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NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD): DISEASE MECHANISMS AND CONTEMPORARY THERAPEUTIC APPROACHES - A LITERATURE REVIEW

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, representing a significant public health challenge. Over the past decades, it has been recognized as a multisystem disease closely associated with type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), and chronic kidney disease (CKD).
Objective: The aim of this review is to discuss contemporary pathogenetic mechanisms underlying NAFLD as well as current and experimental therapeutic strategies, encompassing non-pharmacological, pharmacological, and microbiota-targeted interventions.
Methods: An analysis and synthesis of data from preclinical studies, clinical trials (phases II and III), meta-analyses, and recommendations of scientific societies published over the past two decades was conducted. The review includes works indexed in PubMed, Scopus, and Web of Science databases, with a focus on NAFLD and NASH therapies.
Conclusions: NAFLD is a complex disease with a heterogeneous pathogenesis, in which lipotoxicity, cellular stress, gut dysbiosis, and insulin resistance play key roles. The most well-documented therapeutic approach remains lifestyle modification (Mediterranean diet, physical activity). Promising effects have been demonstrated by certain agents used in the treatment of type 2 diabetes (e.g., GLP-1 receptor agonists, SGLT2 inhibitors, pioglitazone) as well as novel molecules such as FXR agonists, THR-β agonists, and FGF19/FGF21 analogues. Further clinical studies are necessary to validate the efficacy and safety of these therapies.

KEYWORDS

NAFLD, NASH, Non-Alcoholic Fatty Liver, Insulin Resistance, Treatment, Mediterranean Diet, GLP-1RA, SGLT2i, PPAR, Gut Microbiota, Fibrogenesis, FGF19, FGF21, THR-β

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Introduction.

Over the past ten years, a substantial body of evidence has been accumulated indicating that the clinical burden of non-alcoholic fatty liver disease (NAFLD) is not limited solely to increased morbidity and mortality directly associated with liver pathology. An increasing amount of data suggests that NAFLD should be regarded as a multisystem disease that affects numerous extrahepatic organs and various regulatory pathways within the human body [1]. As NAFLD has become the predominant etiological factor of chronic liver disease in many regions of the world [2], it is believed that it may also significantly contribute to the development of chronic complications involving extrahepatic systems, thereby further amplifying its clinical significance.

One phenomenon that remains unexplained is the fact that NAFLD is diagnosed considerably more frequently in men than in women, and precise estimation of its incidence remains challenging due to diagnostic limitations associated with the need for long-term follow-up and the use of sequential assessment methods. Despite these challenges, current data indicate that the incidence rate is approximately 20 cases per 10, 000 person-years, reaching its highest values in populations in their sixth decade of life [3]. Furthermore, it is estimated that the prevalence of NAFLD in the general population is approximately 30–40% among men and 15–20% among women [4], with this prevalence being significantly higher in patients with type 2 diabetes mellitus (T2DM), among whom NAFLD is diagnosed in about 70% of cases [5].

In the past decade, the primary focus of researchers has been on chronic diseases coexisting with non-alcoholic fatty liver disease (NAFLD), particularly its association with chronic liver disease, cardiovascular diseases (CVD), and type 2 diabetes mellitus (T2DM). For instance, a recently published meta-analysis demonstrated that the presence of NAFLD is associated with a 57% increase in overall mortality, with liver diseases and cardiovascular conditions being the leading causes of death. Additionally, NAFLD was found to double the risk of incident T2DM [6].

In recent years, it is worth emphasizing that a growing number of studies have also drawn attention to chronic kidney disease (CKD), which may coexist with NAFLD, with further meta-analyses providing evidence of an approximately twofold increased risk of CKD development in patients with NAFLD [7]. Although there are also reports suggesting an association between NAFLD and a range of other chronic conditions, such as obstructive sleep apnea, colorectal cancer, osteoporosis, psoriasis, and various endocrine disorders (for example, polycystic ovary syndrome) [8], the scope of this review has been limited to those extrahepatic conditions for which the available scientific evidence is most convincing and suggests a potential causal relationship between NAFLD and pathology in extrahepatic organs, namely T2DM, CVD, and CKD.

Pathogenesis

For a long time, the so-called"two-hit hypothesis" predominated in the literature as a model for explaining the pathogenetic mechanisms underlying the development of non-alcoholic steatohepatitis (NASH). This concept assumed that the initial occurrence of hepatic steatosis — that is, non-alcoholic fatty liver (NAFL) — constituted the first stage of the pathological process, whereas progression to NASH required the action of an additional factor, referred to as the"second hit, " which could be, for example, oxidative stress or other disturbances of cellular homeostasis. Although this view was once widely accepted, it is now considered outdated and insufficient in light of current knowledge. It is now known that the development of NASH is the result of a complex interplay of numerous molecular pathways that overlap and influence one another, and, moreover, there is no conclusive evidence that NASH is always preceded by a phase of simple steatosis (NAFL). Additionally, it should be emphasized that the pathogenetic factors responsible for disease development are likely different among individual patients, which is reflected in the significant heterogeneity of both the mechanisms leading to NASH and the clinical manifestations presented by patients [9].

When analyzing the pathogenetic factors underlying the development of non-alcoholic fatty liver disease (NAFL) and non-alcoholic steatohepatitis (NASH), a useful starting point is the conceptual model that assumes the liver's capacity to properly metabolize basic energy substrates — such as carbohydrates and fatty acids — becomes overwhelmed. This situation results in the accumulation of toxic forms of lipids, referred to as lipotoxic lipid species, which has been thoroughly documented in numerous studies [10, 11, 12, 13, 14]. The metabolites produced in this process promote stress within hepatocytes, initiating processes that lead to hepatocyte injury and death, which in turn trigger a cascade of events favoring fibrogenesis and genomic instability. These molecular and structural changes form the basis for the development of advanced liver disease, including cirrhosis and hepatocellular carcinoma. Therefore, understanding the sources, metabolic pathways, and fate of fatty acids in hepatocytes is of key importance for elucidating the fundamental metabolic mechanisms underlying NASH.

When fatty acids are delivered in excess to hepatocytes or when their elimination is insufficient, they can serve as substrates for the biosynthesis of lipotoxic lipid species that induce endoplasmic reticulum (ER) stress and lead to hepatocyte damage. Detailed understanding of the molecular pathways responsible for the development of lipotoxicity, induction of ER stress, and hepatocyte injury has become the basis for developing rational therapeutic strategies targeting these mechanisms [15].

Sources of fatty acids in the liver

Fatty acids reach the liver primarily via the bloodstream as products of lipolysis of triglycerides stored in adipocytes, a process that is under strict control of insulin-mediated regulatory mechanisms in adipose tissue. The occurrence of post-receptor insulin signaling disturbances, which constitutes the essence of insulin resistance in adipose tissue, plays a key role in the pathogenesis of NASH, as it leads to deregulated lipolysis and, consequently, to excessive delivery of free fatty acids to hepatocytes [16]. A crucial element of this process is inflammatory activation, exemplified by phosphorylation of c-Jun N-terminal kinases (JNK) in adipocytes, resulting in significant impairment of insulin signal transduction at the post-receptor level under conditions of ongoing inflammation [17]. This indicates that both metabolic disturbances and inflammatory responses within adipose tissue have the potential to significantly drive pathogenetic mechanisms underlying NASH and, therefore, may represent valuable targets for novel therapeutic strategies [18, 19]. Moreover, it has been demonstrated that even moderate weight reduction contributes to improvement of adipose tissue insulin resistance and overall metabolic homeostasis in humans [20], which may translate into clinical benefits in the context of NASH treatment [21].

The second important source of fatty acids in the liver, alongside delivery from the circulation, is the process of de novo lipogenesis (DNL), in which fatty acids are synthesized from simple sugars, mainly glucose

and fructose. Studies employing stable isotope-based techniques have demonstrated that increased lipid content in hepatocytes in patients with non-alcoholic fatty liver disease (NAFLD) is largely the result of enhanced DNL [22]. While the contribution of glucose to this metabolic pathway is subject to strict regulatory mechanisms, nearly all fructose present in the portal blood is taken up by the liver, where it undergoes phosphorylation and is unrestrictedly incorporated into the de novo lipogenesis pathway. The exact amount of ingested fructose that reaches the portal circulation has not yet been clearly established, as studies conducted in animal models have shown a role for intestinal enterocytes in fructose metabolism [23], whereas data obtained in humans indicate a limited capacity of the intestinal epithelium for fructose absorption [24, 25]. In situations where the body is challenged with a high fructose load, its phosphorylation in hepatocytes leads to activation of the de novo lipogenesis pathway, accompanied by consumption of substantial amounts of ATP, resulting in hepatic ATP depletion, as documented both in humans and in animal models [26]. This phenomenon may further exacerbate cellular stress. Furthermore, the consumption of sugar-sweetened beverages, which contain sucrose (that is broken down in the intestine into glucose and fructose) or a direct mixture of fructose and glucose, shows a strong epidemiological association with excessive hepatic fat accumulation and the development of NASH [27, 28].

The process of de novo lipogenesis (DNL) represents a potential target for pharmacological intervention, and its inhibition may be achieved through modulation of the activity of enzymes involved in this pathway, such as acetyl-CoA carboxylase (ACC), whose function can be effectively blocked using specific inhibitors [29]. Furthermore, a beneficial therapeutic direction in the treatment of non-alcoholic steatohepatitis (NASH) appears to be the reduction of expression of sterol regulatory element-binding protein-1c (SREBP-1c), which acts as the principal transcriptional regulator of genes encoding enzymes participating in DNL, especially given that the activity of this pathway is controlled by the farnesoid X nuclear receptor (FXR). It is also worth noting that the carbohydrate response element-binding protein (ChREBP) plays an important role in inducing the expression of lipogenic enzymes; however, analyses of human liver biopsy samples have shown that ChREBP expression levels are decreased in patients with NASH [30], raising doubts about the validity of targeting this factor in therapy.

A reduction in the influx of fatty acids and carbohydrates into the liver may also be achieved through their redistribution to other tissues, such as peripheral adipose tissue, brown adipose tissue, or skeletal muscle. An example of such an approach is the use of peroxisome proliferator-activated receptor gamma (PPARγ) ligands, such as pioglitazone, which, as specialized nuclear receptor ligands, promote lipid storage in adipocytes. This, on the one hand, may contribute to clinical improvement in patients with NASH, although, on the other hand, it leads to an increase in fat stores in peripheral tissues and weight gain, as demonstrated in clinical studies conducted in populations with type 2 diabetes [31].

Moreover, the redirection of energy substrates from the liver to other tissues may be supported by their increased utilization in active muscle tissue and brown adipose tissue. Brown adipose tissue is a site of intensive energy substrate metabolism, accompanied by uncoupled mitochondrial respiration, which leads to heat production (thermogenesis) rather than the storage of triglycerides in reserve form. This tissue also constitutes an important target of bile acid-induced signaling, which complements the classical function of bile acids as detergents facilitating lipid absorption in the intestine [32]. This action is associated with activation of the TGR5 bile acid membrane receptor in brown adipose tissue, leading to increased thermogenesis [33]. Consequently, one of the potential therapeutic strategies in the prevention and treatment of NASH is the enhancement of the mass and functional activity of brown adipose tissue [34].

Fate of fatty acids in the liver

Fatty acids present in the liver predominantly remain in a non-covalently bound form with fatty acid-binding protein-1 (FABP-1), also referred to as liver fatty acid-binding protein (L-FABP), which enables their proper functioning within the cell. The main metabolic pathways for these fatty acids include mitochondrial β-oxidation and esterification leading to the formation of triglycerides. In some patients with non-alcoholic steatohepatitis (NASH), mitochondrial dysfunction and disturbances in hepatic fatty acid β-oxidation have been observed, and likely also in other tissues of the body [35, 36]. However, it remains unclear whether primary mitochondrial dysfunction constitutes a predisposing factor for the development of NASH, or whether it is a secondary consequence of the cellular stress characteristic of this disease. The process of fatty acid esterification and their conversion into triglycerides is generally regarded as an adaptive and protective cellular defense mechanism that allows for the neutralization of excess free fatty acids when their supply exceeds the

oxidative capacity of hepatocytes [37]. Nevertheless, some reports suggest that the accumulation of triglycerides may not only reflect metabolic disturbances but may itself contribute to their exacerbation [38].

Triglycerides formed in hepatocytes are not entirely exported into the bloodstream as very-low-density lipoproteins (VLDL), but are partially stored as lipid droplets, which are a characteristic morphological feature of non-alcoholic fatty liver disease (NAFLD). These storage lipid droplets can subsequently serve as a source of free fatty acids, released via lipolysis, with the timing and localization of this process in hepatocytes after feeding being tightly regulated.

To date, it has not been possible to definitively identify specific lipotoxic lipid species that play a key role in inducing cellular injury and the development of the NASH phenotype. Nonetheless, preventing their formation remains a logical and promising therapeutic direction. Potential candidates for lipotoxic lipids include, among others, diacylglycerols [39], ceramides [40, 41], and lysophosphatidylcholine [42]. The accumulation of cholesterol in liver cells is also of significance, as it may contribute to NASH progression [43]. This is supported by animal models — in studies on mice and rats, high-cholesterol diets are often used to exacerbate disease course and induce changes characteristic of NASH [44, 45, 46].

Response to lipotoxic lipids

Hepatocyte injury observed in the course of non-alcoholic steatohepatitis (NASH) is characterized by a range of pathological phenomena, among which endoplasmic reticulum (ER) stress [47], impaired response to the presence of misfolded proteins (unfolded protein response) [48], activation of the inflammasome [49], stimulation of apoptosis pathways, as well as chronic inflammation and an enhanced reparative response resembling tissue injury healing [50], all play significant roles. The profile of cellular injury is also influenced by exogenous factors and modulators of the internal environment, including dysregulation of cytokine and adipokine levels [51], ATP deficiency [52], the toxic effects of uric acid [53], intermittent hypoxia associated with obstructive sleep apnea [54], and the action of gut microbiota metabolites [55, 56, 57].

It appears that all these factors may, to varying degrees, contribute to the induction of lipotoxic stress, hepatocyte injury, and the persistence of hepatic inflammation. However, it should be emphasized that the relative contribution of individual abnormalities to the pathogenesis of NASH has not yet been clearly defined and most likely shows significant interindividual variability.

Insulin resistance

Insulin resistance is a commonly observed feature of non-alcoholic fatty liver disease (NAFLD) and plays a key role in its pathogenetic mechanisms [58]. The essence of this disorder lies in the reduced ability of extrahepatic tissues, such as adipose tissue and skeletal muscle, to appropriately uptake and utilize glucose [59]. In adipose tissue, insulin resistance leads to pathologically increased release of fatty acids due to uncontrolled lipolysis, which further exacerbates disturbances in insulin signaling throughout the body and intensifies the development of metabolic disorders characteristic of NAFLD. Numerous studies have demonstrated the existence of a complex and dynamic metabolic interaction between adipose tissue and the liver. Peptides released from adipocytes, such as adiponectin, interleukin 6 (IL-6), and other factors, can exhibit both protective and pro-inflammatory properties toward liver cells, thereby modulating the course of the disease process [60, 61].

Another element linking disturbances in liver and adipose tissue function may be the enzyme dipeptidyl peptidase 4 (DPP-4), whose role in the pathogenesis of insulin resistance is becoming increasingly well understood. DPP-4, secreted by hepatocytes into the circulation, interacts with plasma factor Xa, stimulating the activity of pro-inflammatory macrophages present in visceral adipose tissue, as demonstrated in animal models. This effect leads to the exacerbation of insulin resistance, highlighting the importance of the interplay between the liver and other tissues in the etiopathogenesis of the metabolic dysregulation characteristic of NAFLD [62].

Microbiome

The dynamic increase in the prevalence of non-alcoholic fatty liver disease (NAFLD) recorded over the past 25 years in highly developed countries is largely attributed to the modern dietary pattern, characterized by a high intake of fructose, sucrose, and saturated fats, as well as the increasingly common sedentary lifestyle. The progressive evolution of the human microbiome — reflecting changes in dietary habits as well as the widespread use of antibiotics in both livestock production and medical practice in humans — may also

represent a risk factor for the development of NAFLD. Regardless of etiology, studies conducted in animal models have provided clear evidence that the NASH phenotype can be transmitted via the microbiome [55].

Population studies in humans indicate that the gut microbiome of patients with NASH is characterized by reduced species diversity compared to healthy individuals [63, 64]. Furthermore, it has been shown that weight loss leads to significant changes in the composition of the microbiota. However, a causal relationship between microbiome modification induced by weight loss and regression of NASH-specific lesions has not yet been clearly confirmed [56, 65].

Currently, potential mechanisms linking microbiome composition disturbances with hepatic steatosis are being considered. These include, among others, the ability of bacterial proteins to act as ligands for G protein-coupled receptors [66], and the activity of intestinal bacteria affecting the gut-liver axis by regulating FXR receptor signaling in the intestines and stimulating the secretion of fibroblast growth factor 19 (FGF19) — an intestine-derived hormone that controls bile acid synthesis and also plays a significant role in lipid and glucose metabolism regulation [67, 68, 69]. Moreover, dysbiosis — that is, disruption of microbiome balance — may promote increased intestinal barrier permeability, further amplifying the effects of the mechanisms described above [70]. It should be emphasized that research on the microbiome in the context of NAFLD and NASH remains at a relatively early stage of development; however, significant progress in understanding its role in the pathogenesis of these conditions is anticipated in the coming years.

Fibrogenesis

The accumulation of extracellular matrix within the liver, which leads to the gradual development of fibrosis, cirrhosis, portal hypertension, and ultimately liver failure, constitutes the main mechanism responsible for liver disease-related mortality in the population of patients suffering from non-alcoholic fatty liver disease (NAFLD). The process of fibrogenesis is initiated and driven by signals originating from stressed or injured hepatocytes and activated hepatic macrophages (Kupffer cells). As a result of this signaling, resident hepatic stellate cells become activated, differentiate into myofibroblasts, and begin producing extracellular matrix proteins at a rate exceeding their degradation capacity [71]. An increasing body of evidence indicates the existence of NASH-specific molecular pathways involved in fibrogenesis, which opens new therapeutic possibilities [72]. For example, in murine models of NASH, increased activity of the transcriptional coactivator TAZ signaling pathway in hepatocytes has been observed, promoting the secretion of Indian Hedgehog ligand, which through paracrine signaling stimulates stellate cells to produce fibrotic matrix [73]. Another NASH-specific mechanism is the direct influence of the PNPLA3-I148M genetic variant on the fibrogenic activity of stellate cells [74], suggesting that targeting therapies to modulate PNPLA3 protein function may represent a promising strategy to counteract fibrosis [75].

NAFLD treatment strategy

Although the exact pathogenetic mechanisms underlying the development of non-alcoholic fatty liver disease (NAFLD) remain the subject of intensive investigation and have not yet been fully elucidated, the spectrum of risk factors associated with this condition is well documented. These include, among others, an unhealthy lifestyle, the presence of insulin resistance (IR), type 2 diabetes mellitus (T2DM), excessive lipogenesis occurring in hepatocytes, and disturbances within the gut microbiota. Currently, no standard, clearly defined pharmacotherapy dedicated to the treatment of NAFLD is available. Nevertheless, both the clinical practice guidelines developed by the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), and the European Association for the Study of Obesity (EASO) [76], as well as the guidelines of the American Association for the Study of Liver Diseases (AASLD) [77], emphasize the fundamental importance of lifestyle intervention.

These recommendations indicate that in overweight or obese patients with NAFLD, the implementation of changes involving diet and physical activity can lead to weight loss of 5–10%, which is associated with improvement in clinical parameters. A similar position is presented by the recommendations of the National Institute for Health and Care Excellence (NICE) [78], which also recognize lifestyle modification as the first-line treatment in patients with NAFLD. Consequently, lifestyle optimization, through the adoption of a rational dietary plan and regular physical activity, represents the fundamental and key element of the therapeutic strategy in this condition. Furthermore, it appears that combining such measures with pharmacotherapy aimed at regulating glucose and lipid metabolism, reducing hepatic inflammation, and limiting fibrosis progression may provide additional benefits in the treatment of patients with NAFLD.

Non-pharmacological treatment strategies

Dietary modifications

Significant reduction in total caloric intake, induction of ketosis, or restriction of free sugar and carbohydrate consumption may promote liver protection, making dietary interventions a promising therapeutic approach in the management of non-alcoholic fatty liver disease (NAFLD) [79]. The most commonly used dietary strategy in this patient group is caloric restriction (CR), whose effectiveness in reducing body weight and improving hepatic parameters has been well documented. Meta-analyses have shown that adherence to dietary patterns characteristic of the Western diet is associated with a 56% increased risk of NAFLD development, whereas adherence to the Mediterranean diet (MD) may reduce this risk by 23% [80].

The Mediterranean diet is defined as a dietary pattern based mainly on plant-based products, characterized by a high content of monounsaturated fatty acids (MUFA) and saturated fatty acids (SFA), with total fat accounting for 30–40% of daily energy intake [81]. The MD is based on the consumption of large amounts of fruits and vegetables, fish, whole grains, legumes, and olive oil [82]. According to EASL-EASD-EASO guidelines, the Mediterranean diet can be considered a recommended nutritional model in the treatment of NAFLD, as it has been shown to improve metabolic parameters by reducing insulin resistance and lipid levels, inducing hepatic steatosis regression, and significantly lowering the risk of cardiovascular complications [83, 76, 81, 84, 85]. Therefore, the MD is considered an effective and safe dietary approach for managing patients with metabolic syndrome and NAFLD [86]. Its use contributes to the reduction of overweight and visceral obesity, decreased hepatic steatosis, and inhibition of cirrhosis progression in individuals with NAFLD [87, 88, 89].

Moreover, this diet has a beneficial effect on insulin resistance, which translates into an overall improvement in the clinical condition of patients [81, 90]. A meta-analysis by Takumi Kawaguchi confirmed the ability of the MD to reduce hepatic steatosis and improve insulin resistance parameters in patients with NAFLD [91]. Importantly, increasing evidence indicates the effectiveness of the MD in younger patients — it has been shown that 12 weeks of the MD in children aged 9–17 years leads to improved insulin resistance [92], and in children and adolescents aged 11–18 years, this diet reduced BMI, fat mass, hepatic steatosis, insulin resistance, as well as levels of aminotransferases, inflammatory markers, and oxidative stress markers [93].

In addition to the MD, the ketogenic diet (KD), characterized by a high fat content and significant restriction of carbohydrates, proteins, and other nutrients, is gaining increasing interest. Due to its very low carbohydrate content, KD also has beneficial effects in the treatment of NAFLD [94]. This diet can significantly alter substrate flux in mitochondria and the redox state of hepatocytes, supporting ketogenesis without significantly affecting intrahepatic triglyceride synthesis (IHTG), which ultimately contributes to the reduction of visceral fat and improvement of insulin resistance [95].

Although current studies suggest some therapeutic benefits of KD in patients with NAFLD, it is important to note that both preclinical and clinical studies highlight potential risks associated with its use. For example, animal studies have shown that male C57Bl/6NJ mice with diet-induced NAFLD developed hepatic mitochondrial dysfunction after prolonged KD use [96]. Additionally, cases of acute worsening of hyperlipidemia and increases in liver enzyme activity associated with KD intervention have been reported in the literature [97]. Therefore, the safety of KD in the treatment of NAFLD remains the subject of ongoing research.

In recent years, attempts have also been made to apply novel dietary strategies in NAFLD therapy. For example, a low-calorie, low-fat diet has been shown to significantly reduce liver fat content (LFC) in the short term [98]. A high-protein diet — of both animal and plant origin — has also been found to reduce LFC, improve insulin resistance, and lower levels of inflammatory markers [99]. An eight-week low free sugar diet reduced liver fat content [100] and improved steatosis in adolescent boys with NAFLD [101]. However, due to the limited number of clinical trials on these interventions, it is not currently possible to draw definitive conclusions. Similarly, the insufficient number of data and inconclusive results concern the effectiveness and safety of very low-calorie ketogenic diets (VLCKD), intermittent fasting (IF), and time-restricted feeding (TRF); therefore, their clinical value in the treatment of NAFLD cannot be confirmed at this time.

Exercise intervention

In addition to dietary interventions, regular physical exercise plays an important role in the treatment of non-alcoholic fatty liver disease (NAFLD), as it has the ability to improve metabolic disturbances related to glucose and lipid metabolism [102], as well as reduce liver fat content (LFC) [103], thereby constituting an effective method for managing metabolic diseases. Regular physical activity can bring measurable benefits in both non-obese patients with NAFLD and individuals with excess body weight [104].

In clinical practice, combining resistance training with aerobic exercise is considered the most rational and effective approach, allowing for a comprehensive impact on the body. Resistance exercises have a high safety profile, and their regular application results in improvements in metabolic parameters in patients with NAFLD [105]. For example, a 12-week resistance training program, including activities such as push-ups and squats, may contribute to the prevention of disease progression [106]. Similar effects have been demonstrated for aerobic training — a 12-week aerobic exercise intervention may lead to improvement in the degree of liver fibrosis [107]. Furthermore, it has been shown that 12 weeks of high-intensity interval training (HII) promotes reductions in blood glucose levels and waist circumference in patients with NAFLD [108]. An individually tailored eight-week physical activity program can reduce liver steatosis, decrease concentrations of inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) and ferritin, and limit fibrosis progression [109].

It is worth noting, however, that studies comparing different volumes and intensities of aerobic training have not demonstrated significant differences in their impact on LFC reduction. For example, eight-week programs based on low- or moderate-intensity aerobic exercise, regardless of training volume, resulted in reductions in LFC and visceral adipose tissue (VAT) without significant differences between the protocols [110]. Both continuous high-intensity (HII) and moderate-intensity (MIC) aerobic exercise over eight weeks led to reductions in intrahepatic triglycerides (IHTG) and visceral fat in obese patients with NAFLD coexisting with type 2 diabetes (T2DM) [111].

It should be noted, however, that most available clinical studies on exercise interventions have been limited by small sample sizes, and their main aim was to assess the impact of physical activity on selected clinical parameters, such as BMI, blood glucose levels, or LFC in patients with NAFLD [112]. Importantly, relatively few studies have focused on assessing the effect of physical activity on the degree of liver fibrosis. Consequently, the current state of knowledge does not allow definitive conclusions to be drawn regarding whether exercise interventions provide specific, lasting benefits in limiting fibrosis progression in patients with NAFLD.

Dietary and exercise interventions

The use of therapeutic strategies that combine physical activity with caloric restriction may have a beneficial impact on the course of non-alcoholic fatty liver disease (NAFLD) by increasing the total energy expenditure of the body, reducing excessive lipid overload, and improving overall metabolic homeostasis [89]. This approach, involving the simultaneous implementation of dietary and exercise interventions, may provide more tangible benefits in both preclinical and clinical studies. For example, in an experiment conducted on Sprague Dawley (SD) rats, it was shown that physical activity combined with a switch from a high-fat diet (HFD) to a standard diet helped alleviate HFD-induced hepatic steatosis [113].

In a randomized controlled trial, it was documented that combining physical exercise with the so-called green version of the Mediterranean diet (green-MD) — characterized by restricted intake of red and processed meat along with increased consumption of green plants and polyphenols — led to a greater reduction in intrahepatic fat content and the prevalence of NAFLD compared to both a standard diet and the classical Mediterranean diet model [114]. Similar conclusions were drawn from another randomized controlled trial, which demonstrated that combining exercise with dietary intervention improved parameters related to liver fat content (LFC) and glucose metabolism in patients with NAFLD [115]. The results of these studies suggest that a combined dietary and exercise intervention strategy may have a more favorable effect on the course of NAFLD than either method used alone [116]. Therefore, in patients with NAFLD — particularly those who are overweight or obese and who have the time and energy resources to adhere to recommendations — priority should be given to a comprehensive therapy combining dietary and exercise intervention.

Bariatric surgery

Bariatric surgery constitutes a therapeutic option for patients with non-alcoholic fatty liver disease (NAFLD) and coexisting obesity who have not achieved satisfactory weight reduction despite following dietary and physical activity recommendations or for whom lifestyle modification has proven insufficient. Although this method is widely used in the treatment of obesity in the United States and many European countries, its application in countries such as China remains relatively rare. The Pediatric Committee of the American Society for Metabolic and Bariatric Surgery (ASMBS) recommends metabolic and bariatric surgery (MBS) as an effective therapeutic approach for severe obesity in adolescents and recognizes it as the standard of care [117]. Similarly, guidelines from the American Association for the Study of Liver Diseases (AASLD)

support the consideration of bariatric surgery (including procedures involving the upper gastrointestinal tract) in patients with NAFLD or non-alcoholic steatohepatitis (NASH) when obesity is present [77].

It has been shown that bariatric procedures can lead to improvement in the liver's histological profile, including reduction in fibrosis resulting from NASH. Moreover, these interventions bring additional benefits such as improvement or remission of type 2 diabetes mellitus (T2DM), normalization of lipid profiles, reduction in blood pressure, and decreased cardiovascular disease (CVD)-related morbidity and mortality [118]. Bariatric surgery also contributes to a significant reduction in body mass index (BMI), decreased liver fibrosis, and improvement in all histopathological parameters typical of NAFLD, including fibrosis itself [76, 77, 119, 120].

However, as with any surgical treatment method, bariatric surgery is not entirely devoid of risk or guaranteed efficacy. Cases have been reported in which the health status of patients with NAFLD deteriorated after bariatric surgery. One example is a patient who, despite rapid weight loss of 35% after surgery, developed acute liver failure as a complication [121]. Attention should also be drawn to the increased risk of postoperative complications in patients with cirrhosis, although in individuals with well-compensated cirrhosis, this procedure may serve as an adjunct in improving long-term treatment outcomes [122]. In summary, the clinical efficacy and safety of bariatric surgery in the treatment of patients with NAFLD require further well-designed studies to definitively determine its role in the therapeutic management of this patient population.

Medical treatment

Drugs used in type 2 diabetes mellitus (T2DM)

Although the pathogenetic mechanisms underlying the development of non-alcoholic fatty liver disease (NAFLD) have not yet been fully elucidated, there is general consensus that insulin resistance (IR) is a key factor in the etiopathogenesis of this condition. The prevalence of NAFLD is particularly high in the population of patients with type 2 diabetes mellitus (T2DM), and the presence of this metabolic disease is strongly associated with risk factors such as obesity, elevated glycated hemoglobin (HbA1c), hyperlipidemia, and increased alanine aminotransferase (ALT) activity [123]. For this reason, antidiabetic medications are widely used in clinical practice in the treatment of patients with coexisting T2DM and NAFLD, representing an important component of comprehensive therapy aimed at improving metabolic parameters and limiting the progression of liver disease.

Glucagon-like peptide-1 receptor agonists (GLP-1RA)

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by enteroendocrine cells of the small intestine in response to food intake, which stimulates insulin secretion and inhibits glucagon secretion. Drugs in the GLP-1 receptor agonist (GLP-1RA) class, such as liraglutide, semaglutide, dulaglutide, and exenatide, are modern agents used in the treatment of T2DM. Studies have shown that these drugs not only promote weight loss and improve insulin resistance but also favorably affect liver enzyme activity and reduce liver fat content (LFC) in patients with T2DM, suggesting their potential utility in the therapy of NAFLD and NASH [124]. Consequently, GLP-1RAs are increasingly the subject of clinical investigations in the context of NAFLD.

Liraglutide is the most extensively studied GLP-1RA in research on NAFLD [125]. It has been demonstrated to improve insulin resistance [126] and reduce LFC in patients with T2DM [127]. A phase II clinical trial showed that subcutaneous administration of liraglutide at a dose of 1.8 mg/day in patients with NASH led to improvement in liver histopathology, evidenced by NASH regression, good treatment tolerability, and absence of fibrosis progression [128]. Additionally, a study by Feng et al. found that liraglutide's efficacy in patients with T2DM and NAFLD surpassed that of metformin and gliclazide, particularly regarding weight loss, waist circumference, and LFC reduction [129]. However, it should be noted that liraglutide use was associated with mild gastrointestinal adverse events, such as diarrhea, constipation, or decreased appetite [128].

Studies by Philip Newsome's team showed that obesity and T2DM are major drivers of NAFLD development, and the use of semaglutide resulted in significant reductions in ALT and hs-CRP levels in obese patients with T2DM, suggesting the drug's potential in alleviating the course of NAFLD [130]. Subsequently, a randomized, placebo-controlled phase II trial was initiated to assess the efficacy of semaglutide in patients with NASH, administered in various doses as subcutaneous injections. After 72 weeks of therapy, significant histological liver improvements were observed in the treatment group, mainly in the form of reduced inflammatory infiltrate and hepatocyte ballooning; the proportion of patients without fibrosis progression was also significantly higher than in the placebo group. The optimal dose was 0.4 mg/day, which showed the best therapeutic effect. Nevertheless, semaglutide did not significantly reduce the degree of fibrosis [131], and its efficacy in this area is the subject of ongoing phase III trials [132]. Flint et al. confirmed that administration of

semaglutide at 0.4 mg/day reduced LFC and improved liver enzyme levels, although it did not significantly impact cirrhosis regression [133]. Like liraglutide, semaglutide was associated with adverse effects, mainly nausea [131, 134].

Dulaglutide, administered subcutaneously at a dose of 1.5 mg once weekly, led to reductions in ALT, AST, and GGT activity in patients with T2DM [135], indicating its potential utility in the treatment of NAFLD. Compared to liraglutide, dulaglutide had the advantage of requiring less frequent administration, increasing treatment convenience. Studies by Kuchay et al. demonstrated that dulaglutide at 1.5 mg weekly significantly reduced LFC and GGT levels in patients with T2DM and NAFLD without serious adverse effects, supporting its recommendation as an option for early therapy [136]. This was also confirmed by a Japanese study, where dulaglutide at 0.75 mg weekly for 12 weeks resulted in weight loss and improvement in liver enzyme levels [137].

Exenatide also showed beneficial effects on carbohydrate metabolism, body weight, and liver enzyme activity in patients with T2DM and NAFLD [138]. Due to its hepatoprotective properties, this agent is considered particularly suitable for patients with NAFLD who have coexisting obesity, elevated liver enzyme levels, and T2DM [139]. Studies by Liu et al. demonstrated that subcutaneous administration of exenatide at 10 μg twice daily reduced LFC [140], and a Turkish study confirmed that the same dose favorably affected blood glucose levels, body weight, and liver fibrosis indices [141]. Gastaldelli et al. documented that the combination of exenatide with dapagliflozin was more effective than monotherapy with either agent, indicating the potential of combination strategies, although this requires further verification in prospective studies [142].

Sodium-glucose co-transporter 2 inhibitors (SGLT2i)

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) represent a modern class of oral antidiabetic agents whose mechanism of action is based on blocking renal tubular glucose reabsorption, resulting in a reduction in blood glucose levels. Retrospective analyses have shown that these agents may not only improve glycemic control but also exert beneficial effects on hepatic steatosis and fibrosis in patients with type 2 diabetes mellitus (T2DM), suggesting their potential usefulness in the treatment of NAFLD [143]. For example, a five-year controlled study conducted by Japanese researchers in a group of six patients with T2DM and NAFLD found that half of the participants demonstrated histological liver improvement following SGLT2i therapy [144]. Additionally, an 18-month randomized clinical trial from Korea demonstrated that adding an SGLT2 inhibitor to standard antidiabetic therapy more effectively reduced liver fat content and improved liver enzyme activity [145]. A meta-analysis encompassing 10 clinical trials confirmed that SGLT2i use in Asian patients with T2DM and NAFLD led to reductions in LFC, improvements in liver enzyme levels, decreased BMI, and lower concentrations of inflammatory markers [146], which was further supported by another systematic review [147].

Clinical data support these observations. Gaborit et al. documented that administration of empagliflozin (EMPA) at a dose of 30 mg/kg/day for 12 weeks in C57BL/6 mice reduced LFC, and a similar effect was observed in patients with T2DM treated with EMPA at 10 mg/day for the same period [148]. Moreover, a phase IV randomized, double-blind clinical trial demonstrated that empagliflozin at 25 mg/day for 24 weeks not only effectively controlled glycemia but also reduced LFC [149]. Another study in patients with T2DM and cardiovascular disease (CVD) found that empagliflozin at doses of 10–25 mg/day decreased hepatic steatosis, although it did not significantly affect the risk of fibrosis progression [150]. Interestingly, in patients with NAFLD without coexisting T2DM, administration of EMPA at 10 mg/day for 24 weeks also improved steatosis and fibrosis [151].

Similar effects were observed with ipragliflozin — oral administration at 50 mg/day for 24 weeks led to improvements in liver parameters and fasting glucose levels in patients with T2DM and NAFLD [152], findings that were corroborated by other Japanese researchers [153]. A multicenter, open-label, randomized trial demonstrated that 72 weeks of ipragliflozin therapy contributed to fibrosis improvement, weight reduction, and better glycemic control; notably, none of the patients developed NASH, highlighting this agent's potential role in NASH prevention and treatment [154].

The results for dapagliflozin have also been promising. A randomized, placebo-controlled trial found that dapagliflozin at 10 mg/day for 8 weeks lowered aminotransferase activity and reduced LFC in patients with T2DM [155]. Extending the therapy to 12 weeks yielded further improvements in hepatocyte injury biomarkers such as ALT, AST, and GGT [156]. A prospective Japanese study demonstrated that dapagliflozin at 5 mg/day for 24 weeks improved hepatic steatosis and mitigated fibrosis in patients with advanced fibrosis [157]. Similar beneficial effects, including weight loss and improved liver enzyme activity, were observed in patients with NAFLD without T2DM [158].

Regarding canagliflozin, available data are more limited. Administration of canagliflozin at 100 mg/day for 24 weeks demonstrated therapeutic potential in improving liver function and reducing visceral fat in patients with T2DM and NAFLD, although the study included only five patients [159]. Similar limitations applied to a retrospective study involving seven patients, where long-term canagliflozin therapy improved liver histology in six patients, while one experienced deterioration [160]. These findings indicate the need for further, larger studies to definitively assess the efficacy of canagliflozin in the treatment of NAFLD.

Biguanides

Biguanides, represented by the widely used metformin, constitute one of the most commonly employed drug classes in the treatment of type 2 diabetes mellitus (T2DM). Metformin, as the standard antidiabetic agent, reduces endogenous glucose production, activates AMP-activated protein kinase (AMPK), and inhibits mitochondrial glycerophosphate dehydrogenase activity [161]. Nevertheless, its efficacy and safety in the population of patients with non-alcoholic fatty liver disease (NAFLD) remain a matter of controversy [162].

Preclinical studies have shown that administration of metformin at 300 mg/kg/day in the diet led to a reduced incidence of NAFLD in C57Bl/6J mice compared to a group receiving a high-sugar, high-fat diet alone [163]. However, in contrast to the results obtained in animal models, data from clinical studies have not unequivocally confirmed such beneficial effects of metformin. After 24 weeks of therapy, metformin produced only minor improvements in body weight, waist circumference, and liver enzyme activity in patients with T2DM and coexisting NAFLD [129]. Similarly, a systematic review and meta-analysis demonstrated no significant impact of metformin on histopathological liver improvement in patients with NASH [164].

In recent years, the effectiveness of metformin in the treatment of NAFLD has continued to be debated. Findings from Japanese researchers suggest that the use of higher doses of metformin (1, 500 mg 2–3 times per day for 52 weeks) may contribute to a reduction in hepatic steatosis in patients with T2DM and NAFLD [165]. Additionally, a study by Mitrovica et al. showed that metformin could reduce levels of inflammatory markers such as hs-CRP and ferritin in non-obese patients with T2DM and NAFLD [166].

Moreover, certain clinical studies have evaluated the potential effect of combination therapy with metformin and GLP-1 receptor agonists (GLP-1RA) or sodium-glucose co-transporter 2 inhibitors (SGLT2i) in patients with T2DM and NAFLD. However, the results of these studies have been disappointing. For example, a 24-week randomized, prospective, placebo-controlled trial by Harreiter et al. demonstrated that metformin combined with exenatide or dapagliflozin did not result in an additive effect in reducing hepatocyte lipid content [167].

In summary, there is currently insufficient evidence to conclusively state that metformin has a significant impact on the treatment of NAFLD. Nonetheless, some studies suggest that this agent may play a role in the prevention of hepatocellular carcinoma and other liver malignancies [168], which warrants further, in-depth evaluation in well-designed clinical trials.

Thiazolidinediones

Thiazolidinediones are a class of antidiabetic agents whose mechanism of action involves activation of the peroxisome proliferator-activated receptor gamma (PPAR-γ). These agents contribute to the improvement of insulin resistance (IR), particularly in patients with obesity and coexisting type 2 diabetes mellitus (T2DM). Among thiazolidinediones, pioglitazone is the only antidiabetic agent recommended in current guidelines for the treatment of non-alcoholic steatohepatitis (NASH) [76, 77, 169].

The results of a randomized controlled trial showed that combined treatment with metformin at a dose of 2 g/day and low-dose pioglitazone (mean 26 mg/day) for 12 months led to improvement in liver steatosis, reduction of inflammation, and improvement of insulin resistance in patients with T2DM and NAFLD [170]. The efficacy of pioglitazone monotherapy was assessed in a placebo-controlled trial, in which administration of pioglitazone at 30 mg/day for 96 weeks resulted in histopathological liver improvement, reduction of liver enzyme activity, and enhancement of insulin sensitivity in patients with NASH without coexisting diabetes [171]. Similar effects were observed in a study conducted by Aithal et al. — one year of pioglitazone therapy at 30 mg/day led to improvements in metabolic and histological liver parameters, including reductions in hepatocyte injury and fibrosis in patients with NASH [172].

Additionally, study findings suggest that limited dietary interventions combined with pioglitazone treatment may enhance therapeutic effects in improving hepatic metabolism in patients with NASH. An example is the study by Belfort et al., in which a low-calorie diet (500 kcal/day deficit relative to energy requirements) combined with pioglitazone at 45 mg/day for six months resulted in significant improvements in metabolic parameters and liver

histopathology [173]. Similar results were reported by Kenneth Cusi and colleagues — 18 months of therapy with the same regimen was well tolerated and effective in patients with prediabetes or T2DM and NASH, leading to histopathological liver improvement without fibrosis progression [145].

It should be noted, however, that pioglitazone use is not suitable for all patients. This agent may exacerbate peripheral edema, so its use should be considered with caution in patients with severe obesity, diastolic dysfunction, congestive heart failure, or in those simultaneously using amlodipine or high doses of insulin [169].

Lipid-lowering agents

Statins, one of the most commonly used classes of lipid-lowering agents in clinical practice, act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, thereby suppressing endogenous cholesterol synthesis [170]. The characteristic lipid profile in patients with non-alcoholic fatty liver disease (NAFLD) includes elevated levels of triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C), with cholesterol accumulation in hepatocytes further promoting disease progression [171, 172]. A meta-analysis by Kim et al. showed that statin use reduces the risk of cirrhosis decompensation and mortality in patients with cirrhosis, whereas in patients without cirrhosis, no significant association was found between statin use and cirrhosis development or fibrosis progression [173]. A contrasting view was presented by Athyros et al., who suggested that statin therapy may contribute to reductions in hepatic steatosis, steatohepatitis, and fibrosis [174]. The results of a large, population-based nested case-control study supported this hypothesis, demonstrating that statin use was associated with reduced risk of NAFLD development and decreased risk of fibrosis progression in patients already diagnosed with NAFLD [175].

In another four-year study, atorvastatin therapy at 20 mg/day combined with vitamin supplementation reduced the risk of hepatic steatosis progression by 71% in patients with NAFLD [176]. Similar effects were observed with rosuvastatin — its administration at 5 mg/day for 24 weeks was associated with a reduction in liver fat content (LFC) [177].

Despite these favorable reports, statins were long regarded as potentially hepatotoxic, leading to limited use in patients with NAFLD. An analysis of statin use trends in the United States found that the onset of disease in patients with NAFLD was often not adequately treated with statins at an early stage [178]. However, as research has advanced, perspectives on their use have changed. It is now known that statins may reduce cancer-related mortality in patients with NAFLD [179], and given the high risk of cardiovascular disease (CVD) in patients with NAFLD/NASH, statins are effective in reducing this risk [180]. Furthermore, a post hoc analysis of a trial evaluating pioglitazone in NASH showed that statins lowered total cholesterol and LDL-C without adverse effects on liver enzyme activity over a three-year observation period, suggesting that statins can be safely used in patients with T2DM and NAFLD [181]. Nevertheless, it should be remembered that statins may be associated with an increased risk of hyperglycemia and diabetes development, so their use should be cautious in patients with prediabetes or at high risk of diabetes [182].

Another lipid-lowering agent is ezetimibe, which works by inhibiting intestinal cholesterol absorption. Preclinical studies have shown that this agent can reduce hepatic steatosis in rats by increasing cholesterol efflux transporter activity [183], and in mice fed a high-fat diet, it can prevent and limit hepatic steatosis [184]. In clinical studies, ezetimibe at 10 mg/day for six months led to reductions in serum total cholesterol and improvement in liver fibrosis markers in patients with NAFLD [185]. Similar effects were noted in a study by Park et al., where two years of therapy improved metabolic parameters and liver histology [186]. Combining ezetimibe with rosuvastatin (10 mg/day ezetimibe + 5 mg/day rosuvastatin for 24 weeks) also resulted in significant LFC reduction [177].

On the other hand, a meta-analysis by Lee et al. found no conclusive evidence that ezetimibe effectively improves hepatic steatosis [187]. Another study showed that combining ezetimibe with lifestyle intervention did not improve liver histopathology in patients with NASH [188]. These findings highlight the need for further well-designed studies to definitively determine the efficacy of ezetimibe in the treatment of NAFLD and NASH.

Antihypertensive agents

Increased vascular resistance within the hepatic circulation is a phenomenon observed in both patients in the early stages of non-alcoholic fatty liver disease (NAFLD) and animal models reflecting this condition [189, 190]. This leads to hepatic tissue hypoxia, which plays a significant role in driving disease progression. Hepatic vessels are particularly sensitive to the action of endogenous vasoconstrictors. From a clinical

perspective, NAFLD frequently coexists with arterial hypertension, and persistently elevated blood pressure is associated with accelerated progression of hepatic steatosis and fibrosis [191, 192]. Consequently, one potential therapeutic direction in the treatment of NAFLD is the use of agents that block the action of vasoconstrictors.

Preclinical studies provide promising data regarding the efficacy of such therapies. In a Wistar rat model of diet-induced NAFLD, factors such as endothelin-1 (ET-1), angiotensin II (AT-II), and thromboxane A2 (TxA2) contributed to increased transhepatic pressure gradient (THPG). The use of bosentan (an ET-1 receptor antagonist), valsartan (an AT-II receptor blocker), and celecoxib (a COX-2 inhibitor) reduced these adverse hemodynamic changes. Moreover, in a NASH model in Zucker rats, bosentan therapy compared to placebo led to reduced steatosis and improved liver histology, suggesting the potential use of vasoconstrictor antagonists in improving hepatic vascular function in early-stage NAFLD [191]. In another diet-induced NASH rat model, combined therapy with atorvastatin and ambrisentan led to significant histological improvement of the liver, suggesting that such drug combinations warrant investigation in the NASH patient population [193].

Similarly, data from mouse studies have shown that losartan may prevent hepatic steatosis and adverse macrophage polarization in ob/ob mice by inhibiting hypoxia-inducible factor-1α (HIF-1α) expression. Losartan treatment resulted in increased triglyceride (TG) and free fatty acid (FFA) levels, which appears to protect against NAFLD development [194]. Telmisartan, another potential candidate for NAFLD treatment, inhibits hepatic fibrosis through AT-II receptor blockade [195]. Furthermore, telmisartan acts as a partial PPAR-γ agonist, which translates into improved insulin resistance, better lipid profiles, reduced proinflammatory cytokine expression, and decreased fatty acid and triglyceride levels, thereby potentially limiting hepatic steatosis and fibrosis progression [196].

Hepatoprotective agents

Ursodeoxycholic acid (UDCA) is an endogenous, synthetic bile acid present in the human body that exhibits antioxidant and anti-inflammatory properties and plays a role in preventing mitochondrial dysfunction associated with the progression of obesity-related diseases. Although early clinical studies did not demonstrate significant efficacy of UDCA in the treatment of patients with non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) [197, 198, 199], its potential hepatoprotective effects continue to prompt experimental and clinical research. For example, in ob/ob mice, UDCA was shown to regulate hepatic energy homeostasis and influence macrophage polarization in white adipose tissue [200].

The results of a randomized controlled trial by Ratziu et al. suggested that high-dose UDCA (28–35 mg/kg/day) for 12 months reduced liver aminotransferase activity in patients with NASH and improved glycemic control and insulin resistance, with a favorable safety profile — the most commonly reported adverse effects were abdominal discomfort and diarrhea [201]. Similar findings were reported by Nadinskaia et al., who evaluated the impact of UDCA at 15 mg/kg/day combined with dietary modification and increased physical activity. During the first three months of treatment, patients with NAFLD showed normalization of liver enzyme levels, improved lipid profiles, and reduced hepatic steatosis, and continuation of therapy for six months was associated with reduced cardiovascular risk [202].

Farnesoid X receptors (FXR), members of the nuclear receptor family, play a key role in regulating bile acid synthesis, glycolipid metabolism, hepatic inflammatory processes, and fibrosis. FXR agonists enhance tissue insulin sensitivity, limit bile acid synthesis, and promote mitochondrial fatty acid oxidation. Obeticholic acid (OCA) is one of the best-studied agents in this class [203]. In a phase II trial by Mudaliar et al., OCA at 25 or 50 mg/day for six weeks improved insulin resistance and reduced markers of hepatic inflammation and fibrosis in patients with T2DM and NAFLD; the therapy was well tolerated [204]. Similarly, in a double-blind, placebo-controlled trial, Neuschwander-Tetri et al. found that OCA at 25 mg/day for 72 weeks improved histological features of NASH, although approximately 23% of patients experienced pruritus as an adverse event [205].

Based on these results, Younossi et al. designed a phase III trial to evaluate the impact of OCA on fibrosis in a NASH patient population [206]. Interim analysis after 18 months of treatment showed that OCA at 10 or 25 mg/day was associated with significant fibrosis improvement. However, long-term OCA therapy was linked to adverse effects, such as skin and subcutaneous tissue disorders, gastrointestinal symptoms, and increased cholesterol levels, which may limit its application in the treatment of NAFLD/NASH [207].

Probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT)

In recent years, modulation of the gut microbiota has become the focus of intensive research as a potential therapeutic approach in the treatment of non-alcoholic fatty liver disease (NAFLD). The gut microbiota is believed to play a significant role in the pathogenesis of non-alcoholic steatohepatitis (NASH) through mechanisms involving the release of lipopolysaccharides (LPS), increased ethanol production, and induction of proinflammatory cytokines in intestinal epithelial cells and hepatic macrophages [208]. Furthermore, gut microbes influence NAFLD development by modulating choline metabolism, bile acid transformation, and production of short-chain fatty acids (SCFAs) — such as acetate, propionate, and butyrate — through bacterial fermentation [209]. Gut dysbiosis, characterized by abnormal LPS and SCFA release and excessive ceramide accumulation, can induce hepatic inflammatory processes via enhanced release of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) [210, 211]. Animal models, such as mice, have shown that reduced butyrate levels and increased bacterial LPS translocation may exacerbate NAFLD and insulin resistance (IR). Despite promising experimental findings, the clinical efficacy of these interventions remains only partially confirmed. It is well known that disturbances of the gut microbiota are common in chronic liver diseases and play a significant role in their progression, regardless of etiology [212]. Thus, strategies involving probiotics, prebiotics, synbiotics, or fecal microbiota transplantation (FMT) are increasingly attracting research interest [213].

A placebo-controlled study by Aller et al. demonstrated that oral supplementation with a combination of *Lactobacillus bulgaricus* and *Streptococcus thermophilus* (500 million CFU/day) for three months reduced liver aminotransferase activity in patients with NAFLD [214]. A randomized controlled trial showed that consumption of probiotic-enriched yogurt (220 g/day for 24 weeks) provided greater benefits in improving insulin resistance and reducing liver fat content (LFC) in obese women with NAFLD and metabolic syndrome than milk consumption, while also reducing inflammation, oxidative stress, and improving lipid profiles [215]. Supplementation with *Saccharomyces boulardii* for 12 weeks, alongside diet and physical activity, was associated with improvements in biochemical parameters, including reductions in total bilirubin, aminotransferases, GGT, total cholesterol, LDL-C, and fasting insulin [216].

Other studies have also confirmed the beneficial effects of microbial interventions. Oral administration of probiotic capsules (Lactocare) for eight weeks improved insulin resistance and reduced TNF-α and IL-6 levels [217]. Similar effects were observed with a mixture of 14 probiotic strains (Symbiter), which reduced LFC, TNF-α, IL-6, and transaminase activity [218]; its combination with omega-3 fatty acids provided additional benefits in reducing LFC and inflammatory markers [219]. However, not all studies reported unequivocally positive outcomes — for example, a randomized, double-blind trial using a multi-strain probiotic (30 billion CFU/day for six months) did not significantly affect LFC or fibrosis, although it stabilized gut mucosal immune function [220].

Regarding prebiotics, the use of fructooligosaccharides (FOS) in patients with NASH was shown to reduce histological steatosis [221], and their combination with *Bifidobacterium longum* additionally reduced TNF-α, CRP, AST, and improved liver histology [222]. Synbiotics demonstrated similar potential by positively influencing inflammatory markers [223], although they did not always change LFC or fibrosis [224].

As for FMT, studies such as that by Craven found no significant effect on insulin resistance but suggested a potential improvement in gut permeability [225]. In a recent randomized clinical trial in China comparing FMT and probiotics, FMT more effectively reduced hepatic steatosis in non-obese patients with NAFLD through modulation of the gut microbiota [226].

Peroxisome proliferator-activated receptor (PPAR) agonists

PPAR agonists play a key role in regulating glucose and lipid metabolism, positively affecting glycemic control and lipid profiles, including cholesterol and triglyceride levels. In addition to pioglitazone, widely discussed earlier for use in patients with type 2 diabetes mellitus (T2DM) and NASH, new molecules from this group are currently under active development. One example is saroglitazar — a dual PPAR-α/γ agonist — which modulates carbohydrate and lipid metabolism and has been approved in India for the treatment of NAFLD [227]. Preclinical studies in male Wistar rats with diet-induced NASH showed that saroglitazar significantly reduced hepatic steatosis [228]. Similarly, a randomized, double-blind, placebo-controlled phase II clinical trial found that saroglitazar at 4 mg/day for 16 weeks in patients with NAFLD/NASH improved lipid profiles, reduced hepatic steatosis and triglyceride levels, and decreased insulin resistance [229].

In a phase IIb study evaluating lanifibranor — a pan-PPAR agonist — administration of 1, 200 mg/day for 24 weeks in patients with NASH significantly reduced fibrosis severity (assessed by the SAF-A score),

lowered liver lipid content, and improved liver enzyme activity. Based on these findings, Francque's research team designed a phase III trial to further confirm the drug's efficacy [230].

Similarly, the study by Gastaldelli et al. confirmed that pioglitazone, as a PPAR-γ agonist, can modulate visceral fat content and adiponectin levels, contributing to the alleviation of hepatic steatohepatitis in patients with NASH [231].

Studies by Ratziu et al. demonstrated that elafibranor (a PPAR-α/δ agonist) at 120 mg/day for one year significantly improved liver fat content and reduced liver enzyme levels without worsening fibrosis [232].

It is also worth mentioning pemafibrate, a modern selective PPAR-α modulator. A clinical study conducted by Japanese researchers found that although this agent did not significantly reduce liver fat content, it did reduce liver stiffness, suggesting its potential use in NASH therapy in combination with other agents [233].

Thyroid hormone receptor β (THR-β) agonists

The thyroid hormone receptor β (THR-β) plays a key role in regulating numerous metabolic pathways, including glycolipid and cholesterol metabolism in the liver, making it a promising therapeutic target in the development of new treatments for non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Among the novel THR-β agonists, resmetirom (MGL-3196), a highly liver-selective agent, is of particular interest. Preclinical studies conducted in obese mice with NASH induced by a high-fat, high-sugar diet demonstrated that treatment with MGL-3196 at 3 mg/kg/day significantly reduced liver mass, hepatic steatosis, plasma ALT activity, as well as hepatic cholesterol, plasma cholesterol, and blood glucose levels [234]. These promising results were confirmed in clinical trials — a 36-week, randomized, double-blind, placebo-controlled, multicenter phase II study led by Harrison's team showed a significant reduction in liver fat content after 12 and 36 weeks of oral resmetirom at 80 mg/day in patients with NASH [235]. The extension study of this phase II trial confirmed that both 80 mg/day and 100 mg/day doses were well tolerated and safe, allowing the drug to progress to phase III clinical trials [236].

Another example of a THR-β agonist under development for NAFLD therapy is TG68. Preclinical data indicate that this agent is highly effective in reducing liver fat content and steatosis in a C57BL/6 mouse model of diet-induced NASH, with effects comparable to those of resmetirom [237]. Regardless of the encouraging preclinical findings, further clinical studies are necessary to confirm the efficacy and safety of TG68 in patient populations.

Fibroblast growth factor analogs

Fibroblast growth factors 19 (FGF19) and 21 (FGF21) represent a new class of endocrine mediators that play a crucial role in regulating energy homeostasis, including lipid and carbohydrate metabolism. Initially, their analogs were developed primarily to improve glycemic control in patients with type 2 diabetes mellitus (T2DM), but their marked, consistent, and durable effects on lipid metabolism observed in clinical studies have shifted the focus towards their therapeutic potential in NASH [238].

In a randomized, double-blind, placebo-controlled phase II study, treatment with aldafermin (NGM282), a modified FGF19 analog, at doses of 3 mg/day or 6 mg/day in patients with NASH led to significant reductions in liver fat content while maintaining a good safety profile [239]. Another multicenter, randomized, double-blind, placebo-controlled trial led by Harrison's team confirmed that NGM282 at 1 mg/day or 3 mg/day for 12 weeks improved histological features of the liver and lowered aminotransferase levels (AST and ALT) [240]. Results from a 24-week continuation of this phase II study confirmed reductions in hepatic steatosis and showed a trend toward fibrosis improvement [241]. The latest data from a phase IIb trial indicate that NGM282 at doses of 0.3 mg/day and 1 mg/day was well tolerated, although no significant differences in fibrosis improvement were observed between doses [242]. It was also noted that NGM282 use may lead to increased cholesterol levels, prompting a phase II study combining the agent with statins, which demonstrated better lipid parameter control [243]. Common adverse events associated with NGM282 included mild to moderate nausea, vomiting, and diarrhea.

Regarding FGF21, which belongs to the same fibroblast growth factor signaling subfamily as FGF19, its therapeutic potential in NAFLD has garnered attention. Targeting the FGF21/FGFR/β-Klotho signaling pathway may counteract hepatic fat accumulation, inflammation, and fibrosis progression [244]. One of the leading FGF21 analogs under investigation is pegbelfermin (BMS-986036), a pegylated FGF21 analog. Phase II studies in patients with obesity and T2DM demonstrated that pegbelfermin improved metabolic parameters and fibrosis markers [245]. A phase IIa multicenter, randomized, double-blind, placebo-controlled study found that subcutaneous BMS-986036 at 10 mg/day or 20 mg/week for 16 weeks in patients with NASH significantly

reduced liver fat content with a good safety profile [246]. However, despite these promising results, the number of clinical trials involving FGF21 analogs remains limited, and further studies are required to assess their long-term effects on liver histology, cirrhosis risk, and patient survival [247].

Summary and Conclusions

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide and represents a significant and increasingly important clinical health concern. The pathogenesis of NAFLD is complex and multifactorial, involving excessive influx of fatty acids into the liver, disturbances in de novo lipogenesis, insulin resistance, lipotoxicity, chronic inflammation, dysbiosis of the gut microbiota, and fibrogenesis processes. The disease is strongly associated with type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), and chronic kidney disease (CKD), thus conferring a multi-organ and systemic character to NAFLD.

Currently, the cornerstone of NAFLD management remains lifestyle modification, including caloric restriction, adherence to dietary patterns such as the Mediterranean diet, and regular physical activity. These strategies have demonstrated high efficacy in reducing hepatic steatosis, improving metabolic parameters, and decreasing the risk of complications. An increasingly important role in therapy is played by medications originally developed for the treatment of T2DM — including GLP-1 receptor agonists, SGLT2 inhibitors, and pioglitazone — which have shown beneficial effects on hepatic steatosis and metabolic parameters in patients with NAFLD and coexisting T2DM.

Promising results have also emerged for new therapeutic agents, such as FXR, THR-β, and PPAR agonists, as well as FGF19 and FGF21 analogs, which in preclinical studies and early-phase clinical trials have demonstrated potential for reducing hepatic steatosis and fibrosis. At the same time, there is growing interest in interventions targeting the gut microbiota (probiotics, prebiotics, synbiotics, and fecal microbiota transplantation), although their long-term effectiveness in improving liver histology requires further verification.

In conclusion, the effective management of NAFLD requires a multidimensional approach integrating lifestyle changes, pharmacological treatment, and — in selected cases — procedural interventions such as bariatric surgery. Further clinical research is essential to better assess the efficacy, safety, and long-term benefits of emerging therapeutic strategies targeting the pathogenic mechanisms of NAFLD.

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