

# Current management of non-alcoholic fatty liver disease

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## SUMMARY

Non-alcoholic fatty liver disease (NAFLD) is characterized by hepatic accumulation of lipid in patients who do not consume alcohol in amounts generally considered harmful to the liver. NAFLD is becoming a major liver disease in Eastern countries and it is related to insulin resistance and metabolic syndrome. Treatment has focused on improving insulin sensitivity, protecting the liver from oxidative stress, decreasing obesity and improving *diabetes mellitus*, dyslipidemia, hepatic inflammation and fibrosis. Lifestyle modification involving diet and enhanced physical activity associated with the treatment of underlying metabolic are the main stain in the current management of NAFLD. Insulin-sensitizing agents and antioxidants, especially thiazolidinediones and vitamin E, seem to be the most promising pharmacologic treatment for non-alcoholic steatohepatitis, but further long-term multicenter studies to assess safety are recommended.

**Keywords:** non-alcoholic fatty liver disease, steatosis, steatohepatitis, metabolic syndrome, obesity.

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a clinical/pathological condition characterized by significant lipid deposition in the hepatocytes (steatosis) after the exclusion of significant alcohol intake, viral infection, or other specific liver disease. Steatosis is usually diagnosed using imaging examinations, which may or not be associated with necroinflammatory changes and fibrosis (steatohepatitis) diagnosed by liver biopsy. This disease encompasses a spectrum of changes ranging from steatosis and steatohepatitis to fibrosis and hepatic cirrhosis, and is associated with a higher frequency of hepatocellular carcinoma.<sup>1,2</sup>

NAFLD is considered the hepatic manifestation of metabolic syndrome (MetS),<sup>1</sup> which is defined by the presence of at least three of the following factors: central obesity, hypertension, hypertriglyceridemia, reduced high-density lipoprotein (HDL) cholesterol, and hyperglycemia.<sup>2</sup> The strong association between NAFLD and insulin resistance (IR) and MetS is well documented in the literature.<sup>3</sup> This condition is currently recognized as the most prevalent liver disease in Western populations with average rates estimated at 20 to 30%.

## TREATMENT OF NAFLD

NAFLD treatment aims to reduce insulin resistance and oxidative stress, control the associated conditions (obesity, *diabetes mellitus*, dyslipidemia), and also reduce inflammation and fibrosis of the liver. Considering all patients with NAFLD, the treatment focuses on lifestyle modifications, including a change of eating habits and the regular practice of physical activities, associated with the treatment of all the components of metabolic syndrome. Discontinuation of the use of hepatotoxic drugs is also recommended.

Patients with non-alcoholic steatohepatitis (NASH) should be the main target of treatment given that this group has a higher risk of mortality related to the disease. Among the causes of death in patients with NASH, cardiovascular diseases are in first place, followed by complications from cirrhosis and hepatocellular carcinoma. The ideal management of these patients is not yet well established. Clinical trials currently in progress are focusing on this population. Lifestyle modifications with diet and physical activity, bariatric surgery, drug therapy to improve IR and the use of antioxidants are the therapies

that have been studied the most. Other treatment approaches have aimed at inhibiting proinflammatory or fibrotic pathways.<sup>4,5</sup>

## DIET AND PHYSICAL ACTIVITY

NAFLD is a manifestation of obesity and of MetS, usually associated with excess calorie intake and a lack of physical activity. Weight loss is widely accepted as part of treatment for patients with NAFLD, although there is still a lack of data to provide guidance on how, in what amount of time and how much weight the patient should lose.<sup>6,7</sup> The lack of data makes it difficult to elaborate evidence-based recommendations for the modification of diet and the practice of physical exercise in the treatment of NAFLD. It is recommended to perform exercises for at least 250 minutes per week.<sup>8</sup> In general, 5 to 10% reduction in body weight in obese or overweight people over 6 to 12 months has been advocated through changes to eating habits and the practice of physical activity. This recommendation is based on short-term studies that

showed an improvement in IR and in liver histology with gradual weight loss, as shown in Table 1.

## BIARIATRIC SURGERY

In patients with morbid obesity or obese patients of greater severity (BMI > 40 or BMI between 35 and 40 with comorbidities), bariatric surgery induces long-term maintenance of weight loss and has been recommended by the researchers for motivated candidates. Whatever the surgical procedure, 14 to 25% weight loss is observed 10 years after surgery, associated with improvement in IR, remission of *diabetes mellitus* and few cardiovascular events.<sup>15,16</sup>

In terms of liver damage, various studies have shown improvement of the steatosis after bariatric surgery. A meta-analysis in 2008 that included 15 studies and 766 paired liver biopsies of patients undergoing bariatric surgery showed significant improvement of all NAFLD components: reduction of steatosis in 93%, reduction of steatohepatitis in 82% and reduction of fibrosis in 73%.<sup>17</sup> Other recent studies have suggested potential benefits of

**TABLE 1** Recently published clinical trials on the effect of diet associated with physical activity in patients with NAFLD.

Author/year	Diagnosis	n	Intervention	Results
Baba et al., 2006 <sup>9</sup>	Biopsy	65	Moderate calorie restriction in obese individuals + PA (40' walk 3-4 times per week, 60 to 70% maximum HR)	Beneficial effect limited to patients who fulfilled the dietary programs and PA (n=44)
Thamer et al., 2007 <sup>10</sup>	MRI	112	Reduction of fat intake up to 30% of total calories, reduction of saturated fatty acids up to 10% of total calories, increased daily dose of fiber intake to 15 g/1,000 kcal, and increased PA to 3h/week for 9 months	Reduction of IR and fat in the liver
Albu et al., 2010 <sup>11</sup>	MRI	58	Decreased calorie intake (-500 kcal/day) and increased PA ( $\geq 175$ min/week), during 12 months	Reduction of fasting blood glucose and fat in the liver
Promrat et al., 2010 <sup>12</sup>	Biopsy	65	Caloric restriction (1,000-1,200 kcal/day if baseline weight < 200 lb or 1,200-1,500/day if initial weight > 200 lb) and a daily fat target of 25% and 200 minutes of moderately intense PA per week for 12 months	Significant improvement in steatosis, lobular inflammation, hepatocyte ballooning and NAS in patients with a decrease of at least 7% of total body weight
Lazo et al., 2010 <sup>13</sup>	MRI	5,145	Moderate caloric restriction (1,200-1,500 kcal/day for individuals weighing < 114 kg and 1,500-1,800 kcal/day for those weighing > 114 kg) and increased physical activity with a target of 175 min of moderately intense PA per week for 12 months	Reduction in liver fat
Oh et al., 2014 <sup>8</sup>	Fibroscan	169 (obese)	Calorie restriction of 1,680 kcal/day and PA for less than 250 min per week or 250 min or more per week	Reduction of serum ferritin and adiponectin and reduction of liver fat
Vilar-Gomez et al., 2015 <sup>14</sup>	Biopsy	293	Low-calorie diet (750 kcal/day less than the calculated daily energy need) and PA for 200 min a week for 52 weeks	Histological improvement, including fibrosis, when weight loss was greater than or equal to 10%

PA: physical activity; HR: heart rate; NAS: NAFLD Activity Score; MRI: magnetic resonance imaging.

bariatric surgery.<sup>18-21</sup> However, there is a lack of randomized studies assessing the effect of this procedure on NASH. Therefore, performing bariatric surgery specifically for the treatment of this condition is not recommended.<sup>22</sup> It should be considered that although bariatric surgery may play a role in the treatment of patients with morbid obesity and NASH, the recommendation of this procedure must be individualized and conducted at specialized medical centers with a multidisciplinary approach due to the potential complications, which vary depending on the center where the procedure is performed (mean mortality of 0.3% and morbidity of 10%).

## ANTIOXIDANTS

Antioxidants, especially vitamin E, have been studied in patients with NAFLD because oxidative stress is considered a key mechanism in the pathophysiology of NASH, leading to hepatocellular injury and progression of the disease.

### Vitamin E

Vitamin E is a fat-soluble vitamin with antioxidant properties. Two recently published, large-scale, randomized and controlled studies (PIVENS and TONIC) have assessed its effect on NAFLD in adults and children, respectively.<sup>23,24</sup> In the PIVENS study, a significant histological improvement (a reduction of at least 2 points in the inflammatory activity score – NAS) was noted in patients who received vitamin E compared to patients treated with a placebo (43 *vs.* 19%,  $p=0.001$ ).<sup>23</sup> In children with hepatic steatosis, both vitamin E associated with metformin and the isolated use of vitamin E were not superior to the placebo in reducing alanine aminotransferase (ALT) levels in the TONIC study. However, the children treated with vitamin E that presented NASH proven via biopsy had significant histological improvement.<sup>24</sup>

Some data suggests potential safety concerns with the long-term use of vitamin E, though. A meta-analysis that included 11 trials that tested the effect of vitamin E supplementation in humans showed that high-dose supplementation (400 U/day) was associated with increased mortality due to any cause.<sup>25</sup>

## CYTOPROTECTIVE AGENTS

Drugs classified as cytoprotective agents prevent apoptosis and inhibit the inflammatory cascade, two central mechanisms in the pathogenesis of NASH.

### Ursodeoxycholic acid

Ursodeoxycholic acid (UDCA) is an excellent example of a cytoprotective agent that has been investigated in the

treatment of NASH. The largest study that evaluated UDCA *versus* a placebo showed similar improvement in both groups, despite a high dropout rate and an unexpectedly high rate of improvement in the placebo group.<sup>26</sup> A randomized and controlled study with 147 patients treated with a placebo *versus* UDCA at 23-28 mg/kg/day only found an improvement of ALT serum levels and lobular inflammation, with the absence of a significant overall histological improvement.<sup>27</sup> A study of 126 patients comparing high doses of UDCA with a placebo showed an improvement in the level of aminotransferase, serum markers of fibrosis (FibroTest) and IR after 12 months, although liver histology was not assessed.<sup>28</sup> These controversial results, associated with recent concerns about the increased mortality from all causes with high doses of UDCA in primary sclerosing cholangitis has led to a decrease in research with patients with NAFLD.

### Pentoxifylline

Another approach to the treatment of NAFLD involves using anti-TNF- $\alpha$  drugs, given that this cytokine induces both necroinflammation as well as IR.<sup>29</sup> Pentoxifylline is a TNF- $\alpha$  inhibitor, and has been used in animal models<sup>30</sup> and in patients with NASH. A meta-analysis assessing five randomized, placebo-controlled studies, including only 157 patients, showed that pentoxifylline can reduce transaminase activity and improve histological parameters in NAFLD patients.<sup>31</sup>

A more recent study not included in this meta-analysis and involving 55 NASH patients showed an average improvement of 1.6 points in the NAS score *vs.* 0.1 points in the placebo group. The reduction in fibrosis was not statistically significant, although it occurred in 35% of patients in the pentoxifylline group *vs.* 15% in the placebo group.<sup>32</sup> Therapy with this medication appears to be well tolerated, although other studies are needed before it can be recommended as a therapy for NASH.

## HYPOLIPIDEMIC AGENTS

Hypolipidemic medication such as statins and omega-3 fatty acids are seen as potential options for the treatment of NAFLD due to their effects on hypertriglyceridemia and low levels of HDL cholesterol, which are common changes in patients with MetS.

### Statins

With antioxidant and anti-inflammatory properties, in addition to the frequent coexistence of NAFLD and dyslipidemia, and the increased cardiovascular risk of these patients, statins appear as an attractive therapeutic option

in NAFLD. Important evidence indicates the use of statins in order to reduce cardiovascular disease in patients with dyslipidemia.<sup>33</sup> However, data on the effectiveness of statins for the treatment of NAFLD is scarce. A pilot study in which 16 participants with NASH proven via biopsy were randomized to receive 40 mg of simvastatin or a placebo for 12 months found a significant improvement in the level of aminotransferase in the simvastatin group. Liver histology was not significantly affected by the simvastatin.<sup>34</sup> Similarly, another study using atorvastatin 24 mg/day *versus* a placebo revealed that there was a significant improvement in serum transaminase in the statins group. Furthermore, there was an increase in aminotransferase in the placebo group. Histological changes were not assessed.<sup>35</sup> At the present time, when there is still a lack of evidence of any histological benefit, therapy with statins may not be recommended as a primary therapy for NAFLD but as a treatment for associated hyperlipidemia.

### Omega-3 fatty acids

Omega 3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are potent activators of nuclear receptor proteins such as PPAR $\alpha$  and PPAR $\gamma$ , which regulate various genes involved in the stimulation of fatty acid oxidation, regulate pro-inflammatory genes, such as TNF- $\alpha$  and IL-6, and improve insulin sensitivity.<sup>36,37</sup> In relation to the effects on NAFLD, a recent systematic review and meta-analysis found heterogeneity between the studies and concluded that, although omega-3 supplementation may decrease fat in the liver (without effects on transaminase levels), the optimal dose has not yet been established.<sup>38</sup> A subsequent randomized, double-blind study assessed supplementation with an EPA compound in individuals with NASH confirmed via biopsy. After 12 months, there was no improvement in the histological characteristics of the NASH. A possible explanation for the negative results of this study is that the dose of EPA was not sufficiently suitable for the population (only 2.7 g/day). Furthermore, the response rate to the placebo in this trial was higher than previously reported in other studies.<sup>39</sup> Thus, additional studies are needed to support the routine use of omega-3 in patients with NAFLD, with its use currently restricted to the treatment of hypertriglyceridemia.

## INSULIN SENSITIZERS

Given the importance of IR in the pathogenesis of NASH, insulin sensitizers such as metformin and thiazolidinedio-

nes (TZDs) have been extensively studied in the treatment of NASH.

### Metformin

Metformin is a biguanide that improves IR and hyperinsulinemia by reducing hepatic glucose production, increasing peripheral glucose uptake by the muscles and reversing IR induced by tumor necrosis factor.<sup>40</sup> However, recent meta-analyses have concluded that the use of metformin did not promote a consistent benefit in patients with hepatic steatosis.<sup>41,42</sup> Therefore, its use is reserved for the management of patients with fatty liver and associated type 2 diabetes as it improves the metabolic parameters and promotes moderate weight loss.<sup>43</sup>

### Thiazolidinediones

Thiazolidinediones improve insulin sensitivity in adipose tissue, activating nuclear transcription factor PPAR $\gamma$ .<sup>44</sup> The two drugs in this class that have been studied in the treatment of NASH are pioglitazone and rosiglitazone. A series of well-designed randomized clinical trials has shown the efficacy of these medications in the improvement of fatty liver, inflammation, cell ballooning, and possibly fibrosis.<sup>45-47</sup>

In the multicenter, randomized PIVENS (Study of Pioglitazone *versus* Vitamin E *versus* Placebo for the Treatment of Non-Diabetic Patients with Hepatic Steatosis) study, 247 adults with NASH and without diabetes were randomized to receive one of three treatments (placebo, n=83; vitamin E 800 IU/day, n=84, or pioglitazone 30 mg/day, n=80) for 96 weeks. Although pioglitazone did not achieve its main objective, it improved insulin sensitivity and decreased steatohepatitis (34 *vs.* 19%; p=0.04) compared to the placebo.<sup>23</sup> A recent meta-analysis assessing four randomized clinical trials (three with pioglitazone and one with rosiglitazone) showed improvement in steatosis, inflammation and cell ballooning, but no improvement in fibrosis. However, by limiting the analysis to studies with pioglitazone, a significant improvement in fibrosis is observed (OR 1.68, 95CI 1.02-2.77).<sup>48</sup>

TZD therapy is not free of side effects, which may limit its clinical usefulness. Both pioglitazone and rosiglitazone are associated with an average weight gain of 3 to 4 kg with long-term treatment, and retrospective assessments have linked TZD therapy to decreased bone mineral density and fractures.<sup>49</sup> Recent evidence has associated the use of rosiglitazone with increased rates of myocardial infarction, which has reduced this agent being indicated as a therapeutic option.<sup>50,51</sup> However, piogli-



tazone remains available and is considered as a potential treatment for patients with NASH.

## NEW APPROACHES AND TREATMENT SUMMARY

### Obeticholic acid

Obeticholic acid (OCA), a derivative of chenodeoxycholic acid, is a selective agonist of the farnesoid X receptor (FXR), which is a nuclear hormone receptor that regulates glucose and lipid metabolism. Several preclinical studies have shown that OCA increases sensitivity to insulin and regulates glucose homeostasis, modulates lipid metabolism, and exerts anti-inflammatory and fibrotic effects on the liver, kidney and intestine, the main organs expressing FXR.<sup>52</sup>

A recent multicenter, double-blind, controlled and randomized study has evaluated the effectiveness of OCA in non-cirrhotic NASH patients. Patients were randomly distributed 1:1 to receive the treatment administered orally with OCA (25 mg/day) or a placebo for 72 weeks. OCA was associated with improvement of the histologi-

cal characteristics of NASH in comparison with the placebo.<sup>53</sup> More studies are required to prove the benefits of this drug in the long term and its actual safety, especially in relation to changes in the lipid profile.

Table 2 presents the main options for the treatment of NAFLD.

## CONCLUSION

Lifestyle intervention remains the cornerstone of NAFLD treatment. However, it is well recognized that lifestyle changes in diet and exercise are difficult to achieve and maintain in the long term. Current guidelines recommend that pioglitazone and vitamin E may be used to treat steatohepatitis in non-diabetic patients, despite inconclusive data about their long-term safety. Other conditions associated with NAFLD must also be controlled, such as *diabetes mellitus* and dyslipidemia. Large studies should be performed to better assess the efficacy and safety of antioxidant or cytoprotective drugs and to find possible

**TABLE 2** Treatment options in non-alcoholic fatty liver disease.

Modality	Effect	Comments
<b>Diet</b>		
Weight loss of 5-10%. Moderate calorie restriction. Reduce 500-750 kcal/day	Improves histology in NASH	Only 40% of patients are able to achieve these goals. A loss of at least 10% is necessary to decrease fibrosis
Eliminate or significantly reduce saturated fats and fructose in the diet	Fructose increases lipogenesis through activation of pyruvate dehydrogenase	Prospective studies have shown that fructose consumption is a risk factor for NAFLD
Consider omega-3 supplementation	May decrease hepatic steatosis. Decreases triglyceride levels	The optimal dose is unclear, but some benefit may be achieved with a dose of 1 g/day
<b>Physical activity</b>		
≥ 250 min/week	Decreases insulin resistance and decreases hepatic steatosis	Benefits with aerobic or anaerobic physical activity. Best results associated with diet
<b>Pharmacological treatment</b>		
Vitamin E 800 IU/day	Improves histology in NASH	Benefits must be validated in diabetics and various ethnic groups. May increase the risk of prostate cancer
Pioglitazone 30 mg/day	Improves histology in NASH	Associated with weight gain. Possible increased risk of CHF and osteoporosis
Metformin	Improves metabolic parameters and promote moderate weight loss	No direct improvement in NAFLD. Its use is reserved for the management of patients with fatty liver and associated type 2 diabetes
Statins	Limited data relating to histological improvement	Safe in patients with NAFLD. Decreases the risk of cardiovascular diseases
<b>Bariatric surgery</b>		
Roux-en-Y gastric bypass; adjustable gastric band; vertical gastrectomy	Improves histology in NASH in up to 80% cases, including fibrosis	Few randomized and controlled studies; caution in patients with cirrhosis; lifestyle change should be attempted first

Adapted from Torres et al.<sup>5</sup>

NASH: non-alcoholic steatohepatitis; NAFLD: non-alcoholic fatty liver disease; CHF: congestive heart failure.

medication that could directly affect the pathophysiology of hepatic steatosis.

## RESUMO

Atualidades no tratamento da doença hepática gordurosa não alcoólica

A doença hepática gordurosa não alcoólica (DHGNA) é caracterizada pela deposição significativa de lipídios nos hepatócitos de pacientes que não apresentam história de ingestão alcoólica significativa. É a doença do fígado mais prevalente em populações ocidentais e existe forte associação da DHGNA com a resistência à insulina (RI) e com a síndrome metabólica. O tratamento objetiva reduzir a RI, o estresse oxidativo, a obesidade, a dislipidemia bem como a inflamação e a fibrose hepáticas. O tratamento atual baseia-se principalmente em modificações do estilo de vida, que incluem dieta e prática regular de exercícios físicos, associadas ao tratamento de todos os componentes da síndrome metabólica. Quanto ao tratamento medicamentoso da esteato-hepatite não alcoólica, os agentes insulino-sensibilizantes e os antioxidantes parecem os mais promissores, especialmente as tiazolidinodionas e a vitamina E, mas faltam estudos multicêntricos avaliando sua segurança a longo prazo.

**Palavras-chave:** hepatopatia gordurosa não alcoólica, esteatose hepática, esteato-hepatite, síndrome metabólica, obesidade.

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