Treatment of NAFLD: Diet, Physical Activity, and Potential Pharmacological Options

Justyna Śliz

E-mail: justyna-sliz@wp.pl

ORCID: https://orcid.org/0009-0007-0242-149X

Central Clinical Hospital of the Medical University of Lodz, Pomorska 251, 92-213 Łódź

Natalia Aleksandra Popławska

E-mail: natalia.poplawska2109@gmail.com

ORCID: https://orcid.org/0009-0002-6243-6603

Central Clinical Hospital of the Medical University of Lodz, Pomorska 251, 92-213 Łódź
Marta Skorupska
E-mail: mskorupska71@gmail.com
ORCID: https://orcid.org/0009-0001-6556-3133
Karol Jonscher Municipal Medical Center, Milionowa Street 14, 93-113 Lodz

Magdalena Joanna Czeczetka
E-mail: magda.czeczotka@gmail.com
ORCID: https://orcid.org/0009-0005-6306-8437
Karol Jonscher Municipal Medical Center, Milionowa Street 14, 93-113 Lodz

Krzysztof Woźniak
E-mail: wozniak.krzysztof1998@gmail.com
ORCID: https://orcid.org/0009-0004-1438-0806
Medical University of Lodz, Al. Kościuszki 4, 90-419 Łódź

Martyna Magdalena Martka
E-mail: martyna.martka@stud.umed.lodz.pl
ORCID: https://orcid.org/0009-0006-2295-5459
Karol Jonscher Municipal Medical Center, Milionowa Street 14, 93-113 Lodz
ABSTRACT

Introduction and purpose

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in the world, and according to current data, it affects 38% of the global population. NAFLD includes non-alcoholic fatty liver and the progressive form called non-alcoholic steatohepatitis, which is characterized by damage, inflammation of hepatocytes, and fibrosis. NASH can lead to cirrhosis and hepatocellular carcinoma. Moreover, it increases the risk of diabetes mellitus type 2, lipid disorders, and death due to cardiovascular causes. Currently, no cure is aimed at reducing the severity of NALFD and liver fibrosis. The aim of this study was to provide a total review of the current state of knowledge regarding NAFLD treatment and to identify potential areas for further evaluation.

Materials and method

The PubMed and Google Scholar databases were thoroughly searched to select appropriate sources for this article.

A brief description of the state of knowledge

Diet, weight management, and physical activity constitute fundamental elements of every treatment regimen for NAFLD. Regarding pharmacological treatment, European guidelines recommend the use of vitamin E or pioglitazone in certain patients. Recently, the topic of NAFLD treatment has been a popular subject among scientists who are striving to discover new therapeutic options. A lot of recent research has exhibited promising outcomes for GLP-1 agonists, metformin, SGLT2 inhibitors, FXR, and PPAR ligands.

Summary

The findings of the conducted studies so far are encouraging and offer promise for novel pharmacological interventions in the treatment of NAFLD. Nonetheless, before implementation, further research in this area will be imperative to comprehensively evaluate the efficacy and safety profiles of these pharmaceuticals.

Keywords: non-alcoholic fatty liver disease; metabolic-associated fatty liver disease; NAFLD; MAFLD; NAFLD treatment; MAFLD treatment
INTRODUCTION AND PURPOSE
Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide and is defined as the accumulation of ≥ 5% lipids in hepatocytes in the absence of any additional causative factors for hepatic steatosis, such as prolonged fasting, medication usage, or monogenic diseases, in an individual who abstains from alcohol or consumes it in limited quantities. NAFLD is one of the metabolic diseases, so it has undergone a recent rebranding to metabolic-associated fatty liver disease (MAFLD). This new nomenclature acknowledges the condition as an autonomous disease entity and removes the criterion of excessive alcohol use from its definition. In this review, we will use the term NAFLD to avoid any confusion regarding nomenclature. NAFLD includes nonalcoholic fatty liver (NAFL) and the progressive form called non-alcoholic steatohepatitis (NASH). NAFL may expand to NASH, which is characterized by cellular damage [1,2,3]. The term NASH first appeared in 1980, when Ludwig and co-creators described histologic fatty lesions with lobular inflammation in nonalcoholic patients. In 2020, an international panel of experts studied the nomenclature and established the term MAFLD [4]. The purpose of this study was to provide a total review of the current state of knowledge regarding NAFLD treatment and to identify potential areas for further evaluation.

STATE OF KNOWLEDGE
Risk factors for NAFLD
The main risk factors for NAFLD are components of the metabolic syndrome. Non-alcoholic fatty liver disease is significantly associated with obesity, exhibiting a prevalence of up to 80% in obese patients, while only affecting 16% of individuals without metabolic risk factors and normal BMI. Notably, obesity appears to contribute to both the initial development of simple steatosis and its progression to non-alcoholic steatohepatitis [5,6]. A high-calorie diet, excessive intake of (saturated) fats, consumption of sugar-sweetened beverages, refined carbohydrates, high fructose intake, and adherence to a Western dietary pattern have all been correlated with obesity, weight gain, and NAFLD. The elevated consumption of high fructose may escalate the susceptibility to non-alcoholic steatohepatitis and advanced fibrosis. However, this correlation may be influenced by excessive calorie intake sedentary behavior, and unhealthy lifestyles, which are more prevalent among individuals affected by NAFLD [7]. Genetic risk factors may also play a role in the pathogenesis of NAFLD. PNPLA3 (I148M) was the first identified variant associated with NAFLD. The main site of PNPLA3 expression
regulated by insulin is the liver and adipose tissue. The PNPLA3 protein hydrolyzes triglycerides and retinyl esters, which reduces their deposition in the liver. The impairment of the PNPLA3 protein function is caused by the substitution of isoleucine to methionine at 148 position (PNPLA3-I148M). The result is TAG accumulation in the hepatocytes [8,9]. Also, the TM6SF2 gene has recently been identified as a disease modifier and may offer clinical utility in assisting risk stratification for cardiovascular vs. liver-related morbidity [7].

**Symptoms and progression**

Fatty liver disease usually progresses without symptoms and is often diagnosed incidentally. Occasionally, patients may experience fatigue, weakness, poor general feeling, or discomfort in the right upper quadrant of the abdomen. Objective symptoms often include obesity. In less than 75% of patients, liver enlargement occurs, and in less than 26%, spleen enlargement is observed. Sometimes, other signs of portal hypertension can also be observed in patients [3]. Liver fibrosis usually progresses slowly, but approximately 20% of patients experience rapid progression. In individuals with NASH, there is an increased risk of developing liver cirrhosis and hepatocellular carcinoma. However, cardiovascular diseases are the primary cause of death in these patients [3].

**Diagnostic tests**

During the diagnosis of NAFLD, laboratory tests are performed, such as measuring the activity of ALT and AST, which typically show a slight to moderate increase. The De Ritis ratio (the ratio of AST to ALT activity) is less than 1. GGT levels, bilirubin, glucose, albumin, and lipid metabolism are also assessed. Coagulation parameters are checked (prolongation of PT may occur in advanced liver disease), as well as iron and ferritin levels, which are often elevated. Imaging studies, such as liver ultrasound, computed tomography, or magnetic resonance imaging of the abdomen, are also utilized. In ultrasound, increased echogenicity (steatosis) may be visible, and less frequently, liver enlargement. When cirrhosis is present, ultrasound may reveal signs of portal hypertension. CT provides a good assessment of the liver and other organs, but due to ionizing radiation, it is not recommended for routine use. MRI allows for an accurate assessment of even minimal steatosis. The only validated method for the quantitative measurement of liver fat content is 1H-MRS. Liver fibrosis is assessed using tests such as ultrasound elastography or magnetic resonance elastography. For some patients, a histological examination of a liver biopsy is performed, although this carries a risk of complications due to the need to obtain a liver tissue sample. This examination is
considered the gold standard for diagnosis and is necessary to definitively distinguish NASH from NAFL [3].

**Treatment**
Modifications of lifestyle and weight reduction are fundamental components of the treatment regimen. Additionally, treatment encompasses the regulation of lipid and glycemic levels. In cases of substantial obesity, the consideration of gastric bypass or alternative surgical interventions for weight reduction is warranted. Patients are advised to refrain from the consumption of hepatotoxic drugs or alcohol [10].

**Lifestyle modification**
Diet, weight management, and physical activity constitute fundamental elements of every treatment regimen for NAFLD. Reducing caloric intake by a minimum of 500–1000 kcal has demonstrated efficacy in ameliorating insulin resistance and hepatic steatosis [11,12]. Mariana Lazo et al. were studying the long-term health effects of an intensive lifestyle intervention on obese or overweight people with diabetes type 2. The hypothesis was that lifestyle intervention would decrease hepatic steatosis and the occurrence of non-alcoholic fatty liver disease compared to people in the second group who were receiving diabetes support and education. They found that an intensive lifestyle intervention in people with Diabetes type 2, results in an 8% reduction in body weight and a noteworthy 25% decrease in hepatic steatosis. Furthermore, the occurrence of non-alcoholic fatty liver disease was significantly lower compared to a control group following the 12-month intervention period [13].

Eduardo Vilar-Gomez et al. conducted the study which aimed to examine the correlation between the extent of weight loss resulting from lifestyle modifications and the alterations in histologic characteristics of nonalcoholic steatohepatitis. They discovered that a more substantial degree of weight loss resulting from lifestyle modifications is associated with a higher level of improvement in the histologic characteristics of nonalcoholic steatohepatitis. Patients achieving weight reductions of 10% or more exhibited the most pronounced reductions in NAFLD activity score (NAS), resolution of NASH, and regression of fibrosis [14].

According to research findings, engaging in moderate exercise a minimum of 5 times per week, totaling 150 minutes weekly, or increasing physical activity by more than 60 minutes per week, can serve to prevent non-alcoholic fatty liver disease (NAFLD) or ameliorate its symptoms [15,16].
Hui-Jie Zhang et al. tried to assess the impact of vigorous and moderate exercise on metabolic risk factors and intrahepatic triglyceride content in patients diagnosed with NAFLD. They discovered that moderate and vigorous exercise exhibit equivalent efficacy in reducing intrahepatic triglyceride content. This effect is primarily attributed to the facilitation of weight loss [17].

Catalina M. Mascaró et al. conducted a study to evaluate the physical activity and fitness status following a six-month lifestyle intervention (comprising diet and physical activity) in adults diagnosed with metabolic syndrome and NAFLD. The research findings indicated that a lifestyle intervention spanning six months, incorporating dietary modifications and regular physical activity, led to enhanced functional fitness among middle-aged patients diagnosed with metabolic syndrome and NAFLD. Patients adhering to a Mediterranean diet and engaging in structured training sessions over the same duration exhibited improvements in aerobic capacity [18].

**Pharmacological treatment**

Researchers are still searching for an effective pharmacological treatment for this disease. Below, research on several drugs that may prove effective in treating NAFLD is presented.

According to European recommendations, developed by European scientific societies: the European Association for the Study of the Liver, the European Association for the Study of Diabetes, and the European Association for the Study of Obesity, pharmacotherapy should be considered for patients diagnosed with non-alcoholic steatohepatitis, particularly those presenting with significant fibrosis. Additionally, individuals with less severe disease but deemed to be at high risk of progression may also be suitable candidates for pharmacological intervention aimed at preventing disease advancement. While definitive recommendations are lacking, pioglitazone, vitamin E, or a combination of both may be utilized in the management of NASH [19].

**Vitamin E**

The different forms of vitamin E include alpha, beta, and gamma tocopherols and tocotrienols. The alpha-tocopherol form is the most common and active in human tissues [20]. Vitamin E is a powerful antioxidant in the human body, capable of capturing lipid peroxide radicals. It can target not only reactive oxygen species but also reactive nitrogen species [21]. Supplementation with vitamin E increases the level of superoxide dismutase, an antioxidant enzyme in the body [22]. Additionally, vitamin E inhibits the expression of TGF-beta, which is associated with hepatocyte apoptosis and liver fibrosis. Furthermore, vitamin E is linked to
increased adiponectin levels, which inhibit the synthesis of fatty acids in the liver and reduce inflammation by suppressing the excretion of TNF-alpha, IL-1, IL-2, IL-4, IL-6, and IL-8 cytokines in patients with NASH [23]. Vogli et al. conducted a meta-analysis of randomized controlled trials conducted through April 2023 among patients with NAFLD. They examined the effect of vitamin E on the level of hepatic enzymes. The results showed that vitamin E supplementation with 2 doses of 400-800 IU lowers serum ALT and AST levels compared to placebo. The decrease in ALT was particularly noticeable [24]. Ken Sato et al. conducted a meta-analysis of randomized controlled trials, revealing that vitamin E effectively reduces AST, ALT, ALP, steatosis, inflammation, hepatocellular ballooning, and fibrosis in patients with NASH when compared to the control group [25].

**Pioglitazone**

Pioglitazone is one of the thiazolidinediones and is postulated to function through the activation of PPAR-γ receptors, thereby triggering the expression of numerous genes associated with the metabolism of glucose and fatty acid [26]. Jingxuan and colleagues conducted a meta-analysis to assess the impact of pioglitazone in treating patients with diabetes or prediabetes who also had non-alcoholic fatty liver disease. The study found that pioglitazone significantly improved the steatosis grade, inflammation grade, and ballooning grade compared to the placebo. However, no significant improvement was observed in the fibrosis stage. Additionally, pioglitazone may also help improve blood glucose levels and liver function [27]. Giuseppe et al. conducted a randomized controlled trial to investigate the effects of 1-year treatment with pioglitazone or sulphonylureas on indirect indices of non-alcoholic fatty liver disease in people with type 2 diabetes. Patients, whose metformin 2 g/day treatment was weakly controlled, were randomly allocated to add-on sulphonylureas or pioglitazone. The results showed that even low-dosage treatment with pioglitazone but not with sulphonylureas markedly improved liver inflammation and steatosis, systemic and adipose tissue insulin resistance in patients with type 2 diabetes. These effects are not dependent on controlling blood glucose levels [28]. According to a systematic review conducted by Iqra et al. both pioglitazone and vitamin E exhibit an effective reduction in inflammation, steatosis, and ballooning of the liver, as well as lowering liver markers. However, the available data on the resolution of fibrosis appears to be inconclusive. The review also demonstrated that the combination of vitamin E and pioglitazone is a more effective treatment for NASH than pioglitazone alone. Pioglitazone may be prescribed to
diabetic patients with NAFLD, while vitamin E was found to be effective in non-diabetic patients with NAFLD [29].

**GLP-1 agonists**

GLP-1 analogues are recommended for patients diagnosed with type 2 diabetes, particularly those presenting with obesity, cardiovascular conditions, and chronic kidney disease [30,31]. These pharmaceuticals have been found to mitigate cardiovascular risk, reduce blood pressure, and ameliorate lipid profiles, parameters commonly aberrant in individuals with non-alcoholic fatty liver disease (NAFLD) [31,32]. Furthermore, they induce weight loss, thereby mitigating steatohepatitis. The impact of GLP-1 analogues on the liver encompasses enhancements in hepatocyte mitochondrial functionality, heightened liver insulin sensitivity, and decreased plasma transaminase levels [33]. Notably, Cusi demonstrated a decrease in liver fat among patients receiving incretin-based medications with NAFLD and type 2 diabetes [34]. Philip N. Newsome et al. Conducted a study to examine the impact of semaglutide, one of GLP-1 agonists, on the histologic resolution of nonalcoholic steatohepatitis in individuals with NASH and fibrosis confirmed by biopsy. The study revealed that treatment with semaglutide yielded a notably higher proportion of patients achieving NASH resolution compared to those administered with a placebo. Nevertheless, the trial did not exhibit a significant inter-group disparity in the percentage of patients manifesting an improvement in the fibrosis stage [35].

Matthew James Armstrong et al. examine the efficacy of another GLP-1 analogue called liraglutide, in people with NASH. In this research, liraglutide demonstrated safety, good tolerability, and induced histological resolution of NASH [36]. Other scientists have also studied the properties of liraglutide. Ryotaro Bouchi et al. tried to assess the impact of liraglutide on visceral adiposity and associations between changes in visceral fat and alterations in hepatic steatosis, albuminuria, and systemic chronic low-grade inflammation in individuals diagnosed with type 2 diabetes. As a result of their study, they found that adding liraglutide to insulin treatment demonstrated a reduction in visceral adiposity, simultaneous with a decrease in hepatic fat accumulation, micro-inflammation, and albuminuria while also yielding improvements in quality of life related to diabetes care among individuals with type 2 diabetes [37].

**Metformin**

Metformin is a biguanide medication and exerts its efficacy in reducing blood glucose levels through the inhibition of hepatic glucose production, attenuation of intestinal glucose
absorption, and augmentation of insulin sensitivity. Consequently, metformin effectively ameliorates postprandial and basal blood glucose levels [38].

Sofia de Oliveira et al. showed in their study that consuming a high-fat diet can lead to an increase in liver size, enhanced angiogenesis, micronuclei formation, and neutrophil infiltration in the liver. Such a diet can also result in changes in the morphology and polarization of macrophages, with a higher number of liver-associated TNFα-positive macrophages. However, treatment with metformin can reverse these effects. It can reduce liver size, alter macrophage polarization, and decrease micronuclei formation in NAFLD/NASH-associated HCC larvae. Additionally, a high-fat diet can cause a reduction in T cell density in the liver, but this can be reversed by treatment with metformin [39]. Simon et al. found that NASH led to reduced effectiveness of anti-PD-1 therapy in treating liver cancers in murine models. NASH induced a pro-inflammatory change in hepatic CD8+ T cells. Metformin treatment improved the efficacy of anti-PD-1 therapy against liver tumors in NASH [40]. Scientists have recently discovered a new form of regulated cell death called Ferroptosis. This form of cell death has been linked to the development of non-alcoholic fatty liver disease. Fangzi et al. Their research has investigated the effect of metformin on Ferroptosis and its potential mechanisms in NAFLD. The results showed that metformin can prevent the progression of NAFLD and reduce hepatic iron overload (HIO) and Ferroptosis. Additionally, metformin increases the expression of Ferroportin (FPN) both in vitro and in vivo. This mechanism has a potential therapeutic impact [41]. Nonalcoholic steatohepatitis is a liver disease that is characterized by the presence of hepatocellular ballooning (HB). Iliana et al. conducted a study on the effects of metformin, a medication commonly used to treat nonalcoholic fatty liver disease, on HB. They reviewed studies that included pre- and post-treatment liver biopsies. The study found that metformin improved HB in the population who improved their transaminases and lost weight during therapy. Previous studies have also shown that metformin has other beneficial effects, such as improving insulin resistance, reducing body weight, preventing complications related to diabetes, and reducing the risk of hepatocellular carcinoma. As a result, metformin is a promising treatment option for patients with diabetes, prediabetes, and co-existing NAFLD [42].

**SGLT2 inhibitors**

The sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) are pharmaceutical agents used in the treatment of diabetes. They operate by impeding the reuptake of glucose in the proximal renal tubule, thus promoting the excretion of glucose in the urine and consequent
reduction in serum glucose levels [43]. Recently, more and more research suggests that, in addition to their antidiabetic effects, these drugs may also have a beneficial effect on NAFLD. Sabine Kahl et. al conducted a study in which they assessed the impact of empagliflozin on the risk of NAFLD-related fibrosis and steatosis. They found that the prevalence of individuals at high risk of steatosis decreased slightly with the use of empagliflozin, while empagliflozin did not demonstrate an improvement in the prevalence of individuals at high risk of fibrosis over time in comparison to the placebo group so based on this empagliflozin has been found to potentially lower the risk of steatosis in patients with diabetes mellitus type 2 and cardiovascular disease, although it may not have the same effect on fibrosis risk [44].

The study conducted by Mohammad Shafi Kuchay et. al aimed to assess the influence of empagliflozin on liver fat in individuals diagnosed with diabetes type 2 and NAFLD by using MRI-PDFF (MRI-derived proton density fat fraction). They discovered that incorporating empagliflozin into the standard treatment for type 2 diabetes leads to a reduction in liver fat and improvement in ALT levels among patients diagnosed with diabetes type 2 and NAFLD [45].

Scientists are also investigating the effects of other SGLT2 inhibitors on patients with fatty liver disease. Yumie Takeshita et al. examined the effectiveness of tofogliflozin (one of the SGLT2 inhibitors) and the sulfonylurea glimepiride in participants with NAFLD and diabetes type 2 over a 48-week period. They assessed liver histology, hepatic enzymes, hepatic gene expression profiles, and metabolic markers. They conclude that tofogliflozin, and to a lesser extent glimepiride, demonstrated a significant reduction in liver histology scores over a 48-week period in individuals with diabetes type 2 and NAFLD confirmed by liver biopsy specimens [46].

**PPAR-agonist**

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors known for their pleiotropic effects on metabolism and immunomodulation. These receptors encompass various subtypes. PPAR-α, predominant in the liver, primarily regulates fatty acid oxidation. Conversely, PPAR-γ, highly expressed in adipose tissue, plays a crucial role in adipocyte differentiation and enhances glucose tolerance. Lastly, PPAR-δ, predominantly found in the liver and muscles, modulates glucose metabolism to favor oxidative pathways over glycolysis [47].

Elafibranor functions as an agonist of the peroxisome proliferator-activated receptor-α and also the peroxisome proliferator-activated receptor-δ [48].
Vlad Ratziu et al. conducted a study in which the efficacy and safety of elafibranor in people with nonalcoholic steatohepatitis were evaluated. The intervention group demonstrated significant reductions in liver enzymes, markers of inflammation, lipids, and glucose profiles in comparison to the placebo group. Elafibranor exhibited good tolerability and did not induce cardiac events or weight gain; however, it did elicit a reversible, mild increase in serum creatine [49].

Nidhi P Goyal et al. decided to investigate the use of this drug in the pediatric population. The objective of the study was to delineate the pharmacokinetics, tolerability, and safety of two dosage levels of oral elafibranor (80 and 120 mg) in pediatric patients aged 8-17 years, and to evaluate the impact on aminotransferase levels. The once-daily administration of elafibranor displayed favorable tolerability in pediatric patients with NASH. The group that received 120 mg of elafibranor exhibited a substantial 37.4% relative reduction from the mean baseline ALT. Researchers claimed that this reduction in ALT levels may be indicative of improved liver histology and could be considered a potential surrogate for histological assessment in early-phase trials [50].

Saroglitazar is a dual peroxisome proliferator-activated receptor-α/γ agonist [51]. Saroglitazar prevents the delivery of fatty acids to the liver, increases insulin sensitivity, and regulates the level of adiponectin and leptin in adipose tissue. In hepatocytes, it induces β-oxidation of fatty acids and transcriptionally activates genes that metabolize lipids in peroxisomes [52]. In a study conducted by Gawrieh et al., 106 patients with Non-Alcoholic Steatohepatitis (NASH), BMI >25 kg/m², and elevated liver enzyme ALT were examined. The patients were categorized into 4 groups: placebo, and groups administered with saloglitazar at doses of 1 mg, 2 mg, and 4 mg for a duration of 16 weeks. The administration of saloglitazar at a 4 mg dose resulted in a reduction of ALT activity, liver fat content (LFC), insulin resistance, and atherogenic dyslipidemia in participants with NAFLD/NASH [53].

Pan-PPAR agonists, such as lanifibranor, synergistically harness the beneficial effects of selective PPAR agonists, demonstrating enhanced efficacy in counteracting inflammation and the progression of liver disease [54]. In a double-blind, randomized, placebo-controlled phase 2b study conducted by Francque et al, non-cirrhotic NASH patients were allocated to three groups in a 1:1:1 ratio. These groups were administered either 1,200 mg or 800 mg of lanifibranor, or a placebo, for a duration of 24 weeks. Results indicated a decrease in liver enzyme levels and improvement in most lipid, inflammatory, and fibrosis biomarkers in the lanifibranor groups. Notably, the proportion of patients exhibiting a decrease of at least 2 points in the SAF-A score without exacerbating fibrosis was significantly higher in the 1,200
mg lanifibranor group when compared to the placebo group. These findings advocate for further assessment of lanifibranor in phase III trials [55].

**Obeticholic acid (OCA)**

Obeticholic acid serves as an agonist of the farnesoid X receptor (FXR), presenting a novel therapeutic target for non-alcoholic fatty liver disease (NAFLD) treatment [56]. FXR, prominently expressed in the liver, when activated, exerts inhibitory effects on hepatic fatty acid synthesis, governs the inflammatory response, and confers protection against cholestatic liver injury. Additionally, it modulates vascular remodeling, glucose metabolism, intestinal barrier, and fibrinogenesis [57,58]. In a multicenter, randomized, double-blind study conducted by Zobair et al., patients diagnosed with non-alcoholic steatohepatitis (NASH) and liver fibrosis stages F2 and F3 were included. The study comprised three groups: one administered a placebo, another received obeticholic acid at a daily dose of 10 mg, and a third received obeticholic acid at a daily dose of 25 mg. The findings demonstrated a notable reduction in liver fibrosis and histological activity of NASH in the group receiving a daily dose of 25 mg of obeticholic acid [59]. The conclusions confirm earlier studies by Neuschwander-Tetri and others [60]. A study by Mudaliar and others, involving patients with non-alcoholic steatohepatitis (NASH) and type 2 diabetes treated with a dose of 25 mg or 50 mg of OCA for 6 weeks, also showed the effectiveness of OCA in reducing inflammatory markers and liver fibrosis. Furthermore, the therapy increased the patients' insulin sensitivity compared to the placebo group [61].

**SUMMARY**

Non-alcoholic fatty liver disease is a liver disease that can manifest in various ways and often remains asymptomatic. Patients are at high risk for cardiovascular events and progression to advanced fibrosis or cirrhosis elevates the risk of liver decompensation and hepatic-related mortality. Presently, pharmacological interventions for NAFLD are constrained, with dietary regulation, weight management, and physical activity constituting the fundamental therapeutic approach. Available pharmacotherapies encompass Pioglitazone or Vitamin E but recently a lot of research exhibited promising outcomes for GLP-1 agonists, metformin, SGLT2 inhibitors, FXR, and PPAR ligands. However, more research on their efficacy and safety is needed.
DISCLOSURE

Author’s contribution:

Conceptualization: Natalia Aleksandra Popławska, Justyna Śliz

Methodology: Justyna Śliz, Natalia Aleksandra Popławska, Krzysztof Woźniak

Software: Marta Skorupska, Krzysztof Woźniak, Martyna Magdalena Martka

Check: Marta Skorupska, Krzysztof Woźniak, Magdalena Joanna Czeczetka, Martyna Magdalena Martka

Formal Analysis: Justyna Śliz, Natalia Aleksandra Popławska, Krzysztof Woźniak, Magdalena Joanna Czeczetka

Investigation: Natalia Aleksandra Popławska, Justyna Śliz, Marta Skorupska

Resources: Justyna Śliz, Natalia Aleksandra Popławska, Marta Skorupska, Magdalena Joanna Czeczetka, Martyna Magdalena Martka

Data Curation: Natalia Aleksandra Popławska, Justyna Śliz, Marta Skorupska, Krzysztof Woźniak, Magdalena Joanna Czeczetka

Writing - Rough: Natalia Aleksandra Popławska, Justyna Śliz, Krzysztof Woźniak

Writing - Review and Editing: Marta Skorupska, Magdalena Joanna Czeczetka, Martyna Magdalena Martka

Visualization: Krzysztof Woźniak, Magdalena Joanna Czeczetka, Martyna Magdalena Martka

Supervision: Natalia Aleksandra Popławska, Justyna Śliz, Marta Skorupska, Krzysztof Woźniak, Magdalena Joanna Czeczetka, Martyna Magdalena Martka

Project Administration: Natalia Aleksandra Popławska, Justyna Śliz, Marta Skorupska, Magdalena Joanna Czeczetka

Receiving funding-no specific funding

All authors have read and agreed with the published version of the manuscript.
Funding Statement: The Study Did Not Receive Special Funding.


Informed Consent Statement: Not Applicable.

Data Availability Statement: Not Applicable.

Conflict Of Interest: The authors declare no conflict of interest.

REFERENCES

3. https://www.mp.pl/interna/chapter/B16.II.7.11. (access 28.05.2024 r.)
7. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388-1402. doi:10.1016/j.jhep.2015.11.004


37. Bouchi R, Nakano Y, Fukuda T, et al. Reduction of visceral fat by liraglutide is associated with ameliorations of hepatic steatosis, albuminuria, and micro-


