Chapter

Treatment of Nonalcoholic Fatty Liver Disease through Changes in Gut Microbiome and Intestinal Epithelial Barrier

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a leading liver disease worldwide with a prevalence of approximately 25% among adult population. The highest prevalence is observed in Middle East and the lowest prevalence in Africa. NAFLD is a spectrum of liver disorders ranging from simple steatosis to nonalcoholic steatohepatitis (NASH). Pro-inflammatory diet, overweight/obesity, inflammation, insulin resistance, prediabetes, type 2 diabetes, dyslipidemia, disrupted gut microbiome, and impaired intestinal barrier function are important risk factors associated with and/or contributing to NAFLD. Gut microbiome is a complex and diverse microbial ecosystem essential for the maintenance of human health. It is influenced by several factors including diet and medications. Gut microbiome can be disrupted in NAFLD. Intestinal epithelial barrier is the largest and most important barrier against the external environment and plays an important role in health and disease. Several factors including diet and gut microbiome impact intestinal barrier function. NAFLD can be associated with impaired intestinal barrier function (increased intestinal permeability). There are no specific drugs that directly treat NAFLD. The first-line therapy of NAFLD is currently lifestyle intervention. Weight loss is an important component in the treatment of NAFLD subjects who have excess body weight. Gut microbiome and intestinal epithelial barrier are becoming promising targets for the treatment of several diseases including NAFLD. In the absence of approved pharmacotherapy for the treatment of NAFLD/NASH, in addition to lifestyle intervention and weight loss (in case of excess body weight), focus should also be on correcting gut microbiome and intestinal permeability (directly and/or through gut microbiome modulation) using diet (e.g., low-fat diet, high-fiber diet, and Mediterranean diet), prebiotics (nondigestible food ingredients), probiotics (nonpathogenic living microorganisms), synbiotics (combination of prebiotics and probiotics), and fecal microbiota transplantation (transfer of healthy stool).

Keywords: nonalcoholic fatty liver disease, gut microbiome, intestinal epithelial barrier, targeted treatment

1. Introduction

NAFLD is a leading liver disease worldwide with a prevalence of approximately 25% among adult population. It is the most common cause of chronic

liver disease in Western countries. NAFLD is a spectrum of liver disorders ranging from simple steatosis to NASH [1–9].

Pro-inflammatory diet, overweight/obesity, inflammation, insulin resistance, prediabetes, type 2 diabetes, dyslipidemia, disrupted gut microbiome, and impaired intestinal barrier function are important risk factors associated with and/or contributing to NAFLD [2, 4–27].

In the absence of approved drugs for the treatment of NAFLD/NASH, management relies mainly on lifestyle intervention and weight loss (in case of excess body weight) [1, 2, 8, 28–30].

Gut microbiome and intestinal epithelial barrier are becoming promising targets for the treatment of several diseases including NAFLD [4, 17, 18, 20–22, 24, 25, 31–43].

2. Physiology

2.1 Liver

The liver is the largest visceral organ. It weighs approximately 1.5 kg. Macroscopically, the liver is divided into four lobes. The basic functional unit of the liver is the liver lobule which includes the hepatocytes. Approximately 30% of the liver volume is made up by blood (**Figure 1**) [44].

The liver is a vital organ. It has numerous important roles including secretion of bile (700–1,200 mL/day), metabolism of bilirubin, metabolism of nutrients (e.g., glucose homeostasis, fat synthesis, and albumin synthesis), endocrine function (e.g., production of angiotensinogen and activation of vitamin D), storage of minerals and vitamins (e.g., iron, copper, vitamin A, vitamin B12, and vitamin D), hematologic and vascular functions (e.g., hemostatic function and capacity to store/release large volume of blood), immunologic and protective functions, and metabolic inactivation and detoxification (e.g., catabolism or alteration of hormones, toxins, and drugs) [44].

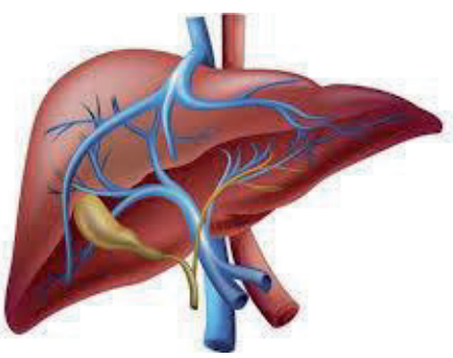

Figure 1.
Normal liver.

2.2 Gut microbiome

Gut microbiome is a complex and diverse microbial ecosystem living in the digestive tract, mainly in the colon. It is established within the few first years of life and contains up to 100 trillion microbes, mainly bacteria (more than 1,000 species) but also fungi, protozoa, archaea, and viruses (**Figure 2**) [45–51].

Gut microbiome is involved in multiple physiological functions and is essential for the maintenance of human health [50–57]. It is influenced by several factors including diet and medications [31, 32, 50, 53, 58–69].

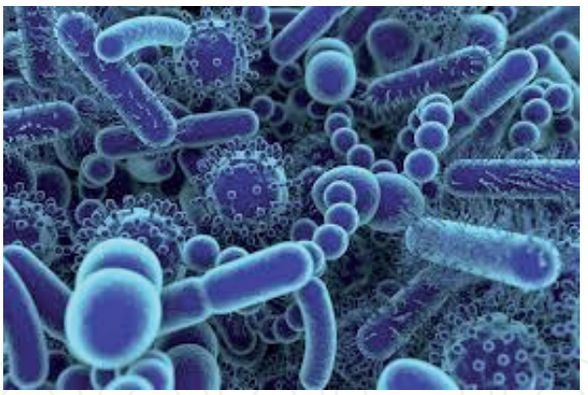

Figure 2.
Gut microbiome.

2.3 Intestinal epithelial barrier

The intestine is lined by layer of epithelial cells that are connected by cell–cell junctions (tight junction, adherens junction, desmosome). These junctions are responsible for maintenance of tissue integrity, creation of a barrier, and signaling. The barrier, which is important for tissue homeostasis, controls the passage of water, ions, molecules, cells, and pathogens across the epithelial layer. Intestinal epithelial barrier is the largest and most important barrier against the external environment (barrier between luminal contents and the underlying immune system). It covers a surface of approximately 400 m^2 and requires approximately 40% of the body energy expenditure (**Figure 3**) [23, 41–43, 70, 71].

Intestinal epithelial barrier is constantly challenged by gut microbiome. It plays an important role in health and disease [23, 41–43, 70, 71]. Several factors including diet and gut microbiome impact intestinal barrier function [20, 41–43]. A high-fiber diet has a beneficial effect while a high-fructose diet and a high-fat diet have a deleterious effect on intestinal barrier function.

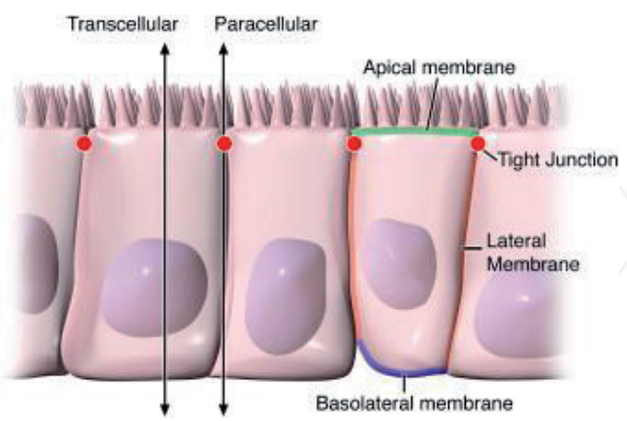

Figure 3.
Intestinal epithelial barrier.

3. NAFLD

3.1 Definition

NAFLD is a liver disease characterized by hepatic steatosis (≥ 5% fat deposit) on either imaging or histology, with no excessive alcohol consumption (< 30 g/day for men and < 20 g/day for women), in the absence of other causes of steatosis (e.g.,

viral hepatitis and medications). It is a spectrum of liver disorders ranging from simple steatosis to NASH. Up to 30% of NAFLD subjects develop NASH. NASH is the aggressive form of NAFLD that can progress to fibrosis, cirrhosis, and hepatocellular cancer. The presence of fibrosis is the strongest predictor of mortality (**Figure 4**) [1–9].

Recently, a consensus of international experts proposed to change the acronym NAFLD to MAFLD (metabolic dysfunction-associated fatty liver disease) [72].

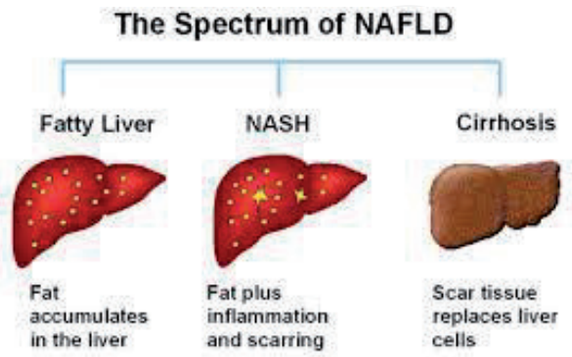

Figure 4.
Spectrum of NAFLD.

3.2 Prevalence

NAFLD is a pandemic with a prevalence of approximately 25% among adult population worldwide. The highest prevalence is observed in Middle East and the lowest prevalence in Africa. More than 1 billion people are affected by NAFLD worldwide (**Table 1**) [3, 8]. The differences in prevalence can be explained, at least partially, by genetic background and lifestyle. NAFLD prevalence continues to rise in all age groups, including in the adolescent population, especially in the setting of the obesity pandemic.

NAFLD is a sexual dimorphic disease. The prevalence of NAFLD is higher in men than in women (protective role of estrogen) [73, 74].

Region	NAFLD Prevalence
World	**25%**
Middle East	32%
South America	30%
Asia	27%
North America	24%
Europe	24%
Africa	13%

Table 1.
Prevalence of NAFLD in adult population by region.

3.3 Pathophysiology

The pathophysiology underlying NAFLD is complex with both non-genetic and genetic components [2, 4–27, 75–79].

Pro-inflammatory diet, overweight/obesity, inflammation, insulin resistance, prediabetes, type 2 diabetes, dyslipidemia, disrupted gut microbiome, and impaired intestinal barrier function are important risk factors associated with and/or contributing to NAFLD [2, 4–27]. In addition, some miscellaneous endocrine disorders including growth hormone (GH) deficiency, hypothyroidism, polycystic ovary syndrome, and hypogonadism and deficiency in epigenetic regulators such as sirtuin 1 have been reported as possible contributing factors to NAFLD [75–79].

There are several genetic forms of NAFLD including variations in patatin-like phospholipase domain-containing protein 3 (*PNPLA3*), transmembrane 6 superfamily 2 (*TM6SF2*), membrane-bound O-acyltransferase domain-containing protein 7 (*MBOAT7*), and glucokinase regulatory protein (*GCKR*) genes [5, 6].

Excessive fat deposition in the liver (hepatocytes) leading to NAFLD can result from one or several combined mechanisms including increased delivery of lipids to the liver from diet or adipose tissue, increased *de novo* synthesis of lipids in the liver, decreased hepatic oxidation of fatty acids, and decreased export of triglycerides from the liver [7–9].

3.3.1 Pro-inflammatory diet

Various common food components have pro-inflammatory potential and by contributing to chronic inflammation, can promote the development of NAFLD [10]. They can either directly alter liver metabolism or act through disruption of gut microbiome. The Western diet which is a diet rich in saturated fat, red meat, fructose, alcohol, and salt is associated with an increased risk of NAFLD.

3.3.2 Overweight/obesity, inflammation

Excess body weight (overweight and obesity) is considered as the main cause of several abnormalities that are contributing to the pathogenesis of NAFLD (e.g., inflammation and insulin resistance). NAFLD is commonly associated with overweight/obesity [74]. It is independently associated with both subcutaneous and visceral obesity. The adipose tissue inflammation observed in overweight/obesity and characterized by increased cytokine production leads to systemic inflammation which is responsible for insulin resistance [10, 11, 80]. Clinical studies have shown that cellular and molecular adipose tissue inflammation correlate with the degree of liver inflammation and the importance of liver disease.

Based on body mass index (BMI), up to approximately 19% of NAFLD subjects do not have excess body weight (lean NAFLD) [74, 81, 82].

The prevalence of NAFLD by BMI in a Chinese population of Shanghai is reported in **Table 2** [74].

BMI	NAFLD Prevalence
< 18.5 (n = 445)	0.4%
18.5 to < 24.0 (n = 4,899)	12.7%
24.0 to < 28.0 (n = 2,801)	49.2%
≥ 28.0 (672)	82.4%

Table 2.
Prevalence of NAFLD by BMI in a Chinese population of Shanghai (n = 8,817).

3.3.3 Insulin resistance, prediabetes, type 2 diabetes

Insulin resistance plays an important role in the in the development of NAFLD. Overweight/obesity and systemic inflammation are responsible for insulin resistance which in its turn is an important contributing factor to the pathogenesis of prediabetes, type 2 diabetes, and NAFLD [2, 10, 80]. NAFLD is highly correlated with prediabetes and type 2 diabetes. There is a reciprocal association between prediabetes/type 2 diabetes and NAFLD [13]. The global prevalence of NAFLD in subjects with prediabetes and type 2 diabetes is around 48% and more than 55%, respectively (**Figure 5**) [5, 10, 12, 15].

Figure 5.
There is a strong association between prediabetes/type 2 diabetes and NAFLD.

3.3.4 Dyslipidemia

Dyslipidemia is a significant risk factor for NAFLD and associated cardiovascular disease. The mechanism by which dyslipidemia increases the risk of NAFLD may be related to an increased accumulation of lipids in the hepatocytes [16].

3.3.5 Disrupted gut microbiome

Profound changes affecting the diversity and the abundance of gut microbiome (dysbiosis) are associated with several metabolic disorders including NAFLD [4, 10, 17–25, 83]. Gut microbiome plays a major role in the pathogenesis of NAFLD. Disrupted gut microbiome (e.g., increase in pro-inflammatory bacteria and decrease in protective bacteria) can promote or aggravate NAFLD through several mechanisms including change in intestinal permeability and change in the amount of absorbed energy (this can cause overweight/obesity, an important risk factor for NAFLD). Microbial metabolites and cell components contribute to the development of inflammation and hepatic steatosis.

Several clinical studies have shown the association of qualitative and quantitative changes in gut microbiome (e.g., increased *Lactobacillus* and Gram-negative bacteria) with NAFLD and its severity [4, 17–19, 24, 25]. The increased gut microbiome taxa may produce more short-chain fatty acids (SCFAs), alcohol, and lipopolysaccharides (LPS). Increased supply of SCFAs, alcohol, and LPS (endotoxins) into the portal circulation is implicated in the pathogenesis of NAFLD and its evolution to NASH (promotion of overweight/obesity and inflammation) [17, 20–23].

3.3.6 Impaired intestinal barrier function

Impaired intestinal barrier function causes increased intestinal permeability ("leaky gut") and is associated with several metabolic disorders including NAFLD [20, 23, 26, 27, 41–43, 70, 71].

Increased intestinal permeability is most likely caused by the disruption of intercellular tight junctions of the intestinal epithelium [26, 71]. It promotes translocation of bacteria-derived products (e.g., SCFAs, alcohol, and LPS) into the portal circulation, exposing the liver to substances capable of inducing hepatic steatosis and fibrosis [17, 20–23]. Several studies have reported that serum zonulin, a marker of intestinal permeability, correlates significantly with the severity of hepatic steatosis in subjects with NAFLD [43].

3.3.7 Miscellaneous endocrine disorders

Several miscellaneous endocrine disorders may contribute to the development of secondary NAFLD [75]. GH deficiency through different mechanisms including inflammation and insulin resistance may promote NAFLD. Hypothyroidism by causing impaired glucose and lipid metabolism and altered energy homeostasis can be linked to NAFLD. Polycystic ovary syndrome through multiple factors (e.g., obesity, inflammation, insulin resistance, and hyperandrogenism) may promote NAFLD. Hypogonadism can be associated with NAFLD through several mechanisms including obesity, insulin resistance, dyslipidemia, estrogen deficiency, and dehydroepiandrosterone deficiency.

3.3.8 Sirtuin 1 deficiency

Sirtuins are a group of proteins belonging to the family of silent information regulator 2. Humans have seven sirtuins. Sirtuin 1 is widely recognized as an important epigenetic regulator involved in multiple biological processes and its deficiency contributes to the pathogenesis of several diseases including NAFLD [76–79]. Exposure to sirtuin 1 inhibitors (e.g., fructose, alcohol, and LPS) leads to defective sirtuin 1 function and can promote NAFLD.

3.3.9 Genetic predisposition

Common genetic forms of NAFLD include variations in *PNPLA3*, *TM6SF2*, *MBOAT7*, and *GCKR* genes (**Figure 6**). These genetic forms of NAFLD are not associated with insulin resistance, type 2 diabetes, and dyslipidemia but can progress to NASH, cirrhosis, and hepatocellular cancer [5, 6].

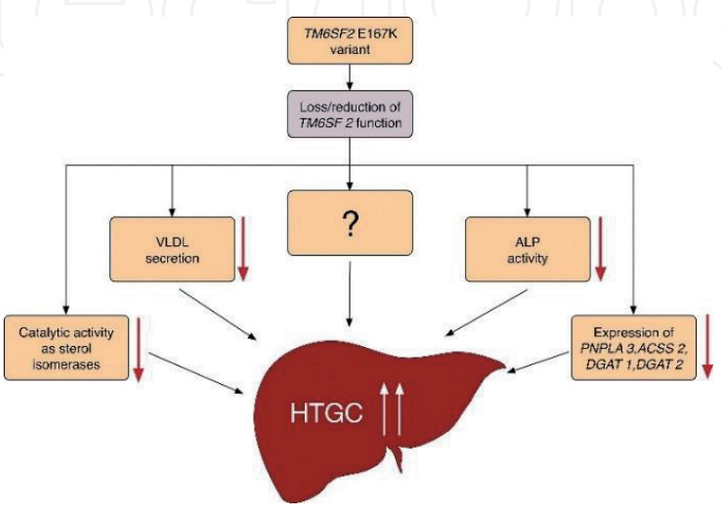

Figure 6.
Several gene variants can contribute to the pathogenesis of NAFLD.

3.3.10 Combination of several factors

Several of the above-mentioned factors can be present in subjects with NAFLD, especially when they are interrelated. For example, a subject with obesity may have inflammation, insulin resistance (with prediabetes or type 2 diabetes), gut microbiome dysbiosis, and leaky gut.

3.4 Diagnosis

NAFLD is a liver disease characterized by hepatic steatosis (≥ 5% fat deposit) on either imaging or histology. Several tests (non-invasive and invasive) can be performed to support and/or confirm the diagnosis of NAFLD and the presence of fibrosis, and optimize the intervention [1, 5, 6, 9, 84–88]. There are several national and international guidelines related to the diagnosis and the management of NAFLD (e.g., American Association for the Study of Liver Diseases "AASLD", National Institute for Health and Care Excellence "NICE", European Association for the Study of the Liver "EASL", Italian Association for the Study of the Liver "AISF", and Asia-Pacific guidelines) [1, 89].

3.4.1 Non-invasive tests

Non-invasive tests of NAFLD include liver biochemistry and imaging examination [1, 5, 6, 9, 84–88].

To establish the diagnosis of NAFLD, conventional liver biochemistry is used first. It may show an increase in liver enzymes including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT). However, up to approximately 75% of subjects with NAFLD may have normal liver enzymes. Additional biomarkers and scores have been proposed (e.g., cytokeratin-18 fragment, fatty liver index, Zhejiang University index, and NAFLD liver fat score) (non-exhaustive list).

Imaging of the liver can be obtained with several tools including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) (**Figure 7**). Based on most guidelines, abdominal ultrasound should be the first-line examination for the identification of hepatic steatosis. Although ultrasound has some limitations in morbidly obese subjects and in subjects with liver fat content below 20%, it has the advantage of being widely available with low cost. MRI remains the gold standard for assessing and quantifying hepatic steatosis since it can detect a liver fat content as low as 5%. However, its use is limited due to high cost and a long time of execution. Another promising imaging technique is the ultrasonography-based transient elastography using continuous attenuation parameter.

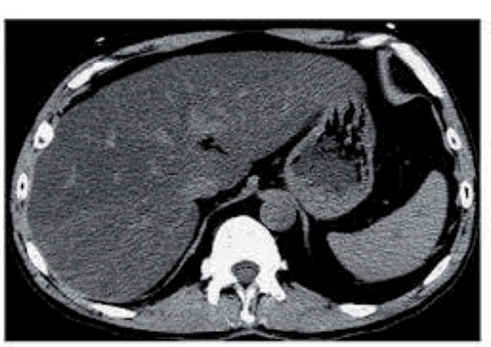

Figure 7.
Abdominal CT scan showing diffuse hepatic steatosis in a subject with NAFLD.

For the assessment of liver fibrosis, several biomarkers, scores, and imaging techniques have been proposed (e.g., AST/ALT ratio, AST to platelet ratio index, enhanced liver fibrosis score, NAFLD fibrosis score, and magnetic resonance elastography) (non-exhaustive list) [6, 84, 88].

All the non-imaging assessments of NAFLD have limitations and alone cannot replace liver biopsy.

3.4.2 Invasive tests

Liver biopsy is the gold standard test in the assessment of NAFLD to diagnose NASH and stage liver fibrosis. It is potentially harmful and carries a low risk of morbidity and extremely low risk of mortality. Therefore, it should be reserved to selected subjects (**Figure 8**) [1, 90]. One important limitation of liver biopsy is that it explores only a small portion of the liver (approximately 1/50,000), not representative of the entire organ.

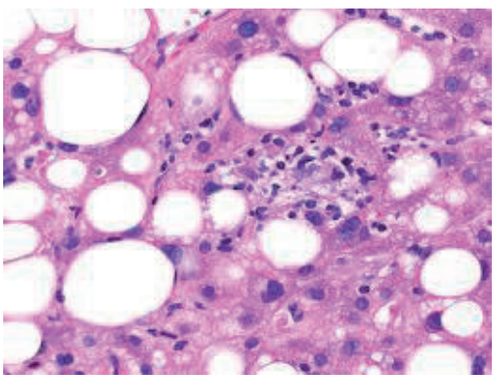

Figure 8.
Liver histology showing macrovesicular steatosis in a subject with NAFLD.

3.5 Treatment

Because NAFLD/NASH is associated with increased morbidity and higher risk of death mainly related to cardiovascular and liver diseases, it is essential to initiate a treatment as soon as the diagnosis is made. In the absence of approved pharmacotherapy for the treatment of NAFLD/NASH, the first-line therapy of NAFLD remains lifestyle intervention with weight loss (in case of excess body weight) [1, 2, 8, 28–30]. Gut microbiome and intestinal epithelial barrier are becoming promising targets for the treatment of several diseases including NAFLD [4, 17, 18, 20–22, 24, 25, 31–43]. When treating NAFLD/NASH, in addition to lifestyle changes and weight loss (in case of excess body weight), focus should also be on correcting gut microbiome and intestinal permeability directly and/or through gut microbiome modulation [4, 17, 18, 20–22, 24, 25, 35–40, 43]. Several drugs for the treatment of NAFLD/NASH are currently under investigation [6, 8, 91]. It is also important to treat the associated morbidities other than overweight/obesity (e.g., type 2 diabetes and dyslipidemia).

3.5.1 Lifestyle intervention

Lifestyle intervention which includes diet and exercise is the first-line therapy in NAFLD but is difficult to maintain (**Table 3**) [1, 2, 8, 28–30]. Diet is a powerful tool in the management of NAFLD. Diet relates to the amount and the composition of food that is consumed on a daily basis. There are several types of

diets with different caloric content and different composition of macronutrients, fiber, minerals, and vitamins. They include hypocaloric diet, low-carbohydrate diet, low-fat, high-protein diet, high-fiber diet, and Mediterranean diet (non-exhaustive list) [8, 29, 30, 92]. In NAFLD subjects, hypocaloric diet is usually a deficit of 500–1,000 kcal/day. For macronutrient composition and according to most recommendations, carbohydrate intake should be between 40 and 50% (with exclusion of fructose from foods and beverages), fat intake no more than 30% (with saturated fat below 10%), and protein intake between 15 and 20% [28]. Even without significant weight loss, anti-inflammatory diets like Mediterranean diet (a mainly plant-based low-carbohydrate and high-unsaturated fat diet) have beneficial properties both in the prevention and treatment of NAFLD [8, 10, 25, 27–29, 93]. The omega-3 polyunsaturated fatty acids present in the Mediterranean diet may reduce hepatic steatosis. A diet containing sirtuin 1 activators (e.g., magnesium and zinc) can be beneficial in NAFLD subjects [79].

The objective in NAFLD subjects with excess body weight is a weight loss of 7–10%. To achieve weight loss, in addition to lifestyle intervention, other tools including drugs, medical devices, and bariatric surgery can also be used when needed and indicated [2, 28, 94–97]. Rapid sudden weight loss should be avoided (risk of aggravation of liver failure).

Lean NAFLD subjects may have visceral obesity that is not detected by BMI. These subjects may also benefit from diet and weight loss.

In addition to the type of diet, the timing and the frequency of the meals may also influence NAFLD. It is recommended to consume more daily calories in the morning versus the evening and avoid skipping meals [29].

Regular exercise including moderate intensity aerobic activities (3–5 weekly sessions with approximately 40 minutes per session) and resistance training can reduce hepatic steatosis even without significant weight loss [1, 8, 28, 29]. Combination of exercise and diet has greater benefit than exercise or diet alone.

Lifestyle Intervention	Description
Healthy diet	Low-carbohydrate diet, Low-fat diet, High-fiber diet, Mediterranean diet, etc.
Diet for weight loss (in case of excess body weight)	Hypocaloric diet
Exercise	Aerobic activities, Resistance training

Table 3.
Lifestyle intervention for the treatment of NAFLD.

3.5.2 Gut microbiome modulation

The prevention and management of NAFLD may benefit from modulation and correction of gut microbiome [4, 17, 18, 20–22, 24, 25, 35–40]. Gut microbiome can be modulated through diet, antibiotics, prebiotics, probiotics, synbiotics, and fecal microbiota transplantation [4, 17, 18, 20–22, 24, 25, 33–40, 58–65]. To optimize the efficacy of these therapies, focus should be on the altered gut microbiome (e.g., taxa responsible for high alcohol and LPS production) [17].

3.5.2.1 Diet

Diet is an important tool for the modulation of gut microbiome. The amount of daily caloric intake and the content of food significantly affect gut microbiome. A diet that is low in calories (when weight loss is needed), low in fat, and high in fiber has a favorable effect on weight control and gut microbiome (increase in richness, decrease in Firmicutes-to-Bacteroidetes phyla ratio) [58–64].

The diet, through the modulation of gut microbiome, could be beneficial in NAFLD subjects [4, 25].

3.5.2.2 Antibiotics

Antibiotics are medications used to fight local or systemic infection [98].

Antibiotics affect gut microbiome [4, 24, 59, 65]. They can deplete or alter gut microbiome (e.g., increase in Firmicutes phylum) and reduce liver disease development. However, their clinical use is limited since they may eliminate important beneficial bacterial species and cause antibiotic resistance.

3.5.2.3 Prebiotics

Prebiotics are chemicals (nondigestible food ingredients) inducing growth and/or activity of intestinal bacteria (e.g., inulin, lactulose, and resistant starch) [31, 69]. Some dietary fibers are prebiotics [25]. Prebiotics can be found in many foods (e.g., leek, asparagus, onion, soybean, apple, and banana) (**Figure 9**).

Prebiotics can positively modulate gut microbiome and improve NAFLD [4, 21, 24, 25, 35]. They lower the production of LPS. Treatment with oligofructose (16 g/day for 8 weeks) in subjects with NASH showed a significant decrease of AST [35].

Figure 9.
Prebiotics can be beneficial in the treatment of NAFLD by modulating gut microbiome.

3.5.2.4 Probiotics

Probiotics are nonpathogenic living microorganisms with direct or indirect effect on gut microbiome [31, 32, 68]. Probiotics can be found in several foods (e.g., yogurt, cheese, and milk) (**Figure 10**).

Probiotics can positively impact gut microbiome and improve NAFLD [4, 21, 24, 36–39]. They reduce the production of LPS. Administration of *Lactobacillus rhamnosus* strain GG (12 billion CFU/day) for 8 weeks in children with NAFLD showed a significant decrease of ALT [36]. Treatment with VSL#3 (a mixture of 8 probiotic strains) for 4 months in children with NAFLD demonstrated a significant decrease of hepatic steatosis [38].

Figure 10.
Probiotics can be beneficial in the treatment of NAFLD by modulating gut microbiome.

3.5.2.5 Synbiotics

Synbiotics are combination of prebiotics and probiotics. They have the potential to induce more effects than prebiotics or probiotics used alone.

There are few studies assessing the effects of synbiotics on NAFLD subjects. They showed several beneficial effects including reduction of inflammation and hepatic steatosis [4, 24, 40]. Administration of *Bifidobacterium longum* with fructo-oligosaccharides for 24 weeks in subjects with NASH showed a significant decrease of AST, serum endotoxin, hepatic steatosis, and NASH activity index [40].

3.5.2.6 Fecal microbiota transplantation

Fecal microbiota transplantation consists of transfer of feces from a healthy donor to a recipient. The addition of healthy stool can be done through colonoscopy, orogastric tube, esophagogastroduodenoscopy, or oral capsule (**Figure 11**) [99].

Fecal microbiota transplantation is an exciting therapy with important potential indications. It was first approved by the United States Food and Drug Administration for the treatment of *Clostridium difficile* infection. Fecal microbiota transplantation can modify gut microbiome for the purpose of obesity and metabolic disorders management [33, 34]. Clinical studies using fecal microbiota transplantation in NAFLD subjects are currently ongoing.

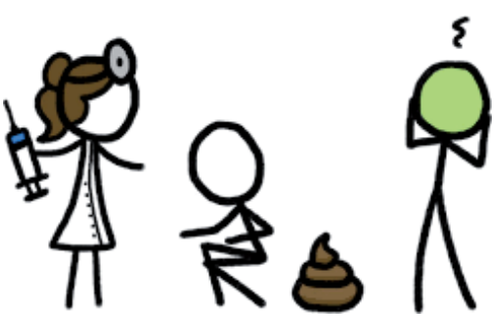

Figure 11.
Fecal microbiota transplantation has the potential to treat NAFLD by modifying gut microbiome.

3.5.3 Intestinal permeability correction

Restoring the intestinal epithelial barrier is an attractive therapeutic approach in NAFLD subjects. Currently, there is no approved drug for this indication. Intestinal permeability can be targeted and corrected directly (with diet) and/or through gut microbiome modulation [17, 18, 43].

A study using high-fiber diet for 6 months in subjects with NAFLD showed a decrease in intestinal permeability as demonstrated by a reduction of approximately 90% of serum zonulin, and a significant reduction of liver enzymes (e.g., AST, ALT, and GGT) and hepatic steatosis [43].

3.5.4 Drugs

There are no approved drugs for the treatment of NAFLD/NASH. Several investigational drugs are currently in various stages of clinical trials. They can impact at least four pathways related to NAFLD development and progression (hepatic fat accumulation, oxidative stress, gut microbiome, and hepatic fibrosis) [7, 8, 91]. Some of these investigational drugs have shown promising preliminary results (e.g., lanifibranor, cenicriviroc, and resmetirom) (non-exhaustive list) [6, 8, 91].

Any drug that is currently used in the treatment of NAFLD/NASH (e.g., antidiabetic drugs, lipid-lowering drugs, and vitamin E) should be considered as an off-label treatment [1, 2, 6–9, 14–16, 28, 91, 100]. Among the antidiabetic drugs, pioglitazone has shown a strong efficacy and became the first-line therapy in subjects who have type 2 diabetes and NAFLD [1, 2, 6, 14, 15, 28, 100].

The summary of different tools available in the United States of America (USA) or under investigation for the treatment of NAFLD/NASH is reported in **Table 4**.

Tool	Description
Lifestyle intervention	Diet, Exercise
Anti-obesity drug	Xenical®, Qsymia®, Contrave®, Saxenda®
Anti-obesity medical device	Lap-Band®, AspireAssist®, Orbera® Intragastric Balloon System, TransPyloric Shuttle®, Obalon® Balloon System, Plenity®
Bariatric surgery	Sleeve gastrectomy, Roux-en-Y gastric bypass
Gut microbiome modulation	Diet, Antibiotics, Prebiotics, Probiotics, Synbiotics, Fecal microbiota transplantation
Intestinal permeability correction	High-fiber diet, Gut microbiome modulation
Off-label drug	Antidiabetic drugs, Vitamin E, etc.
Investigational drug	Lanifibranor, Cenicriviroc, Resmetirom, etc.

Table 4.
Summary of different tools available in the USA or under investigation for the treatment of NAFLD/NASH.

3.5.5 Liver transplantation

NASH is becoming one of the leading causes of liver transplantation. Currently, in the USA, NASH ranks as the second most common reason for liver transplantation after hepatitis C [89].

4. Conclusions

NAFLD is the most common chronic liver disease worldwide. It is a spectrum of liver disorders ranging from simple steatosis to NASH. NAFLD subjects have overweight/obesity in the majority of cases and the disease can be associated with disrupted gut microbiome and impaired intestinal barrier function.

In the absence of approved pharmacotherapy for the treatment of NAFLD/NASH, in addition to lifestyle intervention with weight loss (in case of excess body weight), targeting gut microbiome and intestinal epithelial barrier with diet, prebiotics, probiotics, synbiotics, and fecal microbiota transplantation represents a promising novel therapeutic approach.

Conflict of interest

The author declares no conflict of interest.

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