Dietary Treatment of Nonalcoholic Steatohepatitis

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Abstract and Introduction

Abstract

Purpose of review Nonalcoholic steatohepatitis (NASH) is increasing in prevalence, in tandem with the U.S. obesity epidemic, in both children and adults. Identifying specific dietary components that drive NASH is important for successful management of this disease.

Recent findings Weight loss of 5–10% improves NASH. In addition, fructose and trans-fats, two components of the Western 'fast-food' diet, have unique metabolic effects that suggest they may be key contributors to NASH. However, further research is needed to clarify the utility of restricting these nutrients in treating NASH.

Summary Overall reductions in body weight, through reduced calorie intake and increased physical activity, are the current mainstays of NASH treatment. Reducing fructose and trans-fat intake, independent of weight loss, may be critical to improving or preventing progression of NASH.

Introduction

Nonalcoholic fatty liver disease (NAFLD) encompasses a range of liver diseases. Simple steatosis, or fatty liver, is now found in up to 31% of adults[1] and 16% of children.[2] Of those with steatosis, approximately 5% will develop nonalcoholic steatohepatitis (NASH), in which steatosis is accompanied by inflammation and fibrosis. Up to 25% of NASH patients will progress to cirrhosis.[3,4] NASH is the third leading indication for liver transplantation in the United States and will become the most common if current trends continue.[5] Therefore, understanding its pathogenesis and treatment is of utmost importance.

The Lipotoxicity Model of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Since the term NASH was coined in 1980,[6] treatment recommendations have evolved, as our understanding of its pathogenesis has matured. The original 'two-hit' hypothesis of NAFLD theorized that buildup of triglyceride in hepatocytes preceded – and possibly caused – the inflammation and fibrosis of NASH.[7] However, accumulating evidence implicates lipid in the form of free fatty acids (FFAs) as the major mediator of liver injury in NASH.[8,9] This 'lipotoxicity' model suggests that hepatic steatosis and inflammation develop concurrently. Some FFAs are trafficked into intrahepatocyte triglyceride droplets, leading to steatosis. FFA metabolites not sequestered as triglycerides promote apoptotic and inflammatory pathways, for example, by activating toll-like receptor 4 ligands or destabilizing lysosomes to induce cathepsin B release, both triggers for apoptosis. Reactive oxygen species formed during FFA metabolism may overwhelm mitochondrial antioxidant capacity, eliciting additional inflammation and apoptosis. In this model, sequestering FFA in triglyceride droplets may actually protect against inflammatory liver injury.[8-10]

The lipotoxicity theory explains why simple steatosis is seen in some patients, whereas others develop steatosis and inflammation leading to NASH (Fig. 1).[4] As in the 'two-hit' hypothesis, NAFLD in the lipotoxicity model occurs when lipid influx into the liver exceeds lipid clearance from the liver. This can occur through:

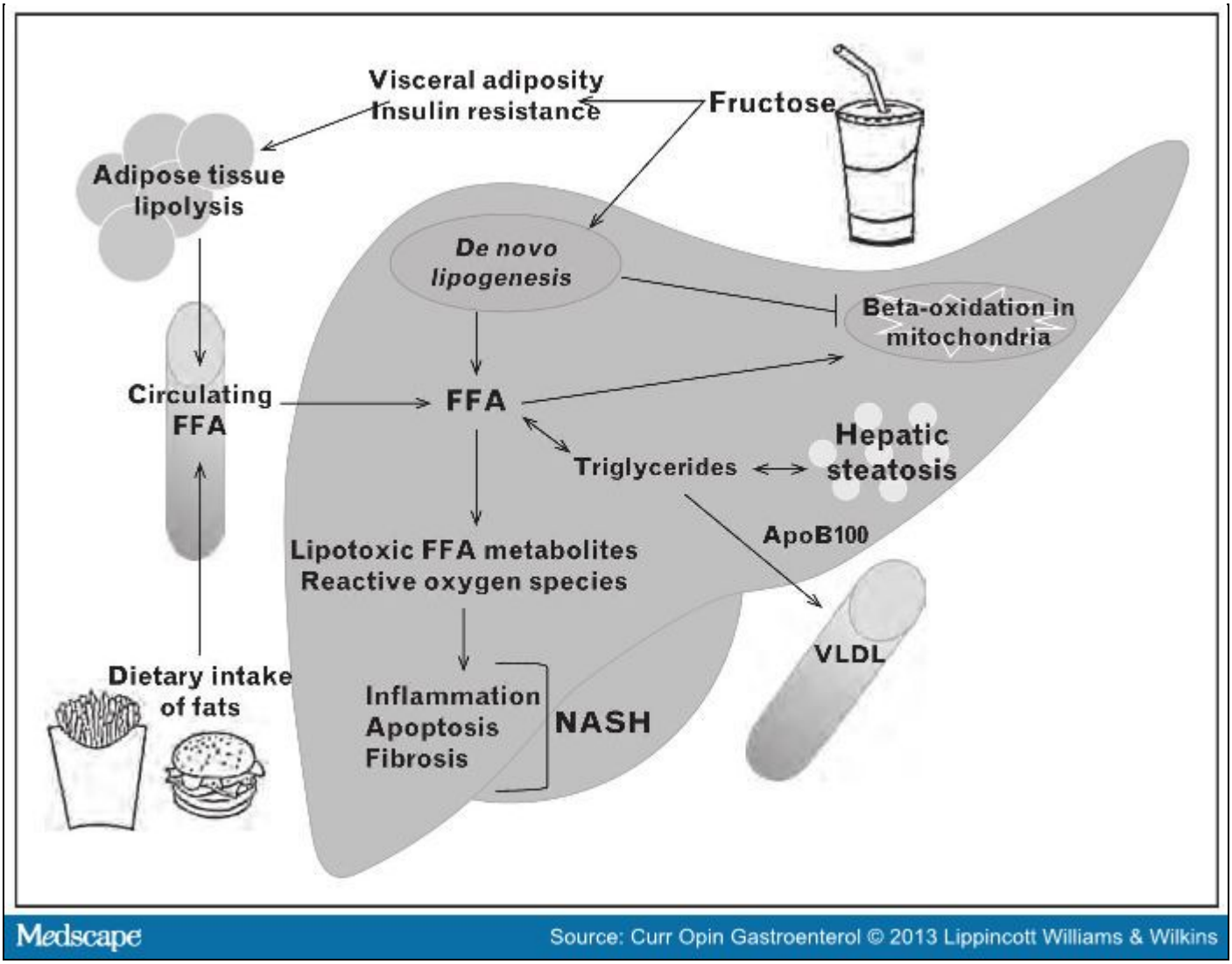

Figure 1.

Diagram illustrating the lipotoxicity model of nonalcoholic steatohepatitis development, highlighting the role of dietary fructose and trans-fats. In this model, free fatty acids (FFA) and their metabolites are thought to drive the steatosis, inflammation and fibrosis that are hallmarks of NASH. Sequestering of fatty acids in triglyceride droplets (hepatic steatosis) may actually protect against the inflammation and fibrosis that drive progressive NASH. NASH develops when lipid influx into the liver exceeds lipid clearance from the liver. This can occur through increased fat consumption, of which trans-fat intake may be a particularly important component; increased liver FFA availability from lipolysis of adipose tissue or intrahepatic triglyceride, which is exacerbated by insulin resistance; increased de-novo lipogenesis (DNL), in which new FFAs are synthesized from excess carbohydrates or amino acids; impaired hepatic beta-oxidation of FFA within mitochondria, which can lead to accumulation of FFA; and impaired very low density lipoprotein (VLDL) secretion. VLDL secretion from the liver is the major mechanism for triglyceride export. Of note, increases in DNL may contribute to impairment of beta-oxidation.

1. Increased dietary fat consumption: However, in stable isotope studies, only 15% of intrahepatic lipid is derived from dietary fat, so the contribution of this pathway remains controversial[11]

2. Increased liver FFA from lipolysis of adipose tissue or intrahepatic triglyceride: A major source of hepatic FFA is lipolysis of adipose tissue.[11] Peripheral insulin resistance increases the rate of adipose tissue lipolysis, increasing the flow of FFA into the liver.[8] However, in patients with hepatic steatosis, lipolysis of hepatic triglyceride droplets and de-novo lipogenesis (DNL) (see #3) may contribute more significantly to FFA levels in the liver.[12]

3. Increased DNL: In DNL, new FFAs are synthesized in the liver from excess carbohydrates or amino acids. DNL contributes most significantly to intrahepatic lipid in obese and insulin-resistant individuals.[13,14]

4. Impaired hepatic beta-oxidation of FFA: During beta-oxidation, two-carbon fragments are successively removed from

FFA in hepatic mitochondria. Impaired beta-oxidation can lead to FFA accumulation. DNL may contribute to impaired beta-oxidation, as the DNL intermediate malonyl-CoA inhibits carnitine palmitoyl transferase-1 (CPT-1), limiting regeneration of carnitine to shuttle FFA into mitochondria for beta-oxidation.

5. Impaired very low density lipoprotein (VLDL) secretion: VLDL secretion from the liver is the major mechanism for triglyceride export. Impaired VLDL export, such as in the genetic condition hypobetalipoproteinemia, causes severe steatosis but does not appear to cause NASH.[8,15]

There are likely multiple factors driving NAFLD in any individual. Weight gain predicts incident NAFLD.[16] Visceral adiposity and insulin resistance are major risk factors, as these increase hepatic lipid processing. The increased risk in some racial/ethnic groups may be partially explained by sociocultural differences in dietary intake. However, differences by race/ethnicity also suggest the contribution of genetic factors. Latinos are at highest risk, whites have intermediate risk and African-Americans have lower than expected prevalence for the degree of obesity and insulin resistance.[17,18] Specific genetic polymorphisms predispose to NAFLD, most notably patatin-like phospholipase 3 (PNPLA3), which may be particularly important in Latinos.[19–21] The sirtuin gene family (*SIRT1, SIRT3*), which is involved in fatty acid oxidation within the mitochondria and regulation of oxidative stress, may also play a role.[22,23]

The 'fast-food diet,' high in fat and sugar, seems to exacerbate development of NAFLD. The high fructose content in sugar-sweetened beverages, and the high trans-fat content in fried and highly processed foods, may be particularly damaging. Sedentary adults who ate two fast-food meals a day for 4 weeks had significant increases in liver fat and in serum alanine aminotransferase (ALT).[24] A more controlled study[25] of fructose and fat overfeeding found that the combination increased hepatic steatosis more than either alone, and that this combination prevented the increase in hepatic VLDL secretion seen with isolated fructose overfeeding. In animal studies, the combination of fructose and medium-chain trans-fats seems to uniquely produce the features of NASH, with hepatic steatosis along with inflammation and fibrosis.[26,27] This finding has not yet been verified in humans.

Weight Loss for Treatment of Nonalcoholic Steatohepatitis

The most effective currently available treatment for NASH is lifestyle intervention to induce weight loss, including dietary modification and increased physical activity. Recent guidelines endorsed by the American Association for the Study of Liver Diseases, American College of Gastroenterology and American Gastroenterological Association recommend lifestyle intervention for weight reduction for adults and children with NASH.[3] European guidelines also support this recommendation.[28]

Two recent systematic reviews conclude that weight reduction reduces hepatic steatosis.[29,30] Study diet and duration vary widely, but all studies restricted calories; all reported a decrease in body weight accompanied by decreases in liver fat of 10–80% and in hepatic aminotransferases of 21–60%.[29] Of note, aerobic and resistance exercise – even without weight loss – decreases hepatic steatosis and other markers of lipotoxicity.[31,32]

Studies in adults and children suggest that loss of 3–5% of body weight decreases hepatic steatosis, but reducing inflammation and progression of NASH may require as much as 10% weight loss.[3] In a 12-month trial of adults with type 2 diabetes, losing 1–5% of body weight reduced hepatic steatosis by 33% compared with a 65% reduction in those who lost 5–10% body weight and 80% reduction in those that lost more than 10%.[33] Similarly, in obese children with NAFLD, BMI reduction by 1–2 kg/m^2 resolved NAFLD in 48%, while a more than 2 kg/m^2 reduction resolved NAFLD in 89–95%.[34]

Few studies of lifestyle interventions for NASH have employed liver biopsy for diagnosis. Liver biopsy is currently the gold standard method for quantifying liver inflammation and fibrosis. Promrat et al.[35] compared patients undergoing 48 weeks of hypocaloric diet along with exercise to controls. Participants in both groups who lost more than 7% of body weight had significant reductions in steatosis, inflammation and hepatocyte ballooning.[35] Similarly, a small study[36] of caloric restriction (<1400 kcal/day) found that body weight loss of at least 9% significantly improved hepatic steatosis, inflammation and ballooning. A study of children with NAFLD found that steatosis, inflammation and ballooning all improved significantly during 2 years of lifestyle intervention. In these children, baseline fibrosis was minimal, with no significant improvement.[37]

Carbohydrate Restriction for Treatment of Nonalcoholic Steatohepatitis

There are few studies that directly compare different diets for NASH treatment. In the largest randomized trial, with 170 overweight adults, 6 months of a low-fat or low-carbohydrate diet produced equivalent reductions in intrahepatic fat, ALT, visceral adiposity, total weight and insulin sensitivity.[38] A 3-month study similarly found that low-carbohydrate and low-fat diets reduced ALT to a similar degree.[39]

Other studies suggest that carbohydrate-restricted diets might be more beneficial for reducing surrogate markers of NAFLD than fat-restricted diets. In a small study, Kirk *et al*. compared a low-carbohydrate with a low-fat diet. Both decreased body weight by approximately 7%. The low-carbohydrate diet decreased intrahepatic fat significantly more after 48 h (-30 vs. -10%), but the diets led to equal decreases in liver fat after 11 weeks (-38 vs. -42%). Neither diet changed aspartate aminotransferase nor ALT[40] In a carbohydrate overfeeding paradigm that induced NAFLD, weight loss did reverse the hepatic steatosis.[41]

Two posthoc analyses of prospective trials found that low-carbohydrate diets were associated with larger reductions in ALT than low-fat diets. In one study,[42] after 18 weeks, serum ALT concentrations decreased twice as much in the low-carbohydrate group, a significant difference even after adjusting for ALT, sex, age and weight loss. Another prospective study followed three groups of type 2 diabetics over 12 months, on one of three diets: American Diabetes Association [60% carbohydrate (CHO), 20% fat]; low glycemic index (50–55% low glycemic index CHO, 30% fat); or modified Mediterranean index (35% low glycemic index CHO, 45% high monounsaturated fat). ALT decreased in all three groups, with the greatest decrease in those on the low-carbohydrate modified Mediterranean diet, from 25 U/l at baseline to 14 U/l at 12 months.[43]

Specific Macronutrient Restriction as Treatment for Nonalcoholic Steatohepatitis

Alcohol is the foodstuff most clearly associated with steatohepatitis. Abstaining from alcohol should definitely be recommended in NASH patients as well. The liver is the primary metabolic clearinghouse for two other dietary components associated with fatty liver disease: fructose and trans-fats. Both are major components of the modern Western diet. These substrates are not insulin regulated and deliver metabolic intermediates to hepatic mitochondria without a 'pop-off' mechanism for excess substrate (e.g. glycogen), enhancing lipogenesis and hepatic FFA.[44] Accumulating evidence argues that they are key contributors to NAFLD.

Fructose Restriction

Fructose is a monosaccharide typically consumed in sweeteners, with sucrose (50% fructose, 50% glucose) or high-fructose corn syrup (42 or 55% fructose, with the remainder glucose) the most common sources. Several lines of evidence point to fructose as an important contributor to NASH pathogenesis and progression (Fig. 1).

Fructose intake has increased in the U.S. in parallel with obesity, metabolic syndrome and NASH. Before World War II, Americans consumed approximately 24 g per day of fructose; by the mid-1970s, it had increased to approximately 37 g per day; and by the early 2000s, to 49–75 g per day.[45–47]

Approximately 33% of fructose intake comes from sugar-sweetened beverages and fruit juices.[48] Thus, sugar-sweetened beverage or added sugar consumption is often used as a proxy for fructose consumption.[49,50] In a population-based cohort of Israelis, even after adjustment for age, sex, BMI and total calories, sugar-sweetened beverage consumption was an independent predictor of NAFLD.[51] In a recent randomized trial, increased sugar-sweetened beverage intake, as soda, increased liver and visceral fat significantly more than did isocaloric, isovolumic milk intake.[52]

Fructose undergoes first-pass metabolism in the liver.[53,54] Its entry into hepatocytes via the Glut5 transporter and subsequent metabolism is not dependent on insulin. Unlike glucose, there is no storage carbohydrate for fructose. Fructose also bypasses two enzymes – glucokinase and phosphofructokinase – that normally prevent excess substrate supply to the liver mitochondria through negative feedback mechanisms.[53,54] Fructose is metabolized directly to fructose-1-phosphate (F1P), and then to pyruvate and acetyl-CoA.[53,54] In the cytosol, acetyl-CoA is carboxylated to malonyl-CoA, which provides the building blocks for fatty acid synthesis and inhibits beta-oxidation by inhibiting CPT-1.[53,55] Thus, hepatocytes are not able to regulate fructose metabolism on the basis of substrate supply or mitochondrial capacity.

In the glycogen-replete or fed state, fructose increases the rate of DNL. This is accentuated by obesity and insulin resistance. Fructose ingestion induces significantly more DNL than isocaloric glucose ingestion.[55–57] Animal studies also suggest that fructose metabolites may stimulate carbohydrate response-element binding protein (ChREBP) and sterol regulatory element binding protein-1c (SREBP-1c); both increase activity of enzymes involved in DNL.[58]

In adults on high-carbohydrate diets over 10 weeks, reduced fat oxidation and increased DNL were seen in those randomized to high-fructose but not high-glucose diets. The largest decreases in postprandial fat oxidation rates were in individuals with metabolic syndrome.[59] In adults, high-fructose diets exacerbate dyslipidemia and insulin resistance more than isocaloric high-glucose diets, with effects most pronounced on adults who already have metabolic syndrome.[56,59] In children, a small study[60] showed that a high-fructose diet caused more postprandial hypertriglyceridemia and high density lipoprotein (HDL) reduction than did a high-glucose diet, with effects exacerbated in those with NAFLD.

In addition to stimulating hepatic steatosis, habitual fructose consumption may promote fibrosis and liver injury, particularly in older patients. In a cross-sectional study of adults with biopsy-proven NASH, consumption of at least one fructose serving daily more than doubled the risk of liver fibrosis, even after adjustment for known risk factors. Fructose consumption was associated with liver inflammation and ballooning – indicators of progressive hepatocyte injury – although paradoxically hepatic steatosis was decreased in patients with severe NASH.[61]

The contribution of fructose to NAFLD may vary on the basis of individual genetics and comorbidities. For instance, the GG allele of PNPLA3 common in Latinos is associated with hepatic steatosis secondary to reduced activation of SREBP-1 in response to feeding[62] For children with the GG allele, increased sugar consumption is associated with increased hepatic steatosis; this interaction was not seen with other allelic variations.[21]

Trans-fat Restriction

High-fat feeding exacerbates NAFLD in some but not all experimental and human models.[63,64] This raises questions about whether specific types of fats are particularly important in NAFLD. Evidence implicating trans-fats remains preliminary but intriguing.

Trans-fats are mono or polyunsaturated fats that contain hydrogen ions in a trans-configuration around one or more carbon–carbon double bonds. They are produced during the partial hydrogenation of oils and fats, a process that prolongs shelf-life and reduces refrigeration needs. In the Western diet, trans-fats are derived primarily from fried foods produced industrially or in restaurants, as they form only under the high temperatures used in commercial cooking.[65]

Trends in trans-fat intake are not as well studied as those for fructose. Average U.S. daily intake was estimated at 5.3 g/day in 1999[66] and may be decreasing slightly with increased public awareness following 2003 U.S. Food and Drugs Administration (FDA) rules that require labels to include trans-fat content.[67]

Similar to fructose, trans-fats are implicated in FFA trafficking to the liver and resultant insulin resistance. Trans-fats may induce or exacerbate metabolic syndrome by effecting lipid metabolism, causing systemic inflammation, and possibly increasing visceral adiposity. They are associated with reduced triglyceride uptake and increased production of FFAs in peripheral adipocytes, leading to increased serum FFA levels.[68]

Mice consuming high trans-fat diets develop NASH-like lesions, larger livers, worse insulin resistance and higher serum triglyceride and cholesterol than mice on diets high in unsaturated or saturated fat. The trans-fat diet enhanced SREBP-1 expression and decreased microsomal transfer protein mRNA compared with the polyunsaturated fat diet, suggesting increased FFA production and diminished liver capacity to export VLDL.[69] In mice with NASH induced by trans-fat feeding, removal of trans-fat from the diet led to improvements in liver disease.[70]

Data linking trans-fat intake to NAFLD in humans remain preliminary. One cross-sectional study[71] found that trans-fat intake was associated with insulin resistance, even after adjustment for other risk factors.

Conclusion

The epidemic of NASH in the U.S. is rising in tandem with the obesity and metabolic syndrome epidemics. If diagnosed before patients have progressed to cirrhosis, NASH is a treatable – even reversible – disease. Although weight loss improves the hepatic steatosis and inflammation of NASH, it is difficult to achieve and maintain.

Reducing intake of specific dietary components may be particularly important in the treatment of NASH. Evidence implicating fructose and trans-fats is growing, as both have high consumption in the U.S., mirroring the increasing NASH prevalence; are associated with obesity and metabolic syndrome; exacerbate insulin resistance; and increase hepatic FFA, by providing substrate for DNL, impairing beta-oxidation and/or decreasing VLDL secretion. The 'fast-food diet,' high in both fructose and trans-fat, is particularly facile at promoting and exacerbating NASH. Further research into the effects of reducing fructose and trans-fat consumption to effectively treat NASH is urgently needed.

Sidebar

Key Points

- As nonalcoholic steatohepatitis (NASH) increases in prevalence, in tandem with the U.S. obesity epidemic, identifying specific dietary components that drive this disease is key to its successful management.

- Free fatty acid metabolites in the liver are thought to cause the hepatic steatosis, inflammation and fibrosis that are hallmarks of progressive NASH.
- Reduction in body weight by 5–10%, through reduced calorie intake and increased physical activity, is the current mainstay of NASH treatment.
- Both fructose and trans-fats increase the hepatic availability of free fatty acids and impair their metabolism, suggesting their important role in NASH. The combination of fructose and trans-fats in the Western 'fast-food' diet may further exacerbate NASH.
- Further research is needed to clarify the utility of restricting fructose, trans-fats and other nutrients in the dietary management of NASH.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 235–236).

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