Nonalcoholic Fatty Liver Disease: Evidence based management

ANUPAM K SINGH, ARVIND KUMAR, S.F HAQUE

INTRODUCTION

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ABSTRACT

The fatty change and the inflammation spectrum are similar to the alcoholic fatty liver disease. While primary or idiopathic NAFLD forms the major part of this disease spectrum, we should always address secondary causes leading to fatty changes in liver. Management consists of general measures of risk reduction like: instituting weight loss program, diet control, exercise, weight loss drugs, use of insulin sensitizers like metformin and thiazolidinediones, use of cytoprotective agents like vitamin E, betaine and hypolipidemics like statins.

INTRODUCTION

Hepatic steatosis (commonly called fatty liver) is mostly an asymptomatic liver disease, which is diagnosed mostly as a part of an unrelated condition. It was considered to be a benign consequence of chronic alcohol intake. In absence of alcohol intake of >20 g/day, it is termed as nonalcoholic fatty liver disease (NAFLD). Nonalcoholic fatty liver disease consists of accumulation of fat within hepatocytes with/without inflammatory changes. The fatty change and the inflammation spectrum are similar to the alcoholic fatty liver disease. While primary or idiopathic NAFLD forms the major part of this disease spectrum, we should always address secondary causes leading to fatty changes in liver. Management consists of general measures of risk reduction like: instituting weight loss program, diet control, exercise, weight loss drugs, use of insulin sensitizers like metformin and thiazolidinediones, use of cytoprotective agents like vitamin E, betaine and hypolipidemics like statins.

In this Review we shall address the mechanism of action of these management strategies, efficacy as seen in clinical trials, and critically evaluate the current evidence for their use in view of recent guidelines and recommendations.

LIFESTYLE MODIFICATION

Weight Reduction

A 1 year weight loss intervention in 15 subjects with nonalcoholic steatohepatitis (NASH) that achieved only an average 3 Kg weight loss resulted in an improvement in histology in 9 subjects.2,3 Those with improved histology were found to have had greater weight loss, improved liver transaminases and decreased liver fat. Weight reduction is one of the most effective strategies to reverse fatty changes accumulated in hepatocytes. It can be achieved by diet control, exercise, use of weight loss drugs or bariatric surgery.

Diet Control

This is currently the most efficacious strategy in countering steatois, biochemical and histological changes. Initial studies were 4–14 inadequately powered to detect effect on various parameters; however, a systemic review of these studies and various case series showed that various types of diet alteration led to significant reduction in liver aminotransferases and hepatic steatosis as seen on ultrasound.15 A preliminary study, done in 6 subjects with NAFLD has shown that the oral administration of 6.5 mL olive oil enriched with omega-3 polyunsaturated fatty acids (ω-3 PUFA) for 12 months improve the liver echo texture and decreased circulating liver enzyme and triglycerides. Recent studies have showed improvement both in steatosis and biochemical parameters16–21 by diet control. Lifestyle modification by diet, exercise or combination of interventions for weight loss has consistently led to up to 40% (range 30–75) change in liver fat as detected in magnetic resonance spectroscopy (MRS). The degree of fat loss was proportional to intensity of weight reduction in these studies provided the weight loss ranged between 5% and 10%.3,8,12 In general 1500 Kcal of deficit per week leads to 1 pound reduction12 of weight each week and energy restriction of 25–30 Kcal/Kg/day leads to a weight loss of up to 10 after 6 months.16–18 However, reports involving more intensive weight reduction up to 1.6 Kg/week in morbidly obese patients has led to increased risk of portal fibrosis, so caution has to be exercised at tempo of weight reduction.

Thus, even though weight reduction as less as 3–5% can lead to improvement both in NAFLD histology and biochemical parameters; a significant reduction of 10% or more will have a beneficial effect on necroinflammation as well.
Exercise

Exercise increases insulin sensitivity; however in various studies it has been shown to be less effective than diet control both in weight reduction and improvement in hepatic histology.6-8 Exercise has not shown consistent effect on other necroinflammatory changes in hepatocytes.21-25

PHARMACOTHERAPY: THERAPEUTIC AGENTS

Insulin Sensitizers

Metformin

Though mode of action of metformin is unclear, it has been postulated that it acts by decreasing hepatic gluconeogenesis and has been shown to decrease steatosis in murine models as well. Initial trials of metformin26,27 showed decreased steatosis and inflammation but no change in fibrosis, while in a open label study using 2 g/day of metformin for 48 weeks NASH was improved only in one-third of the patients, further trials of metformin28-36 revealed a non-significant benefit.

Thiozolidinediones

Thiozolidinediones bind to peroxisome proliferator-activated receptors (PPAR)-γ receptors in adipocytes leading to improved insulin sensitivity. Initial randomized controlled trials (RCTs) on thiozolidinediones improved aminotransferases and hepatic steatosis but had variable effects on necroinflammation and fibrosis.37-40 While study by Aithal showed significant improvement in fibrosis and inflammation though not in hepatic steatosis.41

In PIVENS study though there was an improvement in NASH (47% vs 21%, p = 0.05) on taking pioglitazone at 30 mg/day for 12 month, primary end point of necroinflammation and fibrosis was not affected.42 Even recent meta-analysis have shown a significant benefit with pioglitazone in necroinflammation (odds ratio [OR] 4.05) and hepatic steatosis but not in fibrosis (OR 1.40, p > 0.05).2 Taking into account generally beneficial effect of thiozolidinediones on NASH it is recommended for use in biopsy proven NASH.1

However, recently there have been concerns about side effects pioglitazones in congestive heart failure (CHF), coronary artery disease (CAD), osteoporosis, and bladder cancer and even death.43 This limits the potential number of candidates in whom pioglitazones can be given for treatment. Further since pioglitazones cause weight gain, it further decreases avenues for its use in metabolic syndrome.

However as of date, pioglitazones are definitely the most preferred insulin sensitizers and recommended over metformin in NASH.

Cytoprotective Agents

Vitamin E

Vitamin E acts by decreasing lipid peroxidation and its antioxidant properties prevent hepatocellular injury.44-48 The evidence for vitamin E use is generally based on non-blinded and underpowered studies. Meta-analysis done before PIVENS and TONIC studies49 suggested that vitamin E primarily causes decreases in aminotransferases, improvement in steatohapatitis while having no benefit in hepatic fibrosis.3 PIVENS44 study showed that pure form of alfa-tocoherol administered at 800 IU/day for 96 weeks led to improvement in liver histology of non-diabetic NASH in 42% of participants as opposed to 19% receiving placebo. The NNT (numbers needed to treat) for a significant benefit in this study was low 4.4 and hence clinically important.

However recently there has been a controversy on effect of high dose vitamin E on all–because mortality with some studies finding an association50 –52 while others could not see an association.53-55 A recent RCT suggested that even low dose of vitamin E at 400 IU/day could result in a very small but absolute increase in prostatic cancer risk of 1.6/1000/1000 person years.56

In light of current evidence vitamin E is recommended at a dose of 800 IU/day in biopsy proven non-diabetic NASH while its not recommended in NAFLD in diabetics, on-biopsied NASH patients or cryptogenic cirrhosis.

Ursodeoxy Cholic Acid

Ursodeoxycholic acid (UDCA) is the non-hepatotoxic epimer of chenodeoxycholic acid. Ursodeoxycholic acid replaces endogenous bile acids, which are hepatotoxins, has membrane stabilizing and cytoprotective effects on mitochondria as well as immunological effects. It is believed that by decreasing bile acids, UDCA protects against hepatocyte injury and decreases oxidative stress in patients with NAFLD. Ursodeoxycholic acid has been used in the treatment of some hepatobiliary diseases for nearly two decades.57-60

Omega-3 fatty acids

Omega-3 fatty acids have been used traditionally for hypertriglyceridemia. There have been many animal studies61 but not much has been achieved in human trials. A recent review62 has suggested the role of UDCA in NAFLD but it consists of small number of studies and is limited by methodological limitation.

Hence omega-3 fatty acids are currently not approved for treatment of NAFLD or NASH but may be considered to address hypertriglyceridemia in setting of NASH or NAFLD.

Miscellaneous Therapeutic Approaches

Other therapeutic non-mainstream pharmacological approaches have also been investigated where evidence is less robust based on small clinical trials and animal studies, and these are currently not recommended by standard guidelines. These consist of: Altering Macronutrient Content
This approach focuses on various approaches in modifying type of diet.

1. Altering PUFA to saturated fatty acid (SFA) ratio in NASH patients. A recent review by Zivkovic77 has examined the role of various weight losses—diets to include Atkins, Ornish, Zone, Beach diets in management of NAFLD. It was suggested that diets consisting of lowglycemic index promote insulin sensitivity.

2. Modification of various types of fat. Excess amount of SFA leads to steatosis in endoplasmic stress, hepatic steatosis, and inflammation in animal studies while monounsaturated fatty acids rich foods like olive oil, peanut butter are thought to be beneficial because they decrease triglycerides, LDL, serum cholesterol, and maintain high-density lipoprotein (HDL).

3. Polyunsaturated fatty acid ratio alteration animal studies in obese mice have led to improvement in hepatic steatosis with dietary PUFAs via negative regulation of lipogenesis in liver:78 Ratio-6 to ω-3 PUFA is important in predicting insulin resistance. Increased ω-6/ω-3 PUFA ratio is an important predictor of insulin resistance,79 while consumption of foods like fish oil and walnuts which are rich in ω-3 PUFA (alfa linolenic acid) show improvement in serum triacylglycerol level, liver enzyme level, and hepatic steatosis.61

4. Fructose content—High fructose content has been suggested to lead to hepatic lipogenesis, hypertriglyceridemia, and hepatic insulin resistance.80 This is also in consonance with an animal study showing that rapidly absorbed carbohydrates promote hepatic steatosis.81

5. Trans fatty acid—Studies in healthy subjects show that increase in trans fatty acids mainly found in hydrogenated oils increase inflammatory marker and LDL/HDL ratio. Hence, the use of trans fatty acids is generally discouraged.

Thus despite the macronutrient composition manipulation appears to lack robust evidence. General concept of foods with low glycemic index, no fructose, increased ω-3 PUFA, monounsaturated fatty acid (MUFA), and decreased SFA seem to be generally recommended for healthy lifestyle

### Rimonabant

Activation of lead to peripherally and centrally located cannabinoid receptors lead to alteration of energy homeostasis and weight gain. These receptors are located in liver, skeletal muscle, adipocytes, and pancreas. Inhibition of these receptors has potential to decrease NASH.

Rimonabant has been used in doses of 20 mg/day for 1 year or 6 months in various studies to improve serum triglyceride level, HDL level, and insulin resistance in addition to weight loss. However, it is associated with various psychiatric and neurological side effects. In a meta-analysis NNH (number needed to harm) for discontinuation due to adverse side effect was 14, which were significantly low as compared to NNH of 39 for orlistat. Rimonabant also leads to improvement in liver enzymes and weight loss and decreases hepatic fat but does not lead to any histological improvement.

Due to these reasons it is not recommended as therapy for NASH as of now.

### Incretin Analogs

Peptide derivative of glucagon like protein-1-receptor agonists like exenatide have been explored as therapeutic agents for NASH. They promote insulin secretion, decrease gastric emptying prevent excess glucagon secretion, and cause weight loss. Nausea is a dose dependent effect of exenatide, which is addressed with dose titration. One study in obese mice showed decreased hepatic steatosis and other markers of oxidative stress and insulin resistance.83 There have also been case reports of decreased steatosis and improved liver enzymes in diabetic treated with glucagon-like peptide-1 (GLP-1) analogs.

However, as of now in absence of adequate number of RCTs it is not recommended for specific treatment of NASH.

### Betaine

Betaine is an anti-oxidant which decreases S-adenosylmethionine level and hence decreases fat deposition in liver. A Pilot trial in NASH patients treated with dose of 20 mg/day of betaine for 12 months led to improvement in aminotransferases level and histology.84 It should be noted that the betaine anhydrous used in this pilot study is different from betaine hydrochloride regularly available in nutrition stores. However, RCTs are necessary before betaine can be prescribed as a specific therapy for NASH.

### Pentoxifylline

It is a cytoprotective agent which inhibits tumor necrosis factor-α (TNF-α). It has been widely used in alcoholic hepatitis. Many case reports and pilot trials suggested that anti-inflammatory properties of pentoxifylline might decrease TNF-α and interleukin-6 (IL-6) levels in body and hence they are generally beneficial in steatohepatitis treatment.85,86

The meta-analysis suggests that while studies using pentoxifylline showed a reduction in aminotransferases after use, the liver aminotransferases reduction cannot be used as a surrogate for NASH reversal as many of the patients with normal alanine transferase also have steatohepatitis and fibrosis on biopsy of liver.

A statistical pooling of effects on TNF-α and IL-6 in control and pentoxifylline group did not yield a significant difference in the meta-analysis. Since nausea is a very common and significant side effect of this medication, many patients discontinue it. Drop-out rates of up to 50% has been reported which limits the clinical efficacy of this drug.85,86

Hence, pentoxifylline is not currently recommended for specific therapy of NASH.

### Ezetimibe

Ezetimibe due to its lipid lowering properties on triglycerides and LDL has been suggested for treatment in NASH for some pilot studies. However, there have been no clinical trials to support its use and hence it is not recommended for specific therapy of NASH.

### Angiotensin Receptor Blockers

Angiotensin receptor blockers (ARBs) have been shown to have hepatoprotective properties in addition to their role in treatment of hypertension and CHF. Obese mice showed decreased level of cytokines, histology improvement, and improvement in
liver aminotransferases. These benefits are due to inhibition of satellite cell activity, which leads to improvement in hepatic fibrosis. Even some human pilot studies have suggested that ARBs might improve liver aminotransferases and provide histological benefit.

However, large RCTs are needed before incorporating them for specific treatment of NASH.

Figure 1. Algorithmic approach to nonalcoholic fatty liver disease. NAFLD: non-alcoholic fatty liver disease.

**PERSONALIZED MANAGEMENT IN NONALCOHOLIC FATTY LIVER DISEASE**

Nonalcoholic fatty liver disease classically refers to a spectrum of pathology from steatosis to steatosis with inflammation (NASH), which is not caused by alcohol abuse. It is caused by diverse etiologies ranging from metabolic (diabetes), infectious (hepatitis B, C), auto-immune (SLE), pregnancy and in children due to Reye’s syndrome. Unfortunately as things stand, it is most commonly associated with metabolic syndrome and diabetes, which form the most common etiology of NAFLD. However, since the natural history of these various disease etiologies vary hence even the prognosis and management should vary. Further NAFLD should be thought of as a risk factor for various liver, heart, and kidney pathologies instead of a specific diagnosis.

Pathogenesis of fatty liver is multi-modal. At molecular level defects in nuclear receptor signaling involving lipid sensing, synthesis and oxidation, defects in the lipid influx-efflux channels, proteins involved in insulin signaling, fatty acid catabolism, molecular defects in adipose tissue development, maturation and function and neural signaling can cause steatosis. Individual variability in evaluating alcoholism and histopathological specimens, the variety of genetic defects presenting as fatty liver, together with the absence of reliable disease markers makes the accurate diagnosis of NAFLD difficult.

Clubbing several diverse molecular and epigenetic defects under same diagnosis can result in adverse and inefficient patient management. With the advances in molecular medicine and diagnostics, diseases like NAFLD and diabetes mellitus type-2 that are currently considered and managed as single entities would split into several distinct entities which might differ in management, like what is happening currently in oncology: where we target a drug to a particular receptor. Thus, exploration of the molecular and genetic basis of NAFLD will allow us to classify them separately, manage them appropriately, and reduce the side effects. A simplified algorithm for approach to NAFLD is summarized in Algorithm 1.

**CONCLUSION**

Nonalcoholic fatty liver disease is an important cause of chronic liver disease worldwide. Weight loss, lifestyle modification, and exercise should form the key stone of any treatment regime addressing NAFLD. Insulin sensitizers like thiazolidinediones, antioxidants like vitamin E, and statins also have a role in treatment of biopsy proven NASH. Other therapeutic approaches offer promise but have to be validated in large RCTs before being used as a specific therapy of NASH.

**Clinical Case Approach**

A 45-year-old male resident of Delhi comes to the medicine OPD with elevated liver enzymes over past 1 year. He has a significant history of weight gain in past 5 years. He is a social drinker, is an active smoker, and occasionally complains of right hypochondrial pain and dyspepsia which has been more frequent in past 7 days.

He has past medical history of dyslipidemia, hypertension, and he has impaired fasting glucose. He has been taking telmisartan 40 mg for his blood pressure control for past 3 years.

On physical examination, he is found to be obese with body mass index (BMI) of 31.4, his blood pressure is 138/86, and pulse rate is 82/minute. He has mild Acanthosis nigricans. He has no hepatosplenomegaly or any other stigmata of chronic liver disease. Remainder of physical and other systemic examination is within normal limits.

Investigations reveal hemoglobin (Hb) 13.2 g%, TC 6,800, DC 146, high-density lipoprotein (HDL) 42 mg%, triglycerides 320 mg%, total cholesterol is 252 mg%, his liver profile shows total bilirubin of 0.7 mg/dL, direct bilirubin 0.3 mg/dL, INR 1.1, aspartate aminotransferase (AST) 64, alanine aminotransferase (ALT) 98, alkaline phosphatase (ALP) 106 mg/dL, S. albumin is 4.2 mg/dL, and globulin 2.3 mg/dL. He has been worked up for viral hepatitis, auto-immune disease, hemochromatosis and Wilson’s disease, and all serologies are negative. His ultrasound report says: hepatomegaly with diffuse heterogenosity suggestive of fatty liver.

Q 1. What factors would lead to a suspicion of NAFLD in this patient?

A history of obesity, dyslipidemia, impaired fasting glucose, unexplained rise of liver aminotransferases, and central obesity with acanthosis nigricans raise suspicion of NAFLD.
Q 2. What is difference between NAFLD and NASH?
Nonalcoholic steatohepatitis is a subset of NAFLD that has in addition to steatohepatitis, a histological evidence of hepatocyte injury like inflammation of lobules, ballooning degeneration, and perivenular or perisinusoidal fibrosis. Nonalcoholic fatty liver disease prevalence has been documented to be 18–25% in worldwide studies, while prevalence of NASH is suspected to be 3–6%. Nonalcoholic fatty liver disease prevalence is much higher in patients of diabetes and metabolic syndrome to the tune of 65–75%.

Q 3. What is difference in prognosis of NAFLD and NASH?
Non-alcoholic fatty liver disease has generally low risk of progression to cirrhosis while NAFLD patients with NASH histology follow one-third rule i.e., one-third will be stable, one-third will progress and one-third will regress.

Q 4. How would you differentiate between NAFLD and NASH?
Liver biopsy is the gold standard for providing a clear cut evidence of steatohepatitis.

Other non-invasive approaches are magnetic resonance imaging (MRI), computed tomography (CT) scan, transient elastography (fibro scan). All of these modalities are developing, however, none of them has proven to be a clear cut alternative to liver biopsy. Serum biomarkers like hyaluronic acid, C-reactive protein (CRP), cytokeratin 18, adipocytokines have also been used. Scoring system has been used consisting of combination of clinical indices and biomarkers. But they have not had universal validation as of now.

Q 5. Would you go for liver biopsy in this patient?
Liver biopsy is the gold standard for diagnosis of NASH and its preference may vary according to medical practitioners. In general, indicators which sway clinicians in favor of liver biopsy are presence of diabetes, obesity, age over 50 years, AST/ALT > 0.8, high triglycerides, worsening of liver enzymes on therapy.

In these patients apart from raised triglycerides, other factors don’t support liver biopsy at this point. So a trial of lifestyle changes and medical therapy should be given before doing liver biopsy. However if and when liver biopsy is done: the hepatic histology must be graded (necroinflammatory activity) and staged (fibrosis). There are systems in place for documenting hepatic histology. Brunt classification is a commonly used system.

Q 6. How does treatment of isolated fatty liver (NAFLD without NASH) differ from biopsy proven NASH or patients at high risk of developing NASH?
Lifestyle modification should be applied to both group consisting of weight reduction (energy intake of 25–30 Kcal/Kg/day or targeting a caloric reduction of 500 Kcal initially, increasing the activity level), other methods might consist of taking foods with low glycemic index, altering macronutrient composition (high in tanle of PUFAs, less SFA, increasing intake of ω-3 PUFAs).

However, in addition to these measures a trial of medical therapy should be considered of patients with biopsy proven NASH or at a high risk of NASH (morbidly obese, diabetics, raised AST)

Q 7. What are the drugs with definitive benefit in NAFLD based on current evidence?
Based on recent AASLD guidelines, thiazolidinediones should be preferred as insulin sensitizers; vitamin E in dose of 800 IU/day is beneficial in biopsy proven NASH. Statins might be given in case of dyslipidemia in NASH patients, while omega-3-fatty acids should be given in patients of hypertriglyceridemia.

Q 8. Which of the conventionally used drugs are no longer recommended for therapy of NASH as per latest AASLD guidelines?
Use of metformin and ursodeoxycholic acid is not recommended by AASLD guidelines. Orlistat is also not recommended for weight reduction as a routine in NASH patients.

Q 9. How many patients of NASH deteriorate and go on to require liver transplant
While 15–30% of NASH patients go on to develop progressive liver disease only 2–5% of them actually require liver transplant.

Q 10. What is the role of statin in this patient?
This patient has three risk factors according to adult treatment panel (ATP)-3 guidelines. His Framingham risk score is between 10–20%. Hence, LDL cut off to start drug therapy is >130 mg/dL. Hence he should be started on statins and continued till his LDL goal of <130 mg/dL is met. Nicotinic acid and omega-3-fatty acids might be considered to address hypertriglyceridemia in this patient in case statins are not effective.

Based on evidence and information provided, the patient described in the case above did not go for liver biopsy, was advised lifestyle modification, abstinence from smoking, and caloric reduction. He was started on atorvastatin of 20 mg/day for dyslipidemia; pioglitazone 15 mg/day, and the side effects of these medicines were explained to him.

Liver function tests were repeated after 63 month, there was improvement in aminotransferases AST was 44 IU/L ALT was 52/L, LDL came out to be 120 mg%. Lifestyle modification was continued.

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