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Review Article

# Recent Updates in the Prevention of Nonalcoholic Fatty Liver Disease

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## Abstract

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are the leading causes of hepatic fibrosis and liver-related mortality worldwide, despite efficient hepatitis B and C antiviral therapies that have dramatically lowered the disease load. Although significant efforts have been exerted to understand the molecular basis of disease pathogenesis, there are currently few therapeutic alternatives available for NAFLD-associated fibrosis. Thus, NAFLD prevention is critical before the development of disease-related complications. In this context, there is a tremendous substantial global burden on public health systems to actively search for effective preventive and therapeutic targets for NAFLD. In this review, we highlight the current strategies to prevent progression and poor outcomes of NAFLD and to avoid complications associated with disease fibrosis, notably cirrhosis, portal hypertension, and liver cancer. We discuss different nonpharmacological measures, such as lifestyle modifications (weight loss, exercise, healthy diet) and other pharmacological interventions that could prevent NAFLD.

## Introduction

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in developed countries, affecting a large percentage of the adult population.[1] NAFLD is defined as a spectrum of liver diseases that include cirrhosis, steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, and hepatocellular carcinoma (HCC).[2] In a consensus statement in 2020, an international panel of experts recommended a change in NAFLD to metabolic-associated fatty liver disease owing to the heterogeneous pathogenesis of the disease.[3] The main advantage of this new nomenclature is a move away from alcohol usage or other concurrent liver diseases and toward a diagnosis of inclusion based on the metabolic dysfunction that is the primary cause of the disease,[4] particularly for children.[5] Nonetheless pathogenesis of NAFLD is complex and multifactorial. Environmental factors, obesity, insulin resistance, alterations in the microbiome, and predisposing genetic variations interact in a complicated way to cause disordered lipid homeostasis and an abnormal accumulation of triglycerides and other lipid compounds in hepatocytes.[6]

Frequently associated metabolic dysfunctions such as type 2 diabetes mellitus (T2DM), obesity, or dyslipidemia are seen in NAFLD patients.[1] Fatty liver disease is categorized into NAFLD or NASH based on histology. NAFLD is defined as the presence of more than 5% hepatic steatosis in the absence of hepatocyte injury. NASH is defined as hepatic steatosis with concomitant lobular inflammation and hepatocyte damage (such as hepatocyte ballooning), with or without fibrosis.[7,8]

Promoting a healthy anti-oxidant status is essential for maintaining normal cellular homeostasis. Oxidative stress is considered a major factor that contributes to the pathophysiology of inflammatory chronic liver diseases and, in turn, the development of NAFLD. This highlights the significance of controlling Ox, to prevent the development and progression of NAFLD.[9]

In this context, NAFLD carries a high risk for cardiovascular diseases and cardiovascular events and increases the burden of NAFLDrelated HCC, underscoring the urgent need for early identification and prevention of disease progression.[1]

## Modifiable and nonmodifiable predisposing risk factors for NAFLD

Obesity is a significant driver of NAFLD and NASH,[10] with the

**Keywords:** Nonalcoholic steatohepatitis; Nonalcoholic fatty liver disease; Prevention; Lifestyle modifications; Pharmacological interventions.

**Abbreviations:** ALT, alanine transaminase; BMI, body mass index; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PPAR, proliferator-activated receptor; T2DM, type 2 diabetes mellitus.

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prevalence of NAFLD increasing relative to increases in body mass index (BMI).[11] The increase in T2DM echoes that of obesity worldwide, adding another risk factor for NAFLD and NASH.[11] The prevalence of T2DM among NAFLD and NASH patients is over 60%. T2DM also increases the risk of an accelerated course of NAFLD and is a predictor of advanced fibrosis and mortality.[1,12] Visceral obesity, associated with insulin resistance, is a crucial factor in NAFLD development.[13] Insulin resistance causes increased lipolysis in adipose tissue that causes decreased glucose absorption in skeletal muscle. As a result, the amount of free fatty acids in the circulation and liver rises.[14,15]

The possibility of NAFLD and NAFLD-related fibrosis increases with aging.[11,12] It has been observed that older individuals have higher stages of fibrosis.[16] Female sex is also associated with an increased risk of NAFLD, as stated in some reports from Sri Lanka and Thailand. A study from Thailand including 34,709 individuals (27,073 females and 7,636 males) reported the prevalence of NAFLD at 22.9% in females and 18.3% in males.[17] However, some studies conducted in the USA, China, and Spain reported higher rates of NAFLD in males.[18–20]

As previously mentioned, ethnicity and race can be categorized as nonmodifiable risk factors for NAFLD.[12,21] In many studies conducted in the USA, Hispanic Americans had the highest prevalence of NAFLD, followed by Americans of European origin and African Americans, despite a higher prevalence of obesity among non-Hispanics.[22,23] The higher prevalence of NAFLD among Hispanics may be explained by greater sensitivity to recognized risk factors (*e.g.*, visceral adiposity, diabetes, and an undesirable gene variant) relative to other ethnic subgroups. However, socio-economic and cultural factors that may affect the risk of developing NAFLD are rarely considered in the sense of NAFLD.[23]

Genome-wide association studies have identified multiple loci associated with NAFLD.[24,25] The genes that have been related to NAFLD include transmembrane 6 superfamily member 2, PNPLA3, MBOAT7, glucokinase regulator, and hydroxysteroid 17-beta dehydrogenase-13.[26] Multiple other genes, and reversible epigenetic changes, such as miRNA-122, miRNA-34a, and miRNA-192, have been reported in many studies, suggesting the existence of heritable factors for NAFLD.[27,28]

A functional role for the microbiota in NAFLD pathogenesis has been identified. Gut bacteria from obese and lean humans have different impacts on the risk of fat accumulation in germ-free mice, but there is little data available on the role of gut microbiota in NAFLD in humans.[29] Recently published data suggest that the microbiome and gut microbiome-derived metabolites could be used to predict advanced fibrosis and cirrhosis in NAFLD patients.[30,31]

Smoking has been reported to be an independent risk factor for fibrosis progression in patients with NAFLD.[32] However, drinking coffee was found to prevent liver fibrosis in NAFLD patients while conflicting reports are available about its role in reducing NAFLD incidence in the general population.[33] Additionally, elevated serum markers, such as uric acid and ferritin, have been significantly correlated with the existence and progression of NAFLD.[34,35] The associations of metabolic syndrome, predominantly obesity and insulin resistance, with NAFLD prevalence can increase the likelihood of liver fibrosis progression, leading to cirrhosis, HCC, and death.[36,37]

The burden of NAFLDrelated HCC is increasing rapidly. In 2010, a study from northeast England reported that 35% of diagnosed HCC cases were associated with NAFLD (41 of 118 cases), which was a significant 10-fold increase over a 10-year period.[38] In another study, the reported incidence of HCC among patients with NAFLD was 0.44 per 1,000 person-years. Stages F3 and F4 NAFLD-related fibrosis increased by an estimated 7-fold for the risk of HCC compared to individuals without liver disease. NAFLD-related HCC can also arise in the absence of cirrhosis, as seen in the chronic hepatitis B virus.[39,40] According to published data, there has been a 9% annual increase in NAFLD-related HCC associated with a 1.2-fold higher risk of mortality within 1-year for compared to other liver diseases.[41] Another study demonstrated that NAFLD was associated with a 7.3-fold increased risk of HCC (OR: 7.3, 95%CI 1.52–34.76) in patients with chronic hepatitis B virus infection.[42] Patients with noncirrhotic NASH had an almost 3-fold increase in the risk of HCC development compared to noncirrhotic individuals with liver disease due to other causes (OR 2.61; 95% CI 1.27–5.35; $p$ = 0.009).[43] A study from South Korea including 329 patients reported an increase in NAFLD-related HCC cases from 3.8% in 2001–2005 to 12.2% in 2006–2010.[44]

Figure 1 summarizes the main modifiable and nonmodifiable risk factors for the occurrence and progression of NAFLD.

## Prevention of NAFLD

### *Nonpharmacological measures*

Despite great efforts in finding pharmacological strategies for NAFLD prevention, nonpharmacological measures remain the first and critical issue for NAFLD prevention. Lifestyle modifications, including weight loss, dietary modifications, and exercise, also serve as a primary line of prevention.

### *Lifestyle modification*

#### Dietary change

It is estimated that most consumed fats are saturated and that fresh fruit and vegetable intake rates are low.[45] For example, among Egyptian women, approximately 40% of the diet includes saturated fat.[46] Additionally, weight gain, obesity, and NAFLD have all been linked to increased caloric intake, particularly when combined with the consumption of more saturated fat, complex carbohydrates, sugary beverages, and high fructose intake.[47,48] Lifestyle modification programs, in addition to weight loss, are proven measures for reducing hepatic fat, the disappearance of steatohepatitis, and fibrosis regression, subsequently improving the quality of life of NAFLD patients. Six weeks of a Mediterranean diet were shown to be linked to appreciable reductions in hepatic steatosis based compared with increased fat and reduced carbohydrate diet.[49] Interestedly, some published data suggest that the timing of meals also affects NAFLD; eating before sleep and consuming a majority of calories at dinner increases the chance of developing NAFLD.[50] However, some herbs and foods are thought to be protective against the disease.[51] Green tea catechins are thought to have hepatoprotective effects due to their anti-inflammatory, anti-oxidant, and hypolipidemic qualities. One study involving patients with biopsy-proven NASH reported an improvement in insulin resistance with a decrease in BMI but without a change in alanine transaminase (ALT) and aspartate aminotransferase levels compared to controls. Due to debates in the respective research fields, preclinical models have been developed to address toxicological concerns before conducting further research to explore the possible benefits of green tea in NAFLD.[52]

There is some literature on the effects of coffee and other caffeinated drinks on NAFLD prevention. One study reported that coffee could reverse NAFLD by reducing ALT, macrovesicular steatosis, and hepatocyte ballooning.[52] Several bioactive substances in cof-

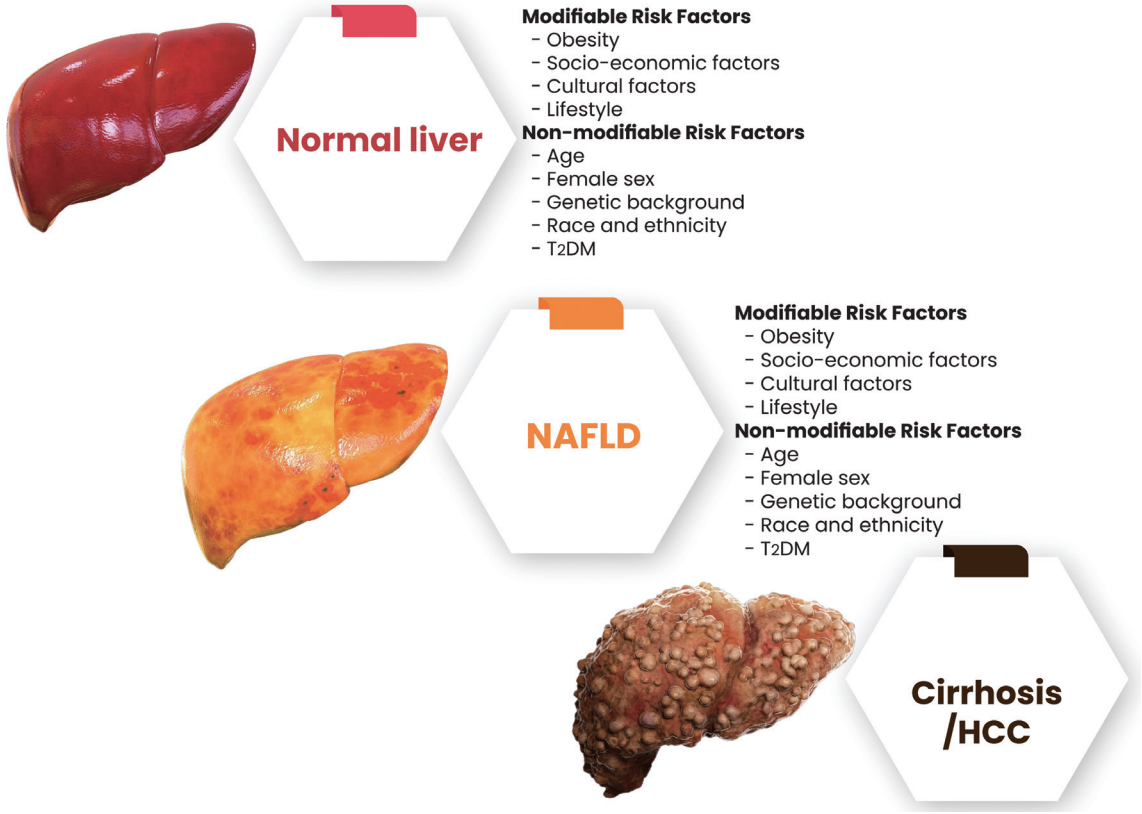


**Fig. 1. The main modifiable and nonmodifiable risk factors for the occurrence and progression of nonalcoholic fatty liver disease.**

fee could mediate this protective mechanism. The antifibrotic action, as a result of caffeine's antagonism of the adenosine receptor A2a, could result in the inactivation of hepatic stellate cells.[53,54] A meta-analysis of 20,064 participants and a large population-based study of a cohort of 18,550 people found that caffeine consumption was protective against NAFLD, as evidenced by altered levels of the liver enzymes aspartate aminotransferase and ALT.[55]

In conclusion, energy intake restrictions, such as reduced saturated fat, carbohydrate, and sugar consumption, and an increase in consumption of green tea, coffee, and caffeine, could be beneficial dietary changes for NAFLD prevention.

### Physical activity

A lack of physical activity is associated with an increased risk of NAFLD; the lower the level of habitual physical activity the greater the risk of intrahepatic fat content.[56] Even without weight loss, a suitable exercise regimen is a crucial factor in NAFLD prevention. However, there is no established ideal physical activity/exercise frequency, intensity, duration, and type to promote NAFLD resolution.[57,58] Both aerobic and resistance exercise are associated with a significant reduction in hepatic fat content, and the choice between both types should be based on patient preference.[47,59] European clinical guidelines for NAFLD suggest resistance training together with 150–200 minutes per week of moderate-intensity aerobic physical activity, such as brisk walking or stationary cycling in 3–5 sessions. This exercise benefit could be associated with improvement in musculoskeletal fitness and metabolic risk factors.[47] A large pool of published data reported an improvement in the degree of hepatic steatosis with exercise; however, there is insufficient data evaluating the impact of exercise on liver histology in NASH.[47] In this context, exercise type and duration should be designed based on patient preference and compliance with the exercise protocol.[58]

### Weight loss

Weight loss can have a significant impact on overweight or obese NAFLD patients.[60] Many studies reported that weight loss via a comprehensive lifestyle program for 12 months could improve histologic NASH-related features.[61] Interestingly, it was reported that a 5% reduction in body weight was associated with an approximate 30% reduction in liver fat content with a subsequent improvement in metabolic abnormalities; meanwhile, a 7–10% reduction in weight loss was reported to be associated with a reduction in hepatocyte inflammation, and a 10% reduction was associated with significant fibrosis regression.[62–64] In contrast, some published data illustrated that weight reduction is not significantly associated with reducing hepatic fat content or restoring normal liver function.[65]

### Sleep

National Sleep Foundation guidelines state that a reasonable sleep duration differs according to age. Normal, healthy adults should sleep between 7 and 9 hours every night, while infants, young children, and teenagers require even more sleep to support growth and development, and persons over 65 years need between 7 and 8 hours of sleep every night.[66] Some studies reported that poor quality of sleep and sleep deviation contribute to NAFLD pathogenesis and that sleep quality is associated with obesity, diabetes, and multiple behavioral influences.[67,68] The underlying mecha-

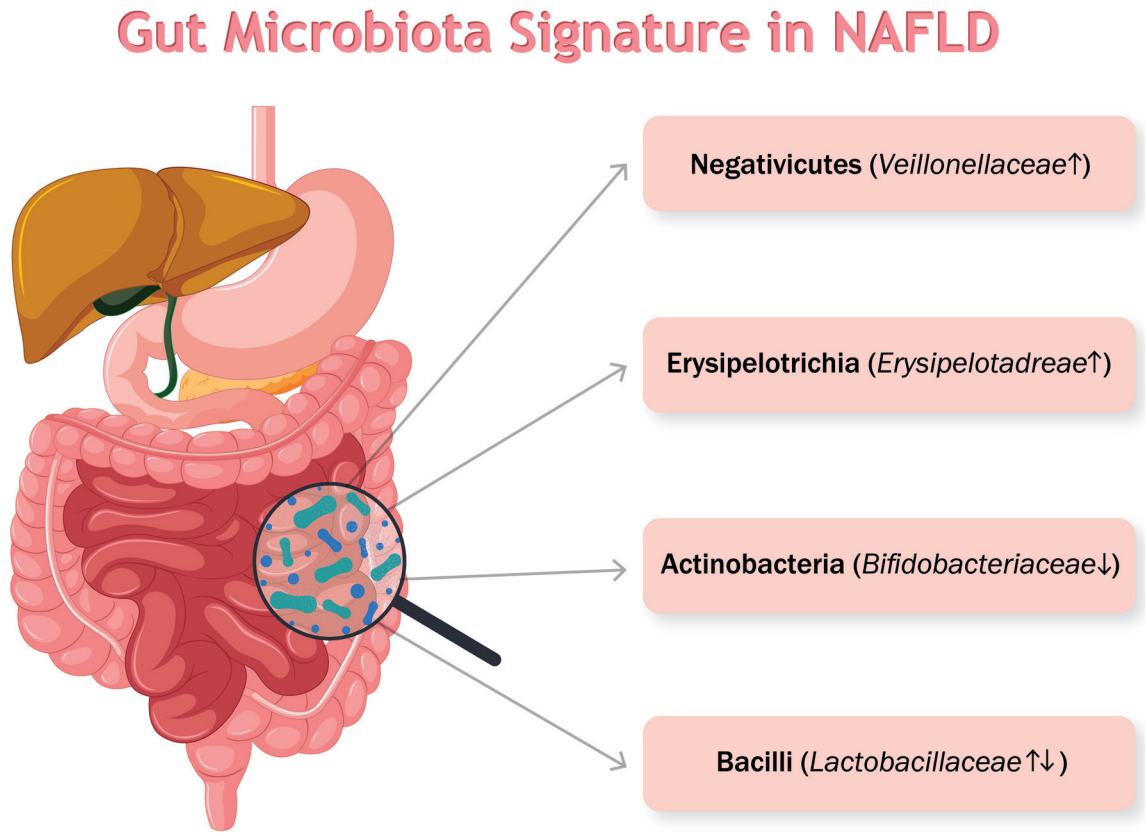


**Fig. 2. Gut microbiota signature in nonalcoholic fatty liver disease.**

nism is attributed to increases in inflammatory cytokines, such as interleukin 6 and tumor necrosis factor-alpha, that are exacerbated by sleep disorders. Such increases, in turn, can enhance adipocyte lipolysis affecting hepatic overflow of free fatty acids.[69] Changes in sleep quality may also lead to increased liver fat storage via its effect on the hypothalamus-pituitary-adrenal axis and cortisol metabolism.[70] Although the discoordination between central and peripheral circadian rhythms plays a crucial role in pathogenesis. Thus, circadian clock proteins that maintain energy homeostasis by coordinating cellular processes within and between organ systems could also lead to NAFLD.[71] Therefore, proper sleep patterns and duration combined with other behavioral factors are important in NAFLD prevention.

## Bariatric (metabolic) surgery

Due to the superior efficacy of sustained weight loss and physical activity in NAFLD prevention, bariatric surgery represents an alternative nonpharmacological management option for obese patients with NAFLD.[72] Recent systematic reviews and meta-analyses reported a marked decrease in mean NAFLD activity score following bariatric surgery.[73,74] Many articles have also reported potential positive effects of bariatric surgery on several outcomes for NASH owing to its effect on reducing BMI, improving insulin resistance, altering glucose metabolism, reducing transaminases levels, and improving histological changes associated with simple steatosis, NASH, and fibrosis.[75,76] However, there is still lack of information on adverse events.[75] Until now, there have been no recommendations to support or reject bariatric surgery in the treatment of NAFLD.[75]

## Gut microbiota

The gut plays a pivotal role in the development of NAFL and NASH.[77] Trillions of microorganisms inhabit the different parts of the gastrointestinal tract at different concentrations.[77] The gut microbiome is responsible for regulating the fermentation and metabolism of food-derived nutrients that impact the aggravation and mitigation of the course of NAFLD. The microbiome also plays an important role in the development and function of the host's innate and adaptive immune systems by depleting harmful substances that promote inflammation, boosting the host immune response, and preventing insulin resistance, steatosis, and, consequently, NAFLD.[78] Increased *Proteobacteria* (phylum), *Enterobacteriaceae* (family), *Escherichia*, *Bacteroides*, *Dorea*, and *Peptoniphilus* (genus) and decreased *Rikenellaceae*, *Ruminococcaceae* (family), *Faecalibacterium*, *Coprococcus*, *Anaerosporobacter*, and *Eubacterium* (genera) are considered the most consistent gut microbiota signatures associated with NAFLD. Other metabolic disorders could overlap with NAFLD-associated microbiota signatures such as reduced levels of *Faecalibacterium prausnitzii*, which is considered a beneficial anti-inflammatory microbe in cirrhotic patients, as well as in obese patients, patients with T2DM, or in some gut diseases, such as irritable bowel syndrome and inflammatory bowel disease. In advanced fibrosis, *Bacteroides vulgatus* is more prevalent and is linked to marked obesity, insulin resistance, and elevated levels of haemoglobin A1c. It is noteworthy that the gut mycobiome is consistent among NAFLD patients, unlike patients with cirrhosis and alcoholic liver diseases.[79] Figure 2 provides an overview of the gut microbiota signature in NAFLD. In this context, microbial metabolic manipulation via the microbiome and its

**Table 1. Recent reports of gut microbial alterations in patients with nonalcoholic fatty liver disease**

| Study | Year | Sample size | Microbiome | Metabolites |
|---|---|---|---|---|
| *Rau et al.*[81] | 2018 | 32 NAFLD; 14 NAFL; 18 NASH; 27 HCs | *Fusobacteria; Fusobacteriaceae; Fusobacterium; Prevotella; Eubacterium biforme* | Propionate; Butyrate; Acetate |
| *Kim et al.*[82] | 2019 | 453 Non-NAFLD; 40 Developed NAFLD; 35 Regressed NAFLD; 238 Persistent (G3) | *Christensenellaceae; Odoribacteraceae; Oscillospira; Odoribacter; Coprococcus; Ruminococcaceae; Porphyromonadaceae; Christensenellaceae; Oscillospira; Ruminococcus; Coprococcus* | Not described |
| *Caussy et al.*[30] | 2019 | 54 Non-NAFLD; 18 NAFLD without advanced; fibrosis; 26 NAFLD-cirrhosis | *Streptococcus; Megasphaera; Bacillus; Lactococcus; Gallibacterium; Faecalibacterium; Prausnitzii; Catenibacterium Rikenellaceae; Mogibacterium; Peptostreptococcaceae* | Not described |
| *Chen F. et al.*[83] | 2020 | 30 Lean control; 46 non-lean control; 99 Lean NAFLD | *Dorea; Marvinbryantia; Christensenellaceae* | Total BA; Total primary BA; Total secondary BA; CDCA; DCA |
| *Adams et al.*[84] | 2020 | 55 Control; 58 NAFLD Fibrosis F0-2; 9 NAFLD Fibrosis F3/4 | *Firmicutes Proteobacteria; Actinobacteria; Bacteroidetes Actinomycetaceae; Lachnospiraceae; Bacteroidaceae* | Total BA; Primary conjugated; BA; GCA; Secondary conjugated; BA; DCA |
| *Behary et al.*[85] | 2021 | 30 Non-NAFLD control; 28 NAFLD-fibrosis; 32 NAFLD-HCC | *Proteobacteria; Enterobacteriaceae; Oscillospiraceae Erysipelotrichaceae; Coriobacteriaceae; Muribaculaceae; Odoribacteraceae; Prevotellaceae; Bacteroides caecimuris; Veillonella parvula* | Xaloacetate; Acetylphosphate; Isocitrate; Acetate; Butyrate; Formate; Butyrate; Propionate |
| *Demir et al.*[86] | 2022 | 16 Controls; 24 NAFL; 54 NASH | *Mucor sp.; Cyberlindnera jadinii; C.albicans Salinispora sp. Babjeviella; inositovora* | Not described |

BA, bile acids; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; HCs, healthy controls; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

metabolites could represent a potential option for NAFLD prevention, but more extensive research is required.[80]

Table 1 demonstrates the most recent reports of gut microbial alterations in patients with NAFLD.[30,81–86]

## Pharmacological interventions

Pharmacological therapies have had significant effects on NAFLD prevention, especially for patients in high-risk groups, such as those with concomitant T2DM.[1] Glucagon-like peptide-1 agonists that stimulate the secretion of insulin in a glucose-dependent manner, as well as sodium-glucose transport protein 2 inhibitors that prevent glucose reabsorption in the kidney, are examples of new antidiabetic medications that could have a positive effect on weight reduction. Liraglutide and semaglutide, glucagon-like peptide-1 receptor agonists, are now being studied in a placebo-controlled phase 2 study in NASH patients.[87] The nuclear receptor obeticholic acid, which can control liver inflammation, lipoprotein composition, bile acid synthesis, and glucose and lipid metabolism, is a new medication that exhibits agonistic farnesoid X receptor activity.[88,89] and has been demonstrated in several placebo-controlled trials to be significantly helpful in enhancing insulin sensitivity in NAFLD patients with T2DM.[90,91] Based on the promising results of a phase 2 trial that demonstrated notable reductions in inflammation and fibrosis in patients with NAFLD, obeticholic acid is currently being investigated in a sizable long-term phase 3 study with more than 2,400 NASH patients, including approximately 2,100 patients with moderate hepatic fibrosis.[92,93]

Proliferator-activated receptors (PPARs) agonists are a group of transcription factors that serve as fat sensors in several tissues and are essential for controlling adipogenesis, triglyceride metabolism, and liver homeostasis.[94] Three different receptors (PPARα, PPARβ/δ, and PPARγ) in this family are antidiabetic targets of the thiazolidinediones class, also known as "glitazones".[95] Pioglitazone and Rosiglitazone target PPARγ, which can ameliorate fibrosis,[96] reduce hepatic fat, inflammation and transaminase levels, and improve histological features in NAFLD.[97,98]

Several other drugs are in phase 2 randomized placebo-controlled trials with promising results. Firsocostat (GS-0976) and PF-05221304 are involved in inhibiting acetyl-coenzyme carboxylase catalyzing the rate-limiting step in *de novo* lipogenesis.[99] Selonsertib, an apoptosis signal-regulating kinase 1 inhibitor, was tested as a target for "anti-inflammatory" interventions in phase 3 trials but with less satisfactory results.[100] Another phase 3 trial evaluating cenicriviroc, a chemokine CCR2/CCR5 receptor inhibitor, in NASH patients with liver fibrosis is currently ongoing.[101] Cenicriviroc is thought to effectively inhibit monocyte recruitment and macrophage accumulation in the liver,[102] which is a crucial step in NASH progression towards fibrosis.[103,104]

Adipokines are secreted from adipose tissues and are considered the primary fatty acid provider, which is the main contributor to NAFLD development.[105] Adiponectin is a vital adipokine that improves hepatic steatosis and inflammation and prevents NAFLD development.[106,107] Coincident dyslipidemia should be treated with LDL-cholesterol-lowering agents, such as statins.[8,15] Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors are also promising medications because of their ability to target the renin–angiotensin–aldosterone system in NAFLD pathogenesis.[6,15] Leptin is an appetite-suppressing hormone secreted by fat cells; however, its effects on NAFLD development in humans are not clear yet.[108] Ghrelin is an anti-inflammatory adipokine that improves hepatic lipid metabolism, inflammation,

oxidative stress, and apoptosis, and could be a promising target for NAFLD prevention.[109]

Many preclinical and clinical studies suggest that various polyphenols, either flavonoids or nonflavonoids, could prevent steatosis and its progression to nonalcoholic steatohepatitis, as well as ameliorate NAFLD. Therefore, adding polyphenol-rich foods to one's diet may be an appropriate recommendation for NAFLD patients. However, more clinical studies are needed to confirm this hypothesis.[110] Several polyphenols, including resveratrol, curcumin, caffeine, and quercetin, are among the micronutrients that were investigated in preclinical and clinical trials by preventing the formation of intracellular reactive oxygen species. These micronutrients include vitamins E, C, and D, which can inhibit circulating blood cells from infiltrating the liver or target signaling pathways and mediators critical to producing extracellular matrix substances. However, most of these benefits have only been shown in experimental models.[111,112] Vitamin E is a widely investigated micronutrients in preclinical and clinical studies for NAFLD management,[113] which led to the recommendation of its use in the 2018 practice guidelines of the American Association of Liver Disease for treating biopsy-proven, nondiabetic patients with NASH.[8] Many studies have reported promising benefits for silymarin which is regulated through a decrease of oxidative stress and inflammation. One large meta-analysis that included five clinical trials found a significant reduction of transaminases when silymarin was administered as a monotherapy.[114] The benefits of using omega-3 fatty acids in NAFLD are still debatable. A meta-analysis including seven trials with omega-3 fatty acid supplementation in patients with NAFLD reported a significant decrease in transaminases, reduction in serum triacylglycerols, and increase in high-density lipoprotein levels compared to placebo. Meanwhile, two extensive well-controlled studies failed to show any benefits of omega-3 fatty acids in the treatment of NAFLD.[115]

## Conclusions

NAFLD prevention is important before the development of disease-related complications. Many efforts are being made toward NAFLD prevention and management, mainly through controlling the modifiable predisposing risk factors, with many pharmacological agents still under investigation.

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## Conflict of interest

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## Author contributions

MEK and AA contributed to the conception and design of the work and literature review. AA wrote the first draft of the manuscript. MEK and NMS provided critical revision and editing. All authors revised and approved the final version of the manuscript.

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