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REVIEW

Dietary Fructose in Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in adults and children. A number of genetic and environmental factors are known to predispose individuals to NAFLD. Certain dietary sugars, particularly fructose, are suspected to contribute to the development of NAFLD and its progression. The increasing quantity of fructose in the diet comes from sugar additives (most commonly sucrose and high fructose corn syrup) in beverages and processed foods. Substantial links have been demonstrated between increased fructose consumption and obesity, dyslipidemia, and insulin resistance. Growing evidence suggests that fructose contributes to the development and severity of NAFLD. In human studies, fructose is associated with increasing hepatic fat, inflammation, and possibly fibrosis. Whether fructose alone can cause NAFLD or if it serves only as a contributor when consumed excessively in the setting of insulin resistance, positive energy balance, and sedentary lifestyle is unknown. Sufficient evidence exists to support clinical recommendations that fructose intake be limited through decreasing foods and drinks high in added (fructose-containing) sugars. (HEPATOLOGY 2013;57:2525-2531)

Nonalcoholic fatty liver disease (NAFLD) is a chronic, obesity-associated liver disease that has become the most common liver disease affecting adults and children. The role of fructose in inducing NAFLD has been a critical, pervasive question, in part because the prevalence of NAFLD increased in parallel to a rapid rise in fructose consumption.[1,2] NAFLD is closely tied to hepatic insulin resistance and has been suggested to be the hepatic manifestation of the metabolic syndrome.[3] As discussed below, the link between insulin resistance, visceral adiposity, and hepatic steatosis may explain how fructose contributes to NAFLD. The prevalence of NAFLD differs markedly by race and ethnicity, raising the possibility of specific genetic susceptibilities and environmental (particularly dietary) effects. In the U.S., Mexican American obese children have the highest prevalence[4,5] and African American children seem relatively protected, despite their high prevalence of obesity and insulin resistance.[4,6] These prevalence differences can also be seen among adult populations.[7] A concerning concomitant of NAFLD is the association of NAFLD with increased cardiovascular disease risk. Natural history studies of adults with NAFLD demonstrate that cardiovascular disease (CVD) is a substantial long-term risk,[8-10] perhaps exceeding risk of death from cirrhosis.[11] The association of CVD and NAFLD begins early, as children with NAFLD already have increased carotid intima media thickness (cIMT).[12,13]

Dysregulated Lipid Metabolism in NAFLD

A healthy liver generally does not store triglycerides in substantial amounts (normal typically defined as <5.5% fat fraction). Steatosis results from an imbalance between import, synthesis, utilization, and/or export of lipid in or from the liver. Defects have been demonstrated in several of these areas of lipid metabolism. Donnelly et al.[14] evaluated the source of fat deposited in the liver in NAFLD and demonstrated that plasma free fatty acids (FFA) returning to the liver represented greater than half of the triglycerides stored in the fasted state (50%-70%). FFA flux is dysregulated in NAFLD, as demonstrated by inadequate suppression of FFA in the postprandial period.[15] Synthesis of fatty acids (*de novo* lipogenesis [DNL]) is 5-fold greater in NAFLD compared to normal individuals

Abbreviations: cIMT, carotid intima media thickness; CVD, cardiovascular disease; DNL, de novo lipogenesis; Eh, redox potential; FFA, free fatty acid; GSH, glutathione; HDL, high density lipoprotein; LDL, low density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; ROS, reactive oxygen species; VAT, visceral adipose tissue; VLDL, very low density lipoprotein.

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(measured by percent of plasma very low density lipoprotein-triglyceride [VLDL-TG]) and DNL fails to increase postprandially in the pattern of healthy individuals.[14] Lipid dysregulation in NAFLD also includes increased VLDL secretion.[16] Cali et al.[17] measured fasting VLDL particle size, number, high density lipoprotein (HDL) and low density lipoprotein (LDL) particle size in 12 adolescents with NAFLD and compared them to 37 adolescents with low hepatic fat and found that hepatic steatosis predicted larger VLDL particles. In adults with NAFLD, elevated fasting TG, LDL, and low HDL are common.[18] Cassader et al.,[19] and others, have demonstrated that in NAFLD there is increased secretion of TG in the form of VLDL, primarily from intrahepatic sources including DNL.[14,20] Delay in TG clearance also contributes to hypertriglyceridemia in NAFLD.[21] In sum, multiple defects in synthesis, secretion, and clearance of lipids in patients with NAFLD result in TG deposition in the liver. This constellation of defects in NAFLD may decrease tolerance of nutrients that are metabolized through similar mechanisms.

Fructose: A Lipogenic Sugar

Fructose is a highly lipogenic sugar present in processed foods and beverages in large amounts throughout the world. Fructose can be found in its monosaccharide form or can be bound to glucose with a disaccharide bond in sucrose. The primary dietary sources of fructose are high-fructose corn syrup and sucrose (cane or beet sugar) because both are commonly used to sweeten beverages and processed foods. Since its introduction in 1967, the use of high-fructose corn syrup (HFCS) has increased relative to sucrose because it is less expensive, transports easily, and stabilizes the texture of some processed foods better than sucrose. The use of HFCS itself did not increase fructose percentage in the diet because it is a mixture (typically 55% free fructose / 45% glucose) similar to cane sugar (which is sucrose, a disaccharide composed equally of glucose and fructose). From the 1970s to the 1990s, consumption of added sweeteners from all sources increased.[22] In the early 1990s, fructose consumption was estimated to be ~54 g/d,[1] ~50% higher than the mean reported in the 1970s.[23] Possibly in part due to increased public awareness of the negative health consequences of excessive sugar, added sugar consumption has decreased in the past decade, although overall consumption remains higher than recommended.[24] In the National Health and Nutrition Examination Survey (NHANES 2007-08) data, adolescents consumed 17% of their total energy as added sugars, decreased from 22% in 1999-2000. Young adults (18-34 years) consumed similar amounts as the adolescents but older adults consumed much less (11% of total energy in 2007-2008).[24]

Hepatic Metabolism of Fructose

After absorption across the brush border of the small intestine into the portal blood supply, fructose is cleared from the blood in the liver on the first pass and primarily metabolized in hepatocytes. After a 1 g/kg dose of fructose, blood levels increase minimally to just ~0.5 mM,[22] much less than the 10 mM increase found with an equivalent dose of glucose. Fructose metabolism also differs from glucose metabolism in that uptake is relatively unregulated by insulin.[25] Fructokinase action is 10 times faster than glucokinase and hexokinase, and fructose accumulates in the liver as fructose-1-phosphate.[26] Perfusion studies of liver tissue show that this step is rapid enough to precipitate a depletion of adenosine triphosphate (ATP) content to 23%, although ATP recovers to normal within 40 minutes.[27] Fructose-1-phosphate is converted into triose phosphates, which become substrates for gluconeogenesis or the downstream steps of glycolysis and DNL. In a 6-hour study tracking the fate of an oral bolus of labeled fructose, 35% of fructose was oxidized, 0.4% appeared as FFA in newly formed VLDL-TG, 38% appeared as glycerol in VLDL-TG, and some remained unaccounted for, likely remaining in the liver in the form of glycogen.[28] In sum, fructose metabolism is unique from glucose; it enters the liver in a relatively unregulated fashion and is metabolized into products of both glycolysis and gluconeogenesis.[29]

Mechanisms of Fructose Action in Humans

Fructose Effects on Insulin Resistance and Visceral Adiposity in NAFLD. Paradoxically, although fructose does not increase insulin acutely, over time it increases insulin resistance, fasting glucose, and insulin. Dirlewanger et al.[30] found that fructose induces hepatic and extrahepatic insulin resistance in healthy adult humans in infusion/clamp studies, although the mechanism of how insulin resistance is induced is not known. High fructose consumption clearly increases visceral fat in healthy adults and in animal models (see Supporting Material). In a 10-week study, subjects consuming fructose beverages gained significantly more visceral adiposity compared to those consuming eucaloric glucose beverages.[31] A cross-sectional study of adolescents also

found a relationship between high fructose consumption and visceral adiposity.[32] It may be that induction of visceral fat results in increased insulin resistance because visceral fat is thought to be inherently "diabetogenic."[33] However, it is also possible that the deposition of lipids in the liver causes insulin resistance and leads to increased visceral adiposity.[33] Stanhope and Havel[34] postulate that decreased insulin stimulation by fructose leads to decreased lipoprotein lipase activity in saturated adipose tissue and increased lipoprotein lipase activity in visceral adipose tissue, thus leading to increased lipid uptake into the hypertrophied adipocytes.

Fructose and Hypertriglyceridemia. In 1970, Mann et al.[35] demonstrated that sucrose reduction in the diet resulted in improved TG levels in healthy men. This finding continues to be supported by numerous studies demonstrating a hypertriglyceridemic effect of fructose in humans. In various exposure duration and dose studies, fructose consistently induces increased plasma triglycerides, particularly postprandium.[31,36-40] Feeding studies in adults show that high doses of fructose and fructose-containing sugars increase plasma triglycerides when compared to glucose feeding in studies lasting 1 day,[38] 6 days,[41] 2 weeks,[40] 4 weeks,[42] and 12 weeks.[34] We recently studied a cohort of healthy children and those with NAFLD and found fructose beverages induced postprandial TG elevation in both compared to glucose beverages.[15] Due to the inherent challenges of collecting accurate diet information, population studies of fructose are limited. Added sugars (all caloric sweeteners added to food/drinks) are a reasonable surrogate for fructose consumption. In U.S. population studies, in both adolescents and adults, high added sugar consumption was associated with increased fasting TG and lower HDL.[43,44] The mechanism responsible for fructose-induced increase in TG appears to be increased DNL through provision of increased precursors. This includes generation of glycerol[28] and resultant increased VLDL secretion, as well as decreased clearance of TG-rich particles. VLDL secreted after fructose is larger[15] and increased apoB suggests that there is increased production of particles.[40] Decreased clearance of VLDL and triglyceride-rich lipoproteins also may play a role because lipoprotein lipase (LPL) was lower after consuming fructose compared to glucose.[45]

A consideration in human feeding studies of fructose relates to the delivery form of the sugar. In a non-experimental diet, pure fructose is rarely consumed because processed and natural foods mostly containing a mixture of fructose and glucose. Stanhope et al.[46] compared fructose with glucose to fructose alone and found that resulting hypertriglyceridemia is potentiated by glucose. Because of this, studies that use the typically consumed substances (sucrose or HFCS) are more relevant to "real life." Others have questioned if it matters whether fructose is delivered as free fructose (HFCS) or as a disaccharide (sucrose). In humans, there does not appear to be an important difference, implying that the health consequences of sucrose and HFCS are similar.[47]

The effects of fructose align with the lipid dysregulation characteristic of NAFLD, rendering fructose as an etiopathogenic suspect (Fig. 1). In NAFLD, apoB and VLDL production is high, possibly precluding an ability to increase export of TG from the liver further. VLDL particle size is already large in NAFLD and DNL is increased. We studied fructose beverages in adolescents with NAFLD, hypothesizing a potentiation of the dyslipidemia.[15] Subjects with NAFLD had substantially increased postprandial triglycerides after fructose ingestion compared to glucose and this response was heightened compared to fructose effects in matched healthy adolescents without NAFLD. VLDL size appeared to be larger and postprandial lipemia prolonged after fructose in the NAFLD subjects compared to healthy controls.[15]

Fructose and the Microbiome: A Link to Inflammation. Dietary fructose is absorbed into the intestine by way of a saturable, facultative glucose transporter (GLUT5). Healthy persons are able to absorb up to 25 g. Malabsorption can lead to increased fructose fermentation by gut bacteria.[48] Findings regarding endotoxin (lipopolysaccharide [LPS]) levels in portal blood in human NAFLD have been mixed, in part because portal blood is difficult to sample in human subjects and circulating levels are inconsistent. Normally, endotoxin released from the gut is cleared rapidly on first pass by Kupffer cells. However, a growing body of evidence supports a role for increased gut permeability and endotoxin in human NAFLD. In type II diabetes, endotoxin contributes to the development of the subclinical inflammatory state and insulin resistance by stimulating the innate immune system and inducing release of proinflammatory cytokines from adipose tissue. While HDL is known to neutralize LPS, this anti-inflammatory function has been shown to be less effective in patients with NAFLD.[49] If HDL protection of LDL is decreased, that could lead to greater levels of oxidized LDL in NAFLD, which has previously been demonstrated.[50,51] Supporting this, in a small study of children with NAFLD, a low fructose diet resulted in diminished oxidized LDL.[51] The relationship of

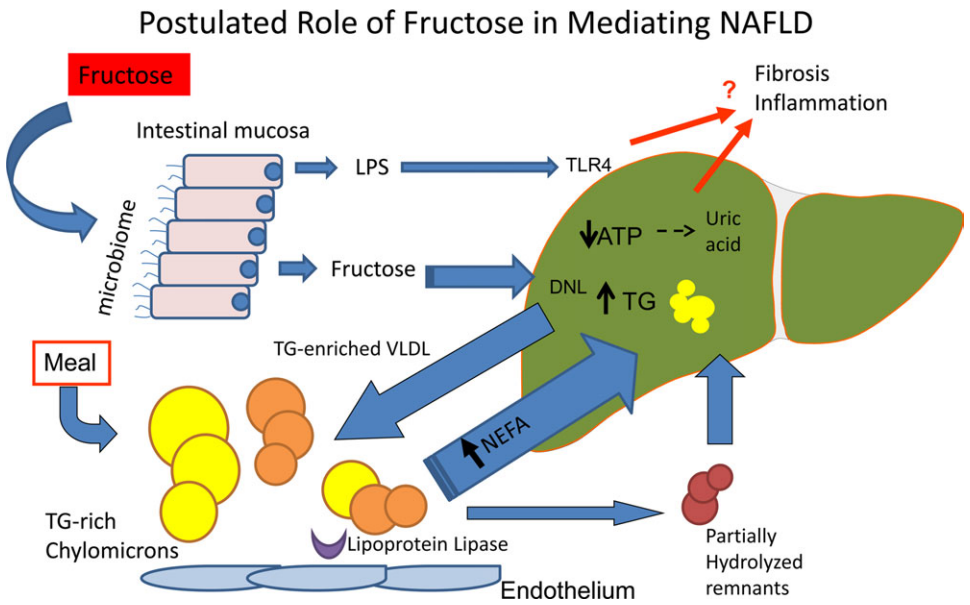

Fig. 1. In NAFLD, ingested fructose may alter the microbiome, increasing movement of endotoxin into the portal system because of increased permeability of tight junctions. Endotoxin and fructose enter the liver where endotoxin increases inflammation and insulin resistance through activation of Toll-like receptor 4 (TLR4). Fructose is rapidly metabolized, consuming adenosine triphosphate (ATP), which may result in increased adenosine monophosphate (AMP) and conversion to uric acid. Excess triglyceride produced through stimulation of *de novo* lipogenesis (DNL) is packaged onto large, TG-rich very low density lipoproteins (VLDL) or in the setting of imbalance can result in increased steatosis in the liver. Steatosis may also be driven by increased return of nonesterified free fatty acids (NEFA) from adipose tissue.

fructose-induced endotoxin to disease in humans is even less well understood than the role of endotoxin in NAFLD; the direct relationships require further exploration.

Fructose Consumption Is Increased in NAFLD. Limited studies suggest an association between fructose consumption and NAFLD. A pediatric study demonstrated increased carbohydrate intake in children with NAFLD identified by ultrasound compared to obese non-NAFLD counterparts.[52] Small case-control studies of adults demonstrate higher fructose and/or soft drink consumption in those with NAFLD.[53-55] A study demonstrating excess soft drink consumption predicted NAFLD in a cohort of adults without typical risk factors for NAFLD lends support for a fructose effect independent of obesity.[56]

Fructose May Increase the Severity of NAFLD. Abdelmalek et al.[57] evaluated histologic features of a large cohort of adults with NAFLD and correlated this to estimated fructose intake. Although steatosis grade was lower in those with increased fructose intake, the degree of fibrosis was increased. In this same study, serum uric acid was substantially higher in those with increased fructose intake. Uric acid has been proposed as a biologic marker of fructose intake because uric acid levels increase with fructose intake.[58,59] In a large cohort of children with NAFLD, histopathology did not correlate with self-reported sugar consumption; however, uric acid was significantly increased in those with NASH compared to those with steatosis alone.[60] It has been proposed that uric acid may mediate some of the abnormalities seen with fructose consumption through induction of retinol binding protein-4 (RBP-4), an adipokine linked to hepatic insulin resistance.[58] This is supported by a fructose feeding study that demonstrated increased RBP-4, uric acid, and GGT after 10 weeks.[58]

Direct Evidence for Fructose Provocation of NAFLD. While evidence supports a potentiation of hypertriglyceridemia and increased severity of NAFLD from excess fructose, it remains unclear if fructose *causes* NAFLD in humans. Possibly, fructose is insufficient to initiate NAFLD in isolation in individuals who are not predisposed to develop hepatic fat. Silbernagel et al.[61] studied the effects of 4 weeks of a high fructose diet compared to a high glucose diet in 20 healthy adults who had normal hepatic fat at baseline (~1.5%), despite an elevated mean body mass index (BMI) of 25.9 kg/m^2. Using magnetic resonance imaging (MRI) to quantify hepatic fat before and after the 4 weeks of fructose, they found no change in intrahepatic fat or insulin resistance, although the hypertriglyceridemic effect was present. A small sample size limited the study. In a slightly larger study of 30 men that tested the short-term (4-7 days) effects of both hypercaloric dietary fructose and fat, both were found

to increase intrahepatic lipid and the effect was synergistic.[62] Another study demonstrated that a 7-day hypercaloric (135%) high fructose diet resulted in a small but significant increase of intrahepatic fat from 0.5% to 0.8% in healthy controls and from 0.8% to 1.5% in the offspring of diabetics.[63] The strongest evidence that fructose induces hepatic lipid storage in humans comes from a 6-month randomized clinical trial comparing sucrose sweetened drinks to noncaloric drinks and milk. The relative changes in hepatic fat measured by MRI were significantly increased in the regular cola group. Liver fat increased between 132%-143%, along with smaller increases in skeletal muscle fat and VAT.[64]

Similar to animal models, fructose likely acts in combination with high saturated fat and/or a hypercaloric state. The "fast food diet" is a good example of this and when tested in a group of healthy men and women for 4 weeks resulted in increased hepatic triglyceride and alanine aminotransferase (ALT).[65] A hypercaloric diet (an additional 1,000 kcal/d as primarily simple sugars) in 16 adults over 3 weeks resulted in a 27% increase in hepatic fat (from ~9% to ~13%) and a 5% increase in VAT. These increases reversed following a 6-month weight loss in the same subjects.[66]

Recent studies evaluated genetic predisposition of fructose influence on the liver. The gain-of-function I148M variant (rs738409 C/G) in the patatin-like phospholipase domain-containing protein 3 (adiponutrin, PNPLA3) gene is associated with hepatic steatosis and severity of NAFLD.[67] Davis et al.[68] tested for an interaction between the PNPLA3 gene and diet in a group of 153 Hispanic children and found that increased sugar strongly interacted with the GG homozygous variant to predict increased hepatic fat. This is in contrast to the findings in 16 overweight adults on a hypercaloric, high sugar diet that increased hepatic fat by 27% over 3 weeks. In this study, PNPLA3 genotype did not affect hepatic or visceral fat gain.[66]

Fructose Avoidance May Improve NAFLD. Decreasing fructose is difficult to implement and few studies have attempted this. A pilot study of a low fructose diet in children demonstrated an improvement in oxidized LDL and a trend towards improved ALT, although hepatic fat fraction was not quantified.[51]

Conclusion and Clinical Implications

Although the evidence remains inconclusive, there is a growing implication of high fructose consumption as an important contributor in the epidemic of NAFLD. The proposed role of fructose is common in diseases: an environmental effect that exacerbates or triggers a disease in the setting of overexposure and/or genetic susceptibility. Thus, despite the possibility that fructose is not the primary provocation for developing NAFLD, fructose reduction population-wide may be critical in turning the tide of this epidemic. There are encouraging recent trends in the food and drink industry, backed by government regulation in some instances, to reduce the amount of caloric sweeteners in products and to reduce portion sizes. Guidelines for adults by the American Heart Association recommend that added sugars compose less than 5% of total calories (corresponding to 2.5% of calories from fructose).[69] We far exceed that level today.[24] While the understanding of the role of fructose in NAFLD is evolving, the evidence demonstrating increased VAT, hypertriglyceridemia, and insulin resistance from high fructose is sufficient to support decreasing consumption as a clinical recommendation for patients with NAFLD.

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