REVIEW ARTICLE

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

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KEY WORDS

arterial hypertension, dyslipidemia, nonalcoholic fatty liver disease, type 2 diabetes

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is a clinical condition that encompasses various forms of liver damage not caused by chronic alcohol consumption. In the absence of other etiologies, it ranges from steatosis to nonalcoholic steatohepatitis and cirrhosis. The prevalence of NAFLD has considerably increased over the last years owing 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. Given the poor prognosis of patients with advanced NAFLD, a practical therapeutic approach is necessary to halt its natural history. However, no licensed drugs have been approved for this purpose to date. Nowadays, we are in a race to find the first drug able to stop the incidence of NAFLD and reverse the disease in patients at more advanced stages. Meanwhile, the management of the NAFLD metabolic overload, including weight loss, cardiovascular protection, insulin sensitization, and lipid reduction, is the only strategy to improve hepatic and extrahepatic outcomes. In this review, we aimed to describe the management of the main metabolic disorders related to NAFLD, such as type 2 diabetes, arterial hypertension, and dyslipidemia.

Introduction Nonalcoholic fatty liver disease (NAFLD) is a clinicopathological syndrome associated with metabolic syndrome, defined as a cluster of 3 of the following features: increased waist circumference, abnormal fasting glucose levels or type 2 diabetes (T2D), arterial hypertension, hypertriglyceridemia, and low levels of high-density lipoprotein (HDL) cholesterol.[1] A recent meta-analysis involving 8.5 million individuals from 22 countries has shown that more than 80% of patients with NAFLD were obese, 72% had dyslipidemia, and 44% had T2D.[2] This association is due to the overlapping of NAFLD pathogenetic mechanisms with those of metabolic syndrome, including genetic predisposition, insulin resistance (IR), oxidative stress, chronic and systemic microinflammation, and reduced adiponectin levels.[3] Owing to this strong association, patients who present with metabolic syndrome need to be examined for the risk of NAFLD and, vice versa, patients with NAFLD should be evaluated for all components of metabolic syndrome.[4]

Physicians face the challenge of the early diagnosis and intervention in NAFLD, and there are few pharmacological agents with proven efficacy. It is necessary to proactively assess the presence of cardiovascular disease in patients with NAFLD, regardless of the presence or absence of classic risk factors.[5] The management of the metabolic overload of NAFLD, including weight loss, cardiovascular protection, insulin sensitization, and lipid reduction, is currently the only strategy to improve hepatic and extrahepatic outcomes. In this review, we aimed to characterize the management of the main metabolic disorders associated with NAFLD, such as T2D, arterial hypertension, and dyslipidemia.

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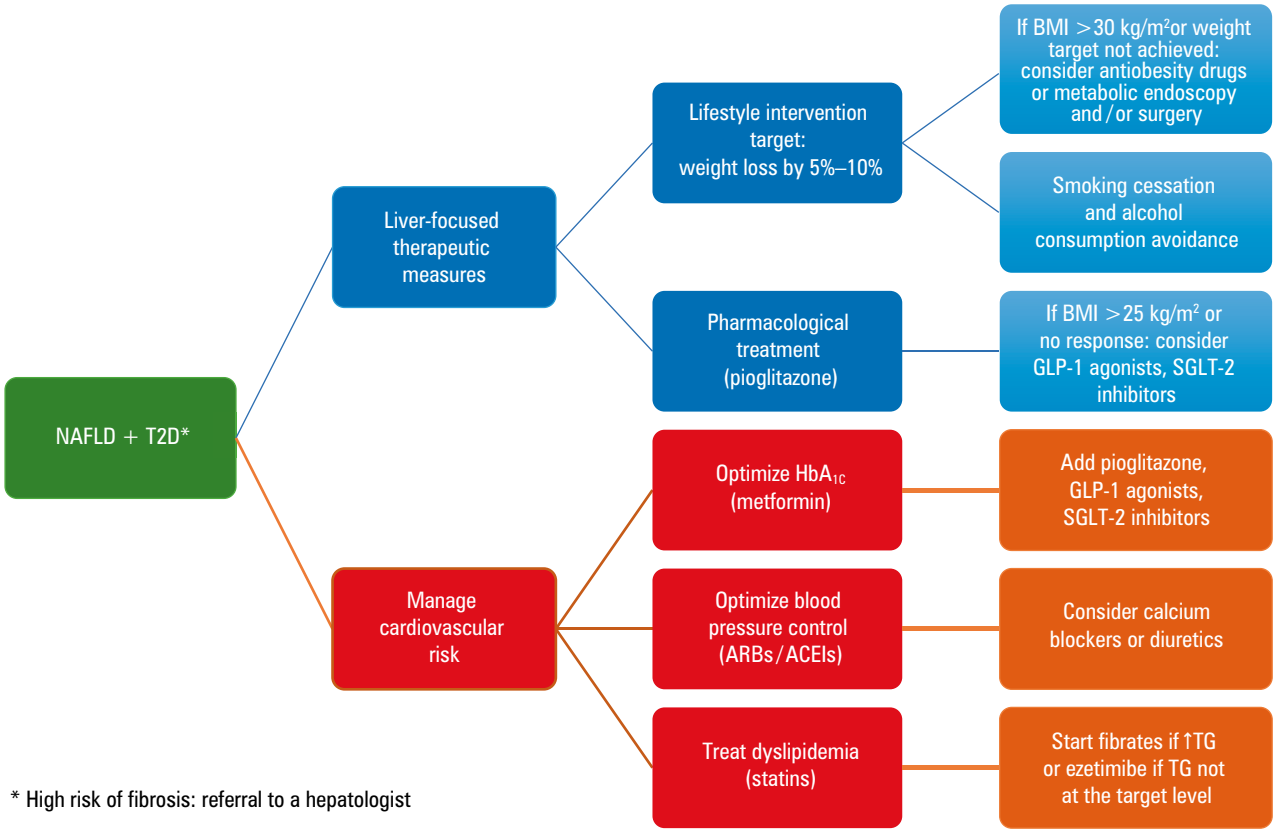
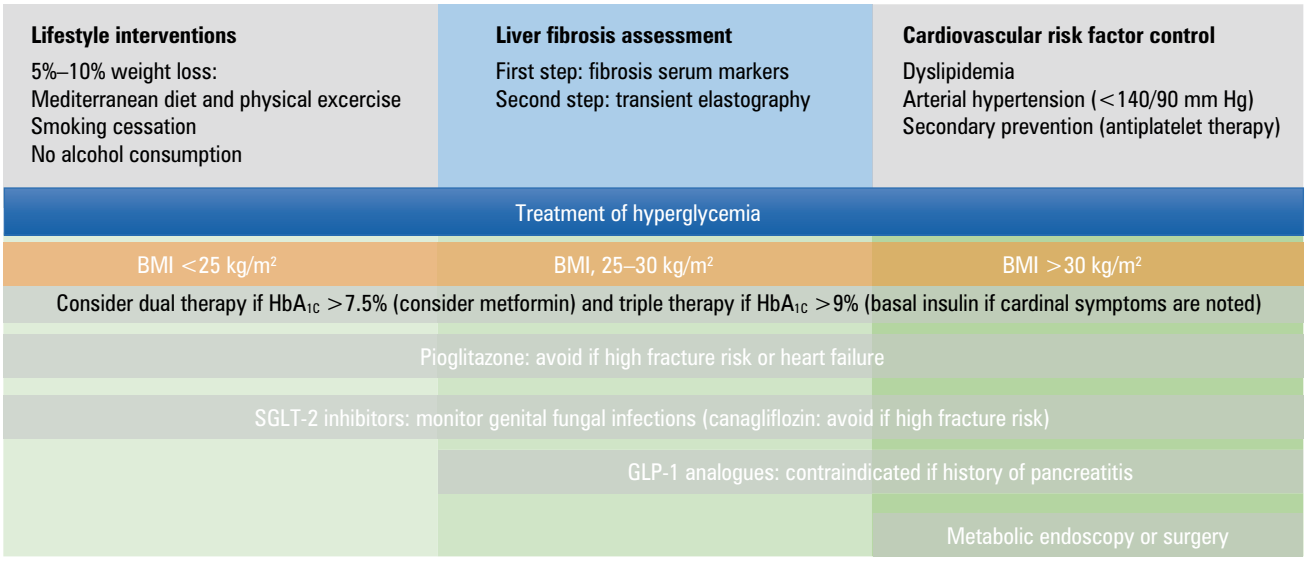


FIGURE 1 The suggested algorithm for the management of type 2 diabetes and prediabetes in the nonalcoholic fatty liver disease scenario
Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; GLP-1, glucagon-like peptide 1; HbA_{1C}, hemoglobin A_{1C}; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SGLT-2, sodium-glucose cotransporter 2; TG, triglyceride; T2D, type 2 diabetes

The first step to manage nonalcoholic fatty liver disease **Lifestyle interventions** The most critical intervention is to endorse a healthy lifestyle that promotes weight loss and control of cardiovascular risk factors (see FIGURE 1).[6,7] The European and American guidelines emphasize the importance of modifying lifestyle in the absence of approved pharmacological agents for the treatment of NAFLD.[5,8,9] A single 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 greater than 7% led to a significant improvement in the NAFLD Activity Score (NAS). Vilar-Gomez et al[11] reported similar results, with the highest rates of NAS reduction and fibrosis regression in patients who achieved weight loss greater than 10%. Based on these studies, at the early stages of NAFLD, recommending a loss of 5% to 7% of body weight might be sufficient.

In the case of T2D, pharmacological treatment should be started as an adjunct to recommending reduction of body weight greater than 7%.[5,8,12] Besides, interventions that improve metabolic abnormalities in patients with T2D have been proven to be beneficial in NAFLD (FIGURE 2). Furthermore, it should be considered that smoking is associated with advanced liver fibrosis mediated by an increase in IR. Therefore, smoking cessation is essential to reduce the effect of 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 patients with NAFLD and T2D.[8] Recently, Xu et al[15] demonstrated that low-to-moderate alcohol consumption was associated with an increased risk of T2D in patients with NAFLD.

The European Society of Cardiology and the European Society of Hypertension guidelines for the management of arterial hypertension suggest that a healthy lifestyle may be sufficient to delay or prevent the need for drug therapy in patients with grade 1 arterial hypertension.[16] The recommendations about the lifestyle associated with blood pressure (BP) reduction include weight loss, regular physical activity, smoking cessation, and dietary interventions.[16] Weight loss and the maintenance of an optimal body mass index (BMI) (approximately 20–25 kg/m²)[17] are recommended to prevent hypertension, reduce BP, and improve the efficacy of medication in hypertensive patients.[16] Epidemiological studies have shown that the treatment and prevention of hypertension may be enhanced by regular aerobic physical activity, which also reduces cardiovascular risk and mortality.[17] A growing body of evidence has suggested that hypertensive patients should



Established heart disease: empagliflozin, canagliflozin, lirgalutide or semaglutide

Heart failure: empagliflozin, canagliflozin, dapagliflozin

Diabetic kidney disease: empagliflozin (eGFR >45 ml/min/1.73 m²), canagliflozin (eGFR >45 ml/min/1.73 m²), dapagliflozin (eGFR >60 ml/min/1.73 m²), lirgalutide or semaglutide (eGFR >15 ml/min/1.73 m²)

Cerebrovascular disease: semaglutide

FIGURE 2 The recommended management of type 2 diabetes in the nonalcoholic fatty liver disease scenario
Abbreviations: eGFR, estimated glomerular filtration rate; others, see **FIGURE 1**

be advised to participate in at least 30-minute moderate-intensity aerobic exercise sessions (walking, jogging, cycling, or swimming) on 5 to 7 days per week.[17] Regarding dietary changes, hypertensive patients should be recommended to follow a healthy, balanced diet containing vegetables, legumes, fresh fruit, low-fat dairy products, whole grains, fish, and unsaturated fatty acids (especially olive oil) and promoting a low consumption of red meat and saturated fatty acids.[18,19] The Mediterranean diet, which includes many of these nutrients,[18,19] significantly reduces blood pressure[20] and has similar beneficial effects on blood glucose and lipid levels.

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

Dietary treatment Reduced caloric intake and improved macronutrient composition may 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 the diet to the individual's taste. Some studies have identified dietary habits that may promote NAFLD directly by modulating hepatic triglyceride accumulation and antioxidant activity and, indirectly, by affecting insulin sensitivity and postprandial triglyceride metabolism.[25] The Western diet, which is generally characterized by a high consumption of carbohydrates, simple sugars, saturated fats, trans fats, animal proteins (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 typical of the Mediterranean diet.[5,24] The Mediterranean diet is a dietary pattern supported by probably the greatest body of evidence of long-term cardiometabolic benefits.[18,24] However, the number of randomized trials examining the effect of the Mediterranean diet on liver histology is limited.[24] Long-term trials on standardized nutritional interventions, evaluating the effect on fibrosis, are necessary.[5,24] In NAFLD, carbohydrate intake should include whole grains, unprocessed cereals, and low–glycemic index foods[24]; fat intake should aim at high monounsaturated fatty acid and omega-3 polyunsaturated fatty acid consumption; 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 caloric intake and favorable microbiota, respectively.[24] Information on dietary treatment in NAFLD is summarized in **FIGURE 3**.[24]

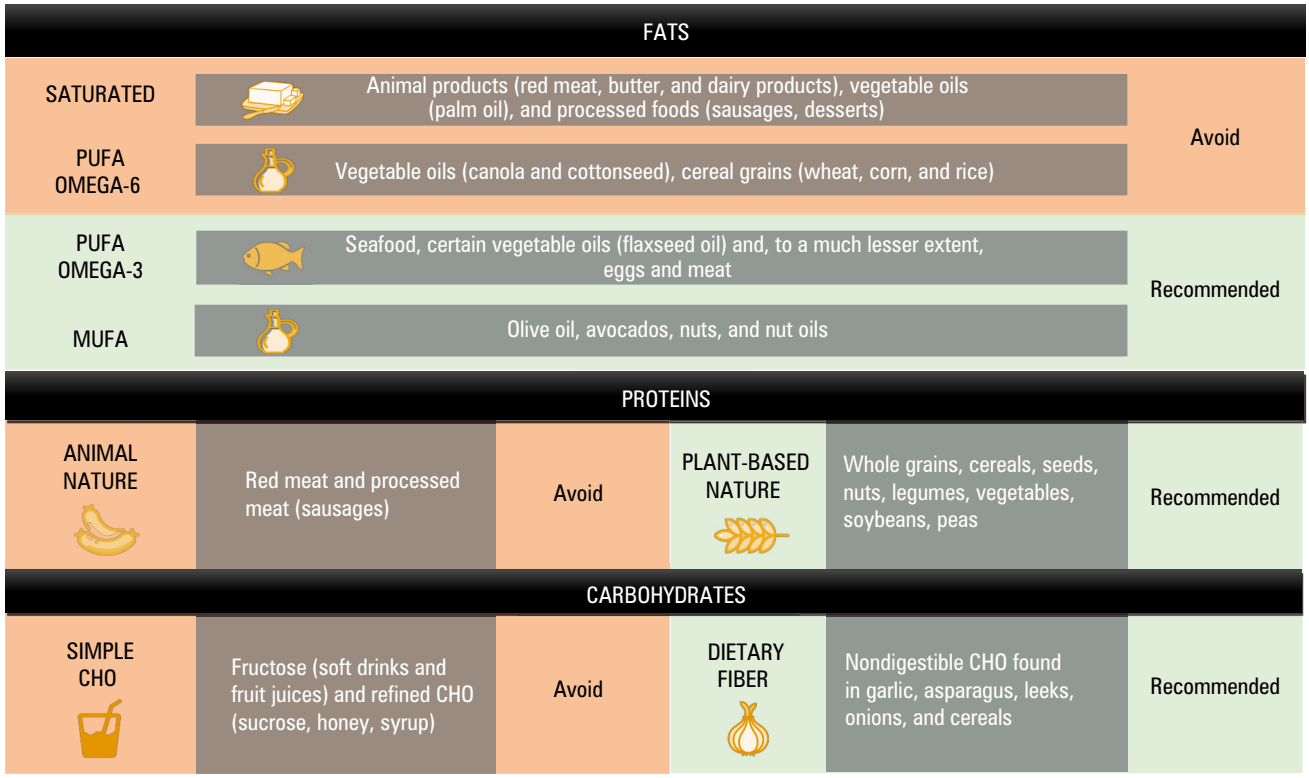


FIGURE 3 Dietary treatment according to macronutrient composition in the treatment of nonalcoholic fatty liver disease and type 2 diabetes
Abbreviations: CHO, carbohydrates; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid

Specific management of type 2 diabetes in nonalcoholic fatty liver disease The coexistence of NAFLD and T2D is dangerous, because it seems to favor quick progression towards more aggressive liver conditions such as nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma,[5,6] especially in patients with other metabolic comorbidities (arterial hypertension, dyslipidemia, and obesity).[5] However, unfortunately, patients and clinicians are unaware of the potentially serious NASH.[8] It has been reported that up to 66% of patients with T2D or obesity who are older than 50 years of age have NASH[21] and it seems to be an additional independent risk factor for cardiovascular disease.[7,8,21] Moreover, patients with T2D 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 hepatologist is required in order to rule out other causes of liver disease, perform liver biopsy if necessary, and maintain closer follow-up.[5,6,8]

How to assess diabetes in nonalcoholic fatty liver disease The diagnosis of T2D is established based on the abnormal levels of the following parameters: fasting plasma glucose level ≥126 mg/dl (7 mmol/l), 2-hour plasma glucose level during a 75-g oral glucose tolerance test ≥200 mg/dl (11.1 mmol/l), or hemoglobin A_{1C} level (HbA_{1C}) ≥6.5% (48 mmol/mol).[27] The HbA_{1C} criteria cannot be used in patients with sickle cell disease, glucose-6-phosphate dehydrogenase deficiency, recent blood loss or transfusion, HIV, in pregnancy, and in those undergoing hemodialysis or receiving erythropoietin therapy. Patients with the classic symptoms of hyperglycemia and a random plasma glucose level ≥200 mg/dl (11.1 mmol/l) do not need to meet any further criteria to be diagnosed with T2D.

Referral to an endocrinologist is recommended if the patient is considered to be a candidate for bariatric surgery, has advanced micro- or macrovascular complications, and HbA_{1C} target levels have not been achieved following intensified oral antidiabetic treatment at the primary care level.[5,27] The target level of HbA_{1C} is individually established in view of comorbidities, life expectancy, risk of hypoglycemia, and micro- and macrovascular complications.[27] In general, a target level of HbA_{1C} <7% is appropriate, but the target level <8% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, or significant comorbid conditions.

Pharmacological treatment Pharmacological treatment should always be considered in T2D and NAFLD, especially if lifestyle recommendations are unsuccessful or challenging to maintain.[8] In patients with T2D, 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 11 international guidelines for the treatment of NAFLD, the initiation of pharmacotherapy was recommended when the patient presented with NASH

TABLE 1 The histological effects of antidiabetic treatment in patients with type 2 diabetes and nonalcoholic fatty liver disease

Antidiabetic agent	Steatosis	Inflammation	Fibrosis
Pioglitazone 45 mg	↓	↓	↓
Pioglitazone 30 mg	↓	↓	⇆
Liraglutide	↓	↓	⇆
Exenatide	↓[a]	NA	NA
Empagliflozin	↓[a]	NA	NA
Canagliflozin	↓[a]	NA	⇆[a]
Dapagliflozin	↓[a]	NA	⇆[a]
Ipragliflozin	↓[a]	NA	↓
Luseogliflozin	↓[a]	NA	⇆[a]
Metformin	⇆	⇆	NA
Sitagliptin	⇆	⇆	⇆
Vildagliptin	↓[a]	NA	NA
Saxagliptin	↓[a]	NA	NA

a No histological evidence
Abbreviations: NA, no data available; ↓, decrease; ⇆, neutral effect

or risk factors for a rapid progression of NAFLD, such as the coexistence with T2D.[22] The effect of various antidiabetics on NAFLD was compared in a recent systematic review.[28] Pioglitazone and glucagon-like peptide-1 (GLP-1) analogues are antidiabetic drugs having the best effect on liver histology,[5,28] and sodium-glucose cotransporter 2 (SGLT-2) inhibitors have also been proven to be beneficial, although drug efficacy may be mediated, at least in part, by weight loss.[6] Among the pharmacological agents for the treatment of T2D, neither insulin, metformin, sulfonylureas, dipeptidyl peptidase–4 (DPP-4) inhibitors, nor acarbose are believed to significantly improve NASH or liver fibrosis, although reduced steatosis has been reported in small studies.[28]

Thiazolidinediones Pioglitazone is an agonist of the peroxisome proliferator–activated receptor γ, which improves insulin sensitivity and mitochondrial dysfunction in hepatocytes.[7] The PIVENS (Pioglitazone Versus Vitamin E Versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis) trial team compared the use of pioglitazone 30 mg/d with vitamin E and placebo for 2 years in patients without diabetes.[29] Pioglitazone significantly reduced steatosis and inflammation, but there was no evidence for fibrosis reduction. In T2D, a single randomized controlled trial included 55 patients with prediabetes or T2D with confirmed NASH who were assigned to either receive a hypocaloric diet and placebo or a hypocaloric diet and pioglitazone 45 mg/d.[30] After only 6 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 adverse 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 the cardiovascular safety of the drugs. Recently, the efficacy and safety of pioglitazone (45 mg/d) in 101 patients with T2D and NAFLD have been proven after 36 months of treatment without significant adverse effects including a mean weight gain of 3.1 kg.[33] Additionally, a subsequent meta-analysis (n = 516) confirmed the efficacy and safety of pioglitazone in the therapeutic management of NAFLD.[34] No major adverse events were reported during the trials, and the adverse effects observed included a slight weight gain and lower extremity edema. Moreover, pioglitazone has been shown to reduce the incidence of stroke and fatal or nonfatal myocardial infarction by 24% in patients with a history of ischemic stroke or transient ischemic attack.[35] Furthermore, the use of pioglitazone reduced the progression from prediabetes to T2D by 50% to 70%.[8]

Glucagon-like peptide-1 agonists Glucagon-like peptide-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 which are approved for the treatment of T2D. The LEAN (Liraglutide Efficacy and Action in NASH) trial showed a histological benefit in 52 patients treated with liraglutide for 48 weeks (39% resolution of NASH versus 9% with placebo).[37] The LEAD (Liraglutide Effect and Action in Diabetes) program team performed individual patient data meta-analysis, in which liver enzyme reduction, weight loss, and glycemic control were achieved.[38] In summary, based on the current evidence and mainly because it induces weight loss, liraglutide use is recommended in T2D and NAFLD.[6] Similar outcomes have been reported for other GLP-1 agonists.[32] A trial demonstrated that exenatide versus insulin therapy during 8 weeks was associated with greater reversal of liver fat (assessed by ultrasonography),[39] and similar results have been recently reported, although liver fat was assessed by magnetic resonance spectroscopy after 24-week treatment.[40] Regarding novel agents, GLP-1 and dual glucose-dependent insulinotropic polypeptide receptor agonists improved NASH and facilitated liver regeneration in mice[41] as well as significantly decreased fibrosis biomarkers and increased adiponectin levels in patients with T2D.[42] Both liraglutide and semaglutide have been shown to reduce cardiovascular risk in patients with T2D.[43,44]

Sodium-glucose cotransporter 2 inhibitors Sodium-glucose cotransporter 2 inhibitors are the major cotransporters involved in glucose reabsorption in the kidney and they are blocked by empagliflozin,

dapagliflozin, canagliflozin, tofogliflozin, luseogliflozin, ertugliflozin, and ipragliflozin, which induce glucosuria in the proximal renal tubule.[45] Based on the evidence of low-to-moderate quality, 2 recent systematic reviews concluded that SGLT-2 inhibitors improve liver enzymes and reduce liver and visceral fat, providing additional beneficial effects on various metabolic parameters in T2D patients with NAFLD.[46,47] In Japan, ipragliflozin has been shown to have a similar effect on hepatic fat content (measured by computed tomography) as compared with pioglitazone.[48] Similarly, luseogliflozin has been found to be superior to metformin in reducing hepatic fat content (measured by computed tomography).[49] There have been no studies evaluating the effect of SGLT-2 inhibitors on liver histology, but these drugs show promising results due to their potential to promote weight reduction (2%–4%), improve glycemic control, improve cardiovascular disease (dapagliflozin and empagliflozin), and slow the progression of chronic kidney disease in T2D.[45,50]

Other antidiabetic agents Metformin is the first--line drug in the management of T2D. Despite the fact that its main function is to improve insulin sensitivity, metformin did not cause histological improvement of steatosis,[51] although it has been recently 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 owing to its recognized effect on glycemic control[8] and 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 been demonstrated to reduce liver fat content assessed by magnetic resonance spectroscopy in patients with T2D and NAFLD.[40] Dipeptidyl peptidase–4 inhibitors (sitagliptin, linagliptin, vildagliptin, saxagliptin, teneligliptin, and alogliptin) act by blocking the enzyme that breaks down GLP-1, enhancing the effects of incretins and duration of their activity.[45] They have been proven to help achieve good glycemic control in T2D[31]; however, large randomized controlled trials with sitagliptin failed to show benefit in NAFLD.[54,55] Conversely, vildagliptin seems to improve steatosis assessed by ultrasonography after 12 weeks of treatment compared with placebo,[56] and, more recently, preliminary data have shown that saxagliptin improved IR as well as reduced IL-6 levels and liver steatosis.[57] Based on the current evidence and owing to the fact that they do not induce weight loss, DPP-4 inhibitors should not be the first-line therapy in the NAFLD treatment of T2D.

Nonpharmacological treatment Bariatric surgery Bariatric surgery should be considered in severely obese patients (with BMI >40 kg/m^2 or ranging between 35 to 40 kg/m^2 and comorbidities).[58] It has been suggested to expand the indications for metabolic surgery to the BMI as low as 30 kg/m^2 in patients with T2D who do not achieve permanent weight loss and comorbidity improvement with nonsurgical treatments.[58] Bariatric surgery may induce a 25% weight loss even 10 years after the procedure.[59] Additionally, bariatric surgery facilitates better glycemic, lipid, and blood pressure control. A long-term reversal of NASH has been reported regardless of the fibrosis stage and through various types of surgical interventions.[8,21] A prospective study provided evidence on an 85% fibrosis improvement a year after the surgery.[60] However, no randomized controlled trials have evaluated the effect of different surgical approaches versus lifestyle intervention plus pharmacological treatment on T2D and NAFLD. Of note, bariatric surgery should be performed in high-volume centers and by a multidisciplinary team to ensure patient safety.[61]

Specific management of arterial hypertension in nonalcoholic fatty liver disease The global prevalence of hypertension was estimated at 1.3 billion in 2015, with a prevalence of 150 million cases in Central and Eastern Europe; in adults, the prevalence is around 45% and becomes 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 around 50% of patients with NAFLD suffer from this condition.[63] Moreover, fatty liver is significantly more prevalent in nondiabetic hypertensive patients (31%) compared with normotensive controls (13%).[64] Besides, hypertension is associated with the development of severe NAFLD.[64]

How to assess arterial hypertension in nonalcoholic fatty liver disease Hypertension is predominantly an asymptomatic condition detected by screening programs or an incidental measurement of BP and, therefore, patients with NAFLD should undergo screening for hypertension. Hypertension is defined as office systolic BP (SBP) of at least 140 mm Hg and / or diastolic BP (DBP) of at least 90 mm Hg, although the last European Society of Cardiology / European Society of Hypertension guidelines[65] considered SBP of 130 to 139 mm Hg and / or DBP of 80 to 89 mm Hg as high-normal values, SBP of 120 to 129 mm Hg and DBP of 80 to 84 mm Hg as normal values, and SBP above 120 mm Hg and DBP below 80 mm Hg as optimal values. Arterial hypertension should be evaluated periodically, depending on severity, ranging from every 3 months to 5 years.[65]

Pharmacological treatment Apart from lifestyle modification, a wide range of agents has been tested for the treatment of NAFLD (TABLE 2). A large body of evidence has suggested

TABLE 2 The histological effects of antihypertensive treatment in patients with arterial hypertension and nonalcoholic fatty liver disease

Antihypertensive agent	Steatosis	Inflammation	Fibrosis
Atorvastatin	↓[a]	↓[a]	⇆
Rosuvastatin	↓[a]	↓[a]	⇆
Pitavastatin	⇆	⇆	⇆
Ezetimibe	⇆	⇆	⇆
Fibrates	⇆	⇆	⇆
Omega-3 fatty acid supplements	⇆	⇆	⇆
PCSK9 inhibitors	NA	NA	NA

a No histological evidence

Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9; others, see TABLE 1

TABLE 3 The histological effects of lipid-lowering treatment in patients with dyslipidemia and nonalcoholic fatty liver disease

Lipid-lowering agent	Steatosis	Inflammation	Fibrosis
Telmisartan	↓	↓	↓[b]
Losartan	⇆	⇆	⇆
Olmesartan	⇆	↓[a]	⇆
Valsartan	↓	⇆	⇆
Candesartan	NA	NA	NA
Ramipril	NA	NA	NA
Perindopril	NA	NA	NA
Captopril	NA	NA	NA

a No histological evidence

b Insufficient data to make recommendations

Abbreviations: see TABLE 1

that the renin–angiotensin system (RAS) may play a relevant role in the pathogenesis of NAFLD and indicated angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) as potential therapeutic drugs.[66] In fact, ACEIs and ARBs are the most widely used antihypertensive drugs.[65]

Consistent data have shown that RAS intervention in NAFLD could influence adipogenesis as well as adipokine and cytokine production, interact with insulin receptors and intracellular signaling pathways, and interfere with pancreatic β-cell insulin secretion.[66] The local hepatic effect is mediated by angiotensin II receptor 1, which is localized in hepatocytes, bile duct cells, hepatic stellate cells, and vascular endothelial cells (where it mediates the action of angiotensin II in the liver).[66] On the other hand, angiotensin II receptor 2 has antifibrogenic effects. Hence, the inhibition of the RAS could improve the activity of intracellular signaling pathways, adipose tissue proliferation, and adipokine production, as well as lead to a more stable release of cytokines and chemoattractant factors.[66]

Angiotensin-converting enzyme inhibitors There are 2 classes of agents to antagonize the RAS: ACEIs and ARBs. Unfortunately, there are little data about their role in NAFLD, particularly regarding ACEIs. Gillespie et al[67] reported that ACEIs improved the insulin sensitivity index by a mean (SD) of 12.1% (15.8%) in the analysis of 20 clinical trials, while Abuissa et al[68] performed a meta-analysis of 12 randomized controlled clinical trials and concluded that ACEIs reduced the incidence of diabetes by 27%. A study that examined the in vivo effect of perindopril on 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 also reduced collagen accumulation in the model of pig serum–induced liver fibrosis. In a rabbit model, ramipril significantly reduced the development of steatosis, lobular inflammation, and hepatic fibrosis as well as significantly diminished the development of NASH.[70] However, data on the evaluation of the impact of ACEIs in NAFLD patients are too scarce to make any recommendation about their role in this population.

Angiotensin II receptor blockers Losartan and telmisartan are the most commonly investigated ARBs in the scenario of NAFLD, demonstrating an excellent side-effect profile.[71,72] Losartan (50 mg/d for 48 weeks) was tested in 3 small human studies (a total of 19 patients) that evaluated biochemical parameters and histological markers in patients with biopsy-proven NASH.[73] Yokohama et al[74] included 7 biopsy-NAFLD patients and found an improvement of hepatic necroinflammation in 5 patients, reduction of hepatic fibrosis in 4, and resolution of iron deposition in 2. Besides, another study assessing 48-week losartan treatment showed a remarkable decrease in the number of activated hepatic stellate cells and a mild increase in quiescent phenotypes in 7 patients.[75] Despite these findings, further studies are needed to make any 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 period. A significant improvement in cytolysis was noted in all patients, similar for telmisartan and valsartan. Besides, both valsartan and telmisartan improved IR, although the effect was more remarkable with the latter drug; patients receiving telmisartan had an improved NAS and fibrosis stage.[76] Another randomized clinical trial assessed the role of prescribing telmisartan in 50 patients with biopsy-proven NASH who underwent lifestyle modification. Adding telmisartan improved the NAS and fibrosis scores in NASH and was associated with nonsignificant adverse events.[77] On the other hand, olmesartan 20 mg/d and telmisartan 40 mg/d were tested in patients with NAFLD for 6 months, and the study demonstrated that

both drugs significantly improved IR and transaminase levels.[78]

Therefore, ARBs are effective drugs for arterial hypertension, which have shown the ability to improve insulin sensitivity, and could play a partial role in the necroinflammatory activity.[78] They could be an excellent choice to treat arterial hypertension in patients with NAFLD (telmisartan in particular), probably better than ACEIs. However, their use as NAFLD treatment needs further large clinical trials to establish their efficacy in this entity.

Specific management of dyslipidemia in nonalcoholic fatty liver disease Dyslipidemia is frequent in individuals with NAFLD, which, in turn, is independently associated with increased triglyceride and low-density lipoprotein (LDL) cholesterol levels, and decreased HDL cholesterol levels.[79] On the other hand, hypertriglyceridemia is present in 20% to 80% of patients with NAFLD.

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

Pharmacological treatment Statins Statins are among the most frequently prescribed drugs worldwide. Reducing cholesterol biosynthesis in the liver by inhibiting 3-hydroxy-3-methylglutaryl–coenzyme A reductase is the fulcrum in the 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 excellent drugs for the treatment of NASH, but the use of statins has long been limited due to their potential hepatotoxicity in patients with liver disease. Statin metabolism takes place in the liver, and the use of these drugs has been related to higher transaminase levels.[83] Liver toxicity associated with statins is rare, and the incidence of acute liver failure is estimated to be similar in subjects exposed and unexposed to statins.[84] In 2006, data from an extensive analysis of the Dallas Heart Study suggested that no damage should be expected for the statin use in individuals with liver disease, including patients with fatty liver.[85] Currently, the European Society of Cardiology / European Atherosclerosis Society guidelines for the management of hypertension suggest that statin therapy may be continued if alanine transaminase levels are lower than or equal to the 3-fold value of the upper limit of normal and may be reduced or discontinued if alanine transaminase levels rise above this value.[86]

Statins have been proposed to treat NAFLD and NASH because of their anti-inflammatory, antioxidant, and antithrombotic effects. Nevertheless, unfortunately, only a few and limited studies have tested the benefits of statins in the treatment of NAFLD (TABLE 3). In a cross-sectional study from 2015, the statin use was associated with protection from steatosis, NASH, and significant fibrosis.[87] Atorvastatin and rosuvastatin have shown a beneficial effect on both biochemical and ultrasonographic evidence of NAFLD.[88,89] Besides, numerous studies have confirmed that statins may reduce the risk of advanced liver disease and mortality as well as might reduce portal hypertension, promoting fibrosis regression and stopping disease progression.[90] NAFLD Clinical Practice Guidelines,[5] published by the European Association of Liver Disease, strongly recommend the use of statins to strictly control the cardiovascular risk, but they do not recommend them as a therapeutic therapy for NAFLD.

Ezetimibe Ezetimibe is a selective inhibitor of the Niemann–Pick C1-like 1 protein that regulates cholesterol absorption from the small intestine to enterocytes and it has been demonstrated to significantly reduce LDL cholesterol levels and cardiovascular risk, especially in combination with statins.[91] It has also been reported that ezetimibe reduces lipid levels, IR, and cardiovascular risk as well as improves liver function and hepatic histology in NAFLD.[91] In an experimental study, ezetimibe was found to improve diet-induced steatosis and fibrosis, while attenuating dyslipidemia in obesity and the insulin-resistant animal model.[92] In the MOZART (Magnetic Resonance Imaging and Elastography in Ezetimibe Versus Placebo for the Assessment of Response to Treatment in NASH) trial, a randomized, double-blind, placebo-controlled trial, 50 patients with

biopsy-proven NASH were randomized to either oral ezetimibe 10 mg/d or placebo for 24 weeks.[93] The aim of the study was to examine the efficacy of ezetimibe versus placebo in reducing liver fat assessed by magnetic resonance imaging–proton density fat fraction 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 for the treatment of patients with NAFLD beyond the management of dyslipidemia.

Fibrates and omega-3 fatty acid supplements Fibrates are the first-line pharmacological therapy in patients with severe hypertriglyceridemia. Their primary function is to decrease plasma triacylglycerol levels, increase HDL synthesis, and increase reverse cholesterol transport. Furthermore, fibrates may ameliorate insulin sensitivity[94] as well as vascular and systemic inflammation.[95] In a study by Fernández-Miranda et al,[96] fenofibrate was administered in 16 patients with NAFLD for 48 weeks, and the authors noted that the transaminase levels decreased and ballooning improved, but no effect on histological steatosis, inflammation, or fibrosis was observed. Another placebo-controlled study using fenofibrate for 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 lipid levels, but they have not demonstrated the ability to improve histological outcomes, which would support their use in patients with NAFLD. [98]

Proprotein convertase subtilisin/kexin type 9 inhibitors Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition is a promising therapeutic option for patients with familial hypercholesterolemia or statin intolerance. These drugs significantly decrease LDL cholesterol and triglyceride levels, increase HDL cholesterol levels, and reduce the number of cardiovascular events.

The link between PCSK9 inhibitors and liver steatosis remains unclear. Numerous studies have indicated that a high level of intrahepatic and circulating PCSK9 increase liver lipid storage, adipose energy, and hepatic fatty acid storage as well as triglyceride secretion and storage.[99] In 201 consecutive patients with biopsy-confirmed NASH, circulating PCSK9 levels were associated with the steatosis grade, necroinflammation, ballooning, and the fibrosis stage.[100] Indeed, circulating PCSK9 levels increase with hepatic fat accumulation and correlate with the severity of steatosis. Therefore, reducing the PCSK9 expression by using PCSK9 inhibitors seems to protect the liver from NAFLD by decreasing IR.[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 regarded as the liver component of metabolic syndrome, because it is closely related to comorbidities such as diabetes, 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 key role in the progression of this condition, thus requiring prompt and effective therapeutic interventions to avoid hepatic and extra-hepatic complications.

While no pharmacological treatment has been 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 to implement pharmacological therapies that improve glycolipid metabolism and blood pressure. On the other hand, the current understanding of the NAFLD pathophysiology has expanded the possibilities of treatment, so several promising drugs are being studied in randomized controlled trials. We expect that they will facilitate early intervention in NAFLD, leading to individualized treatment for all patients.

ARTICLE INFORMATION

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