Review Article Pol J Public Health, Vol. 132 (2022): 11-15

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Gut microbiome in non-alcoholic fatty liver disease

Abstract

The human gut microbiome is composed of communities of bacteria, viruses and fungi. Bacteria live in each part of digestive tract, increasing their density and changing composition in distal parts. The composition of gut microbiome mainly depends on method of childbirth, age, gender, diet, stress, infections, alcohol intake, diurnal variation, smoking, drugs (antibiotics), physical activity. Dysbiosis is defined as an imbalance or maladaptation in the gut microbial community. This imbalance favors many pathological states and it could be due to some diseases. Non-alcoholic fatty liver disease (NAFLD) has become increasingly common in parallel with the increasing prevalence of obesity and other components of the metabolic syndrome. In year 2020, a more comprehensive new definition of NAFLD was proposed – fatty liver disease associated with metabolic dysfunction (MAFLD). NAFLD/MALFD will become the major form of chronic liver disease in adults and children and could become the leading indication for liver transplantation within a decade. An increased level of *Bacteroidetes* and decreased level of *Firmicutes* is observed in fatty liver disease. This imbalance favors the collection of energy and insulin resistance. The prevention and treatment of dysbiosis in NAFLD/MAFLD is essential.

The purpose of this review is an understanding related to the dysbiosis and non-alcoholic fatty liver disease in order to help physicians of different specialties in their clinical practice because of growing in population patients with metabolic syndrome and liver steatosis.

Keywords: gut microbiome, dysbiosis, non-alcoholic fatty liver disease, probiotics, eubiotics, prokinetics.

DOI: 10.2478/pjph-2022-0002

INTRODUCTION

The human gut has 100 trillion microbes and the mass of gut microbiome amounts to perhaps 2000g [1]. The number of microbes is greater than the cells in the human body [1]. It is composed of communities of bacteria, viruses, archaea, fungi and eukaryotes that inhabit the human body. Collectively referred to as the "second human genome" [2]. Bacteria live in each part of digestive tract, increasing their density and changing composition in distal parts (Table 1). The entire mass of stool consist of 40-55% bacterial biomass. The composition of gut microbiome is variable, depends on many factors: method of childbirth, age, gender, diet, stress, infections, alcohol intake, diurnal variation, smoking, drugs (antibiotics), physical activity [3]. Main gut bacteria in human are from six types [4]. Dysbiosis (also called dysbacteriosis) is defined as an imbalance or maladaptation in the gut microbial community. This imbalance favors many pathological states and it could be due to some diseases. One of these diseases is non-alcoholic fatty liver disease (NAFLD). NAFLD has become increasingly common in parallel with the increasing prevalence of obesity and other components of the metabolic syndrome [5]. In year 2020, a more comprehensive new definition of NAFLD was proposed – fatty liver disease associated with metabolic dysfunction (MAFLD). This new definition is related to a change in the approach to the diagnosis and treatment of primary fatty liver disease. The creation of this name was a consequence of the lack of a clear nomenclature of liver diseases that are not caused by alcohol use disorders [6,7]. NAFLD/MAFLD will become the major form of chronic liver disease in adults and children and could become the leading indication for liver transplantation within a decade [5]. Increased level of *Bacteroidetes* and decreased level of *Firmicutes* are observed [8]. This imbalance of *Bacteroidetes/Firmicutes* favors the collection of energy and insulin resistance.

TABLE 1. The density of bacteria in next parts of digestive tract.

Stomach	Duodenum	Jejunum	Ileum	Colon
10^2CFU/ml	10^3CFU/ml	10^{3-4}CFU/ml	10^{7-9}CFU/ml	10^{10-12}CFU/ml

In prevention and treatment of dysbiosis in NAFLD/MAFLD, the modification of gut microbiome is taken into consideration. The first place is supplementation of probiotics. The second place is treatment by eubiotics, prokinetics.

The purpose of this review is a deeper understanding in aspect of public health related to the dysbiosis and non-alcoholic fatty liver disease in order to help general practitioners, internal medicine physicians, gastroenterologists and physicians of other specialties in their clinical practice because of growing

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population of patients with metabolic syndrome and liver steatosis.

It is still not clear whether NAFLD/MAFLD is the consequence of dysbiosis or dysbiosis is the adverse effect of insulin resistance, metabolic disorders and obesity.

Etiopathogenesis of NAFLD

Over the years, development theory of NAFLD has evolved from the "double hit theory" [9]: "first hit" – accumulation of triglycerides and insulin resistance preventing fatty liver (fat accumulation over 5%) which makes the liver more sensitive to "second hit" – contains mitochondrial dysfunction, oxidative stress and activates inflammation factors: cytokines, proteoglycans (endocan) [10]. All of this leads to fibrosis, cirrhosis [11] and complication of cirrhosis (spontaneous bacterial peritonitis, sepsis). The "multiparallel hits" theory [12] in which the intestinal factors and adipose tissue are of great importance. The development of NAFLD is influenced by many factors, such as diet (high saturated fat and fructose diet), sedentary lifestyle, obesity [12], genetic determinants such as the genetic variation of PNPLA3 (patatin-like phospholipase domain-containing protein 3) [13-15] or a variant of the lipid transporter in the endoplasmic reticulum (associated with increased triglyceride deposition) [14]. Single nucleotide polymorphism in the PNPLA3 gene is strongly related to the increased fat content in hepatocytes [16]. Disturbances in the intestinal flora lead to the damage of the intestinal barrier, increased penetration of bacterial toxins, which contributes to chronic inflammation [12]. Inflammation is an essential player in both endothelial and cardiac pathology in prediabetes and diabetes [17]. However, insulin resistance and type 2 diabetes appear to be key in the development of NAFLD. Insulin resistance is associated with a defective response in liver, muscle, and adipose tissue cells that are targets for insulin. In the muscles, it reduces glucose uptake. In the liver, it reduces the supersuppressive effect of insulin on glucose production while maintaining lipogenesis. In the adipose tissue it blocks the ability of insulin to inhibit lipolysis. This increases the pool of free fatty acids (FFAs) that are then trapped and deposited in the liver [18] to cause steatosis. FFAs associated with the acetyl coenzyme A synthase pathway and then trigger B-oxidation or esterification pathways [11]. Incretin hormones, like GLP-1 (glucagon like peptide 1) and GIP (glucose-dependent insulinotropic peptide) are released in response to dietary components that increase insulin secretion. Stimulation of receptors in GLP-1 on hepatocytes increases fat oxidation, reduces the intracellular fat load, and activates macroautophages which is crucial in removing toxic fatty acids from cells. The incretin effect is significantly reduced in patients with diabetes type 2 [12]. Also in diabetes, the composition of bile acids changes because of reduction mobility of the gallbladder. Disturbances in the composition of bile acids combined with a decrease in the secretion of incretin hormones affecting the decrease in insulin secretion [12]. Nevertheless, NAFLD deals with hyperinsulinemia, which promotes liponeogenesis *de novo* [12].

Bile acids (BA) influence metabolic homeostasis and insulin sensitivity. The correlation between bile acid levels and the severity of non-alcoholic steatohepatitis (NASH) was investigated. Changes in BA concentration in serum and feces were confirmed, increasing the amount of secondary BA which may be harmful to the liver contributing to the progression of NASH [19].

In the homeostasis of BA, glucose and lipid, the Farnesoid X receptor (FXR) is also involved. This receptor is present on the cells of the liver, intestine, adrenal glands and kidneys. It is responsible for the control of the synthesis and enterohepatic circulation of bile acids. It increases glycogen synthesis, decreases hepatic gluconeogenesis and glycolysis [19].

The mechanism of steatosis also involves lipogenic transcription factors such as chREBP (carbohydrate responsive element binding protein), SREBP1c (sterol regulatory binding protein 1c), PPARγ (peroxisome proliferator activated receptor gamma) [14], the activation of which is also influenced by diet, intestinal microflora and genetic factors.

In obese people, fatty acids accumulate in the ectopic tissue (liver, skeletal tissues) instead of adipose tissue, which is facilitated by fatty acid transport proteins (FATP) [14].

Steatosis affects the activity of the transcription factor NF-κβ which induces the production of inflammatory mediators (TNF-α, Il-6, Il-1B, adiponectin, leptin) produced by adipose tissue, activating hepatic macrophages (Kupffer cells) [12,14] intermediating in NASH development. Liver fat overload leads to mitochondrial dysfunction, which causes increased oxidation of fatty acids to produce reactive oxygen species that damage hepatocytes and lead to their death. In the multivariate model, the microbiome, which may be the engine of insulin resistance, holds an important place. Changes in the composition of micophores can lead to changes in the permeability of the bowel barrier and the passage of endotoxins, which promotes chronic inflammation [12,20] which, in turn, is associated with the progression of NAFLD to NASH. In year 2020, a more comprehensive new definition of NAFLD was proposed – fatty liver disease associated with metabolic dysfunction (MAFLD). This new definition is related to a change in the approach to the diagnosis and treatment of primary fatty liver disease. The creation of this name was a consequence of the lack of a clear nomenclature of liver diseases that are not caused by alcohol use disorders [6,7]. MAFLD is considered a more appropriate term for the diagnosis of fatty liver disease associated with known metabolic disorders.

Dysbiosis in NAFLD

Gut microbiome is dynamic community of different microorganisms belonging to *Bacteria, Archaea* and *Eukarya*. These microorganisms might participate in different important processes that affect the human metabolism and immune system providing protection against pathogens. Composition of gut microbiota is variable, depends on lifestyle, on many factors such as gender, age, diet, alcohol intake, diurnal variation, smoking, antibiotics, physical activity [3,21,22]. Among these many factors, diet is the main factor influencing species richness characterizing a healthy microbiota.

Three different phyla of bacteria create about 90% of gut microbiota: *Firmicutes*, *Bacteroidetes* and *Proteobacteria*, whereas the remaining 10% belongs to *Verrucomicrobia, Actinobacteria* and *Fusobacteria* [4,23]. The contribution of anaerobic bacteria in the gut increases from its proximal to distal part and anaerobic bacteria completely dominate in the large intestine.

Community of microorganism in gut maintains gut eubiosis by controlling unrestricted bacterial overgrowth. Bacterial microbiota shape the intestinal homeostasis by the education of gastrointestinal immune system, the regulation of intestinal hormone production, the fermentation of dieting polysaccha-

rides and influence on the energy harvest. Changes of gut microbiota might affect the condition of the liver because of close anatomical and functional relationship. The liver is exposed to nutrients, toxins and antigen from food because it receives about 70% blood from portal vein. The relationship between the liver and gastrointestinal tract is bidirectional and the liver communicates with the intestine by releasing BA and bioactive mediators, that affects the composition of gut microbiota. This functional, bidirectional relationship between the liver and gastrointestinal tract is known as the gut-liver axis (GLA) [24].

Dysbiosis is also defined as any changes of gut bacterial composition, that means decrease beneficial microbiota, unrestricted overgrowth of pathogenic microbiota, reduction of species number and any alteration of an individual microbiota comparing with others in the community. Under change in the composition of gut microbiota, the local homeostasis is disturbed.

Animal model studies have been used to examine the consequences of the absence of gut microbiota and its influence on physiology process and fat accumulation in liver leading to NAFLD. Backhed et al. observed that the germ-free mice models are resistant to the obesity caused by obesitogenic diet (high-fat, high-sugar) [25]. Moreover, in another study Backhed et al. reported that fecal microbiota transplantation (FMT) could trigger development of NAFLD [26]. Turnbaugh et al. suggested that the obese microbiome contribute to assimilation more energy from the diet [27]. Gut microbiota transplantation in germ-free mice has been used to prove the connection between microbiota composition and NAFLD development. The microbiome can transmit a tendency to obesity. Fecal microbiota from the obese twin led to increase in body mass and fat mass. Le Roy et al. showed that the gut microbiota composition influences progression of NAFLD [28]. Transplantation of gut microbiota from mice with NAFLD to germ free mice caused hyperglycemia and steatosis, which are features of NAFLD. These observations suggested significant role of the gut microbiota in mechanisms of progression of NAFLD.

Clinical researches show clearly that fatty liver diseases contain a spectrum of diseases from simple liver steatosis to NAFLD and NASH. In several published studies patients with NAFLD have a higher prevalence of gut dysbiosis and small intestinal overgrowth (SIBO). In Wang's et al. study [29], gut microbiota of NAFLD patients contains larger number of bacteria belonging to phylum *Bacteroidetes* and lesser to *Firmicutes* (genus *Lachnospiracae*, *Lactobacillaceae* and *Ruminococcaceae*) in comparison to healthy adults. The increase of Gram negative bacteria was also observed in children suffering from NAFLD comparing to healthy control, what was also described [30]. The differences in microbiome composition in healthy, obese and with NASH patients [31] are presented in Table 2.

TABLE 2. The differences in gut microbiome composition in healthy, obese and with NASH patients.

Bacteria	Healthy human	Obese patient	Patient with NASH
Firmicutes	66.78%	42.62%	42.39%
Bacteroidetes	28.65%	50.28%	49.11%
Proteobacteria	0.87%	3.13%	6.03%
Verrucomicrobia	0.18%	0.06%	0.06%
Actinobacteria	3.17%	2.42%	1.29%
Fusobacteria	0.00%	0.92%	0.36%
Other	0.35%	0.57%	0.76%

The composition of gut microbiome is different between NAFLD with concomitant fibrosis. *Firmicutes* were observed in mild NAFLD, but in case of concomitant advanced fibrosis, more prevalent was *Proteobacteria*. In the study conducted by Boursier et al. the relationship between the composition of microbiota and the form of fatty liver disease was proved. They noticed dependence on more highly represented *Bacterioides* in NASH and increased abundance in species of *Ruminococcus* in concomitant fibrosis [32].

Zhu et al. reported correlation between NASH and the higher amount of the bacterial ethanol producers belonging to *Proteobacteria* in microbiota of obese children. This higher abundance of alcohol producing bacteria was associated with elevated ethanol concentration in blood and oxidative stress increased hepatic inflammation and finally aggravated course of NASH [31].

Probiotics and other drugs modulating microbiome in NAFLD

Existing treatment for NAFLD and NASH is focused on reducing its risk factors by lifestyle modification and pharmacotherapy [33,34] (Table 3).

Current researches have shown that there is a correlation between intestinal dysbiosis and the presence of NAFLD. The manipulation of the gut microbiome improves liver phenotype in NAFLD patients. Therefore, it is possible to promote changes in microbiota composition to resemble a healthier profile. There is a lot of interest in methods of microbiota modification. These methods include the use of probiotics, postbiotics, eubiotics and prokinetics.

TABLE 3. The methods of NAFLD treatment.

Lifestyle modification	Pharmacotherapy
Weight loss	Ursodeoxycholic acid
Healthy diet	Vitamin E
Avoidance of alcohol	
Motility	
Sports	

According to the WHO (World Health Organization), probiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. Prebiotics are non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improve host's health. The term synbiotics is used when a product contains both probiotics and prebiotics. Postbiotics are substances produced by probiotics microorganisms with a direct or indirect pro-health effect. Eubiotic, in turn, is a substance that, when introduced into the body, shapes the balance of microflora in the digestive tract so that it is as optimal as possible for the functioning of the body.

Many clinical trials have been conducted using probiotics in NAFLD/MAFLD treatment. The use of probiotics bacteria improves the gut endothelial barrier functioning and increases genetic diversity of the microbiota. In one 12-week study it was proved that the use of high dose probiotics containing strains of *Lactobacillus* and *Bifidobacterium* (1x10CFU per day) has a positive effect on the concentration of lipopolysaccharides and reduces the weight of adipose tissue, the content of subcutaneous fat tissue, waist circumference, concentration

of uric acid, insulin, glucose, total cholesterol, LDL cholesterol, triglycerides and the Homa-IR index [35].

Another example is the clinical trial, where the beneficial effects of original Professor De Simone's probiotic formulation in obese children with NAFLD were seen. This formulation is a multistrain probiotic containing *Streptococcus*, *Bifidobacterium*, *Lactobacillus*. The main outcome was the change in fatty liver severity detected by ultrasonography after 4 months of supplementation. At the end of the study children supplemented with this probiotic had more probability of none or light fatty liver, while in placebo group moderate and severe NAFLD were present. Furthermore, BMI (body mass index) decreased and GLP-1 increased in this original probiotic group. Also the administration of original Professor De Simone's probiotic to genetically obese mice improved liver histology, reduced serum aminotransferase alanine level and hepatic fatty acid content [36].

Next probiotic, that plays a crucial role in the preservation and restoration of intestinal barrier functioning in multiple disorders is non-pathogenic yeast *Sacharomyces boulardii*. It has demonstrated its effectiveness as a probiotic in the prevention and treatment of antibiotic-associated, infectious and functional diarrhea. *Sacharomyces boulardii* alters the composition of intestinal microbiota in NALFD patients, which prevents the progression of disease. *Escerichia coli* constitute about 0.15% of gut microbiota. In patients with NAFLD its level is initially higher than in healthy people. A 90-day treatment with *Sacharomyces boulardii* significantly reduced *Escherichia coli* decreasing the risk of liver damage by endogenous ethanol and inhibiting the choline deficiency. It also lowered *Bacteroides fragilis* group reducing the risk of endotoxemia. There were no meaningful changes in other gut microbiota. *Sacharomyces boulardii* lowered VLDL cholesterol level and atherogenic index. It also led to reductions in body weight. In patients with NAFLD there was no progression in hepatosteatosis as assessed by FibroMax test, liver ultrasonography and telomere test [37].

There were also few studies that showed positive effect of probiotic in yogurts on liver. In Nabavi's et al. trial consumption of 300g per day of probiotic in yogurt containing *Lactobacillus acidophilus La5 and Bifidobacterium lactis Bb12* for 8 weeks by patients with NAFLD resulted in improvement activity of hepatic enzymes (aminotransferase alanine, aminotransferase asparagine), serum level of total cholesterol and LDL cholesterol [38].

Examples of prebiotics are inulin and arabinogalactan. Prebiotics and synbiotics do not apply. However, it was shown that the administration of probiotics (not prebiotics and not synbiotics) led to a significant decrease in BMI.

Postbiotics, as byproducts of probiotics, are functional bioactive compounds, generated in a matrix during fermentation, which may be used to promote health [39], such as: SCFAs (short chain fatty acids) or lactic acid, peptidoglycans, cell-wall polysaccharides. As they are not live microorganisms, there are fewer risks associated with their intake. Postbiotics have a positive effect on the host directly, but also can be a nutrient for probiotic bacteria and strengthen the intestal microbiome. The most important actions of postbiotics are immunomodulation, lipid metabolism, anti-inflammatory and antioxidative activity [40]. For example SCFAs, that is butyric acid, propionic acid and acetic acid, may influence the pathogenesis of NAFLD because of their involvement in obesity and improvement of lipid metabolism. Butyric acid is basic source of energy for colonocytes. Its administration has therapeutic effects in gastrointestinal diseases, hepatic diseases, also heart diseases and several neurological conditions, such as dementia and depression, due to the normalization of physiological stress pathways. Butyric acid has a positive effect on mitochondrial dysfunction observed in healthy and autistic children under the influence of physiological stress [41]. Studies showed that *Lactobacillus strains* can produce different types of SCFAs. A significant reductions in plasma total cholesterol and LDL-cholesterol were observed in 12-weeks administration of *Lactobacillus plantarum* [42].

Eubiotic, in turn, such as rifaximin, is a non-absorbable from the gastrointestinal tract antibiotic that has a broad spectrum of antibacterial activity against Gram negative and Gram positive, aerobic and anaerobic bacteria, including those producing ammonia and other toxic substances. However, it should be emphasized that it promotes the growth of beneficial bacteria (*Lactobacillus, Bifidobacterium species* and *Faecalibacterium prausnitzii*). It prevents dysbiosis and modulates balanced intestinal microbiota.

In addition, it also shows a direct anti-inflammatory effect by reducing serum endotoxins and reducing the expression of pro-inflammatory cytokines by binding the pregnane X receptor. One study showed that after 6 months of rifaximin therapy (1100 mg per day), patients with NAFLD showed a significant reduction in LPS (lipopolysaccharide) levels, Homa-IR index, aminotransferase alanine, aminotransferase asparagine, gamma-glutamylotransferase activity, TLR-4 (toll-like receptor 4), IL-6, TNF-α, CK-18 (cytokeratin 18) and NAFLD-liver fat score, but had no effect on lipid profile and BMI values [43].

Prokinetics can also be used to manage NAFLD. It has been suggested that SIBO correlates with NAFLD. This association was observed in meta-analysis conducted by Wijarnpreecha et al. [44]. In another meta-analysis 3 studies were included, which reported that children with SIBO were more likely to have NAFLD [45]. There is also an inverse relationship – increased prevalence of SIBO is observed in patients with NAFLD [8]. The exact mechanisms of this association are unknown, but an intestinal leakage and endotoxemia might be a cause. Prokinetics enhance gastrointestinal motility, so there is reduced intestinal transit time and gut microbiota changes. Mosapride citrate treatment suppresses NASH development in a rodent model [46] by changing the composition of the gut microbiota.

CONCLUSIONS

A review study has shown that NAFLD/MAFLD is the complicated disease and the composition of gut microbiome is variable, depends on many factors. Intestinal microbiota dysbiosis and leaky gut syndrome contribute to the pathogenesis of NAFLD. It is still unclear whether NAFLD is consequence of dysbiosis or dysbiosis is bad effect of insulin-resistance, metabolic disorders and obesity. The modulation of intestinal microbiota is a promising therapeutic strategy for obesity-associated diseases. However, it is not entirely certain whether the changes in gut microbiota are the cause or the result of metabolic disorders and obesity.

Finally, the dependence of the NAFLD and gut microbiome is still clinical management thst could lead to new interesting perspectives diagnosis and therapy research.

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