Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease that exposes patients to a great risk of emerging cardiovascular diseases and could develop to cirrhosis or hepatocellular carcinoma if left unmanaged.

Objective of the Study: this article is intended to provide an overview and explore the optimal intervention for management of NAFLD in the short and long term.

Methods: Electronic search in the scientific database from 1966 to 2017– (Medline, Embase, the Cochrane Library as well as NHS center websites were searched for English Publications were obtained from both reprint requests and by searching the database. Data extracted included authors, country, year of publication, age and sex of patients, epidemiology, geographical distribution, pathophysiology, risk factors, clinical manifestations, investigations and types of surgical treatment.

Conclusion: It was concluded from the extensive review of the literature that Lifestyle modification including diet, physical activity and controlling metabolic disorders are the cornerstone in current management of NAFLD. Nevertheless, Insulin-sensitizing agents and antioxidants, particularly thiazolidinediones and vitamin E, seem to be a very promising pharmacologic treatment for non-alcoholic steatohepatitis, yet further long-term multicenter studies need to be conducted for confirmation and assessment.

Keywords: Cirrhosis, steatosis; steatohepatitis; metabolic syndrome, NAFLD, NASH.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is defined by the presence of hepatic macrovesicular steatosis in the presence of less than 20 g of alcohol ingestion per day [(1)].Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disease from land steatosis (NAFLD) to steatohepatitis (NASH) to progressive fibrosis and, ultimately, cirrhosis with portal hypertension to irreversible cirrhosis [(2)].

At the least advanced end of the spectrum, non-alcoholic fatty liver (NAFL) is an excess of fat in the liver (steatosis) present in 20-30% of the general population and is largely asymptomatic [(3)].

Most people with NAFLD have simple fatty liver. Only a small number of people with NAFLD have NASH. Experts estimate that about 20 percent of people with NAFLD have NASH [(4)]. Between 30 and 40 percent of adults in the United States have NAFLD. About 3 to 12 percent of adults in the United States have NASH [(4)].

NAFLD can progress without clinical manifestations for many years. The symptoms can be unspecific (for example, fatigue, elevated liver injury markers). The diagnosis is typically established though liver biopsy and exclusion of other causes of liver disease. The treatment is centered on management of comorbidities (life style modification, weight loss, antidiabetic medication) [(5)].

For the meantime, no drugs have been approved by the American agency for Food and Drug Administration (FDA) for treatment of NAFLD. Safe and effective medication and noninvasive biomarkers that could distinguish patients at risk of progression to advanced disease are urgently needed [(6)].

It's important to first understand the predisposing factors of NAFLD before concluding on the appropriate intervention.

Predictors of Progressive Fibrosis in Non-Alcoholic Fatty Liver Diseases

1. Genetic Polymorphisms

Polymorphisms in the *PNPLA3* and *TM6SF2* genes are common in the general population with minor allele frequencies of 20%–50% and 10%, respectively [(7)].The rs738409 and rs58542926 single nucleotide polymorphisms (SNP's) of these respective genes have been identified by genome-wide association studies to be

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associated with an increased risk of NAFLD, as well the presence of more severe liver histology (*i.e.*, NASH and fibrosis) [7].

One study enrolling 1000 patients with biopsy proven NAFLD, demonstrated these SNPs were associated with a 40% to 88% increased risk for advanced (F2-4) fibrosis after adjustment for age, sex, and metabolic variables [8]. Likewise, a SNP in the *IFNL4* gene, which is associated with response to interferon based treatment in chronic hepatitis C, has also been associated with fibrosis in NAFLD and has been amalgamated into a predictive score in conjunction with other clinical factors [7].

2. Age

Cross-sectional studies have demonstrated that increasing age was consistently associated with more severe fibrosis in NASH patients; however, this may reflect the cumulative sum of metabolic exposures and longer duration of NAFL/NASH in these populations [9].In contrast, longitudinal studies have not consistently demonstrated age to impact the rate of fibrosis progression [10].

3. Metabolic Status

Diabetes and obesity have been demonstrated to be predictive of a higher rate of fibrosis progression in some but not all longitudinal studies [11].An increase or decrease in body mass index over time, has been associated with progression or resolution of liver fibrosis respectively in NAFLD patients and the emergence of diabetes also appears to parallel fibrosis progression, whereas improved glycemic control parallels fibrosis improvement [11].One meta-analysis examining the full spectrum of NAFLD found hypertension to be a risk factor for fibrosis progression, however an earlier meta-analysis limited to NASH patients did not [9].

4. Histological Factors

The degree of hepatic steatosis does not appear to predict disease progression in NASH. The degree of inflammation however, has been associated with progression to advanced fibrosis in a meta-analysis, but not in any single cohort study [9].

5. Sex

No consistent relationship between sex and fibrosis has been found in NASH, with cross-sectional studies reporting conflicting findings [12]. The relationship between sex and fibrosis may be influenced by menopausal status; cross-sectional studies have found men and post-menopausal women to have a higher risk of fibrosis compared with pre-menopausal women, and early menopause and duration of menopause to be associated with a higher risk of fibrosis [13].

6. Race and Ethnicity

Hispanic patients have an increased prevalence of NAFLD compared to Caucasians; however, there appears to be no difference in degree of liver injury between these ethnic groups [14].In contrast, Asian patients may be prone to more severe histological changes including ballooning, whereas African-Americans may have less severe histology, although factors such as diet may be confounding this relationship [15].

MANAGEMENT OF NFLAD:

A. *Life Style Intervention (DIET AND Exercise)*

Lifestyle intervention can be effective when treating non-alcoholic fatty liver diseases (NAFLD) patients. Weight loss decreases cardiovascular and diabetes risk and can also regress liver disease. Weight reductions of ⩾10% can induce a near universal non-alcoholic steatohepatitis resolution and fibrosis improvement by at least one stage. However, modest weight loss (>5%) can also produce important benefits on the components of the NAFLD activity score (NAS)[16].

It is recommended to perform exercises for at least 250 minutes per week [17]. 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 presented in table 1.

TABLE 1 Recently published clinical trials on the effect of diet associated with physical activity in patients with NAFLD [18].

Authors	Year	Diagnosis	n	Intervention	Results
Thameret al. [19]	2007	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
Lazo et al. [20]	2,010	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
Albu et al.et al. [21]	2010	MRI	58	Decreased calorie intake (-500 kcal/day) and increased PA (≥ 175 min/week), during 12 months	Reduction of fasting blood glucose and fat in the liver
Promratet al. [22]	2010	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
Ohet al. [17]	2014	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. [23]	2015	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.

B. *Bariatric Surgery and NAFLD*

The goal of bariatric surgery is not only to achieve satisfactory weight loss but also to obtain improvements in obesity-related comorbidities, including T2DM, obstructive sleep apnea syndrome, hyperlipidemia, and hypertension. However, no randomized controlled trials examining the effects of bariatric surgery on NAFLD were found in the literature search. Two meta-analyses evaluated the effect of bariatric surgery on the liver histology of patients with NAFLD [24]. Mummadi et al. [24] reported that the improvement or resolution rates of steatosis, steatohepatitis, and fibrosis of 15 studies and 766 paired liver biopsies after bariatric surgery were 91.6, 81.3, and 65.5%, respectively [24].Complete resolution of NASH was archived in 69.5% of patients. However, a recently published Cochrane review concluded that the lack of randomized clinical trials or quasi-randomized clinical studies has prevented a definitive assessment of the benefits and harms of bariatric surgery as a therapeutic approach for patients with NASH [25].

In a recent systematic review, post-operative resolution or improvement of T2DM occurred in 73% of patients [26].Potential mechanisms of T2DM remission underlying the direct anti-diabetic impact of bariatric surgery include enhanced nutrient stimulation of GLP-1, altered physiology from excluding ingested nutrients from the upper intestine, compromised ghrelin secretion, improved hepatic insulin sensitivity, and improved peripheral insulin sensitivity. The changes in the rate of eating, gastric emptying, intestinal transit time, nutrient absorption, and sensing, as well as bile acid metabolism, may also be implicated [27].Bariatric surgery, which offers the effects of metabolic surgery, should be considered for T2DM patients having difficulty continuing with medical treatment and a potential for future deterioration and diabetic complications.

C. ***Oxidative stress/inflammation***

- **ANTIOXIDANTS**

Oxidative stress is important in the pathogenesis of NASH, and antioxidants (vitamin E) may decrease levels of profibrinogenic TGF-β, improve histology, and inhibit hepatic stellate cell activation.

- **Vitamin E and Vitamin C**

Pilot studies with vitamin E have been conducted [28].with promising results in reducing aminotransferases. One randomized placebo controlled trial looked at the combination of vitamin E and vitamin C [29].Improvement in hepatic inflammation and fibrosis was detected. However, these differences were not significantly different from the placebo arm. A recent open label study compared vitamin E to metformin and weight loss [28].Vitamin E was inferior to metformin and/or weight loss in improving aminotransferases.

A recent meta-analysis of high dose vitamin E in the general population revealed an increase in overall mortality [30].Due to the possible increase in mortality with general use of antioxidants and the mixed results from clinical trials in NASH, the use of antioxidants is not recommended.

- **Pro-biotics/pre-biotics**

Probiotics may reduce hepatic injury in animal models where intestinal derived bacterial endotoxin sensitizes fatty livers to the effects of TNF-α. A 3-month treatment period of a commercially available probiotic, VSL #3, given to 22 patients with NAFLD did improve ALT levels and markers of lipid peroxidation [31].Histology was not evaluated in this trial.

- **Anti-cytokines**

Pentoxifylline

TNF-α is a pro-inflammatory cytokine that triggers the production of additional cytokines that recruit inflammatory cells and leads to the destruction of hepatocytes and induction of fibrogenesis. This cytokine is increased in NASH. Pentoxifyl-line is a methylxanthine compound that inhibits TNF-α and is a promising agent in the treatment of alcoholic hepatitis. A pilot study on 20 cpatients detected improvement gastrointestinal side effects led to early withdrawal in many patients[33]. It was in liver enzymes in patients with NASH [32].However, the high incidence of found that pentoxifylline reduced mean transaminase levels, reduced serum TNF-α levels, and improved insulin resistance in 18 patients over a 6 month period**[33]**. Another trial carried by by **Lee *et al.*[34]** investigated 20 patients with NASH and randomized them to 3 months of pentoxifylline or placebo. Both groups had significant decreases in BMI and aminotransferase levels, but there were no significant differences between groups. More patients who received pentoxifylline achieved normal AST. Both groups reported a significant decrease in TNF-α, Il-6, Il-8, and serum hyaluronic acid.

- **Glutathione precursors**

Betaine

Betaine is a component of the metabolic cycle of thionine and may increase S-adenosylmethionine levels. This process may protect against steatosis in alcoholic liver disease animal models. A small, 1-year trial showed that betaine significantly improved aminotransferase levels versus baseline [35]. In addition, a marked improvement in the degree of steatosis, necroinflammatory grade, and stage of fibrosis was observed. Abdelmalek*et al.*[35] then conducted a placebo-controlled, 12-month trial on 55 patients and reported that betaine did not significantly improve aminotransferases or liver histology.

- **Angiotensin II receptor antagonists**

Lorsartan

In a historically controlled study [36], losartan 50 mg daily was associated with improved aminotransferases, serum markers of fibrosis, and plasma TGF-β1. Histological improvements were detected in several of the patients: necroinflammation (5 patients), reduction of hepatic fibrosis (4 patients), and reduced iron disposition (2 patients).

D. Insulin-Sensitizing Drugs

Metformin and glitazones

Considering the close relationship between IR and the pathogenesis of fatty liver disease, insulin sensitizers could be regarded as the treatment of choice. Metformin and glitazones (TZDs) are the most popular drugs tested against NAFLD/NASH.

Metformin improves IR by decreasing hepatic glucose production and increasing skeletal muscle glucose uptake. This drug also reduces the hepatic expression of TNF-α, a mediator of hepatic insulin resistance and necro-inflammation; increases FFA oxidation; and suppresses lipogenesis through AMP-kinase activation. Metformin has been demonstrated to be safe and well tolerated in different studies, with poor cases of lactic acidosis and gastrointestinal intolerance emerging as the most common side effects but not generally requiring discontinuation of the therapy[37]. Despite these positive results regarding tolerance, further well-designed studies are needed to elucidate the significance of metformin treatment for NAFLD. In fact, not all studies have reported the same results for both serum liver enzymes and liver histology. The TONIC trial, which was the most recent randomized study of metformin, compared metformin with vitamin E and placebo in children and adolescents[38]. Again, the results were not satisfactory; in fact, there was no significant reduction in transaminases compared with placebo in the metformin group, and there was no significant change in histology, except for hepatocellular ballooning. Based on the results of these studies and others, metformin is not recommended as a specific treatment for liver disease in adults with NASH[39].

Thiazolidinediones

Thiazolidinediones improve insulin sensitivity in adipose tissue, activating nuclear transcription factor PPARγ[40].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[41].

In the multicenter, randomized PIVENS (Study of Pioglitazone *versus* Vitamin E *versus* Placebo for the treatment of Non-Diabetic Patients with Hepatic Steatosiss. A study on 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[42]. 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)[43].

Conversely, discontinuing TZD therapy has been shown to cause an immediate NASH recurrence. Long-term use is required for the achievement of treatment results; however, the duration can cause medical complications, such as edema, congestive heart failure, osteoporosis and weight gain[44].Overall, pioglitazone is commonly used as a treatment for NASH, as indicated by AASLD guidelines [45].However, the long term safety and efficacy of pioglitazone in patients with NASH have not been established.

E. New Approaches

Obeticholic acid

Non-alcoholic steatohepatitis is a heterogeneous disorder and diverse mechanisms of liver injury that promote disease progression might exist in different patient populations. Altered bile acid metabolism—the rationale for use of semisynthetic bile acids—has been more convincingly shown in individuals with diabetes than in those without[46], which might explain the absence of response to obeticholic acid in individuals without diabetes

FLINT trial[47] that investigate the effect of obeticholic acid on liver histology in non-alcoholic steatohepatitis. A remarkable yet overlooked result in the appendix of this trial was the difference in histological response between participants with diabetes and those without: for participants with diabetes, liver histology improved in 53% of patients who received obeticholic acid versus 19% for placebo (odds ratio [OR] for improvement with obeticholic acid 4·6, 95% CI 2·0–10·6, p=0·0003), while for patients without diabetes, liver histology improved in 37% patients with obeticholic acid versus 23% with placebo (OR 2·0, 95% CI 0·8–4·7, p=0·12). The effect of glucose intolerance on histological response to obeticholic acid was also shown across the progressive stages of pancreatic β cell dysfunction, as estimated by HOMA β cell index[47].

Moreover, consistent with other randomised trials of non-alcoholic steatohepatitis, the percentage of responders was less than 50% in the

FLINT trial, leaving a substantial proportion of patients without an effective treatment[46].

CONCLUSION AND RECOMMENDATION

Overall, NAFLD treatment is chiefly aiming at weight loss as well as controlling insulin resistance or dyslipidemia. Bariatric surgery has proved effective. However, no pharmacologic therapy has been yet approved, emerging data on Thiazolidinediones have shown improvement in both liver enzymes and histology. There are fewer, but promising data, with statins which have been shown to be hepatoprotective in other liver diseases.

Current guidelines recommend that pioglitazone and vitamin E may be used to treat steatohepatitis in non-diabetic patients, not withstanding unsettled 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 medication that could directly affect the pathophysiology of hepatic steatosis.

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