

## CURRENT MANAGEMENT OF NAFLD

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### *Abstract*

*Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in Western countries. It affects about 1 billion individuals worldwide. While people with simple steatosis have no higher risk of death than the general population, people with non-alcoholic steatohepatitis are at increased risk of death compared to general population. Current management for NAFLD includes diet and lifestyle changes, management of underlying metabolic risk factors and pharmacological therapies. The objective of therapy is to prevent the complications. The problem with dietary and lifestyle interventions is that they are hard to implement. Compliance is the key. Until now, there is still no approved drug for the treatment of NAFLD. Insulin resistance is the main target of pharmacological therapy, but the question that we ask ourselves as physicians is who should receive medical treatment among NAFLD patients and for how long.*

**Keywords:** NAFLD, NASH, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, fatty liver

### **Introduction**

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in Western countries. It affects around one-third of adults, which means about 1 billion individuals worldwide [1]. NAFLD represents the spectrum of liver disease ranging from simple steatosis (fatty infiltration of >5% of hepatocytes), non-alcoholic steatohepatitis (NASH - steatosis, hepatocyte ballooning and focal inflammation), fibrosis and cirrhosis, in the absence of alcohol consumption, less than 20 g/day for women and less than 30g/day for men [2]. Other causes of steatosis, such as viral, autoimmune, iron overload, drugs, must be excluded. NASH is the progressive form of NAFLD, which can gradually develop advanced fibrosis, cirrhosis, hepatocellular carcinoma and, eventually, liver-related mortality [1]. NAFLD is strongly associated with features of metabolic syndrome (MS), especially obesity and diabetes, therefore considered to be

the hepatic manifestation of the metabolic syndrome [1]. The prevalence of NAFLD in patients with obesity and diabetes is much higher, ranging from 70% to 90% [3].

While people with simple steatosis run no higher risk of death than the general population, people with NASH are at increased risk of death compared to the general population, the causes of death being cardiovascular, malignancy and liver-related [4]. NAFLD is expected to become, by 2030, the main indication for liver transplantation worldwide [5].

Until now, there is still no approved drug for the treatment of NAFLD. This is due to several misconceptions. NAFLD was first considered a benign manifestation of obesity, then it was considered as one of the complications of diabetes, and finally there were believes that clinical trials regarding NAFLD therapies would require histological documentation of NASH [6]. Other obstacle for drug development in NAFLD is the fact that some pharmacological therapies only work well in rodent models of NASH, not in humans [6]. This is due to the differences between rodent NASH models and humans regarding the replication of insulin resistance (IR), associated metabolic

conditions, genetic variants and progression to advanced fibrosis [6].

### **Management of NAFLD**

Current management for NAFLD includes diet and lifestyle changes for achieving weight loss, management of underlying metabolic risk factors and pharmacological therapies, where there is evidence of NASH, or of advanced fibrosis.

#### ***Diet and lifestyle changes***

Patients with NAFLD have unhealthy lifestyle consisting in both inappropriate diet and absence of physical activity [6]. The usual diet of the NAFLD patient is characterized by overconsumption of fructose, soft drinks, meat, saturated fat, and underconsumption of fiber, fish omega-3 fatty acids, some vitamins [6]. The good news is that relatively small amounts of weight loss result in significant reductions in liver fat with hepatic IR improvement [7].

There are very few randomized controlled trials (RCTs) of dietary and lifestyle interventions in NASH patients. In a small well-designed RCT 32 patients were randomized to receive diet and healthy lifestyle interventions, over a period of 48 weeks, involving dietitians, nutritionists, psychologists, physical coaches [8]. The authors concluded that a 7% weight loss led to histological improvement of NASH in terms of steatosis, ballooning injury, lobular inflammation and NAS score (an aggregate score of steatosis and NASH histological activity) [8]. However, such a wide lifestyle intervention, involving such a complex intervention team, is unlikely to be implemented in every day practice. Weight loss also results in ALT improvement and normalization, which is expected, given the histological benefit of slimming [9].

Caloric restriction seems to be the most important factor in dietary interventions, because it is the main driver for weight loss, for reduction of liver and subcutaneous fat, and for visceral adiposity [10]. The macronutrient composition seems to have no effect on weight loss, as long as it is achieved [6]. Recent data suggest that Mediterranean diet might bring some benefits in terms of liver fat and hepatic IR, even without weight loss [11]. This stresses the importance of monounsaturated and polyunsaturated fatty acids on a healthy diet.

Massive weight loss after bariatric surgery can improve substantially liver histology, including resolution of NASH, reduction of fibrosis, even partial reversal of cirrhosis [6]. These benefits are obtained through reduction of adipose tissue pro-inflammatory mediators (TNF- $\alpha$ , IL-6), thus improving hepatic IR and inhibiting hepatic inflammation [12]. However, bariatric surgery for NASH is not recommended as first-line treatment, while in obese patients requiring bariatric surgery, NASH does not represent a contraindication [13].

About one third of NAFLD patients have no physical

activity and half of them are inactive [14]. The benefits of physical exercise consists in reduction of the risk of type 2 diabetes, hypertension, dyslipidemia, metabolic syndrome, and IR [15]. Also, all-cause mortality and cancer mortality are reduced by a minimum of 15 minutes of daily exercise [16]. Regarding NAFLD, exercise reduces hepatic fat content, apoptosis, visceral adipose tissue, plasma free fatty acids, and it reduces the likelihood of having NASH and, in the context of NASH, the likelihood of having advanced fibrosis [6]. Besides exercise, reducing sedentary time is also important, because sedentary time increases all-cause mortality independent of physical activity [17]. Sedentary time also predicts higher levels of IR [18]. There are no studies yet on sedentary times in NAFLD patients, but, reducing to a minimum the sedentary time, should be a general recommendation for this patients.

The problem with dietary and lifestyle interventions is that it is hard to implement them and, once implemented, most of the patients will fail to maintain them long term. The best approach is to combine caloric restriction with exercise, but keeping in mind to set realistic goals for this patients, given the fact the long-term success of these measures is based on compliance.

#### ***Pharmacological therapies***

The question that we ask ourselves as physicians is who should receive medical treatment among NAFLD patients. The American guidelines recommend that only biopsy-proven NASH should receive medical treatment [13].

There are several drugs tested for the treatment of NAFLD that are not yet recommended. Among these, are pentoxifylline, UDCA, omega-3 fatty acids, metformin [19]. All those therapies have discordant results, and this is why there is a need for further studies to confirm their usefulness [19].

Insulin sensitizing medication has been the cornerstone of NASH medical treatment for several years. Glitazones are the class of drugs with the best evidence-based data so far. Glitazones increase the synthesis and uptake of the fatty acids by the adipocytes, leading to fatty acids loading of the adipose tissue, instead of other organs, such as liver and muscle [6]. They also upregulate adiponectin, an adipokine with anti-steatogenic and insulin-sensitizing properties [20]. Pioglitazone has been shown to improve histological NASH in terms of steatosis, inflammation, ballooning, NAS score and resolution of NASH [21]. It is not known if the efficacy of pioglitazone is related to the degree of IR or to the diabetic state and which is the optimal duration of treatment [6]. Therapy with rosiglitazone for three years did not show any additional histological benefit compared to the one observed after the first year of treatment [22]. This might suggest some limited benefit that glitazones have over the liver, once a certain limit of metabolic improvements is achieved. However, such a long follow-up study regarding pioglitazone does

not exist at this time. Three months after discontinuation of therapy, the beneficial effects of pioglitazone are gone, ALT and HOMA values return to baseline and histological NASH reappears [23]. Due to side effects, especially cardiovascular and metabolic (weight gain), and because long term safety and efficacy of pioglitazone is not established, long term use of pioglitazone is under debate [6,13]. However, for diabetic biopsy-proven NASH patients, pioglitazone may be considered [13].

Vitamin E is a fat soluble compound. It is part of the cell membrane, and protects it from oxidative damage induced by free radicals [6]. It prevents liver injury by blocking intrinsic apoptotic pathways and by protecting against mitochondrial toxicity [24]. Vitamin E improves histological NASH in terms of steatosis, inflammation, ballooning, NAS score, and resolution of NASH at a dose of 800 IU/day [21]. The reduction in ALT is correlated with histological improvement, which means that histological non-responders patients do not have reduced ALT levels [25]. However, there are some concerns about the long term use of vitamin E. Its long term use is associated with increased all-cause mortality, increased incidence of hemorrhagic stroke and increased risk of prostate cancer [26]. In non-diabetic biopsy-proven NASH patients, vitamin E may be considered [13].

Neither pioglitazone nor vitamin E have any effect on fibrosis [21]. This is of interest, considering that fibrosis is the only histological determinant that can predict both all-cause mortality and liver-related mortality, patients with fibrosis stage 3-4, irrespective of NAS, having increased mortality [27].

Obeticholic acid is a potent activator of the farnesoid X nuclear receptor (FXR). Once activated in the liver, FXR reduces bile acid synthesis, improves insulin sensitivity and decreases gluconeogenesis, and reduces inflammation, lipogenesis and fibrosis [28]. Recently, obeticholic acid, 25mg/day for 72 weeks, for non-cirrhotic NASH, has been shown to improve all histological lesions of NASH, including fibrosis [29]. The side effects of the therapy included pruritus and an increase of LDL cholesterol levels [29]. Further studies are awaited in order to assess if the increased LDL cholesterol levels translate into increased cardiovascular risk, given that the therapy with obeticholic acid emerges as a promising one.

Liraglutide is a long acting GLP-1 (glucagon-like peptide-1) agonist. GLP-1 is a peptide secreted after meal by the L cells of the small bowel and proximal colon which stimulates insulin secretion by the pancreatic beta cells, decrease hepatic glucose production, increasing satiety by delaying gastric emptying, and has cardioprotective effects [30]. GLP-1 has a half-life of less than 2 minutes, while, Liraglutide, the synthetic analogue, has a half-life that allows single day administration [30]. In a phase II trial, administered once daily, 1.8mg in subcutaneous injection, produces resolution of NASH and improves key metabolic

risk factors (weight, body mass index, glucose level, HDL cholesterol) with minimum of side effects, mainly gastrointestinal, such as diarrhea [30]. Phase III trials are awaited to confirm these preliminary data, but it seems like a promising medication to treat NASH.

An innovative insulin sensitizer is the dual PPAR $\alpha$ / $\delta$  (peroxisome proliferator-activated receptor alpha/delta) agonist called GFT505. PPAR $\delta$  induces hepatic fatty acid oxidation, inhibits hepatic lipogenesis, reduces glucose production by the liver and improves liver inflammation [31]. Human studies on obese, insulin-resistant patients, with or without diabetes, have shown that this compound improves inflammation and liver function tests, peripheral and hepatic insulin sensitivity and dyslipidemia [32]. Based on this data, there is an ongoing phase IIb randomized trial on NASH patients.

Therapy under development for NASH includes cenicriviroc (a CCR2-CCR5 antagonist) with anti-inflammatory and antifibrotic effects, aramchol (a fatty acid-bile acid conjugate, arachidic acid and cholic acid) with antisteatogenic and metabolic effects, simtuzumab (a humanized, anti-lyzyl-oxidase-like 2 monoclonal antibody) with antifibrotic effects.

#### ***Mangement of underlying metabolic risk factors***

All patients with NAFLD require treatment of associated metabolic risk factors, such as diabetes, hypertension and dyslipidemia. The treatment of patients with type 2 diabetes and NAFLD can include metformin, pioglitazone, GLP-1 agonist, insulin or sulfonylureas [26]. Antihypertensive medication can bring additional benefit, besides lowering hypertension, when there are used blockers of the renin-angiotensin- aldosterone system, and in particular, sartans [33]. Statins are safe to use in NAFLD population [19]. In addition to the beneficial effect on dyslipidemia, they improve liver function [34] and reduce the risk of HCC [35].

#### **Conclusions**

Lifestyle changes with weight loss and exercise along with control of underlying risk factors remains the cornerstone of the therapy. The objective of therapy is to prevent the complications. Attention should be focused on reducing the cardiovascular risk. This is of particular interest, since NASH is not included in current heart risk models. This raises the question about how often should NAFLD patients get cardiovascular monitoring. Regarding dietary and lifestyle changes, compliance is the key. On the other hand, one should not wait too long to initiate pharmacological therapy if these patients fail to achieve the minimum weight loss required. There are no data regarding a limit up to which lifestyle changes are efficient and if severe disease can respond to lifestyle changes. IR is the key to be targeted with pharmacological therapy. But we definitely need better approaches since not all insulin-

sensitizing therapy is effective. Once pharmacological therapy is started a question to be raised is how long to maintain it. Is it indefinitely? We do not have enough data for this. Is it response-limited? In this case, the need for reinstating medical therapy will occur once the benefit is gone. All these questions might receive some answers from the new promising therapies under investigation and from non-invasive methods for monitoring the disease progress. In the end, the question still remains: who needs therapy and who needs monitoring, or perhaps all patients need both.

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