Nonalcoholic fatty liver disease and the risk of metabolic comorbidities: how to manage in clinical practice

Authors: Carolina Perdomo, Paola D’Ingianna, Javier Escalada, Salvatore Petta, Manuel Romero Gómez, Javier Ampuero

Article type: Review article

Received: June 15, 2020.

Accepted: June 16, 2020.

Published online: July 14, 2020.

ISSN: 1897-9483
Title: Nonalcoholic fatty liver disease and the risk of metabolic comorbidities: how to manage in clinical practice

Short title: NAFLD and management of comorbidities

Authors: Carolina Perdomo1*, Paola D'Ingianna2*, Javier Escalada1,5, Salvatore Petta2, Manuel Romero Gómez3,4, Javier Ampuero3,4

* Both authors contributed equally.

Affiliations:

1 Department of Endocrinology and Nutrition, Universidad de Navarra. IdiSNA, Navarra, Spain.

2 Hepatology, PROMISE, University of Palermo, Palermo, Italy.

3 Hospital Universitario Virgen del Rocío. Universidad de Sevilla. Instituto de Biomedicina de Sevilla, Sevilla, Spain.

4 CIBERehd, Madrid, Spain.

5 CIBEROObn, Madrid, Spain.

Correspondence to:

Javier Ampuero MD, PhD

Digestive Disease Department and CIBERehd, Virgen del Rocio University Hospital, Avenida Manuel Siurot s/n, 41013 Sevilla, Spain

E-mail: jampuero-ibis@us.es
EXTERNAL FINANCIAL SUPPORT

This project has been partially funded by the “Consejería de Salud de la Junta de Andalucía” (PI-0075-2014), the “Spanish Ministry of Economy, Innovation and Competition, Instituto de Salud Carlos III” (PI19/01404, PI16/01842, PI17/00535 and GLD19/00100).

*The funders have not had any role in the design, analysis, writing, or interpretation of this project.

POTENTIAL CONFLICT OF INTEREST

None.
ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a clinical-pathological condition that encompasses a wide range of liver damage not caused by chronic alcohol consumption. It ranges from steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis, in the absence of other etiologies. The prevalence of NAFLD has increased considerably over the last years due to the current lifestyle (unhealthy diet and sedentarism). Besides, it is associated with metabolic risk factors such as obesity, arterial hypertension, dyslipidemia, and type 2 diabetes mellitus. Given the poor prognosis of NAFLD patients showing advanced disease, a practical therapeutic approach is mandatory to halt its natural history. However, no licensed drugs are approved to date. Nowadays, we are attending to a race to find the first drug able to stop the incidence of the NAFLD and reverse the disease in patients with further stages. Meanwhile, the management of the metabolic overload of NAFLD, including weight loss, cardiovascular protection, insulin sensitization, and lipid reduction, is the only strategy to improve the hepatic and extra-hepatic outcomes. In this review, we aim to describe the management of the main metabolic disorders related to NAFLD, such as type 2 diabetes mellitus, arterial hypertension, and dyslipidemia.

KEYWORDS: Arterial hypertension; dyslipidemia; non-alcoholic fatty liver disease; type 2 diabetes mellitus.
INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological syndrome associated with metabolic syndrome, defined as a cluster of three of the following features: increased waist circumference, impaired fasting glucose or type 2 diabetes mellitus (T2DM), arterial hypertension, hypertriglyceridemia and low high-density lipoprotein (HDL-cholesterol)[1]. A recent meta-analysis involving 8.5 million individuals from 22 countries reported that more than 80% of patients with NAFLD were obese, 72% had dyslipidemia, and 44% showed T2DM[2]. This association is due to the overlapping of NAFLD pathogenetic mechanisms with the metabolic syndrome ones, including genetic predisposition, insulin resistance (IR), oxidative stress, chronic and systemic micro-inflammation, and reduced adiponectin levels[3]. Due to this strong association, patients who are presenting metabolic syndrome needs to be examined for the risk of NAFLD and vice versa, any patients with NAFLD should lead to an evaluation of all components of the metabolic syndrome[4].

Physicians face the challenge of NAFLD early diagnosis and intervention, albeit there are few pharmacological agents with proven efficacy. It is necessary to proactively assess the presence of cardiovascular disease (CVD) in patients with NAFLD and inversely regardless of the presence or absence of traditional risk factors[5]. The management of metabolic overload of NAFLD, including weight loss, cardiovascular protection, insulin sensitization, and lipid reduction, is currently the only strategy to improve the hepatic and extra-hepatic outcomes. In this review, we aim to describe the management of the main metabolic disorders related to NAFLD, such as T2DM, arterial hypertension, and dyslipidemia.
FIRST STEP TO MANAGE NAFLD: LIFESTYLE INTERVENTION

The most critical intervention is to endorse a healthy lifestyle that promotes weight loss and control of cardiovascular risk factors (Figure 1)[6][7]. European and American guidelines[5][8][9] emphasize the importance of modifying lifestyle in the absence of approved pharmacological agents for the treatment of NAFLD. One randomized controlled trial examined the effect of lifestyle intervention using a combination of diet and exercise (200 min/week)[10]. After 48 weeks of intervention, a weight reduction higher than 7% had a significant improvement in NAS score. Vilar-Gomez et al. evidenced similar results[11], with the highest rates of NAS reduction and fibrosis regression occurring in patients with weight losses higher than 10%. Based on these studies, in the early stages of NAFLD, recommending a weight loss between 5 and 7% might be sufficient.

In T2DM, a pharmacological treatment should be started, additionally to the recommendation of weight reduction of more than 7%[5][8][12]. Besides, interventions that improve metabolic abnormalities in patients with T2DM have proven to be beneficial for NAFLD (Figure 2). Furthermore, it is necessary to consider that smoking is associated with advanced liver fibrosis mediated by an increase in insulin resistance. Therefore, smoking cessation is essential to reduce the cardiovascular risk factors enhanced by this condition[5][8]. Concerning alcohol consumption, although the effect of some degree of regular alcohol consumption over lifetime is controversial[13][14], alcohol intake should be discouraged in NAFLD and T2DM patients[8]. Recently, Xu et al.[15] evidenced that light-moderate alcohol consumption was associated with an increased risk of T2DM in patients with NAFLD.

The European Society of Cardiology and the European Society of Hypertension guidelines for the management of arterial hypertension[16] suggest that a healthy
lifestyle may be sufficient to delay or prevent the need for drug therapy in patients with grade 1 arterial hypertension. The recommendations about the lifestyle associated with blood pressure (BP) reduction are weight loss, regular physical activity, smoking cessation, and dietary interventions[16]. Weight loss and maintenance of optimal BMI (approximately 20-25 kg/m²)[17] is recommended to prevent the occurrence of hypertension and to reduce BP and improve the efficacy of the medication in hypertensive patients[16]. Epidemiological studies show that the treatment of hypertension and its prevention may be beneficiated by aerobic regular physical activity that also reduces the cardiovascular risk and its related mortality[17]. A growing body of evidence suggests that hypertensive patients should be advised to participate in at least 30 minutes of moderate-intensity aerobic exercise (walking, jogging, cycling, or swimming) on 5-7 days/week[17]. Regarding dietary changes, hypertensive patients should be advised to eat a healthy balanced diet, containing vegetables, legumes, fresh fruits, low-fat dairy products, whole grain, fish, and unsaturated fatty acids (especially olive oil) and low consumption of red meat and saturated fatty acid[18][19]. Mediterranean diet, which includes many of these nutrients[18][19], significantly reduces blood pressure[20], showing similar beneficial effects than blood glucose and lipid level.

**Physical Exercise**

Regardless of weight loss, physical exercise reduces IR and improves metabolic risk factors in patients with NAFLD[9][21]. The intensity and duration of physical exercise necessary to significantly reduce liver fat have not yet been defined. Guidelines suggest performing between 150-250 minutes per week of moderate aerobic exercise[22], although better results may be achieved if exercising for more than 250 minutes per week[21]. Likewise, resistance or high-intensity intermittent exercises (3 series of 10
repetitions at 70%-80% of the maximum amount of weight that a person can possibly lift for one repetition, with 1 minute of recovery between series) are also beneficial for patients with NAFLD[23].

**Dietary Treatment**

Reduced calorie intake and improved macronutrient composition may act individually to prevent NAFLD progression, independently of weight loss[24]. Dietary adherence is an essential determinant of weight loss sustainability. Therefore, in the dietary treatment of NAFLD, it is important to provide practical highlights customizing diet to the individual’s taste. Investigations have identified dietary habits that may directly promote NAFLD by modulating hepatic triglyceride accumulation and antioxidant activity and, indirectly, by affecting insulin sensitivity and the postprandial triglyceride metabolism[25]. The Western pattern diet, which is generally characterized by high consumption of carbohydrates, simple sugars, saturated fats, trans fat, animal protein (red meat), processed food, and low fiber intake, is associated with NAFLD development and progression[26].

Dietary advice should include caloric restriction and adherence to the macronutrient composition according to the Mediterranean diet[5][24]. The Mediterranean diet is probably the dietary pattern with the greatest evidence of long-term cardiometabolic benefit[18][24]. However, randomized trials examining the Mediterranean diet histologic liver effect are limited [24]. Long-term trials of standardized nutritional interventions evaluating the effect on fibrosis are necessary [5][24]. In NAFLD, the carbohydrate intake should include whole grains, unprocessed cereals, and low glycemic index foods[24]; the fat intake should aim at high monounsaturated fatty acids (MUFAs) and omega-3 polyunsaturated fatty acids (PUFAs) consumption; the protein intake should favor vegetable protein, seafood, egg, and white meat consumption. The
intake of prebiotic fiber and probiotic enriched products may be recommended to
promote a reduced calorie intake and a favorable microbiota, respectively[24]. Figure 3
summarizes the dietary treatment in NAFLD [24].

**SPECIFIC MANAGEMENT OF TYPE 2 DIABETES MELLITUS IN NAFLD**

The coincidence of NAFLD and T2DM is dangerous because it seems to favor quick
progress towards more aggressive liver conditions like non-alcoholic steatohepatitis
(NASH), cirrhosis and hepatocellular carcinoma[5][6], especially in patients with other
metabolic comorbidities (arterial hypertension, dyslipidemia, obesity)[5]. However,
unfortunately, patients and clinicians are unaware of the potentially serious condition of
NASH[8]. It has been described that up to 66% of patients over 50 years old with T2D
or obesity have NASH[21], and it seems to be an additional independent risk factor for
cardiovascular disease[7][8][21]. Moreover, patients with T2DM and NAFLD have
more micro and/or macrovascular complications in relation to worse glycemic control
and atherogenic dyslipidemia. In high-risk patients, referral to a liver specialist is
required in order to rule out other causes of liver disease, perform, if necessary, a liver
biopsy and maintain a closer follow-up[5][6][8].

**How to assess diabetes mellitus in NAFLD**

T2DM diagnosis requires two abnormal test results of the following criteria: fasting
plasma glucose ≥126 mg/dl (7.0 mmol/L), a 2-h plasma glucose value during a 75-g
oral glucose tolerance test ≥200 mg/dl (11.1 mmol/L) or hemoglobin A1C (HbA1C)
≥6.5% (48 mmol/mol)[27]. HbA1C criteria cannot be used in patients with sickle cell
disease, glucose-6-phosphate dehydrogenase deficiency, recent blood loss or
transfusion, HIV, pregnancy, hemodialysis, or erythropoietin therapy. Patients with
classic symptoms of hyperglycemia and a random plasma glucose ≥200 mg/dl (11.1
mmol/L) does not need any further criteria to make the diagnosis of T2DM.
Endocrinologist referral is recommended if the patient is considered to be a candidate for bariatric surgery, has advanced micro or macrovascular complications, and if HbA1C goals are not achieved after primary care intensification of the oral antidiabetic treatment[5][27]. The HbA1C goal is individually established in order of comorbidities, life expectancy, risk of hypoglycemia, and micro and macrovascular complications[27]. In general, an HbA1C goal of <7% is appropriate, but an HbA1C goal <8% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, or important comorbid conditions.

**Pharmacological Treatment**

Pharmacological treatment should always be considered in T2DM and NAFLD, especially if lifestyle recommendations are unsuccessful or challenging to maintain[8]. In T2DM patients, glycemic control is essential to prevent NAFLD progression. For now, no drug has been approved by international agencies for the treatment of NAFLD, although there are antidiabetic drugs with proven histological efficacy (Table 1). In a systematic review of eleven international guidelines for the treatment of NAFLD, the initiation of pharmacotherapy is recommended when the patient presents NASH or risk factors for a rapid progression of NAFLD, such as the coexistence with T2DM[22]. The effect on NAFLD of different antidiabetics was compared in a recent systematic review[28]. Pioglitazone and glucagon-like peptide-1 (GLP-1) analogs are the antidiabetics drugs with the best effect on liver histology[5][28], and sodium-glucose cotransporter 2 inhibitors (iSGLT2) has also proven to be beneficial, although it may be mediated, at least in part, by weight loss[6]. Among the pharmacological agents for the treatment of T2DM, neither insulin, metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, or acarbose are believed to significantly improve NASH or liver fibrosis, although decreases in steatosis have been reported in small studies[28].
Thiazolidinediones

Pioglitazone is an agonist of the peroxisome proliferating factor-activated receptor \( \gamma \) (PPAR \( \gamma \)) that causes an improvement in insulin sensitivity and improves mitochondrial dysfunction in the hepatocytes[7]. The PIVENS[29] trial compared the use of 30 mg/day of pioglitazone with that of vitamin E and placebo for two years in patients without diabetes. Pioglitazone revealed significant steatosis and inflammation reduction without evidence of a reduction in fibrosis. In T2DM, one randomized controlled trial included 55 patients with prediabetes or T2DM with confirmed NASH, and they were assigned to either receive a hypocaloric diet and placebo versus a hypocaloric diet and pioglitazone 45 mg/day[30]. After only six months of treatment, pioglitazone showed a significant reduction in steatosis, ballooning necrosis, and inflammation. In clinical practice, there is still some reluctance to prescribe this medication probably due to its known side effects: weight gain, bone mineral density reduction, heart failure decompensation in patients with unknown diastolic dysfunction or patients with established heart failure and its controversial relationship with bladder cancer[31][32]. However, various trials have been carried out to establish cardiovascular safety. Recently, the efficacy and safety of pioglitazone (45 mg/day) in 101 patients with T2DM and NAFLD has been evidenced after 36 months of treatment without significant adverse effects, being the average weight gain of 3.1 kg[33]. Additionally, a subsequent meta-analysis[34] (n=516) confirmed the efficacy and safety of pioglitazone in the therapeutic management of NAFLD. No major adverse events were reported during the trials, and the side effects observed were a discrete weight gain and low extremities edema. Moreover, pioglitazone has proven to reduce by 24% the incidence of stroke and fatal or nonfatal myocardial infarction in patients with a previous ischemic
stroke or transient ischemic attack[35]. Furthermore, the use of pioglitazone reduces the progression from prediabetes to T2DM by 50-70%[8].

**GLP-1 agonists**

GLP-1 agonists promote insulin secretion, decrease postprandial glucagon levels, reduce hepatic glucose production, and induce satiety and weight loss[36]. Commercially available GLP-1 agonists include liraglutide, semaglutide, exenatide, lixisenatide, and dulaglutide, all of them are approved for the treatment of T2DM. The LEAN trial evidenced a histological benefit in 52 patients treated with liraglutide for 48 weeks (39% resolution of NASH versus 9% placebo)[37]. The LEAD program performed an individual patient data metanalysis where liver enzymes reduction, weight loss, and glycemic control was significantly achieved[38]. In summary, with the current evidence and mainly because it induces weight loss, liraglutide use is recommended in T2DM and NAFLD[6]. Similar outcomes have been reported with other GLP-1 agonists[32]. A trial of exenatide versus insulin therapy during eight weeks was associated with greater reversal of liver fat (assessed by ultrasound)[39], and comparable results were recently reported though liver fat was assessed by MRS (magnetic resonance spectroscopy) after 24 weeks treatment[40]. Regarding novel agents, GLP-1/glucose-dependent insulinotropic peptide receptors dual agonist improves NASH and liver regeneration in mice[41] and significantly decreased fibrosis biomarkers and increased adiponectin in patients with T2DM[42]. Both liraglutide and semaglutide have shown to improve cardiovascular risk in patients with T2DM[43][44].

**Sodium-Glucose cotransporter 2 inhibitors**

SGLT2 is the major cotransporter involved in glucose reabsorption in the kidney, and it is blocked by empagliflozin, dapagliflozin, canagliflozin, tofogliflozin, luseogliflozin, ertugliflozin, and ertugliflozin, inducing glucosuria in the proximal renal tubule[45].
Two recent systematic reviews concluded that, based on low to moderate quality of evidence, SGLT-2 inhibitors improve liver enzymes and decrease liver and visceral fat, with additional beneficial effects on various metabolic parameters in T2DM patients with NAFLD[46][47]. In Japan, ipragliflozin has shown a similar effect on hepatic fat content (measured by computed tomography) when compared to pioglitazone[48]. Similarly, luseogliflozin has shown to be superior to metformin on reducing hepatic fat content (measured by computed tomography)[49]. There are still no studies evaluating their effect on liver histology, but they are drugs with promising results due to their potential to promote weight reduction (2-4%), improve glycemic control, reduce CVD (dapagliflozin and empagliflozin) and reduce the progression of chronic kidney disease in T2DM[45][50].

Other antidiabetic agents

Metformin is the first-line drug in the management of T2DM. Despite the fact that its main action is to improve insulin sensitivity, metformin has not shown histology improvement of steatosis[51], although recently, it has shown to prevent the development of NAFLD in a mice model[52]. Its use, together with pioglitazone or liraglutide, is recommended in the treatment of NAFLD due to its recognized effect on glycemic control[8] and in relation to the associated weight loss[31][32]. There are few studies evaluating the effect of sulfonylureas on NAFLD. Paradoxically, an association with advanced liver disease and an increased risk of hepatocellular carcinoma has been found since hyperinsulinemia may promote cancer progression[53]. However, insulin has recently shown to reduce liver fat content assessed by MRS in patients with T2DM and NAFLD[40]. DPP-4 inhibitors (sitagliptin, linagliptin, vildagliptin, saxagliptin, teneligliptin, and alogliptin) work by blocking the enzyme that breaks down GLP-1, enhancing the effects and duration of incretins[45]. DPP-4 inhibitors have proven to
achieve good glycemic control in T2DM[31]; however, large randomized controlled trials with sitagliptin failed to show benefit in NAFLD[54][55]. Conversely, vildaglaptin seems to improve steatosis on ultrasound after 12 weeks of treatment compared with placebo[56], and more recently, preliminary data showed that saxagliptin improved IR, reduced IL-6 and liver steatosis[57]. With the actual evidence, and because they do not induce weight loss, DPP-4 inhibitors should not be first-line therapy in the NAFLD treatment of T2DM.

**Non-pharmacological treatment**

**Bariatric Surgery**

Bariatric surgery should be considered in severely obese patients (body mass index (BMI) higher than 40 kg/m² or a BMI between 35–40 kg/m² with comorbidities)[58]. It has been suggested to expand the indications for metabolic surgery to a BMI as low as 30 kg/m² in patients with T2DM who do not achieve permanent weight loss and comorbidities improvement with nonsurgical treatments[58]. Bariatric surgery may induce a 25% weight loss even ten years after surgery[59]. Additionally, bariatric surgery facilitates better glycemic, lipidic, and blood pressure control. Long-term reversal of NASH has been evidenced regardless of the fibrosis stage[8][21] and through different types of surgical interventions. A prospective study evidenced an 85% fibrosis improvement one year after the surgery[60]. However, no randomized controlled trials have evaluated the different surgical approaches versus lifestyle intervention plus pharmacological treatment on T2DM and NAFLD. In the meantime, bariatric surgery should be performed in high-volume centers with the participation of a multidisciplinary team to ensure a safe procedure[61].
SPECIFIC MANAGEMENT OF ARTERIAL HYPERTENSION IN NAFLD

The global prevalence of hypertension was estimated to be 1.3 billion in 2015, with a prevalence of 150 million in Central and Eastern Europe; in adults, the prevalence is around 45% and becomes progressively more frequent with advancing age, adopting a more sedentary life, and increasing body weight[62].

Several epidemiological studies have shown the relationship between NAFLD and essential hypertension, estimating that about 50% of NAFLD patients suffer from this entity[63]. Moreover, fatty liver is significantly more prevalent in non-diabetic hypertensive patients (31%) compared to normotensive controls (13%)[64]. Besides, hypertension is associated with the development of severe NAFLD[64].

How to assess arterial hypertension in NAFLD

Hypertension is predominantly an asymptomatic condition that is detected by screening programs or opportunistic measurement of BP and, therefore, screening of hypertension should be the practice in NAFLD patients. Hypertension is defined as office systolic blood pressure (SBP) values at least 140 mmHg and/or diastolic blood pressure (DBP) values at least 90 mmHg, though the last ESC/ ESH guidelines[65] consider SBP values 130-139 mmHg and/or DBP values 80-89 mmHg as high-normal values, SBP 120-129 mmHg and DBP 80-84 mmHg as normal values and SBP <120 mmHg and DBP <80 mmHg as optimal values. Arterial hypertension should be evaluated periodically, depending on the severity, ranging from every three months to five years[65].

Pharmacological Treatment

Beyond lifestyle modification, a wide range of agents has been tested for the treatment of NAFLD. Many pieces of evidence suggest that the renin-angiotensin system (RAS) may be important in the pathogenesis of NAFLD and indicate angiotensin-converting
enzyme (ACE) inhibitors and angiotensin II receptors blockers (ARB) as potential therapeutic drugs[66]. In fact, ACE inhibitors and ARBs are the most widely used antihypertensive drugs[65].

Consistent data show that RAS intervention in NAFLD could influence adipogenesis, adipokine and cytokine production, as well as interact with insulin receptors and intracellular signaling pathways, and interference with pancreatic B-cell insulin secretion[66]. The local hepatic effect is mediated by ATR1, which is localized in the hepatocytes, bile duct cells, hepatic stellate cells, and vascular endothelial cells (where mediates the actions of Ang-II in the liver[66]. On the other hand, ATR2 has anti-fibrogenic effects. Hence, the inhibition of the RAS system could improve intracellular signaling pathways, the adipose tissue proliferation, the adipokine production, and lead to a more stable release of cytokines and chemoattractant factors[66].

**Angiotensin-converting enzyme (ACE) inhibitors**

There are two targets to antagonize the RAS system: ACE inhibitors and ARBs. Unfortunately, there is little data about their role in NAFLD, particularly regarding ACE inhibitors. Gillispie *et al.*, [67] found that ACE inhibitors improved the insulin sensitivity index by 12.1±15.8% in a set of 20 clinical trials, while Abuissa *et al.*, [68] performed a meta-analysis of 12 randomized controlled clinical trials, concluding that ACE inhibitors reduced the incidence of diabetes mellitus by 27%. A study that examined the in vivo effect of perindopril on a pig serum-induced liver fibrosis development in rats showed that this drug significantly blocked hepatic fibrosis induced by pig serum[69]. The same study showed that captopril inhibited the growth of fibroblasts in vitro, and it also reduced the collagen accumulation in the pig serum-induced liver fibrosis model. In a rabbit model, ramipril significantly reduced the development of steatosis, lobular inflammation, and hepatic fibrosis and significantly
diminished the development of NASH[70]. However, the evaluation of the impact of the ACE inhibitors in NAFLD patients is scarce to make any recommendation about their role in these patients.

**Angiotensin II receptors blockers**

Losartan and telmisartan are the most investigated ARB in the scenario of NAFLD, demonstrating an excellent side-effect profile[71][72]. Losartan has been tested in three small human studies (a total of 19 patients) that evaluated biochemical parameters and histology markers in biopsy-proven NASH patients (50 mg/day for 48 weeks)[73]. Yokohama et al. included seven biopsy-NAFLD patients and found an improvement of hepatic necroinflammation in five patients, reduction of hepatic fibrosis in four patients, and disappearance of iron deposition in two patients[74]. Besides, another study assessing 48-wk losartan treatment observed a remarkable decrease in activated hepatic stellate cells and a mild increase in quiescent phenotypes in seven patients[75]. Despite these results, more studies should perform before making recommendations about the use of losartan as NAFLD treatment.

Telmisartan and valsartan were assessed in a blinded pilot study, including 54 patients with biopsy-proven NASH and mild or moderate arterial hypertension[76]. Paired blinded biopsies were performed at the beginning and the end of the experimental treatment. Significant improvements in cytolysis were noted in all patients, similar for telmisartan and valsartan. Besides, both valsartan and telmisartan improved insulin resistance, although it was more remarkable with this latter; patients receiving telmisartan improved the NAS score and fibrosis stage[76]. Another randomized clinical trial assessed the role of prescribing telmisartan in 50 NASH biopsy-proven patients who underwent lifestyle modification. Adding telmisartan improved NAS and fibrosis scores in NASH with insignificant adverse events[77]. On the other hand,
olmesartan 20 mg/day and telmisartan 40 mg/day were tested in NAFLD patients for six months, and the study concluded that both drugs significantly improved insulin resistance and transaminase levels[78].

ARBs are, therefore, effective drugs for arterial hypertension and have shown the ability to improve insulin sensitivity and could have a partial role in the necro-inflammatory activity[78]. ARBs could be an excellent choice to treat arterial hypertension in patients with NAFLD (particularly, telmisartan), probably rather than ACE inhibitors. However, their use as NAFLD treatment needs more large clinical trials to establish their efficacy in this entity.

**SPECIFIC MANAGEMENT OF DYSLIPIDEMIA IN NAFLD**

Dyslipidemia is frequent in individuals with NAFLD, which in turn, is independently associated with increased triglycerides and low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C)[79]. On the other hand, hypertriglyceridemia is present in 20-80% of patients with NAFLD.

**How to assess dyslipidemia in NAFLD**

The main aim of lipid management is to reduce the atherosclerotic risk by substantially lowering the LDL-C levels. For patients at very high cardiovascular risk (secondary prevention or rarely in primary prevention), LDL-C reduction of >50% from baseline or <55 mg/dl is recommended[80]. For people at high CV risk, an LDL-C reduction of >50% from baseline, and an LDL-C goal <70 mg/dl are recommended. In patients with moderate CV risk, the goal should be LDL-C <100 mg/dl, while for low CV risk individuals, the therapeutic goal should be LDL-C <116 mg/dl. For HDL-C, the specific goal should be 30 mg/dl higher than the corresponding LDL-goal[80]. Moreover, non-HDL-C, which is a measure of atherogenic lipoproteins (including very-low-density
lipoproteins, intermediate-density lipoproteins, and lipoprotein A) is increased in NASH patients. Non-HDL-C is calculated from a standard formula (non-HDL-C = total cholesterol – HDL-C), and guidelines cite its values less than <85-100-130 mg/dl for patients at very high, high and moderate CV risk, respectively (as a secondary target for lipid-lowering therapy). On the other hand, no specific goals for triglycerides levels have been determined in clinical trials, but values <150 mg/dl indicate lower CV risk[80].

**Pharmacological Treatment**

**Statins**

Statins are one of the most prescribed drugs worldwide. Reducing cholesterol biosynthesis in the liver by inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, is the fulcrum in primary and secondary prevention of cardiovascular risk, as demonstrated in several controlled trials[81][82]. Moreover, their anti-inflammatory, antioxidant, and antifibrotic effects would make them an excellent drug for the treatment of NASH, but the use of statin has long been limited for their potential hepatotoxicity in patients with liver disease. Statin metabolism occurs in the liver, and the use of them has been related to higher transaminase levels[83]. Liver toxicity linked to statins is rare, and data from literature estimate an incidence of acute liver failure similar in exposed and unexposed subjects to statins[84]. In 2006, data from an extensive analysis of Dallas Heart Study[85] suggested that no damage was to be expected for the statin use in subjects with liver disease, including patients with fatty liver. Currently, ESC/EAS guidelines for the management of hypertension[86] suggest that statin therapy may be continued if ALT ≤ 3 x ULN and may be reduced or discontinued if ALT levels rise ≥ 3 x ULN.
Statins have been proposed to treat NAFLD and NASH due to their anti-inflammatory, antioxidant, and anti-thrombotic effects. Nevertheless, unfortunately, only a few and limited studies have tested the benefit of statin in the treatment of NAFLD. In 2015, statin use was associated with protection from steatosis, NASH, and significant fibrosis in a cross-sectional study[87]. Atorvastatin and rosuvastatin have shown a beneficial effect on both biochemical and ultrasonographic evidence of NAFLD[88][89]. Besides, many studies have confirmed that statins may reduce the risk of advanced liver disease and mortality and might also reduce portal hypertension, promoting fibrosis regression, and stopping disease progression[90]. NAFLD Clinical Practice Guidelines[5], published by the European Association of Liver Disease (EASL), strongly recommend the use of statins to strict control the cardiovascular risk, but they do not recommend them as a therapeutic approach for NAFLD.

Ezetimibe

Ezetimibe is a selective inhibitor of Niemann-Pick C1-like 1 (NPC1L1) protein that regulates cholesterol absorption from the small intestine to enterocytes, and it has been demonstrated to significantly reduce LDL cholesterol and cardiovascular risk, especially in combination with statins[91]. It was also reported that ezetimibe reduces lipid levels, insulin resistance, cardiovascular risk, and improves liver tests and hepatic histology in NAFLD[91]. In an experimental study, ezetimibe was found to improve diet-induced steatosis and fibrosis and while attenuating dyslipidemia in obesity and insulin-resistant animal model[92]. In the Mozart trial, a randomized, double-blind, placebo-controlled trial, 50 patients with biopsy-proven NASH were randomized to either ezetimibe 10 mg orally daily or placebo for 24 weeks[93]. The aim was to examine the efficacy of ezetimibe versus placebo in reducing liver fat by MRI-PDFF and liver histology in patients with biopsy-proven NASH. Ezetimibe did not
significantly reduce liver fat in NASH, and there were no significant differences in histologic response rates between the experimental drug and placebo[93]. Therefore, ezetimibe is not recommended to treat NAFLD patients beyond the management of dyslipidemia.

**Fibrates and omega-3 fatty acid supplements**

Fibrates are first-line pharmacological therapy in patients with severe hypertriglyceridemia. Their primary outcomes are to decrease plasma triacylglycerol, increase high-density lipoprotein synthesis, and increase reverse cholesterol transport. Furthermore, fibrates may ameliorate insulin sensitivity[94], and vascular and systemic inflammation[95]. Fenofibrate was administrated in 16 patients with NAFLD for 48 weeks, and the authors found that the transaminase levels decreased and ballooning improved, but no effect on histological steatosis, inflammation, or fibrosis was observed[96]. Another placebo-controlled study using fenofibrate on NAFLD did not show any effect on hepatic triglyceride content[97]. Therefore, fibrates are not recommended in NAFLD guidelines. On the other hand, omega-3 polyunsaturated fatty acids reduce plasma and liver lipids, but they have not demonstrated to improve histological outcomes to support their use in NAFLD patients[98].

**PCSK9 inhibitors**

PCSK9 inhibition is a promising therapeutic option in patients with familial hypercholesterolemia or statin intolerance. These drugs significantly decrease LDL cholesterol and triglyceride levels, increase HDL cholesterol, and reduce cardiovascular events.

The link between PCSK9 and liver steatosis is unclear. Many studies indicate that a high level of intrahepatic and circulating PCSK9 levels increase the liver lipid storage,
adipose energy, and hepatic fatty acids storage, as well as triglycerides secretion and storage[99]. In 201 consecutive biopsy-confirmed NASH patients, circulating PCSK9 levels were associated with steatosis grade, necroinflammation, ballooning, and fibrosis stage[100]. Indeed, circulating PCSK9 levels increase with hepatic fat accumulation and correlate with the severity of steatosis, and reducing the PCSK9 expression by using PCSK9 inhibitors seems to protect the liver from NAFLD, because of decreasing insulin resistance[99]. Thus, the modulation of the PCSK9 synthesis and release might be used to treat NAFLD. However, further research is needed to establish the definite role of PCSK9 inhibitors in the management of NAFLD.

CONCLUSIONS

NAFLD could be considered the liver component of the metabolic syndrome because it is closely related to comorbidities such as diabetes mellitus, arterial hypertension, dyslipidemia, and obesity. Also, we should consider the screening of metabolic syndrome features and cardiovascular risk in patients with NAFLD. An unhealthy lifestyle plays a determinant role in the progression of this entity, thus requiring prompt and effective therapeutic interventions to avoid hepatic and extra-hepatic complications.

While no pharmacological treatment is approved by international agencies for the treatment of NAFLD, the therapeutic strategy includes lifestyle change and pharmacological treatment of metabolic syndrome components. In this setting, lifestyle intervention is still the most crucial measure. However, it is necessary the implementation of pharmacological therapies that improve glycolipid metabolism and blood pressure. On the other hand, the current understanding of NAFLD pathophysiology has expanded the possibilities of treatment, so several promising drugs are being studied in randomized controlled trials. We expect they make an easier early intervention of NAFLD, leading to individualized treatment for all patients.
REFERENCES

1. Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology. 2003; 37: 917-923.

2. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016; 64: 73-84.

3. Abenavoli L, Milic N, Renzo L Di, et al. Metabolic aspects of adult patients with nonalcoholic fatty liver disease. WJG. 2016; 22: 7006-7016.

4. Ampuero J, Aller R, Gallego-Durán R, et al. Significant fibrosis predicts new-onset diabetes mellitus and arterial hypertension in patients with NASH. J Hepatology. 2020; 73: 17-25.

5. 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: 1388-1402.

6. American Diabetes Association. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes. Diabetes Care. 2020; 43: S37–S47.

7. Budd J, Cusi K. Non-Alcoholic Fatty Liver Disease: What Does the Primary Care Physician Need to Know? AJM. 2020; 133:536-543.

8. Bril F, Cusi K. Management of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Call to Action. Diabetes Care. 2017; 40:419-430.
9. National Guideline Center, Royal College of Physicians. National Institute for Health and Care Excellence (NICE) guideline NG49. Non-alcoholic fatty liver disease (NAFLD): assessment and management, 2016.

10. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology. 2010; 51: 121–129.

11. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology 2015; 149: 367-378.

12. Lassailly G, Caiazzo R, Pattou F, et al. Perspectives on Treatment for Nonalcoholic Steatohepatitis. Gastroenterology 2016; 150: 1835–1848.

13. Dunn W, Sanyal AJ, Brunt EM, et al. Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with non-alcoholic fatty liver disease (NAFLD). J Hepatol. 2012; 57: 384-391.

14. Kwon HK, Greenson JK, Conjeevaram HS. Effect of lifetime alcohol consumption on the histological severity of non-alcoholic fatty liver disease. Liver Int. 2014; 34: 129-135.

15. Xu L, Xie J, Chen S, et al. Light-to-Moderate Alcohol Consumption Is Associated with Increased Risk of Type 2 Diabetes in Individuals with Nonalcoholic Fatty Liver Disease. AJG. 2020; 115: 876-884.

16. Williams B, Mancia G, Spiering W, et al. 2018 practice guidelines for the management of arterial hypertension of the European society of cardiology and the European society of hypertension ESC/ESH task force for the management of arterial hypertension. J Hypertens. 2018; 36:1953-2041.
17. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016; 37: 2315-2381.

18. Sofi F, Abbate R, Gensini GF, et al. Accruing evidence on benefits of adherence to the Mediterranean diet on health: An updated systematic review and meta-analysis. Am J Clin Nutr. 2010; 92:1189-1196.

19. Dickinson HO, Mason JM, Nicolson DJ, et al. Lifestyle interventions to reduce raised blood pressure: A systematic review of randomized controlled trials. J Hypertens. 2006; 24: 215-233.

20. Doménech M, Roman P, Lapetra J, et al. Mediterranean diet reduces 24-hour ambulatory blood pressure, blood glucose, and lipids: One-year randomized, clinical trial. Hypertension. 2014; 64:69-76.

21. Rinella ME. Nonalcoholic fatty liver disease a systematic review. JAMA. 2015; 313: 2263-2273.

22. Zhu JZ, Hollis-Hansen K, Wan XY, et al. Clinical guidelines of non-alcoholic fatty liver disease: A systematic review. World J Gastroenterol. 2016; 22: 8226-8233.

23. Bacchi E, Negri C, Targher G, et al. Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 randomized trial). Hepatology 2013; 58: 1287-1295.
24. Perdomo CM, Frühbeck G, Escalada J. Impact of nutritional changes on nonalcoholic fatty liver disease. Nutrients. 2019; 11: 1-25.

25. Musso G, Gambino R, De Michieli F, et al. Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. Hepatology. 2003; 37: 909–916.

26. Oddy WH, Herbison CE, Jacoby P, et al. The western dietary pattern is prospectively associated with nonalcoholic fatty liver disease in adolescence. Am J Gastroenterol. 2013; 108: 778-785.

27. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2020. Diabetes Care. 2020; 43: S14-S31.

28. Tang W, Xu Q, Hong T, et al. Comparative efficacy of anti-diabetic agents on nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized and non-randomized studies. Diabetes Metab Res Rev. 2016; 32: 200-216.

29. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010; 362: 1675-1685.

30. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med. 2006; 355: 2297–2307.

31. Blazina I, Selph S. Diabetes drugs for nonalcoholic fatty liver disease: a systematic review. Syst Rev. 2019; 8: 295.

32. Mazzotti A, Caletti MT, Marchignoli F, et al. Which treatment for type 2 diabetes associated with non-alcoholic fatty liver disease? Dig Liver Dis. 2017; 49: 235-240.
33. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus a randomized trial. Ann Intern Med. 2016; 165: 305-315.

34. Musso G, Cassader M, Paschetta E, et al. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: A meta-analysis. JAMA Intern Med. 2017; 177: 633–640.

35. Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. N Engl J Med. 2016; 374: 1321-1331.

36. Barb D, Portillo-Sanchez P, Cusi K. Pharmacological management of nonalcoholic fatty liver disease. Metabolism. 2016; 65: 1183-1195.

37. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016; 387:679-690.

38. Armstrong MJ, Houlihan DD, Rowe IA, et al. Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program. Aliment Pharmacol Ther. 2013; 37: 234-242.

39. Shao N, Kuang HY, Hao M, et al. Benefits of exenatide on obesity and non-alcoholic fatty liver disease with elevated liver enzymes in patients with type 2 diabetes. Diabetes Metab Res Rev. 2014; 30: 521-529.

40. Liu L, Yan H, Xia M, et al. Efficacy of exenatide and insulin glargine on nonalcoholic fatty liver disease in patients with type 2 diabetes [published online ahead of print, 2020 Jan 18]. Diabetes Metab Res Rev. 2020; e3292.
41. Valdecantos MP, Pardo V, Ruiz L, et al. A Novel Glucagon-Like Peptide 1/Glucagon Receptor Dual Agonist Improves Steatohepatitis and Liver Regeneration in Mice. Hepatology. 2017; 65: 950-968.

42. Hartman ML, Sanyal AJ, Loomba R, et al. Effects of Novel Dual GIP and GLP-1 Receptor Agonist Tirzepatide on Biomarkers of Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes. Diabetes Care. 2020; 43: 1352-1355.

43. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016; 375: 311-322.

44. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016; 375: 1834-1844.

45. Athyros VG, Polyzos SA, Kountouras J, et al. Non-Alcoholic Fatty Liver Disease Treatment in Patients with Type 2 Diabetes Mellitus; New Kids on the Block. Curr Vasc Pharmacol. 2020; 18: 172-181.

46. Raj H, Durgia H, Palui R, et al. SGLT-2 inhibitors in non-alcoholic fatty liver disease patients with type 2 diabetes mellitus: A systematic review. World J Diabetes. 2019; 10: 114-132.

47. Xing B, Zhao Y, Dong B, et al. Effects of sodium-glucose cotransporter 2 inhibitors on non-alcoholic fatty liver disease in patients with type 2 diabetes: A meta-analysis of randomized controlled trials [published online ahead of print, 2020 Feb 21]. J Diabetes Investig. 2020; 10.1111/jdi.13237.

48. Ito D, Shimizu S, Inoue K, et al. Comparison of Ipragliflozin and Pioglitazone Effects on Nonalcholic Fatty Liver Disease in Patients With Type 2 Diabetes: A Randomized, 24-Week, Open-Label, Active-Controlled Trial. Diabetes Care. 2017; 40: 1364-1372.
49. Shibuya T, Fushimi N, Kawai M, et al. Luseogliflozin improves liver fat deposition compared to metformin in type 2 diabetes patients with non-alcoholic fatty liver disease: A prospective randomized controlled pilot study. Diabetes Obes Metab. 2018; 20: 438-442.

50. Muthiah MD, Sanyal AJ. Current management of non-alcoholic steatohepatitis. Liver Int. 2020; 40: 89-95.

51. Haukeland JW, Konopski Z, Eggesbø HB, et al. Metformin in patients with non-alcoholic fatty liver disease: A randomized, controlled trial. Scand J Gastroenterol. 2009; 44: 853-860.

52. Brandt A, Hernández-Arriaga A, Kehm R, et al. Metformin attenuates the onset of non-alcoholic fatty liver disease and affects intestinal microbiota and barrier in small intestine. Sci Rep. 2019; 9: 6668.

53. Zhou YY, Zhu GQ, Liu T, et al. Systematic Review with Network Meta-Analysis: Antidiabetic Medication and Risk of Hepatocellular Carcinoma. Sci Rep. 2016; 6:33743.

54. Joy TR, McKenzie CA, Tirona RG, et al. Sitagliptin in patients with non-alcoholic steatohepatitis: A randomized, placebo-controlled trial. World J. Gastroenterol. 2017; 23: 141–150.

55. Cui J, Philo L, Nguyen P, et al. Sitagliptin vs. placebo for non-alcoholic fatty liver disease: A randomized controlled trial. J Hepatol. 2016; 65: 369-376.

56. Hussain M, Majeed Babar MZ, Hussain MS, et al. Vildagliptin ameliorates biochemical, metabolic and fatty changes associated with non alcoholic fatty liver disease. Pak J Med Sci. 2016; 32: 1396-1401.
57. Li JJ, Zhang P, Fan B, et al. The efficacy of saxagliptin in T2DM patients with non-alcoholic fatty liver disease: preliminary data. Rev Assoc Med Bras (1992). 2019; 65: 33-37.

58. American Diabetes Association. 8. Obesity management for the treatment of type 2 diabetes: Standards of Medical Care in Diabetes 2020. Diabetes Care. 2020; 43: S89–S97.

59. Radaelli MG, Martucci F, Perra S, et al. NAFLD/NASH in patients with type 2 diabetes and related treatment options. J Endocrinol Invest. 2018; 41: 509-521.

60. Lassailly G, Caiazzo R, Buob D, et al. Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients. Gastroenterol. 2015; 149: 379-388.

61. Arrese M, Barrera F, Triantafilo N, et al. Concurrent nonalcoholic fatty liver disease and type 2 diabetes: diagnostic and therapeutic considerations. Expert Rev Gastroenterol Hepatol. 2019; 13: 849-866.

62. Zhou B, Bentham J, Cesare M Di, et al. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19·1 million participants. Lancet. 2017; 389: 37-55.

63. Bedogni G, Miglioli L, Masutti F, et al. Prevalence of and risk factors for nonalcoholic fatty liver disease: The dionysos nutrition and liver study. Hepatology. 2005; 42: 44-52.

64. Donati G, Stagni B, Piscaglia F, et al. Increased prevalence of fatty liver in arterial hypertensive patients with normal liver enzymes: Role of insulin resistance. Gut. 2004; 53: 1020-1023.

65. Williams B, Mancia G, Spiering W, et al. 2018 Practice guidelines for the management of arterial hypertension of the European Society of Cardiology
(ESC) and the European Society of Hypertension (ESH). Eur Heart J. 2018; 39: 3021-3140.

66. Bataller R, Sancho-Bru P, Ginès P, et al. Activated human hepatic stellate cells express the renin-angiotensin system and synthesize angiotensin II. Gastroenterology. 2003; 125: 117-125.

67. Gillespie EL, White CM, Kardas M, et al. The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. Diabetes Care. 2005; 28: 2261-2266.

68. Abuissa H, Jones PG, Marso SP, et al. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. J Am Coll Cardiol. 2005;46:821-826.

69. Yoshiji H, Kuriyama S, Yoshii J, et al. Angiotensin-II type 1 receptor interaction is a major regulator for liver fibrosis development in rats. Hepatology. 2001; 34: 745-750.

70. Sturzeneker MCS, de Noronha L, Olandoski M, Wendling LU, Precoma DB. Ramipril significantly attenuates the development of non-alcoholic steatohepatitis in hyperlipidaemic rabbits. Am J Cardiovasc Dis. 2019; 9: 8-17.

71. Israili ZH. Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. J Hum Hypertens. 2000; 14: S73-S86.

72. Oparil S. Newly emerging pharmacologic differences in angiotensin II receptor blockers. Am J Hypertens. 2000; 13: 18S-24S.

73. Georgescu EF, Georgescu M. Therapeutic options in non-alcoholic steatohepatitis (NASH). Are all agents alike? Results of a preliminary study. J Gastrointest Liver Dis. 2007; 16: 39-46.
74. Yokohama S, Tokusashi Y, Nakamura K, et al. Inhibitory effect of angiotensin II receptor antagonist on hepatic stellate cell activation in non-alcoholic steatohepatitis. World J Gastroenterol. 2006; 12: 322-326.

75. Yokohama S, Yoneda M, Haneda M, et al. Therapeutic efficacy of an angiotensin II receptor antagonist in patients with nonalcoholic steatohepatitis. Hepatology. 2004; 40: 1222-1225.

76. Georgescu EF, Ionescu R, Niculescu M, et al. Angiotensin-receptor blockers as therapy for mild-to-moderate hypertension-associated non-alcoholic steatohepatitis. World J Gastroenterol. 2009; 15: 924-954.

77. Alam S, Kabir J, Mustafa G, et al. Effect of telmisartan on histological activity and fibrosis of non-alcoholic steatohepatitis: A 1-year randomized control trial. Saudi J Gastroenterol. 2016; 22: 69-76.

78. Enjoji M, Kotoh K, Kato M, et al. Therapeutic effect of ARBs on insulin resistance and liver injury in patients with NAFLD and chronic hepatitis C: A pilot study. Int J Mol Med. 2008; 22: 521-527.

79. Zhang QQ, Lu LG. Nonalcoholic Fatty Liver Disease: Dyslipidemia, Risk for Cardiovascular Complications, and Treatment Strategy. J Clin Transl Hepatol. 2015; 3: 78-84.

80. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41: 111-188.

81. Patti G, Cannon CP, Murphy SA, et al. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: A collaborative patient-level meta-analysis of 13 randomized studies. Circulation 2011; 123: 1622-1632.
82. Jain A, Davis AM. Primary Prevention of Cardiovascular Disease. JAMA. 2019; 322: 1817-1818.

83. Tziomalos K, Athyros VG, Paschos P, et al. Nonalcoholic fatty liver disease and statins. Metabolism. 2015; 64: 1215-1223.

84. Onofrei MD, Butler KL, Fuke DC, et al. Safety of statin therapy in patients with preexisting liver disease. Pharmacotherapy. 2008; 28: 522-529.

85. Browning JD. Statins and hepatic steatosis: Perspectives from the Dallas heart study. Hepatology 2006; 44: 466-471.

86. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016; 37: 2999-3058.

87. Dongiovanni P, Petta S, Mannisto V, et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. J. Hepatol. 2015; 36: 705-712.

88. Foster T, Budoff MJ, Saab S, et al. Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial. Am J Gastroenterol. 2011;106:71-77.

89. Mitsiou E, Boutari C, Kotsis V, et al. Effect of Low (5 mg) vs. High (20-40 mg) Rosuvastatin Dose on 24h Arterial Stiffness, Central Haemodynamics, and Non-Alcoholic Fatty Liver Disease in Patients with Optimally Controlled Arterial Hypertension. Curr Vasc Pharmacol. 2018; 16: 393–400.

90. Kim RG, Loomba R, Prokop LJ, et al. Statin Use and Risk of Cirrhosis and Related Complications in Patients With Chronic Liver Diseases: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2017; 15: 1521-1530.

91. Oza N, Takahashi H, Eguchi Y, et al. Efficacy of ezetimibe for reducing serum low-density lipoprotein cholesterol levels resistant to lifestyle intervention in patients with non-alcoholic fatty liver disease. Hepatol Res. 2014; 44: 812-817.
92. Deushi M, Nomura M, Kawakami A, et al. Ezetimibe improves liver steatosis and insulin resistance in obese rat model of metabolic syndrome. FEBS Lett. 2007; 581: 5664-5670.

93. Loomba R, Sirlin CB, Ang B, et al. Ezetimibe for the treatment of nonalcoholic steatohepatitis: assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART trial). Hepatology. 2015; 61: 1239-1250.

94. Gandhi N, Lenton R, Bhartia M, et al. Effect of fibrate treatment on liver function tests in patients with the metabolic syndrome. Springerplus. 2014; 3: 14.

95. Nseir W, Mograbi J, Ghali M. Lipid-lowering agents in nonalcoholic fatty liver disease and steatohepatitis: Human studies. Dig Dis Sci. 2012; 6: 738-744.

96. Fernández-Miranda C, Pérez-Carreras M, Colina F, et al. A pilot trial of fenofibrate for the treatment of non-alcoholic fatty liver disease. Dig Liver Dis. 2008; 4: 200-205.

97. Fabbrini E, Mohammed BS, Korenblat KM, et al. Effect of fenofibrate and niacin on intrahepatic triglyceride content, very low-density lipoprotein kinetics, and insulin action in obese subjects with nonalcoholic fatty liver disease. J Clin Endocrinol Metab. 2010; 95: 2727-2735.

98. Argo CK, Patrie JT, Lackner C, et al. Effects of n-3 fish oil on metabolic and histological parameters in NASH: A double-blind, randomized, placebo-controlled trial. J Hepatol. 2015; 62: 190-197.
99. Theocharidou E, Papademetriou M, Reklou A, et al. The Role of PCSK9 in the Pathogenesis of Non-alcoholic Fatty Liver Disease and the Effect of PCSK9 Inhibitors. Curr Pharm Des. 2018; 24: 3654-3657.

100. Ruscica M, Ferri N, Macchi C, et al. Liver fat accumulation is associated with circulating PCSK9. Ann Med. 2016; 48: 384-391.
Table 1. Histological effects of antidiabetic treatment in patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease.

| Antidiabetic agent | Steatosis | Inflammation | Fibrosis |
|--------------------|-----------|--------------|----------|
| Pioglitazone 45 mg | ↓         | ↓            | ↓        |
| Pioglitazone 30 mg | ↓         | ↓            | ⇝        |
| Liraglutide        | ↓         | ↓            | ⇝        |
| Exenatide          | ↓*        | NA           | NA       |
| Empagliflozin      | ↓*        | NA           | NA       |
| Canagliflozin      | ↓*        | NA           | ⇝*       |
| Dapagliflozin      | ↓*        | NA           | ⇝*       |
| Ipragliflozin      | ↓*        | NA           | ↓        |
| Luseogliflozin     | ↓*        | NA           | ⇝*       |
| Metformin          | ⇝         | ⇝            | NA       |
| Sitagliptin        | ⇝         | ⇝            | ⇝        |
| Vildagliptin       | ↓*        | NA           | NA       |
| Saxagliptin        | ↓*        | NA           | NA       |

NA: no data available.

* No histological evidence.
**Table 2.** Histological effects of antihypertensive treatment in patients with arterial hypertension and non-alcoholic fatty liver disease.

|                | Steatosis | Inflammation | Fibrosis |
|----------------|-----------|--------------|----------|
| Atorvastatin   | ↓*        | ↓*           | ⇋        |
| Rosuvastatin   | ↓*        | ↓*           | ⇋        |
| Pitavastatin   | ⇋         | ⇋            | ⇋        |
| Ezetimibe      | ⇋         | ⇋            | ⇋        |
| Fibrates       | ⇋         | ⇋            | ⇋        |
| Omega-3 fatty acid supplements | ⇋ | ⇋ | ⇋ |
| PCSK9 inhibitors | NA   | NA           | NA       |

NA: no data available.

* No histological evidence.
**Table 3.** Histological effects of hypolipidemic treatment in patients with dyslipidemia and non-alcoholic fatty liver disease.

|                | Steatosis | Inflammation | Fibrosis |
|----------------|-----------|--------------|----------|
| Telmisartan    | ↓         | ↓            | ↓**      |
| Losartan       | ⇋         | ⇋            | ⇋        |
| Olmesartan     | ⇋         | ↓*           | ⇋        |
| Valsartan      | ↓         | ⇋            | ⇋        |
| Candesartan    | NA        | NA           | NA       |
| Ramipril       | NA        | NA           | NA       |
| Perindopril    | NA        | NA           | NA       |
| Captopril      | NA        | NA           | NA       |

NA: no data available.

* No histological evidence.

** Insufficient data to make recommendations.
Figure 1. Suggested algorithm for the management of type 2 diabetes and prediabetes in the non-alcoholic fatty liver disease scenario.
### Lyfestyle Interventions
- 5-10% Weight Loss: Mediterranean Diet and Physical Exercise
- Smoking cessation
- No alcohol consumption

### Liver Fibrosis Assessment
- First Step: Fibrosis serum markers
- Second Step: Transient elastography

### Treatment of Hyperglycemia

| IMC <25 kg/m² | IMC <25-30 kg/m² | IMC >30 kg/m² |
|---------------|------------------|---------------|
| Consider dual therapy if HbA1c >7.5% (consider Metformin) and triple therapy if HbA1c >9% (basal insulin if cardiac symptoms) | Ploglitazone: avoid if high fracture risk or heart failure | SGLT-2 inhibitors: monitor genital fungal infections (canagliflozin: avoid if high fracture risk) |
| GLP-1 analogs: contraindicated if history of pancreatitis | Metabolic Endoscopy or Surgery |

**Established heart disease:** Empagliflozin, Canagliflozin, Liraglutide or Semaglutide.

**Heart Failure:** Empagliflozin, Canagliflozin, Dapagliflozin.

**Diabetic Kidney Disease:** Empagliflozin (FR>45 ml/min/1.73²), Canagliflozin (FR>45 ml/min/1.73²), Dapagliflozin (FR>60 ml/min/1.73²), Liraglutide or Semaglutide (FR>15 ml/min/1.73²).

**Cerebrovascular disease:** Semaglutide.

---

**Figure 2.** Recommended management of type 2 diabetes in the non-alcoholic fatty liver disease scenario.
**FATS**

| SATURATED | Avoid |
|-----------|-------|
| Animal products (red meat, butter and dairy products), vegetable oils (palm oil) and processed foods (sausages, desserts) |

| PUFA OMEGA-6 | Avoid |
|--------------|-------|
| Vegetable oils (canola and cottonseed), cereal grains (wheat, corn and rice) |

| PUFA OMEGA-3 | Recommended |
|--------------|-------------|
| Seafood, certain vegetable oils (flaxseed oil) and, to a much lesser extent, eggs and meat |

| MUFA | Olive oil, avocados, nuts and nut oils |

**PROTEIN**

| ANIMAL NATURE | Avoid |
|---------------|-------|
| Red meat and processed meat (sausages) |

| PLANT-BASED NATURE | Recommended |
|--------------------|-------------|
| Whole grains, cereals, seeds, nuts, legumes, vegetables, soybeans, peas |

**CARBOHYDRATE**

| SIMPLE CHO | Avoid |
|------------|-------|
| Fructose (soft drinks and fruit juices) and refined CHO (sucrose, honey, syrup) |

| DIETARY FIBER | Recommended |
|---------------|-------------|
| Non-digestible CHO found in garlic, asparagus, leeks, onions and cereals |

PUFA: polyunsaturated fats; MUFA: monounsaturated fats; CHO: carbohydrate.

**Figure 3.** Dietary treatment according to macronutrient composition in the treatment of non-alcoholic fatty liver disease and type 2 diabetes.