https://doi.org/10.46389/rjd-2021-1048
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2021; volume 28, issue 3, pages 316-324

Review

Management of non-alcoholic fatty liver disease in patients with diabetes mellitus

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Received: 5 August 2021 / Accepted: 17 September 2021

Abstract

Non-alcoholic fatty liver disease (NAFLD) is an emerging global epidemic, closely related to obesity, diabetes and metabolic syndrome. Its association with obesity, dyslipidemia, insulin resistance and type 2 diabetes supports the notion that NAFLD is the hepatic manifestation of the metabolic syndrome. NAFLD, nowadays the most common cause of abnormal liver function tests, affects approximately 25% of the general population and includes a wide spectrum of liver disease, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) with the possibility of progression to cirrhosis and hepatocellular carcinoma (HCC).

The aim of this paper is to describe the therapeutic strategies contributing to the management of fatty liver disease in type 2 diabetes patients and the pathways these drugs interfere with to stop the development or even induce the regression of the liver disease.

The progression of NAFLD to its various stages needs to be stopped. Besides insulin resistance, which is the main target in the therapeutic strategy, the ongoing studies provide new evidence on mechanisms that need to be interfered with to help deal with the metabolic syndrome components and improve the cardiovascular disease (CVD) risk factors.

Dietary changes and other lifestyle modification measures form the primary line of treatment. New molecules are currently developed for the management of NAFLD that act on various therapeutic targets, besides the anti-diabetic treatment. Metabolic surgery remains the last option of NAFLD therapy, as it is highly invasive, even though it provides good results.

Keywords: type 2 diabetes, non-alcoholic fatty liver disease, insulin resistance, metabolic diseases.

Introduction

Diabetes mellitus (DM) and non-alcoholic fatty liver disease (NAFLD) are two chronic metabolic diseases that usually coexist and do not initially determine obvious modifications, but can eventually lead to metabolic complications.

Non-alcoholic fatty liver disease features excessive hepatic fat accumulation commonly associated with obesity and insulin resistance [1]. NAFLD includes a spectrum of progressive pathological conditions which start with steatosis and can progress to non-alcoholic steatohepatitis (NASH), cirrhosis or even hepatocellular carcinoma (HCC) [2]. The association of type 2 diabetes mellitus (T2DM) and NAFLD increase the risk of developing micro- and macro-vascular complications of diabetes [1].

NAFLD has been classically defined as the presence of steatosis affecting more than 5% of all hepatocytes (documented by liver biopsy puncture or by abdominal ultrasound), the absence of significant alcohol consumption and of secondary causes of steatosis such as drugs (corticosteroids,

amiodarone, tamoxifen), hepatitis C virus infection, autoimmune diseases, hereditary liver disease or hypothyroidism [3].

Following recent research in the field of NAFLD pathophysiology and aiming to facilitate the risk stratification and the management of this condition, it has been suggested to introduce a new acronym, MAFLD (Metabolic Dysfunction Associated Fatty Liver Disease), which highlights the relevant risk factors for this pathology [4]. Besides histology, imaging and biomarkers evidence of liver fat accumulation, the presence of one of the following criteria is required: obesity, type 2 diabetes or documentation of metabolic syndrome [5].

The heterogeneity of MAFLD justifies the need for detailed phenotyping, which can lead to the development of new effective therapies for each patient, depending on the dominant subphenotype [6].

Epidemiology

Due to the current unhealthy and sedentary lifestyle, NAFLD has an increased prevalence, especially in patients with obesity and T2DM.

NAFLD prevalence is proportional to obesity ubiquity. While the prevalence of NAFLD is about 25% in the general population, it increases up to 50–75% in individuals with T2DM, depending on ethnicity. On the other hand, the prevalence of diabetes in patients with NAFLD is higher than in the general population [1, 3]. NAFLD is a predictor and a risk factor for the development of diabetes, increasing the risks of morbidity and mortality associated with the advance of other extrahepatic manifestations [4].

NAFLD is also prevalent in patients with type 1 DM. A prolonged duration of diabetes leads to an increased cardiovascular risk, and the increased prevalence of obesity in type 1 DM individuals also contributes to hepatic steatosis [7].

Cirrhosis secondary to non-alcoholic steatohepatitis is the leading cause of hepatocellular carcinoma and ranks second as an indication for liver transplantation in the United States [8].

Pathogenesis

Numerous pathways involved in NAFLD pathophysiology are under investigation. Mechanisms like insulin resistance (IR), lipotoxicity, oxidative stress, immunology or cytokine-related anomalies, mitochondrial damage and apoptosis can lead to the development of fatty liver disease [9].

Apart from the genetic predisposition, at least partly linked to factors such as patatin-like phospholipase domain-containing protein 3 (PNPLA3) or transmembrane 6 superfamily member 2 (TM6SF2), the determinants of progression in NAFLD are related to unhealthy sedentary lifestyle and eating behavior (saturated fatty acids or fructose intake, excessive carbohydrate intake causing *de novo* lipogenesis), microbiome-related metabolites and metabolic comorbidities (insulin resistance, dyslipidemia, obesity, T2DM, metabolic syndrome, hypopituitarism) [2, 10].

Therapeutic options

The treatment of NAFLD/NASH should be personalized once the mechanisms underlying this condition in each patient are understood. Patients are likely to develop the NASH phenotype by multiple mechanisms, therefore diagnosis and therapy should be correspondingly individualized.

As there are no drugs authorized solely for NAFLD therapy yet, the treatment aims to slow the progression of extrahepatic manifestations; therapeutic measures are addressed more to the metabolic syndrome and are represented by lifestyle optimization, including weight loss, regular physical activity, and dietary measures [5]. The latest drug therapy recommendations come from the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) Clinical Practice Guidelines [10]; pharmacotherapy should be implemented for progressive NASH and also for early-stage NASH with increased fibrosis progression (age over 50 years, diabetes, metabolic

syndrome, increased alanine aminotransferase – ALT) or active NASH with high necroinflammatory activity [8, 10].

This article reviews the available treatment options, including lifestyle changes, bariatric surgery, insulin sensitizers, lipid lowering-agents, weight loss medications, cytoprotective agents, antioxidants, and other novel pharmacological approaches that are under investigation (Table 1).

Substantial questions about NAFLD prevention still need answers. A healthy lifestyle is the most important step in the prevention of any disease, all the more of metabolic diseases like diabetes mellitus and its complications, cardiovascular diseases, liver disease.

Lifestyle optimization

A healthy lifestyle is the cornerstone for the prevention and management of NAFLD, so lifestyle intervention is the primary step in the treatment of patients with NAFLD or metabolic syndrome. Lifestyle optimization aims at weight loss, reduction of saturated fats intake, increased

Table 1: Therapeutic options for NAFLD.

Target	Treatment
Obesity	Weight loss • Diet • Physical exercise • Pharmacologic - Orlistat - Lorcaserin • Bariatric (metabolic) surgery
Insulin resistance	Insulin sensitizing agents • Metformin • Thiazolidinediones • Dipeptidyl peptidase 4 (DPP-4) inhibitors • Sodium-glucose co-transporter-2 (SGLT-2) inhibitors • Glucagon-like peptide-1 (GLP-1) receptor agonists
Hyperlipidemia	Lipid lowering agents • Statins • Fibrates • Ezetimibe • Omega-3 fatty acids
Oxidative stress	Antioxidants • Vitamin E
Increased endotoxin levels	Probiotics
Apoptotic pathway	Cytoprotective agents • Ursodeoxycholic acid (UDCA) • Silymarin
Pro-inflammatory cytokines	Anti-tumor-necrosis-factor (TNF) agents • Pentoxifylline
Other	Novel treatments • Angiotensin converting enzyme (ACE) inhibitors • Elafibranor • Cenicriviroc • Fibroblast growth factor 21 (FGF21) • Obeticholic acid • Resmetirom

https://doi.org/10.46389/rjd-2021-1048

physical activity in overweight or obese people, all leading to a reduction in hepatic steatosis and NASH regression. The guidelines recommend a 7–10% weight loss for the improvement of NAFLD [11]. Weight loss of more than 10% can even lead to the regression of liver fibrosis [4]. Sustained physical activity, both in the form of aerobic exercise and active training, is effective in reducing hepatic steatosis [10]. In addition, exercise can improve changes in the intestinal microbiota. A randomized controlled trial of 50 participants described a significantly lower liver fat content and improvements in the peripheral insulin sensitivity with supervised moderate-intensity exercise, although these improvements were not sustained after exercise cessation [12].

Nutritional intervention contributes to the improvement of NAFLD by modulating the intestinal-liver axis, whether or not weight loss is considered [11]. Several studies have revealed that NAFLD patients had a higher intake of soft drinks and meat and a lower intake of omega-3 polyunsaturated fatty acid (PUFA) than healthy controls, independently of age, body mass index (BMI), and total calories [13]. The first step is thus the avoidance of NAFLD-promoting elements, such as processed foods, sugary drinks, and high fructose intake, restoring a healthy gut microbiota [11]. A crossover trial of 80 healthy persons showed the modulatory role of the glycemic index (GI) of carbohydrates. The authors noted an increase in the liver fat fraction with a high GI diet, whereas liver fat decreased with a low GI diet [12].

The Mediterranean diet improves cardio-metabolic parameters and reduces weight. Several studies have shown that a low-carbohydrate Mediterranean diet decreases liver fat deposits more than a low-fat diet [4]. Monounsaturated fats reduce IR and relieve NAFLD.

Coffee appears to have protective properties against liver inflammation by its antioxidant content [9].

Pharmacologically-induced weight loss

Among the drugs approved for obesity therapy, orlistat, a reversible inhibitor of pancreatic and gastric lipase, showed mixed results in NASH, but generally demonstrated a beneficial effect in subjects who lost more than 5% of body weight [14, 15]. Lorcaserin is a serotonin 2C receptor agonist that causes weight loss and improves glycemic control; however, further studies are needed to establish its efficacy as a treatment for NAFLD in patients with type 2 diabetes [15].

Bariatric surgery

For individuals with severe obesity (BMI >40 kg/m^2) or with BMI >35 kg/m^2 and comorbidities, gastric bypass or other weight-loss surgical methods should be considered [16]. A systematic review of 15 studies evaluating the effects of weight loss on NAFLD after bariatric surgery showed a decrease in BMI between 19.1% and 41.8%. The proportion of patients with subsequent steatosis improvement or resolution was 91.6%, followed by an 81.3% rate for steatohepatitis and 65.5% for fibrosis. The complete NASH resolution was seen in 69.5% of patients [15].

Liu et al. prospectively used liver stiffness measurement (LSM) by transient elastography to monitor the improvement of non-alcoholic fatty liver disease following bariatric surgery. The study showed a significant reduction of 54.3% in LSM at 1 year, 48.6% at 3 years, and 45.8% at 5 years after surgery. The effectiveness of bariatric surgery in treating NAFLD was not related only to weight loss. Bariatric surgery achieved better postoperative glycemic control by improving insulin resistance and reversing inflammatory pathways that lead to NAFLD [17].

T2DM medication and NAFLD

Insulin therapy

The administration of exogenous insulin to patients with T2DM seems to be beneficial on hepatic steatosis, as it is the most effective for obtaining glycemic control regardless of the stage of liver damage. Although insulin promotes lipogenesis and decreases lipid oxidation *in vitro*, the reduction of steatosis is achieved by improving hepatic insulin sensitivity and reducing gluconeogenesis [1].

Metformin

The majority of patients with T2DM and NAFLD enrolled in the recent clinical studies were treated with metformin. Metformin monotherapy showed modest effects during the 12–24 weeks after administration, by decreasing liver transaminases, hepatic fat content and hemoglobin A_{1c} (HbA_{1c}), and improving insulin resistance in NAFLD patients with T2DM [4]. Data referring to the improvement of liver fibrosis are inconsistent. Reports from *in vitro* studies pointed out that metformin controls lipogenesis in NAFLD by reducing lipid accumulation and *de novo* fatty acid synthesis. The metformin treatment also showed protection against lipid-induced necrotic cell death, abilities to induce oxidative stress reduction and anti-apoptotic activity. Several *in vivo* studies were performed on genetically modified mice exhibiting features of hepatic steatosis, or dietary models of NAFLD rats that received metformin treatment. Metformin treatment was shown to reduce the gene expression of proteins involved in hepatic lipogenesis via activation of AMP protein kinase (AMPK). Such proteins include the acetyl-CoA carboxylase enzyme (ACC), sterol regulatory element-binding protein 1 (SREBP-1c), fatty acid synthase (FAS), and stearoyl-CoA desaturase-1 (SCD1) [18].

Although metformin is the first line of therapy in the management of T2DM, its effect as an insulin sensitizer is weak in NASH, possibly due to the inability to restore adiponectin levels in the short-term [10].

Thiazolidinediones

Thiazolidinediones act as an agonist of the PPAR-γ receptor (peroxisome proliferator-activated receptor-γ), improving insulin sensitivity. In all studies in which pioglitazone was administered, a significant increase in adiponectin levels (80–178%) and steatosis improvement were seen [8]. Despite safety and tolerability concerns, pioglitazone may be used for certain patients with NASH, especially those with T2DM, where the drug is already approved [10]. The PIVENS study compared low-dose pioglitazone with vitamin E and placebo for 2 years in patients without diabetes. Pioglitazone improved all histological features except for fibrosis and obtained NASH resolution more frequently than placebo. Vitamin E (800 IU/day) showed an improvement in steatosis, inflammation and induced NASH resolution in 36% of patients (compared to 21% in the placebo arm) [10]. Promising treatment options are the newer selective peroxisome proliferator-activated receptor-γ modulators (SPPARMs) and dual PPAR agonists that seem to have a positive impact by increasing insulin sensitivity [8].

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide 1 (GLP-1) is an incretin hormone secreted by the body in response to food which leads to anti-hyperglycemic effects. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of non-insulin drugs approved for the treatment of type 2 diabetes. Exenatide, liraglutide, dulaglutide, and semaglutide have been studied in patients with NAFLD, with some results in reducing liver inflammation and fibrosis. GLP-1RAs stimulate insulin secretion, slow gastric emptying, reduce appetite and body weight. Supraphysiological glucagon receptor agonism might be the new treatment target after new data indicated that glucagon receptor signaling is disrupted in NAFLD. However, GLP-1RAs are not currently recommended for the treatment of NAFLD in patients with T2DM due to limited data [14, 15]. In T2DM and NAFLD, liraglutide and semaglutide had similar effects to metformin but superior to gliclazide, reducing hepatic steatosis, body weight, and HbA_{1c} levels and improving liver function [8]. Synergistic effects can be obtained by combining the activation of GLP-1 receptors with that of the glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptors. Tirzepatide, a dual GIP and GLP-1RA, showed decreased levels of NAFLD biomarkers and increased adiponectin in patients with T2DM [19, 20].

Sodium-glucose co-transporter-2 inhibitors

The efficacy of the sodium-glucose co-transporter-2 (SGLT-2) inhibitors on hepatic fibrosis evaluated by the fibrosis-4 (FIB4) index

https://doi.org/10.46389/rjd-2021-1048

was significantly decreased after 12-month SGLT-2 inhibitor treatment [21].

A meta-analysis of seven randomized clinical trials with dapagliflozin, empagliflozin, canagliflozin, or ipragliflozin evaluated their effect on NAFLD in individuals already treated for T2DM for approximately 6 months. Compared with placebo, SGLT-2 inhibitors such as empagliflozin, canagliflozin, or ipragliflozin demonstrated modest improvement of steatosis, weight loss (approximately 2–3 kg), and HbA_{1c} reduction (approximately 0.8–1%). In contrast, a study with dapagliflozin versus placebo did not show significant reductions in hepatic steatosis, despite weight loss and glycemic control [22].

In a prospective randomized, double-blind, placebo-controlled trial on 106 patients with NAFLD and T2DM who received 10 mg empagliflozin once daily for 24 weeks, improvement of hepatic steatosis and fibrosis (assessed by measuring CAP score as an index of steatosis and liver FibroScan for fibrosis) compared with pioglitazone or placebo were noted. No change in insulin resistance was reported with empagliflozin, while pioglitazone showed a significant decrease in the fasting insulin level [23].

Dipeptidyl peptidase 4 (DPP-4) inhibitors

The hepatocyte-specific overexpression of DPP-4 is associated with hepatic insulin resistance and liver steatosis [24]. Oral daily DPP-4 inhibitors are known to increase pancreatic beta-cell secretion and insulin sensitivity in the liver, muscle and adipose tissue, being an established treatment for patients with diabetes. DPP-4 inhibitors also demonstrated anti-inflammatory and anti-atherogenic effects, but no effect on the reduction of insulin resistance [25]. An *in vitro* study on genetically obese melanocortin 4 receptor-deficient (MC4R-KO) mice fed with a Western diet demonstrated that anagliptin effectively inhibits the progression from NAFLD to NASH, preventing the development of inflammation and fibrosis, without affecting systemic glucose and lipid metabolism. The mechanism of action still needs to be elucidated, suggesting that macrophage activation of "hepatic crown-like structures" (hCLS), which is functioning as a driver of liver fibrosis, is attenuated by anagliptin treatment during progression from steatosis to NASH, independently from the glucose metabolism effects on NASH and HCC development [26]. The ability of omarigliptin, a weekly oral DPP-4 inhibitor, to improve liver function and the levels of inflammation and insulin resistance was examined in type 2 diabetic patients with NAFLD. A single-center, open-label, randomized, prospective study including 84 patients aimed to determine whether inflammation and insulin resistance is more effectively decreased by omarigliptin 25 mg once weekly than by sitagliptin 50 mg once daily or linagliptin 5 mg once daily for 12 months. Omarigliptin significantly reduced the values of ALT, AST, gamma-glutamyl transpeptidase, HOMA-IR, and high-sensitivity C-reactive protein, with no significant differences in HbA_{1c}, BMI, and estimated glomerular filtration rate [24, 25]. Another *post hoc* analysis of this study confirmed these results. Therefore, omarigliptin benefits in improving intrahepatic adipose inflammation and decreasing intrahepatic fat content may be an option for the treatment of NAFLD in non-obese, insulin resistant, diabetic patients [24].

Lipid lowering agents

Although polyunsaturated omega-3 fatty acids and ezetimibe have shown beneficial effects on NASH in animal studies, various lipid-lowering agents (statins, ezetimibe, fibrates, colesevelam, niacin, or polyunsaturated omega-3 acids) have not been able to demonstrate any improvement in steatosis in patients with NAFLD [15]. The use of statins in NAFLD is safe, with no increased risk of hepatotoxicity, even with a possible reduction in transaminase levels [10].

Adjuvants

Probiotics

Probiotics seem to have a positive impact based on their ability to improve intestinal barrier function, reduce endotoxemia and reduce

Toll Like Receptor-4 (TLR4) activation, leading to amelioration of NAFLD. A small study showed that a 6-month administration of a probiotic cocktail led to a significant reduction in the intrahepatic triglyceride content observed by magnetic resonance spectroscopy. Prebiotics, symbiotics, polyphenols, and fecal transplantation, which have shown benefits in animal studies, are also discussed [11].

Antioxidants

Silymarin has been used to prevent liver fibrosis due to its anti-fibrotic and anti-inflammatory actions [14]. In addition to these properties, *in vitro* studies have shown improvements in liver function in NAFLD. In a study in male albino Wistar rats, the silymarin-treated groups showed improvement in oxidative stress, dyslipidemia, and steatosis [27].

Vitamin E is an antioxidant that relieves liver steatosis, but not fibrosis in people without diabetes. Due to the increased cardiovascular risk in patients with diabetes, vitamin E is not recommended in people with type 2 diabetes and NAFLD [14].

Cytoprotective agents

Ursodeoxycholic acid (UDCA) is a secondary bile acid that can reduce oxidative stress and has antiapoptotic properties. UDCA has been investigated in several randomized clinical trials, at different doses and for up to 2 years, showing improvement in transaminases and hepatic steatosis in patients with NAFLD, without histological changes in NASH [15].

Anti-tumor-necrosis-factor agents

Pentoxifylline is a phosphodiesterase inhibitor that suppresses tumor necrosis factor-α secretion, displaying a positive impact on NASH in an animal study [15]. A study by Singh and colleagues compared glitazones, obeticholic acid (OCA), vitamin E and pentoxifylline to placebo and one another in nearly 1000 patients with biopsy-proven NASH. The results demonstrated that pentoxifylline and OCA ameliorate fibrosis, whereas glitazones, vitamin E, and OCA improved ballooning degeneration [28].

Antihypertensives (angiotensin converting enzyme inhibitors or angiotensin II receptor blockers)

Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) have shown an antifibrotic effect in the liver. Losartan, an ARB, inhibits TLR-4 and transforming growth factor-beta (TGF-β) and leads to regression of fibrosis in animal models [29]. A clinical study of losartan vs. placebo for 96 weeks in 45 patients with histological modifications of NASH was not concluding. Therefore, further research is required to confirm this data [28].

New therapeutic data

Many new potential agents are currently tested for NAFLD, even though they are not antidiabetic drugs. They aim to target the metabolic syndrome features and CVD risk factors.

Elafibranor is a dual activator of PPAR-α and PPAR-δ and has been shown to ameliorate liver histology; it is further evaluated in the RESOLVE-IT study. Among drugs acting on PPAR-α and PPAR-γ, saroglitazar continues to be evaluated in NASH. The preliminary results showed improvements in liver function and steatosis, but with the risk of weight gain at 16 weeks. The pan-PPAR agonist lanifibranor is being evaluated in an ongoing study [19].

Cenicriviroc (CVC) is a potent chemokine 2 and 5 receptor antagonist (CCR2/CCR5) that has shown anti-inflammatory and antifibrotic potential in animal models. The CENTAUR study demonstrated histological improvement of fibrosis in patients with NASH after CVC administration for 1 year [15, 19]. The results are pending in another phase 3 trial (AURORA) of subjects with NASH and different stages of fibrosis [19].

The hepatokine Fibroblast Growth Factor (FGF21) is another potential therapeutic agent with beneficial metabolic effects; FGF21 levels

https://doi.org/10.46389/rjd-2021-1048

are elevated in NAFLD and are proportional to the amount of liver triglycerides [2]; in studies on mice, administration of this peptide hormone led to improved insulin sensitivity, body weight, lipid profile and even to a modulating effect on the proinflammatory mechanisms that cause NASH [2, 19].

Obeticholic acid, a modified farnesoid X receptor agonist, improves insulin resistance in type 2 diabetes. In the phase IIb FLINT trial, obeticholic acid administered for 72 weeks to patients with NASH showed improvement in NASH and fibrosis lesions. The disadvantage is represented by its side effects, i.e. pruritus and increased LDL-cholesterol levels [10]. Its promising effects are currently being tested in an international phase 3 trial (REGENERATE) [19].

A phase 3 trial named MAESTRO has been initiated with Resmetirom, a thyroid hormone receptor β agonist (THR-β), to evaluate its efficacy in patients with NASH and fibrosis. Preexisting data suggests that resmetirom improves liver histology and reduces alanine transaminases and low-density lipoprotein cholesterol [19].

The last solution in the advanced stages of the disease is liver transplantation, although the recurrence risk on the transplanted liver remains high if the factors that caused the liver injury have not been removed [10].

Conclusions

Non-alcoholic fatty liver disease is closely related to type 2 diabetes; their central pathogenic mechanism is insulin resistance, which is the main target in the therapeutic strategy. NAFLD has a much higher prevalence in patients with T2DM than in the general population; the incidence of both metabolic disorders rises worldwide. Management of patients with DM should also include the assessment of NAFLD severity and cardio-metabolic risk [3]. Despite advances in understanding the pathogenesis of NAFLD, the only approved treatment option is lifestyle optimization. Ongoing randomized trials will provide new evidence and additional information to enable individualized treatment of patients with NAFLD and type 2 diabetes [15].

Conflicts of interest

The authors have no conflicts of interests regarding this paper.

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