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Diet in Non-Alcoholic Fatty Liver Disease

by Jennifer B. Miller, Zachary Henry

Non-alcoholic fatty liver disease (NAFLD) is quickly becoming one of the leading causes of end stage liver disease, and many physicians will encounter these patients in the clinical setting. It has been proven that a hypercaloric diet, loaded with high fructose corn syrup is directly correlated with the amount of fatty deposition in the liver. A 7-10% weight loss has been associated with a decrease in liver fat content and improvement in liver fibrosis. Therefore, the goal of treating these patients should be weight loss. This can be achieved with exercise, which alone has proven to be advantageous for the NAFLD patient, in concert with dietary change. Diets that reduce carbohydrates, especially high fructose corn syrup, and increase anti-oxidants have a positive impact on NAFLD. The following review highlights the epidemiology, pathogenesis, and treatment goals for patients with NAFLD.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a leading cause of end-stage liver disease and is considered the third-most common indication for liver transplantation in the United States.^{1,2} The term NAFLD encompasses the spectrum of fatty liver diseases including non-NASH fatty liver (NNFL), nonalcoholic steatohepatitis (NASH), and NASH cirrhosis. NAFLD is defined by the presence of $\geq 5\%$ hepatic steatosis, confirmed by imaging or histology, and lack of secondary causes of hepatic fat accumulation.³ A meta-analysis of over eight million patients estimated that the overall global prevalence of NAFLD diagnosed by imaging was 25.24%.⁴ The prevalence of NAFLD

has been reported to be higher in patients with metabolic syndrome, and autopsy data indicates that NASH is at least six times more prevalent in obese patients compared to lean patients.⁵ NAFLD is present in 65% of persons with Class I or II obesity (BMI 30-39.9 kg/m²) and 85% of persons with a BMI ≥ 40 kg/m.^{4,6} NAFLD is strongly linked to both insulin resistance and cardiovascular disease and is considered to be the hepatic manifestation of the metabolic syndrome.^{7,8} With the increasing prevalence of metabolic syndrome and consequently the NAFLD population, there is an urgency to identify efficacious management strategies, as these patients are at risk to develop complications of end stage liver disease.

Pathophysiology of NAFLD

The cornerstone of our current understanding of the progression of hepatic steatosis to NASH fibrosis

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was described by Day and colleagues as the “2-hit” phenomenon. This hypothesis proposed that accumulation of fat in the liver is followed by an oxidative stress state resulting in liver injury/inflammation and resultant scarring i.e. fibrosis.⁷ In the hepatocyte mitochondria, free fatty acids undergo a process of oxidation, esterification and synthesis into phospholipids and cholesterol esters, which are exported from the liver as very low density lipoprotein. Accumulation of hepatic fat can overwhelm the above described process. This hepatic fat accumulation can occur by different mechanisms including delivery from the intestine as chylomicrons, delivery from lipolysis through the action of lipase on insulin resistant adipocytes and thirdly, de novo lipogenesis.⁹ A recent study revealed that patients with higher hepatic fat content derive a greater proportion of liver fat from de novo lipogenesis, compared to matched controls. Interestingly, specific components of the modern American diet, specifically high fructose corn syrup, have been shown to augment the amount of hepatic de novo lipogenesis in patients with NAFLD.⁶

Therapies for NAFLD

The prognosis of a patient with NAFLD is variable, and determining that patient's risk for liver related morbidity is essential to gauge therapeutic intervention. Ekstedt et al. performed a thirty-three year cohort study evaluating 229 biopsy proven NAFLD patients, which found that patients with NAFLD had an increased mortality compared with the referenced population (HR 1.29, CI 1.04-2.15, P=0.02). The causes of death in patients with NAFLD included cardiovascular disease (41%), non-gastrointestinal malignancy (19%) and hepatocellular carcinoma (5%). Those patients with baseline fibrosis stage 3 or 4 (per biopsy) had the worst prognosis.¹⁰ Given the complex underlying physiology of NAFLD, there are many potential targets for therapeutic drugs. Unfortunately, medical therapies up to now have been unsuccessful in reversing fibrosis and have only been marginally effective at improving the underlying components of NAFLD – steatosis, inflammation, and balloon cell degeneration.¹¹

Weight reduction in patients with NAFLD leads to a decrease in liver fat content, serum

liver enzymes, and hepatic inflammation; it may also improve fibrosis.³ A 7%-10% reduction in body weight results in improvement in histological findings including lobular inflammation and hepatocyte ballooning.¹² Small decreases in body weight equate to more substantial decreases in liver fat, and the method by which a patient loses weight is irrelevant.¹³ In a prospective trial of 293 patients on a low-fat hypocaloric diet, 750 kcal/d less than their daily energy needed, a greater than 10% weight loss resulted in a reduced fibrosis score of at least 1 point in 13 of 16 (81%) patients with baseline fibrosis.¹⁴ This study along with many others supports the fact that weight loss is independently linked to an improvement in histological outcomes in patients with NAFLD.

It is important to also recognize that physical activity, independent of weight loss, can improve fatty liver disease by reducing hepatic fat content. Studies have shown that exercise improves the body's peripheral sensitivity to insulin. This decreases the action of lipase, resulting in less adipocyte lipolysis and less delivery of free fatty acids to the liver. Exercise has also been shown to decrease the amount of de novo lipogenesis in patients dedicated to an exercise program.¹⁵ Therefore, in addition to encouraging patients to follow a healthy diet, clinicians should also encourage dedicated exercise programs to maximize potential impact on NAFLD as well as metabolic syndrome in general.

Specific Diets in NAFLD

Lifestyle modifications have shown proven benefit in patients with NAFLD. Accomplishing weight loss can occur through healthy dietary modifications that decrease calories and result in a net negative energy balance. In order to achieve this, expert opinion recommends patients should undergo a multidisciplinary approach, which includes education by a registered dietitian nutritionist. Overall, there are limited data to support one particular diet over another for NAFLD due to small numbers of patients in lifestyle studies. In addition, a recent large trial suggested that a patient's response to a particular diet may be based upon individualized factors as of yet unidentified and predicting success is more difficult than previously thought.¹⁶ However, we will present

Table 1. Summary of Recommendations for Patients with NAFLD

- Weight loss is key – lose weight if overweight.
 - Goal of 7-10% weight loss through diet and exercise.
- Exercise 150 minutes per week.
- Avoid high fructose corn syrup.
- Avoid saturated and monosaturated fats.
- Consider diets high in antioxidants and in polyunsaturated fats; i.e. the Mediterranean Diet.

current data below to support our recommendations for lifestyle modification in patients with NAFLD.

Previously, it was theorized that a hypercaloric diet leading to increased delivery of fat to the liver was the primary driver of NAFLD. To investigate this theory, Kechangias et al. explored the effects of a four week hypercaloric diet in the form of fast-food on intrahepatic triglyceride concentrations and noted an increase in intrahepatic triglyceride content by 1.1-2.8% and an increase in serum ALT levels from 22 U/I to 69 U/I.¹⁷ Hypercaloric diets also appear to increase fasting hepatic glucose output and increase hepatic insulin resistance index by almost two-fold, suggesting both these mechanisms contribute to the development of NAFLD.¹⁸

A growing body of evidence suggests that specific macronutrients (carbohydrates) may have a more profound effect on fatty liver disease. Macronutrients in the portal vein can be as high as ten times greater than that of the systemic circulation, and therefore the liver is in the direct line of fire.² High fructose corn syrup, a predominant component of the western diet, is extensively metabolized in the liver and is thought to be a dominant driver of NAFLD by means of de novo lipogenesis. It has been shown to increase intrahepatic fat accumulation and also cause a decrease in hepatic lipid oxidation.⁶ Americans ingest between 15-25% of their total daily calories from refined sugars; the most commonly consumed sugar is high fructose corn syrup.² Le et al.

compared the effects of seven days of hypercaloric feeding with high-fructose corn syrup on healthy male offspring of parents with and without diabetes mellitus (DM), but with no history of NAFLD. After seven days of a high fructose corn syrup diet, intrahepatic triglyceride concentrations increased by 79% in the male offspring of parents with DM and 76% in the control group.¹⁹ In a second study, Sevastianova et al. studied the effects of short term carbohydrate overfeeding (“candy diet” including 1000 extra carbohydrate kilocalories/day) on liver fat in sixteen overweight patients for three weeks and found that carbohydrate overfeeding increased weight by 2% and liver fat by 27%. When the same cohort of patients were then restricted to a hypocaloric diet for a six month period, they lost 4% of their body weight, and liver fat content decreased by 25%. The authors then took the study a step further by measuring the lipogenic index, i.e., the ratio of saturated fatty acids to unsaturated fatty acids as a marker of de novo lipogenesis. The authors found that three days of high-carbohydrate feeding stimulated de novo lipogenesis by increasing the lipogenic index in measured VLDL triglycerides.¹³ The ability of high fructose corn syrup to instigate de novo lipogenesis seems to be a substantial part of the development of NAFLD. Based on this data, clinicians and registered dietitian nutritionists should encourage patients with NAFLD to eliminate high fructose corn syrup from their diet.

Conversely, polyunsaturated fats have gained positive attention. This can be explained by the fact that polyunsaturated fatty acids upregulate genes responsible for the expression of proteins associated with fatty acid oxidation and decreased hepatic fat accumulation. Furthermore, polyunsaturated fats downregulate the genes responsible for the expression of proteins that boost hepatic fat.⁶ The complexity of diet and its composition should be carefully reviewed by not only the clinician and patient, but also between the patient and registered dietitian nutritionist. The goal of dietary counseling should be to eliminate those components that are worsening the patient’s liver fat content and potentially adding those macronutrients which may down regulate the accumulation of fat in the liver and the inflammatory process that ensues.

The Mediterranean Diet (MD), which is

high in polyunsaturated fats, consists of eating primarily fresh fruits, olive oil, nuts, fish, white meat and legumes in moderation and limiting red meat and sweets. This diet has both anti-oxidant and anti-inflammatory properties and was first noted to decrease risk of cardiovascular disease and diabetes mellitus in the 1960s.²⁰ In regards to NAFLD, a study of overweight/obese patients showed that patients with a low adherence to the MD had a prevalence of NAFLD at 96.5% and those with high adherence to the MD had a NAFLD prevalence of 71.4%, $P < 0.001$.²⁰ Other studies have also suggested a similar benefit of the MD on NAFLD, and hence the European Association for the Study of the Liver guidelines have encouraged the MD for management of NAFLD; however, many of these studies were limited by population based study designs, and so further investigations are needed to solidify the efficacy of this diet in NAFLD management.²⁰

CONCLUSION

Non-alcoholic fatty liver disease is quickly becoming the most prominent liver disease in the world and mirrors the ongoing global epidemic of obesity. In an effort to manage this growing problem, clinicians need to counsel patients on lifestyle modifications with the goal of a 7-10% reduction in total body weight. The bottom line when focusing on dietary intervention in patients with NAFLD is that dietary changes that result in weight loss are beneficial, regardless of the specific dietary modifications undertaken. However, there may be added benefits in those diets that decrease the amount of high fructose corn syrup, increase polyunsaturated fats, and decrease the inflammatory state of NAFLD via antioxidant nutrients such as those found in the Mediterranean diet. Finally, to help clinicians with the management of these patients it is very important to consider referring them to a registered dietitian nutritionist and exercise physiologist or trainer as lifestyle changes are very difficult to undertake alone and require persistence and constant reinforcement. ■

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