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Management of Nonalcoholic Fatty Liver Disease (NAFLD)

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<http://dx.doi.org/10.5772/intechopen.72000>

Abstract

Although there is an epidemic of NAFLD throughout the world, the management of NAFLD is not very satisfactory at the present time. Lifestyle modification is the main mode of therapy. Other modalities like pharmacotherapy and bariatric endoscopy or surgery should be individualized. Various pharmacological agents are being investigated to optimize the treatment of NAFLD.

Keywords: nonalcoholic fatty liver disease, fatty liver, hepatic steatosis, nonalcoholic steatohepatitis, NASH, treatment of NAFLD

1. Introduction

When we consider the management of Nonalcoholic Fatty Liver Disease (NAFLD), two aspects should be considered. One is that it can be a part of the metabolic syndrome [1]. About 80% of patients with metabolic syndrome have NAFLD [2]. Although the prevalence of NAFLD is 20–40% in the general population, about 70% of type 2 diabetes mellitus [3] and 85% of patients with morbid obesity (BMI ≥ 40) have NAFLD [4]. In the general population, 80% of patients with NAFLD are overweight and 20% of NAFLD patients have normal weight as per ultrasonography [5]. Another aspect is that it covers a spectrum of hepatic involvement as it progresses slowly from one stage to another. Initially, it starts as simple steatosis or benign fatty liver disease or nonalcoholic fatty liver (NAFL), where there is only macrovesicular hepatic steatosis ($>5\%$ of hepatocytes are affected) without any inflammation, hepatocellular injury or fibrosis [6]. The second phase is nonalcoholic steatohepatitis (NASH) where there is not only hepatic steatosis but also ballooning degeneration of hepatocytes and mixed inflammatory cells (lymphocytes, plasma cells, monocytes, neutrophils and eosinophils) infiltrates mainly involving the hepatic acini [7]. The third phase is hepatic fibrosis

which generally starts from zone 3 and progresses to bridging fibrosis, cirrhosis of liver and hepatocellular cancer. Prognosis depends on the degree of liver fibrosis [8].

2. Purpose

The main purpose of management of NAFLD is to halt the process as soon as it is diagnosed. The three main modalities of therapy include lifestyle modification, pharmacotherapy and bariatric surgery. Lifestyle modification is applicable to all stages of NAFLD, whereas pharmacotherapy and bariatric surgery should not be considered for patients with simple steatosis. Pharmacotherapy should be considered only for patients with biopsy-proven NASH and hepatic fibrosis as per the guideline of American Association for the Study of Liver Diseases (AASLD).

3. Lifestyle modification

As NAFLD is related to insulin resistance, gradual weight loss is extremely important in overweight and obese individuals [9]. Rapid weight loss can cause portal inflammation and fibrosis [10]. About 7–10% of weight loss over one year by lifestyle changes has been associated with histological improvement in simple steatosis and NASH [11]. Another study showed vigorous and moderate exercises were equally effective in reducing hepatic triglyceride content largely through weight loss [12]. Diet and moderate aerobic exercise are the first line measures to reduce weight and improve insulin resistance [13]. Dietary counseling should be highly encouraged. Consumption of high fructose containing food is the main cause of epidemic of obesity [14]. Patient should avoid high fructose containing foods like sweet, soda, desserts, breakfast cereals, granola bars and cakes. One study showed that in patients with NAFLD, fructokinase and fatty acid synthase activity are increased [15]. NAFLD may occur when there is a combination of genetic predisposition, sedentary life style and consumption of high-calorie foods [16]. One meta-analysis suggested that Omega-3 fatty acid supplementation in diet was beneficial in patients with NAFLD/NASH [17]. Patients should be encouraged to eat food rich in Omega-3 fatty acid (fish, canola, olive, perilla and chia). Food with high glycemic effects and saturated fat should be avoided [18].

In summary, lifestyle modification is the first line intervention in the management of NAFLD. This includes [1] weight loss of about 7–10% of body weight by a combination of diet and exercise [2], low-calorie diet [3], diet with high fructose and saturated fat should be avoided [4], diet with Omega-3 fatty acid supplement should be encouraged.

4. Pharmacotherapy

There are various pharmacological agents available for the management of NAFLD. Many of them have been found to be ineffective and some of them have high risk-benefit ratio [19]. There are various clinical trials ongoing. Here, we discuss the common agents available and the agents recommended by the American Association for the Study of Liver Diseases (AASLD).

4.1. Antioxidants

Progression of simple steatosis to steatohepatitis is related to oxidative stress and free radical formation. Vitamin E has been studied in different clinical trials. One study showed that patients with vitamin E deficiency and NAFLD did not respond to the classical diet for NAFLD [20]. In PIVENS trial, vitamin E 800 units per day was associated with improvement of serum transaminases and liver histology in nondiabetic NAFLD patients [21]. Fibrosis scores were not improved in this trial [22]. In SELECT trial, vitamin E supplementation 400 units per day in healthy individuals was associated with significant increase in prostate cancer [23].

Currently, vitamin E 800 units per day is recommended in nondiabetic individuals with biopsy-proven NASH [19].

4.2. Insulin sensitizing agents

4.2.1. *Thioglitanones (TZD)*

They are agonists/selective ligands of nuclear transcription factor PPAR- γ (peroxisome proliferator-activated receptor-gamma) which is present in pancreatic β -cells, adipocytes, skeletal muscles, endothelial cells and macrophages. They increase insulin sensitivity in NAFLD and thus, promote fatty acid transportation from liver and skeletal muscles into adipose tissue, decrease serum-free fatty acid concentration and increase fatty acid oxidation in the liver [24]. Pioglitazone 30 mg/day improved hepatic steatosis, steatohepatitis and transaminitis in nondiabetic patients with NASH in the PIVENS trial but histological response did not reach statistical significance [22]. Another study showed that in prediabetic and diabetic patients, long-term treatment with pioglitazone 45 mg/day improved not only steatotic and inflammatory activity but also hepatic fibrosis [25]. There are few concerns about the side effects of TZD and these include weight gain [26], bone loss [27] and congestive heart failure [28].

As pioglitazone improves histology of NASH in both diabetic and nondiabetic individuals, it can be used in biopsy-proven NASH. Patients should be informed about the efficacy and side effects of this medication.

4.2.2. *Incretin-based therapy*

Glucagon-like peptide 1 (GLP-1) receptor agonists (liraglutide and exenatide) not only improves insulin sensitivity but also causes weight loss by suppressing appetite and inhibiting gastric emptying [29]. They are primarily used to control diabetes mellitus at this time. There are case reports of improvement of hepatic steatosis by GLP-1 receptor agonists [30]. Another study found that liraglutide given daily improved steatohepatitis and decreased progression of fibrosis [31].

Although incretin mimetics have been found to be helpful in diabetic patients with NAFLD, they are currently not recommended solely to treat NASH or NAFLD [19].

4.2.3. Bariatric surgery

As sustained weight loss is achievable by bariatric surgery, all the features of metabolic syndrome improve and there is reduction in mortality [32]. In a prospective study, NASH disappeared in 70% (severe NASH) to 94% (mild NASH) of patients 1 year after bariatric surgery [33]. There are various bariatric surgical and endoscopic procedures available and approved for morbid obesity at the present time. Laparoscopic sleeve gastrectomy is most commonly done in the United States [34]. Other surgical procedures include gastric bypass, biliointestinal bypass, biliopancreatic diversion with duodenal switch, vertical band gastroplasty and gastric banding. Various endoscopic procedures include intragastric balloon placement, endoscopic sleeve gastroplasty [35] and duodenal mucosal resurfacing [36]. Bariatric endoscopy is successful in reducing more weight than pharmacological agents but less effective than bariatric surgery but has less complications than bariatric surgery. Bower et al. found in a systematic review of studies that bariatric surgery improved steatosis, steatohepatitis and fibrosis in NAFLD [37]. Patients with cirrhosis of liver due to NAFLD are at a higher risk for bariatric surgery [38]. Another study showed that perioperative mortality was higher in patients with NAFLD with cirrhosis than in patients with NAFLD without cirrhosis [39].

Nowadays, bariatric surgery is not recommended as a primary treatment of NAFLD but it can be considered in obese individuals with noncirrhotic NAFLD [19].

4.2.4. Ursodeoxycholic acid (UDCA)

UDCA has cytoprotective effect and can improve serum transaminases in NAFLD but cannot alter liver histology [40].

UDCA is not recommended for the treatment of NAFLD or NASH [19].

4.2.5. Omega-3 fatty acids

Although in animal models, omega-3 fatty acid treatment improved hepatic steatosis [41, 42], recent studies did not show any significant effect on serum transaminases or liver histology [43]. Omega-3 fatty acid is not recommended for the treatment of NAFLD or NASH.

4.2.6. Obeticholic acid (OCA)

OCA is a ligand of farnesoid X receptor (FXR) which is a nuclear receptor present in liver, kidneys, intestine and adipose tissue. FXR controls target genes involved in bile acid synthesis and transport as well as lipid and carbohydrate metabolism. In the farnesoid X receptor ligand obeticholic acid in NASH treatment (FLINT) trial, OCA induced weight loss and improved hepatic fibrosis but resolution of NASH was not statistically more than placebo. OCA decreased serum transaminases but increased serum alkaline phosphatase, LDL and blood glucose levels [44].

Currently, OCA is not recommended in the routine management of NAFLD awaiting the completion of phase 3 trial (REGENERATE) of OCA for the treatment of NASH patients with liver fibrosis [45].

5. Elafibranor

Elafibranor is an agonist of PPAR- α and δ receptor. It has anti-inflammatory activity and can improve insulin sensitivity and lipid metabolism. It was evaluated in a phase II international study for the treatment of NASH [46]. In the post hoc analysis, elafibranor (120 mg/day for 1 year) group showed resolution of NASH without progression of fibrosis more than placebo (19% vs. 12%).

As the improvement was marginal, further studies are needed before using this agent in the treatment of NAFLD.

5.1. Statins

Hyperlipidemia is frequently seen in patients with NAFLD as part of the metabolic syndrome. Statins are commonly used for the treatment of hyperlipidemia, and low-to-moderate dose of statins have been found to be safe with low hepatic toxicity [47]. Statins decrease hepatic transaminases and hepatic fat but have no effect on hepatic fibrosis [48, 49].

Statins are not currently recommended solely for the treatment of NAFLD unless the patient has concomitant hyperlipidemia.

5.2. Orlistat

Orlistat is used as a weight reducing agent as it induces fat malabsorption by inhibiting enteric and pancreatic lipase [50]. A randomized controlled trial showed that orlistat improved transaminitis and hepatitis steatosis in obese individuals with NAFLD [51]. Subsequent study suggested that orlistat did not have any direct effect on NAFLD, overweight subjects improved their hepatic histology if they achieved $\geq 5\%$ weight loss irrespective of taking orlistat [52].

Currently, orlistat cannot be recommended primarily for NAFLD.

5.3. NAFLD and cirrhosis

Patients should be managed the same way as in other cirrhosis. Patients with NAFLD-cirrhosis have 2.6% annual cumulative risk of developing hepatocellular cancer [53]. For every 6 months, abdominal ultrasound is recommended for screening of hepatocellular carcinoma. In obese individuals, if ultrasound is technically difficult, CT or MRI should be considered. As obesity and hyperinsulinemia are risk factors for malignancy, liver cancer can occur even in noncirrhotic NAFLD [54]. Screening for esophageal and gastric varices should be done at base-line of diagnosis of cirrhosis and at regular intervals—no varices: every 2–3 years, small varices—every 1–2 years and decompensated cirrhosis—yearly once [55].

With the epidemic of NAFLD, NASH-cirrhosis and hepatocellular carcinoma will be the leading indication of liver transplantation in future. As patients with NAFLD have multiple metabolic and cardiovascular comorbidities, they should be managed posttransplant appropriately. Management of NAFLD involves multiple specialties which include primary care physicians, gastroenterologists, hepatologists, endocrinologists, bariatric surgeons, transplant surgeons, dietitians and nutritionists.

6. Future therapy

As hepatic inflammation, fibrosis, cirrhosis and subsequent malignancy are the main concerns of NAFLD, plenty of research and studies on anti-inflammatory and anti-fibrotic agents are on-going.

7. Summary

The management of NAFLD patients should be individualized (**Table 1**).

- Lifestyle change is the first line therapy: healthy food habit, increased physical activity, exercise and weight loss of 7–10%.
- Pharmacotherapy is to be considered when lifestyle changes fail to achieve the goal: vitamin E in nondiabetic biopsy-proven NASH, pioglitazone in both diabetic and nondiabetic biopsy-proven NASH, incretin mimetics in diabetes mellitus and NAFLD, statins in hyperlipidemia and NAFLD, orlistat in NAFLD and obesity when life-style changes fail to reduce weight loss.
- Bariatric surgery should be considered in obese individuals and noncirrhotic NAFLD.

Lifestyle changes	First line therapy of NAFLD
Vitamin E	Nondiabetic biopsy-proven NASH
Pioglitazone	Both diabetic and nondiabetic biopsy-proven NASH
Incretin mimetics	Diabetes mellitus and NAFLD
Statins	Hyperlipidemia and NAFLD
Orlistat	NAFLD and obesity when lifestyle changes fail
Bariatric surgery	Morbid obesity and noncirrhotic NAFLD

Table 1. Summary of management of NAFLD.

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