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Fructose and Sugar: A Major Mediator of Nonalcoholic Fatty Liver Disease

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Abstract

Nonalcoholic Fatty Liver Disease (NAFLD) is the hepatic manifestation of metabolic syndrome, and its rising prevalence parallels the rise in obesity and diabetes. Historically thought to result from overnutrition and sedentary lifestyle, recent evidence suggests that diets high in sugar (from sucrose and/or high fructose corn syrup (HFCS)) not only increases the risk for NAFLD, but also, nonalcoholic steatohepatitis (NASH). Here we review the experimental and clinical evidence that fructose precipitates fat accumulation in the liver, due to both increased lipogenesis and impaired fat oxidation. Recent evidence suggests that the predisposition to fatty liver is linked with metabolism of fructose by fructokinase C, resulting in ATP consumption, nucleotide turnover and uric acid generation that mediate fat accumulation. Alterations in gut permeability, microbiome,

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and associated endotoxemia contributes to the risk of NAFLD and NASH. Early clinical studies suggest that reducing sugary beverages and total fructose intake, especially from added sugars, may have a significant benefit on reducing hepatic fat accumulation. We suggest larger, more definitive trials to determine if lowering sugar/HFCS intake, and/or blocking uric acid generation, may help reduce NAFLD and its downstream complications of cirrhosis and chronic liver disease.

Keywords

hepatic steatosis; hepatic inflammation; insulin resistance; sugar consumption; uric acid

> "Apicius made the discovery, that we may employ the same artificial method of increasing the size of the liver of the sow, as of that of the goose; it consists in cramming them with dried figs, and when they are fat enough, they are drenched with wine mixed with honey, and immediately killed."
>
> Pliny the Elder (*The Natural History 1ST Century AD, eds John Bostock, Thomas Henry Riley)*

Fructose is a simple sugar that is present in fruit and honey, but is also a major component in the two most commonly used sweeteners, sucrose (table sugar, a disaccharide of fructose and glucose), and high fructose corn syrup (HFCS, a mixture of fructose and glucose monosaccharides). Intake of fructose has increased markedly over the last several hundred years in parallel with the rise in intake of sucrose and HFCS, and currently the intake of added sugars approaches 15 percent of overall energy intake in the average western diet, with higher intakes among younger individuals (adolescents and adults in their twenties) and among ethnic minorities (African American, Hispanic, Native American, and Pacific Islanders) (1–4).

The association of fructose with fatty liver dates back to Pliny the Elder who noted that the famous Roman chef, Marcus Apicius, would make fatty liver (*foie gras*) by feeding geese dates (a rich source of fructose). Later the German chemist, Justus von Liebig, made the observation that simple carbohydrates stimulated fat accumulation in the liver. Indeed, by the 1960s numerous scientists reported that fructose was distinct from glucose in its unique ability to increase both plasma triglycerides and liver fat (5–7). Metabolic studies in which fructose was labeled further showed a 2 to 3-fold greater labeling of plasma and liver triglycerides than that observed with glucose (8). However, overall the amount of fructose being converted to triglycerides was relatively small (1 to 3% of the fructose), and did not account for the lipogenic response observed (9, 10). This led some scientists to question the importance of fructose as a means for stimulating lipid synthesis and accumulation.

However, the importance of fructose reemerged with a report in this journal linking intake of sugary sweetened beverages, and in particular fructose, with non-alcoholic fatty liver disease (NAFLD) (11), an association that has been confirmed in numerous other studies and is now a major area of research (12–15). Here we provide an update on the association and potential mechanisms by which fructose causes fatty liver. One of the key findings is that it is not the fructose molecule itself that is primarily responsible for making triglycerides, but rather fat accumulates in the liver by the general activation of lipogenesis while at the same time

blocking fatty acid oxidation (16, 17). Indeed, the weight of studies strongly suggest that sucrose and HFCS are likely major risk factors for NAFLD.

The Discovery of NAFLD and Its Association with Metabolic Syndrome

An association of diabetes with liver disease and gout has been known for over 120 years (18) and is strongly associated with insulin resistance. Type 2 diabetes mellitus is the strongest predictor for NAFLD-related hepatic fibrosis and cirrhosis (19). However, the recognition that people with obesity and prediabetes could develop NAFLD emerged only in the last several decades (20–22). Many patients with NAFLD show characteristics observed in subjects with metabolic syndrome, including elevated plasma triglycerides, low HDL cholesterol, impaired fasting glucose levels, an increased waist circumference, and elevated blood pressure (23). Indeed, NAFLD can be viewed as another clinical manifestation of metabolic syndrome, similar to that of hyperuricemia, systemic inflammation (elevated C reactive protein), and microalbuminuria.

NAFLD was not recognized as a clinical entity until the 1980s (20–22), but has been increasing in prevalence, and may progress to nonalcoholic steatohepatitis (NASH) or cirrhosis and eventual liver transplantation (24, 25). NAFLD is also the most common chronic liver disease in children and adolescents especially in obese patients and has even been detected in infants of mothers with gestational diabetes, making this disorder relevant across a wide spectrum of ages (26–28). Thus, identifying the etiologies of NAFLD represents a major goal.

Soft Drinks and Added Sugar are Associated with Fatty Liver

While fructose is present in honey and fruits, the major source of fructose is from sucrose and HFCS, especially in sugary sweetened beverages. While sucrose containing drinks have equal amounts of glucose and fructose, HFCS-containing beverages have varying ratios, usually varying from a 55/45 or 65/35 fructose:glucose ratio (29).

Experimental Studies

Dietary fructose, sucrose, or HFCS have been shown to have a special tendency to induce fatty liver in experimental animals (6, 17, 30–34), as well as inflammation (35). To develop the fatty liver, it usually takes atleast 8–24 weeks on high fructose diet with more progressive disease with longer exposure (36). Often the administration of fructose also induces other features of metabolic syndrome as well, including elevated blood pressure, elevated serum triglycerides, and insulin resistance (37). In part the fatty liver may be due to increased energy intake, as high fructose intake induces leptin resistance in rats (38, 39). However, if diet is controlled so that the control group ingests the same amount of total energy, the fructose-fed rats will still develop features of metabolic syndrome, although weight gain will not be different between groups (37, 40). Indeed, one can even induce fatty liver with a calorically restricted diet if the diet is high (40%) in sugar (41). Others have also reported that high fructose diet can induce fatty liver in the absence of weight gain (35).

Fructose has also been administered to primates. In one study in cynomolgus monkeys (*M. fascicularis*), the administration of fructose was shown to result in both an increase in liver fat and hepatic fibrosis after seven years, with the degree of fibrosis correlating with time of fructose exposure (42). Fructose-induced metabolic syndrome can also be induced in rhesus monkeys (43).

Based on comparative studies in which isocaloric diets were administered using sucrose (glucose-fructose disaccharide) or a 50:50 mixture of glucose and fructose monosaccharides, the monosaccharide mixture appears to induce more fatty liver, although the differences are slight (34). This may relate to differences in absorption or other pharmacokinetics.

Endogenously generated fructose may also have a role in fatty liver and NAFLD (44). For example, the administration of high concentrations of glucose in drinking water will lead to obesity, insulin resistance and fatty liver in mice over time (44). Our group reported that the high portal vein levels of glucose can induce the expression of aldose reductase in the liver, which can convert the glucose to sorbitol, which is then further metabolized to fructose by sorbitol dehydrogenase (the polyol pathway). Indeed, glucose fed mice show increased fructose levels in their liver, and when fructose metabolism is blocked (by giving glucose to fructokinase knockout mice) the animals are almost completely protected from fatty liver and insulin resistance, and are partially protected from obesity (44).

The NAFLD so commonly observed in diabetes may also represent the effects of endogenous fructose accumulation. Indeed, either knocking down aldose reductase mRNA in the liver, or treatment with aldose reductase inhibitors, can attenuate hepatic steatosis in the type 2 diabetic (*db db)* mouse (45).

Clinical Studies

Sugary sweetened beverage drink intake is also strongly associated with NAFLD in humans. Ouyang *et al.* (11) compared NAFLD subjects without cirrhosis to controls that were matched for age, sex and BMI. Subjects with NAFLD had a 2 to 3-fold higher intake of fructose from sugary sweetened beverages than controls, and this was associated with an increased expression of fructokinase in the liver (11). Subsequently the association of fructose from soft drinks has been associated with NAFLD in children, adolescents and adults, where it correlates in a dose-dependent manner with the severity of hepatic fibrosis (11, 13, 46–52). Fructose intake has also been shown to predict the development of NAFLD (53).

Clinical studies also suggest a role for fructose in NAFLD. For example, the administration of sugary beverages for 6 months to humans resulted in increases in liver fat confirmed by magnetic resonance spectroscopy (54). Conversely, the restriction of fructose for 9 days in children with a high baseline fructose intake resulted in both a reduction in liver fat and *de novo* lipogenesis compared to controls fed an isocaloric diet (55). In a subset of the same study, there was also an improvement in other features of the metabolic syndrome, including diastolic blood pressure, serum triglycerides and insulin resistance (56).

While the experimental and clinical studies suggest an association of fructose intake with NAFLD, there is one epidemiological study from Finland that found an inverse relationship between fructose intake and NAFLD, but in this population less than 10 percent consumed soft drinks, and fruit intake was much more prevalent (57). While fruits contain fructose, they are less likely to induce metabolic syndrome due to the lower fructose content per fruit (compared to a soft drink) and also because they contain constituents (flavonols, epicatechin, ascorbate, and other antioxidants) that may combat the effects of fructose (58).

In addition to the aforementioned clinical studies, Figure 1 shows the rise in documented NAFLD prevalence in the National Health and Nutrition Examination Survey (NHANES) database, using a validated, noninvasive measurement (59), the United States Fatty Liver Index (US FLI), in relationship to the rise in obesity and also the rise in added sugar consumption (refined beet, and sugar cane sucrose and HFCS) intake in the periods from 1988–1991, 1999–2000, 2003–2004 and 2011–2012 (60–62). As can be seen, there is a definite association between fructose intake from added sugars and the rise in obesity and NAFLD.

Fructose Effect on Lipogenesis and Fat Oxidation

Fructose intake has been shown to stimulate *de novo* lipogenesis in animals, as well as to block hepatic β-fatty acid oxidation (16, 17, 63). Similarly, studies in humans have also shown that fructose stimulates *de novo* lipogenesis and blocks fatty acid oxidation in the liver (13, 63–66). Acutely (hours) fructose stimulates thermogenesis and metabolic rate (67, 68), but chronically fructose (days to weeks) has been shown to reduce resting energy expenditure (66). The mechanisms for these effects are discussed below, but it is readily evident how these processes could lead to fat accumulation in the liver and elsewhere.

Differences in Fructose and Glucose Metabolism

In order to understand how fructose intake might predispose to the development of fatty liver, one must know how fructose metabolism is distinct from glucose metabolism. Glucose is metabolized primarily by glucokinase or hexokinase, whereas fructose is principally metabolized by fructokinase. Fructokinase utilizes ATP to phosphorylate fructose to fructose-1-phosphate, followed by the metabolism by aldolase B to generate D-glyceraldehyde and dihydroxyacetone phosphate. From this stage on, fructose metabolism is similar to glucose metabolism, and results in the generation of glucose, glycogen, and triglycerides (69). Thus, the unique aspect of fructose metabolism lies in its first two enzymatic steps (Figure 2).

The principal isoform of fructokinase in the liver is fructokinase C, which phosphorylates fructose rapidly and without any negative feedback control, resulting in a drop of ATP and intracellular phosphate (70–73). The fall in intracellular phosphate activates the enzyme, adenosine monophosphate (AMP) deaminase, that converts AMP to inosine monophosphate (IMP), resulting in purine nucleotide turnover that culminates in the formation of uric acid (74). Fructose also stimulates the synthesis of uric acid from amino acid precursors (75, 76). The ability of fructose to induce ATP depletion was shown in humans with both intravenous

(49, 70, 77, 78) and orally (79) administered fructose. Likewise, an acute rise in uric acid also occurs following fructose ingestion (80–82).

Thus, the unique aspect of fructose compared to glucose is that when fructose is metabolized there is a transient decrease in intracellular phosphate and ATP levels associated with nucleotide turnover and uric acid generation. This fall in ATP level induces a series of reactions, including a transient block in protein synthesis, an induction in oxidative stress, and mitochondrial dysfunction that turn out to have a key role in fructose-mediated effects (17, 70, 83).

Fructokinase, the Principal Enzyme Driving Fructose-Induced Fatty Liver

As mentioned, the hepatic metabolism of fructose by fructokinase C results in the breakdown of AMP to IMP and the generation of uric acid (Figure 2), which is primarily due to a fall in intracellular phosphate that occurs following the rapid phosphorylation of fructose by fructokinase C in the liver (70, 71). In contrast, fructokinase A is a second isoform of fructokinase and is more ubiquitously expressed, but differs from fructokinase C in that it phosphorylates fructose less efficiently and does not cause significant ATP depletion (84, 85). We have observed that mice lacking both fructokinase C and A are protected from fructose-induced fatty liver, while fructokinase A-knockout mice develop worse fatty liver compared to wild type animals despite ingesting similar amounts of fructose (85). These animals also show evidence for greater metabolism of fructose through the fructokinase C pathway and have higher intrahepatic uric acid levels (85). In addition, another study by Softic, *et al.* (85) found fructose, but not glucose drove lipogenic enzymes, and insulin resistance through fructokinase, and that fructokinase levels are elevated in fructose fed mice as well as obese humans with NASH (86). Thus, these studies suggest that there is a unique property of the fructokinase C pathway that leads to hepatic steatosis, and raises the possibility that it may relate to the transient ATP depletion, intracellular phosphate depletion or uric acid generation (16).

Gut Permeability and the Microbiome

One potential mechanism by which fructokinase may drive fatty liver is via actions on the gut. While fructokinase C is the main enzyme in the liver that metabolizes fructose, it is also highly expressed in the small intestine. We have found that the metabolism of fructose in the intestine results in disruption of the tight junctions and that this is not observed in fructokinase knockout mice (87). This likely is responsible for the increased gut permeability that has been observed with fructose ingestion (88, 89). Indeed, studies by Bergheim's group have shown that the increase in gut permeability results in endotoxin getting into the portal vein, which is an important trigger for fatty liver formation (90). Indeed, the administration of antibiotics to reduce the endotoxemia can improve the fatty liver (88, 89). Endotoxemia has also been shown to be elevated in children with NAFLD (91). Thus, the microbiome may have a role in fructose-induced fatty liver through an interaction with fructose metabolism in the intestinal wall. Finally, fructose has been found to alter the gut microbiome, which also favors NAFLD development along with increased gut permeability through loss of tight junctions leading to more progressive disease (92–94).

Role of the Immune System

As noted, endotoxemia has been identified as a mechanism by which fructose may augment NAFLD (88). Endotoxemia acts in part by activating the innate immune system, and inflammation is known to have a role in NAFLD, especially for the transition from steatosis to steatohepatitis and cirrhosis (95). In this regard, a role for T cells and NK cells (but not B lymphocytes) in fructose-induced NAFLD has been shown experimentally through the use of mice genetically modified that lack T cell or NK cell function (96).

Uric acid and its Role in Fructose-Mediated NAFLD

Fructose generates Uric acid—As discussed earlier, fructose is the only common carbohydrate that generates uric acid during its metabolism (Figure 2), and levels rise in the circulation within minutes, and can be noted postprandially in subjects eating fructose-rich meals (80, 82, 97). Fructose also increases uric acid levels in the liver (17). Fructose also stimulates the synthesis of uric acid from amino acid precursors (75, 76), and diets high in fructose are associated with increases in fasting serum uric acid levels (98). Some, but not all epidemiological studies, have also linked high fructose intake with increases in fasting serum uric acid (99, 100).

Experimental studies—One of the striking findings was the observation that fructose-induced metabolic syndrome could be partially inhibited by treatment with allopurinol, a xanthine oxidase inhibitor that blocks uric acid generation (37). Subsequent studies showed that xanthine oxidase inhibitors such as allopurinol or febuxostat could reduce fatty liver from fructose (33) as well as in a genetic model of NAFLD (101), diabetes-induced fatty liver (102), high fat diet associated NAFLD (103), and alcohol-induced fatty liver (104). This effect appears to be mediated by improvement of uric acid and/or effects of blocking xanthine oxidase-induced oxidative stress. Furthermore, acutely raising uric acid by the administration of a uricase inhibitor resulted in an acute increase in liver triglycerides and hepatic expression of fatty acid synthase (FAS) (105), and incubation of liver cells (HepG2 cells) with uric acid also resulted in an increase in intracellular triglycerides (17, 83).

Additional studies identified potential mechanisms by which fructose-induced rise in uric acid can stimulate hepatic lipogenesis. First, fructose was found to induce mitochondrial oxidative stress that was mediated by uric acid-induced activation of NADPH oxidase with its translocation to mitochondria (17). The mitochondria contains a large number of enzymes, but two in particular are known to be sensitive to oxidative stress, that being aconitase-2 (in the Kreb cycle) and enoyl CoA hydratase (involved in β-fatty acid oxidation) (106, 107). Fructose and uric acid have been shown to reduce aconitase-2 activity, leading to an accumulation of citrate that moves into the cytoplasm and activates lipogenesis by stimulating ATP citrate lyase (17). Choi *et al.* (82) further showed that the initial oxidative stress in the mitochondria is due to NADPH oxidase, but later there is stimulation of mitochondrial oxidative stress via the electron transport chain, and that these lead to endoplasmic reticulum (ER) stress, the activation of SREBP-1c, and further stimulation of lipogenesis via activation of acetyl CoA carboxylase-1 and FAS (83). Others have also shown fructose-induced induction of the transcription factor, SREBP-1c (83, 108–110) as well as the carbohydrate Responsive-Element Binding Protein (ChREBP) (33, 111). The

stimulation of ChREBP results in the stimulation of glucose-6-phosphatase that may mediate some of the gluconeogenic effects of fructose (112).

We also documented that fructose-induced uric acid can impair fatty acid oxidation. While mitochondrial oxidative stress may be partially responsible for lowering enoyl CoA hydratase-1 activity, we also found that the activity of this enzyme is regulated by AMP-activated protein kinase (AMPK) and AMP Deaminase-2 (AMPD) (16). As mentioned, the rapid metabolism of fructose leads to intracellular phosphate, GTP and ATP depletion, with the stimulation of both AMPK and AMPD activity. However, the stimulation of AMPD tends to dominate, possibly by removing AMP substrate, but also by generating uric acid which feeds back to inhibit AMPK (16, 113). The combined effects of inhibition of AMPK, coupled with AMPD overactivity, results in an inhibition of enoyl A CoA hydratase and the accumulation of lipid (16), as well as the stimulation of gluconeogenesis (113).

This process of reducing AMPK and stimulating AMPD can also result in a reduction in hepatic intracellular ATP levels. Baseline resting ATP levels are low in diabetic subjects with NAFLD and fall further following fructose challenge (77). Subjects with NAFLD who have a higher serum uric acid level show a greater fall in ATP levels following the same fructose challenge (49). Thus, one potential consequence of uric acid is that it may have a role not only in stimulating lipogenesis and gluconeogenesis, but also in blocking fatty acid oxidation, and this may lead to a relatively low hepatic ATP state.

Thus these studies document that the lipogenic response to fructose is not from metabolism of the fructose molecule itself, but rather from the general stimulation of lipogenesis with a block in fatty acid oxidation. Thus, studies using labeled acetate document lipogenesis better (65) than by following labeled fructose (9, 10).

Soluble uric acid has also been shown to have other proinflammatory effects that could play a role in NAFLD, including the activation of the transcription factor NFκB, stimulation of chemokines such as monocyte chemoattractant protein-1, and the stimulation of NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasomes (114, 115).

Clinical Studies—Epidemiological studies have also linked hyperuricemia with NAFLD in both adults (11, 116–122) and children (117–119) in both cross-sectional and longitudinal studies (123, 124) (Table 1). A liver biopsy study also found that in subjects with NAFLD, the higher the serum uric acid the greater the NAFLD score, lobular inflammation and steatosis grade (122). In addition, a meta-analysis found a dose-dependent rise in incidence of NAFLD by 3% for every 1 mg/dL increase in serum uric acid, even after accounting for factors of the metabolic syndrome and other lifestyle factors (125). Finally, a larger meta-analysis of 55,573 patients found a OR of 1.92 (1.59–2.31) for NAFLD occurrence when comparing the highest to lowest serum uric acid (126). While most subjects with NAFLD are obese, NAFLD can also occur in subjects with normal and low BMI, and elevated uric acid also is common in these subjects (17, 127).

Hyperuricemia is also associated with NASH, the intermediate stage and progressive form of NAFLD. In a study of adolescents, hyperuricemia independently predicted [OR 2.5 (1.87–

2.83)] the presence of NASH after adjusting for age, sex and other components of the metabolic syndrome (51). Hyperuricemia in males has also been found to associate more strongly with NASH than simple steatosis and was significantly associated with hepatocyte ballooning, BMI, and younger age in multivariate analysis (128).

One small randomized controlled study evaluated patients with ultrasound-diagnosed NAFLD to determine whether allopurinol treatment (n=17) was superior to placebo (N=14). They reported significant reductions in cytokeratin 18 (a marker for hepatic apoptosis and NASH (129)) (P=0.006), lower ALT and AST levels (P<0.001 and P=0.013), and improved total cholesterol and triglycerides levels (P=0.01 and P=0.038) at 3 months (130).

A diagram showing how fructose with its metabolite uric acid may play a role in NAFLD is shown in Figure 3. This does not include a larger role uric acid likely plays in the metabolic syndrome including effects on adipose tissue and islet cells (131).

Modulating Factors

Factors that may Exacerbate Fructose-induced NAFLD

High fat diets may also contribute to fatty liver. Indeed, when fructose is combined with high fat diet, much more severe fatty liver occurs in mice (132). One potential mechanism is that high fat diets also induce mitochondrial oxidative stress (133), similar to fructose. Nevertheless, mice lacking fructokinase show marked protection from fatty liver and insulin resistance, documenting the key role for fructose in western diet-induced NAFLD (132).

Alcohol ingestion also is well known to induce fatty liver and chronic liver disease that can be histologically similar to NAFLD. Alcohol combined with fructose was associated with worsening metabolic features (hyperlipidemia), although interestingly there did not appear to be a synergistic effect on inducing liver injury (134).

As mentioned, high glycemic diets can induce endogenous fructose production (44). However, we have found that high salt diets can also induce hepatic aldose reductase expression (due to effects on osmolarity) leading to endogenous fructose production and NAFLD in mice, and mice lacking fructokinase are protected (Lanaspa MA, manuscript under review). High salt diets are independently associated with metabolic syndrome/ diabetes (135, 136) and NAFLD (137). Thus, it seems likely that both high glycemic diets and/or high salt diets might exacerbate fructose-induced NAFLD.

In addition, genetic factors also likely play a role in fructose-induced NAFLD. For instance, Hispanic children who were homozygous for the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene variant rs738409 were found to have a positive correlation between liver fat content and carbohydrate (r=0.38, p=0.02) and total sugar (r=0.33, p=0.04) intake (138). A similar correlation was made in Italian adolescents with the variant and liver fat content and SSB intake (139). Also of note in 18 adult NAFLD patients (matched for liver fat content), a 6 day low calorie, low carbohydrate diet revealed reductions in liver fat content, but was 2.5 fold greater in those who were *PNPLA3* GG homozygotes (n=8) vs CC homozygotes (n=10) (140). Less is known about interaction with

other genes such as transmembrane 6 superfamily member 2 (TM6SF2) which regulates VLDL secretion and Glucokinase Regulatory Gene (GCKR) that regulates glycolytic pathway. Overall, further investigations are warranted in this area, but initial data suggest a role of genetic polymorphisms interacting with fructose in the pathogenesis of NAFLD.

Protective Factors for Fructose-Induced NAFLD

Omega 3 fatty acids, such as found in fish oils and in Mediterranean diets, may also protect against NAFLD (141). For example, mice on a western diet (high fat, high fructose) were partially protected from developing NAFLD if they were supplemented with combined omega-3 fatty acids with flavanols (142). Likewise, fish oil treatment was found to improve hypertriglyceridemia and insulin resistance in fructose-fed macaques, although liver fat was not assessed in that study (143). A short term fructose feeding study in humans also suggested fish oil might blunt the development of hypertriglyceridemia and *de novo* lipogenesis (64). Further studies investigating this pathway are needed.

Likewise, there is evidence that many substances found in natural fruits, such as the flavanols, epicatechin, vitamin C and other antioxidants may also protect against fructose-induced metabolic syndrome (58, 144, 145). This may explain why intake of natural fruits are not associated with NAFLD. Fruit juices, which are associated with metabolic syndrome, contain higher amounts of fructose and are often ingested rapidly, leading to higher fructose concentrations that would cause greater ATP consumption and depletion.

Other Amplifying Mechanisms

High Sugar Exposure May Enhance the Metabolic Effects of Fructose— Repeated exposure to sugar is known to upregulate the transport of fructose through the Glut5 transporter (41, 146) and also increase fructokinase levels in the liver (41). Uptake of fructose is also enhanced by glucose (147). Interestingly, this may increase the risk for fatty liver. A study by Sullivan et al investigated the absorption of fructose in lean children, obese children, and obese children with biopsy proven NAFLD. While fructose malabsorption was common in lean children, it was less in obese children and children with NAFLD absorbed almost all of the oral fructose challenge (119). In addition, blood levels of fructose were lower in the obese children with NAFLD, suggesting they also metabolized the fructose more rapidly. Furthermore, Jin et al reported that children with NAFLD show a greater rise in serum triglycerides in response to fructose compared to lean controls (148).

Uric acid as an Amplification Mechanism—An elevated serum uric acid may also function to amplify fructose effects by creating a positive feedback system. For example, uric acid may feedback to increase endogenous fructose production by stimulating AR (149, 150) and may also stimulate fructose metabolism by increasing expression and activity of fructokinase (33). In contrast, high concentrations of uric acid can block xanthine oxidase (151, 152). Thus, high concentrations of uric acid may act to stimulate upstream metabolism of fructose and which will further promote purine metabolism end-products including uric acid.

Limitations

While the evidence for fructose as a risk factor for NAFLD seems very likely, large clinical trials are still lacking. Nevertheless, there are some groups that have argued that fructose intake may not increase the risk for NAFLD, especially in short term (4 weeks or less) trials that compare fructose to isocaloric diets (153) as well as in studies in which fructose-associated hypercaloric diets (154). However, the development of fatty liver with fructose takes months in animals (85, 132) and most of the trials were probably too short to note this effect. Table 2 lists some of these trials, with the longest ones done by Stanhope, et al. and Maersk, et al. at 10 weeks and 6 months respectively showing differences in either visceral fat, or liver and visceral fat being higher in fructose diet compared to glucose or other isocaloric beverage despite similar changes in weight. Other studies noted are shorter duration, although the majority supports fructose worsening lipid profiles or insulin sensitivity compared to glucose that are likely mechanisms in the development of NAFLD. Of note, studies funded by the food industry, and/or in which the authors are funded by the food industry, often fail to show a relationship between sugar intake and metabolic disease (155, 156).

Experimentally, the data that uric acid may have a role in NAFLD is countered by a report in which exogenously administered uric acid reversed hepatic steatosis since it can function as an antioxidant (157). However, there may be differences from exogenous uric acid from intracellular uric acid in terms of its effects on oxidative stress (17, 158). Finally, there is still much to learn about fructose metabolism that is not well understood. For example, fructose is now known to stimulate FGF21, which may counter some of the negative effects of fructose on craving, metabolic syndrome and liver disease (159, 160). Identifying how this factor modulates fructose responses is clearly of major interest.

Conclusions

In summary, there has been a marked rise in sugar and HFCS intake that has paralleled the rise of NAFLD. Experimentally the fructose component of sugar and HFCS appears to have a major role in inducing fatty liver by both stimulating *de novo* lipogenesis and blocking β-fatty acid oxidation. Evidence suggests these effects are due to the unique metabolism of fructose by fructokinase that leads to a fall in ATP with nucleotide turnover and uric acid generation. The prooxidative and proinflammatory effects of uric acid lead to increases in gut permeability and endotoxemia that exacerbates the lipogenic process in the liver, and coupled with mitochondrial dysfunction results in NAFLD. Clinically the intake of sugary sweetened beverages is strongly linked with NAFLD. Reducing sugar or HFCS intake may have a major benefit on NAFLD. Clinical studies to investigate the potential benefit of lowering uric acid should also be performed. While there are many causes of NAFLD, the intake of fructose containing sugars is likely to have a major role.

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Abbreviations

NAFLD	Nonalcoholic Fatty Liver Disease
NASH	Nonalcoholic steatohepatitis
HFCS	high fructose corn syrup
NHANES	National Health and Nutrition Examination Survey
US FLI	United States Fatty Liver Index
FAS	fatty acid synthase
AMPD	AMP-activated protein kinase, AMP Deaminase 2
NLRP3	NOD-like receptor family pyrin domain containing 3
AR	aldose reductase
SDH	sorbitol dehydrogenase
PNPLA3	patatin-like phospholipase domain-containing protein 3
TM6SF2	transmembrane 6 superfamily member 2
GCKR	Glucokinase Regulatory Gene

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Lay Summary

In this paper we discuss the role of fructose, a monosaccharide sugar, in the development of NonAlcoholic Fatty Liver Disease (NAFLD). We examine evidence both in animal models, and clinical data to support the notion that fructose is a kye player in the recent NAFLD epidemic.

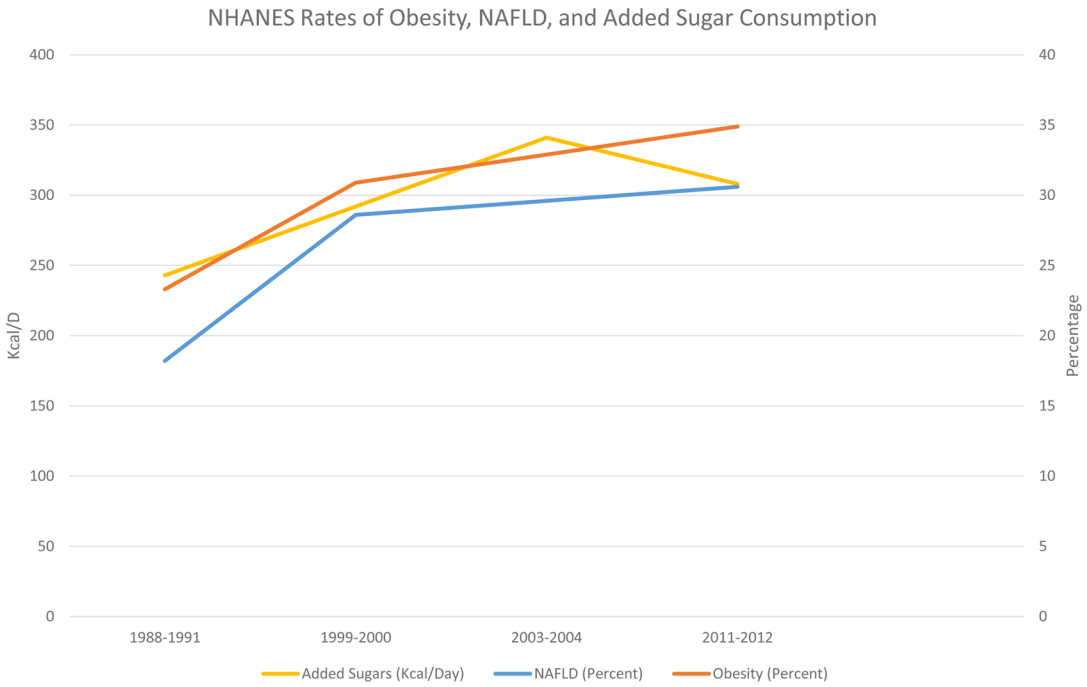

Figure 1.
Association of Added Sugar Consumption with rates of NAFLD, Obesity in NHANES data.

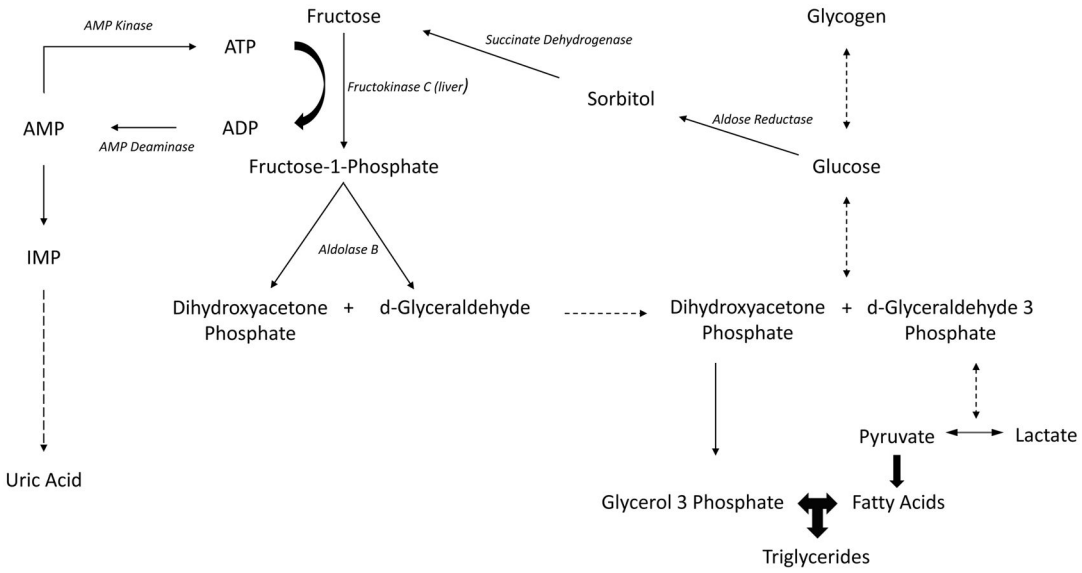

Figure 2.
Interaction of Fructose, Glucose and Polyol Pathway with uric acid and triglycerides

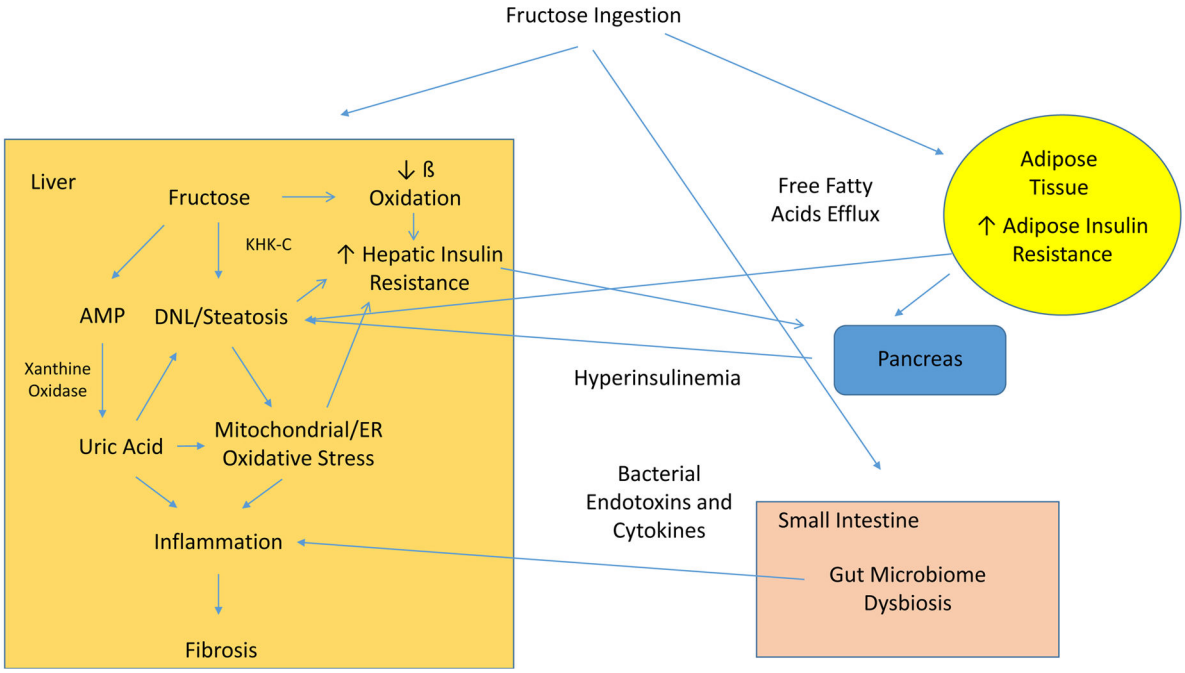

Figure 3.
Fructose Mechanism mediating development and progression of NAFLD

Table 1

Studies with reported Uric Acid in NAFLD patients compared to non-NAFLD patients.

Study	Uric Acid (mg/dL) and NAFLD	P Values
Ouyang X, et al. (2008), *Journal of Hepatology*	NAFLD 6.8 ± 1.6 vs non- NAFLD 4.8 ± 0.9	P=0.03
Sirota JC, et al. (2013), *Metabolism*	Non-NAFLD 5.09 ± 0.02 vs Mild NAFLD 5.19 ± 0.06 vs Moderate NAFLD 5.89 ± 0.06 vs Severe NAFLD 6.35 ± 0.10	P<0.0001
Liu J, et al. (2016), *Hepatol Res*	Obese Hyperuricemia (>7.0mg/dL males and >6.0mg/dL females) OR 1.692(1.371–2.087) Non-obese hyperuricemia 2.559(1.870–3.503)	Not calculated
Liang J, et al. (2015), *Eur Rev Med Pharmacol Sci*	OR for NAFLD[+]: Uric Acid <3.7 OR 1, 3.7–<4.49 OR 1.53(1.17–1.99), 4.49–<5.24 OR 2.22(1.71–2.89), 5.24–<6.11 OR 2.64(2.02–3.44), ≥6.11 OR 3.71(2.83–4.88)	P<0.001
Ryu S, et al. (2011), *Metabolism*	Hyperuricemia (>7.0mg/dL males only) OR 1.21(1.07–1.38) for NAFLD[=]	P=0.004
Sartorio A, et al. (2007), *European Journal of Clinical Nutrition*	NAFLD 6.6 ± 1.7 vs non-NAFLD 5.9 ± 1.6	P<0.0001
Sullivan JS, et al. (2015), *Pediatr Obes*	NAFLD 7.5 ± 1.4 vs obese non-NAFLD 6.1 ± 1.6* vs lean non-NAFLD 4.5 ± 1.6[#]	*P=0.04 [#]P=0.0007
Li Y, Xu C, Yu C, Xu L, & Miao M (2009), *Journal of Hepatology*	NAFLD 6.2 ± 1.5 vs non-NAFLD 5.4 ± 1.4	P<0.001

[+]Model adjusted for sex, age, BMI, Systolic Blood Pressure, Diastolic Blood Pressure, total cholesterol, HDL, LDL, log of triglycerides, Log AST, Log ALT.

[=]Model adjusted for age, BMI, smoking, alcohol intake, exercise, total cholesterol, HDL, triglycerides, glucose, systolic blood pressure, insulin, hsCRP, and presence of metabolic syndrome

Table 2

Studies comparing fructose compared to glucose or other isocaloric intake on NAFLD, Insulin Resistance and Lipids

Study	Corhort	Intervention	NAFLD Measurement	Liver Enzymes	Insulin Resistance	Lipids
Maersk M, et al., 2012(54)	47 overweight nondiabetic patients (30 female)	1L/d SSB (10), isocaloric milk (12), diet cola (12), and water (13) for 6 months	132–143% increase in liver fat over other beverages	NA	NA	NA
Johnson RD, Et al., 2013(161)	32 centrally overweight males age 18–50.	Overfeeding fructose (25%) (n=15) vs glucose (25%) (n=17) 2 weeks	No difference	No Difference	No difference HOMA-IR	No difference in triglycerides
Aeberli I, et al., 2013.(162)	9 healthy normal weight males age 21–25.	3 weeks crossover of medium fructose (40 g/d) (MF), and high fructose (HF), high glucose (HG), and high sucrose (HS) beverage at (80 g/d)	NA	NA	Decreased hepatic insulin sensitivity in HF compared to HG	Increased total cholesterol and LDL in MF, HF, and HS, but not HG. Free fatty acids only elevated in MF.
LeCoultre V, et al. 2013 (163)	55 normal weight males (mean age 22.5)	6–7 days on weight maintenance diet followed by 6–7 day 1.5g/kg/d (n=7), 3g/kg/d (n=17), or 4g/kg/d fructose, 3g/kg/d glucose (n=11) or 30% saturated fats overfeed.	Higher intrahepatic fat in 3g/kg/d and 4g/kg/d fructose, 3g/kg/day glucose, and saturated fat compared to baseline, with tendency for higher levels in fructose diets	NA	4g/kg/d Fructose and 3g/kg/d of Glucose increased hepatic glucose production. 4g/kg/d and 3g/kg/d Fructose decreased hepatic insulin sensitivity	NA
Silbernagel G, et al., 2011. (164)	20 healthy normal weight (mean age 30.5) (12 males, 8 females	4 week over feeding with 150g fructose or glucose	No difference	No difference	No difference	Increased triglycerides in fructose compared to glucose
Stanhope K, et al. 2009. (65)	32 patients (age 42–71) Overweight or obese (25–35 kg/m^2) (16 female)	10 week trial with 25% glucose vs 25% fructose added to diet; 2 weeks inpatient energy balanced diet, followed by 8 week ad libitum diet	Not assessed though visceral adipose tissue, a marker for liver fat, was significantly higher in fructose, but not glucose diet	NA	Fasting insulin, glucose, and decreased insulin sensitivity in fructose diet, but not glucose diet	Increased fasting triglycerides in glucose, not fructose, but higher post prandial triglycerides as well as fasting apoB, LDL, and oxidized LDL in fructose diet only
Schwarz JM, et al., 2015 (165)	8 healthy males (age 18–65) with BMI <30kg/m^2	Cross over 9 day study on isocaloric weight maintaining diet of either 25% fructose or fructose portion substituted with complex carbohydrates	Significant increase in liver fat by 137% in fructose diet compared to complex carbohydrate diet	NA	Higher endogenous glucose production during hyperinsulinemia in high fructose vs complex carbohydrate diet	Increased *de novo* lipogenesis in high fructose as compared to complex carbohydrate diet