The effect of the intestinal microbiota on non-alcoholic fatty liver disease.** High fat diets (HFD) produce dysbiosis and small bowel intestinal overgrowth (SBIO). There is an increase in energy extraction and fermentation of dietary fibers to oligo- and mono-saccahrides and short chain fatty acids (SCFA). There is also an increase in ethanol (ETOH) production. The microbiota metabolize choline to trimethylamine (TMA). There is a choline deficiency which decreases very low-density lipoprotein (VLDL) efflux and hepatic steatosis. In addition the intestinal microbiota suppresses the production of fasting induced adipocyte factor (Fiaf) in intestinal epithelia, which increases the activity of lipoprotein lipase and the levels of free fatty acids (FFA). Dysbiosis results in a disruption of tight junctions in the enterocytes *via* chemokine (C-C motif) ligand 5 (CCL-5). The resulting increase in intestinal permeability results in the translocation of microbial products to the liver and inflammation; MS: Monosaccharides; LPL: Lipoprotein lipase.

leads to an increase in bacterial products including LPS and bacterial DNA in the portal vein. The ensuing hepatic inflammatory response promotes progression of NAFLD to NASH (Figure 1). This change in phenotype can be transmitted by co-housing wild-type and NASH-prone mice[46].

Thus, intestinal dysbiosis can induce colonic inflammation and bacterial translocation which accelerates the progression of simple steatosis to NASH. As a result of these findings attention is beginning to be directed at fecal microbiota transplantation (FMT). FMT was first used in China more than 1500 years ago[47]. In 1958, 4 cases of treatment of pseudomembranous colitis by fecal enemas were reported[48]. This is now an established treatment[49]. At present there is only one report of FMT for metabolic syndrome. Vrieze *et al*[21] reported 18 patients with the metabolic syndrome who underwent a stool transplant that was either autologous or from lean healthy volunteers. Six weeks following the FMT there was a significant increase in insulin sensitivity together with an increase in the levels of butyrate-producing intestinal microbiota.

In summary, there appears to be an effect of the fecal microbiome on the development of the metabolic syndrome and its hepatic manifestation NAFLD and NASH. Further investigation of this relationship will increase our understanding of this connection. There is evidence that manipulation of the fecal microbiome may result in a change in the metabolic syndrome and an improvement in the features of NAFLD. This needs to be explored further in order to investigate if there will be an improvement in clinically significant end points.

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