Editorial

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Sugar sweetened beverages and fatty liver disease: Rising concern and call to action

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Non-alcoholic fatty liver disease (NAFLD) affects 75–100 million US adults and is increasingly recognized worldwide. The intermediate stage of non-alcoholic steatohepatitis (NASH) may progress to advanced hepatic fibrosis and/or cirrhosis. Thus, it is imperative for the medical community to identify and modify potential risks for NAFLD disease acquisition and progression. Recently, increased sugar intake, in particular fructose, has experienced a resurgence of interest and controversy. The rise in dietary fructose consumption, primarily from sugar sweetened beverages (SSB), is at the forefront of interest and controversy from a public health perspective. Fructose, likened to addictive drugs and reviled as a scourge of the modern diet [1] has been implicated as a unique modifiable dietary risk factor for the rise of obesity [2], diabetes [4], cardiovascular disease [2], and recently NAFLD [3,4].

SSB contribute to obesity through their "add-on" caloric load. Several randomized trials of SSB show that sucrose, 50% of which is fructose, or fructose alone increases body weight, visceral adipose tissue, muscle fat, and liver fat. Metabolized rapidly and primarily through first-pass metabolism in the liver via fructokinase, fructose metabolism increases *de novo* lipogenesis, serum triglycerides, and uric acid thereby inducing mitochondrial oxidant stress and a transient depletion of intracellular phosphate and ATP. By virtue of its metabolic consequences, the increased intake of fructose and/or sucrose, has been proposed to be hazardous to the health of some people and deemed a risk factor for NAFLD acquisition and progression.

The inherent challenges of studying excess sugar consumption and in particular fructose as a single dietary nutrient in humans include inaccurate assessment of carbohydrate consumption, inability to isolate fructose from other dietary carbohydrates and the current lack of well-designed clinical studies. The complexities and controversies over study designs pertains to the relevance of the doses of fructose administered, whether total caloric intake is isocaloric or hypercaloric, relatively small sample sizes, lack of long-term follow-up, lack of accurate measures for determining the presence or absence of NAFLD, as well as the uncertainty of defining the most appropriate cohort of patients at risk (i.e. healthy controls without risks for metabolic disease versus those with insulin resistance).

In the current issues of the *Journal of Hepatology*, Ma *et al.* examine the cross-sectional association between habitual SSB, diet soda intake, liver fat measured by multidetector computed tomography (MDCT) and alanine aminotransferase (ALT) levels in the Framingham Heart Study cohorts. The analysis included 2634 participants with interpretable MDCT scans, food frequency questionnaire (FFQ) data, low levels of alcohol consumption and available ALT measures. Participants were categorized as either non-consumers or consumers (three categories: 1 serving/month to <1 serving/week, 1 serving/week to <1 serving/day, and $\geqslant$1 serving/day) of SSB or diet soda. After adjustment for confounding, the odds of NAFLD were 1, 1.16 (0.88, 1.54), 1.32 (0.93, 1.86), and 1.61 (1.04, 2.49) across SSB consumption categories ($p = 0.04$). SSB consumption was also positively associated with ALT levels ($p = 0.007$). The effects of SSB in overweight and obese subjects were more pronounced than those with normal BMI. The latter findings were not observed with diet soda consumption.

At first blush, it is encouraging to note that the prevalence of NAFLD in the study cohort is lower (17%) than current prevalence estimates for NAFLD in the general population. The relatively lower prevalence of NAFLD in this study could reduce the ability to detect significant differences among SSB categories and results in a non-differential misclassification effort of MDCT; however, a significant increasing trend of NAFLD across SSB consumption categories was still noted. Interestingly, daily SSB consumers had a 56% higher risk of NAFLD compared to non consumers. SSB consumption was associated with higher liver fat content and increased ALT among overweight and obese but not in normal weight persons. After controlling for potential confounders, diet soda intake was not associated with NAFLD or changes in ALT. Using strict ALT cut-off values of 19 U/L for women and 30 U/L for men [5], daily SSB consumption was independently associated with a 36% increased risk of elevated ALT levels (OR = 1.36, 95% CI 1.09, 1.70). The association of SSB with increased ALT in this study as well as with increased fasting plasma insulin levels and HOMA-IR [6] lend weight to the concern that SSB also increases the risk of NASH.

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The acquisition and progression of NAFLD have been previously been reported to be associated with SSB intake. Patients with NAFLD consume more simple carbohydrates than the general population [7] and consumption of SSB is a common risk factor for NAFLD in the absence of other classic risk factors [8]. Patients with biopsy-proven NAFLD compared to matched controls without NAFLD consume 2–3 fold more SSB and this was associated with increased expression of fructose-metabolizing enzymes in the liver [4]. The associated alterations in hepatic energy homeostasis [9] and/or the fermentation of fructose endogenously to ethanol by the gut-microbiome [1] may serve as an alternative mechanism for the variable risk of fructose-related liver injury in susceptible individuals [10]. In this regard, SSB intake has previously been associated with increased NASH and hepatic fibrosis in patients with NAFLD [3].

Several investigators have argued that the role of excess carbohydrates in general, as opposed to fructose *per se*, is the cause of metabolic syndrome and NAFLD; however, this remains controversial [11]. A feeding study of either 25% calories from glucose- or fructose-sweetened beverages, demonstrated that fructose- but not glucose-sweetened beverages increases visceral adiposity, serum lipids, and decreases insulin sensitivity in overweight and obese subjects [12]. Fructose, but not glucose, led to significant increases of 24 hour uric acid profiles (p <0.0001) and retinol binding protein-4 concentrations (p = 0.012), as well as plasma GGT activity (p = 0.04) [12]. Because glucose and fructose are often consumed together in the form of sucrose, the same group of investigators performed a subsequent study comparing fructose as 25% calories to an isocaloric glucose-containing diet. Unlike glucose, fructose increased post-prandial triglycerides, low-density lipoprotein cholesterol, and apolipoprotein B levels suggesting that fructose increases *de novo* lipogenesis and hepatic steatosis compared to glucose [13]. However, another study reported that overweight men fed a high fructose or a high-glucose isocaloric diet for two weeks did not develop any significant changes in hepatic concentration of TAGs or serum levels of liver enzymes. However, a high fructose and high glucose hypercaloric diets produced significant increases in TAGs and serum liver enzymes without any significant difference between the two groups indicating an energy-mediated, rather than a specific macronutrient-mediated, effect [14]. Although very few studies of the long-term effects of fructose consumption exist, one study compared the effects of sucrose-sweetened soft drinks with those of isocaloric milk and a diet soft drink which demonstrated increased ectopic fat in the liver and muscle tissue and increased serum lipids compared to milk, diet soft drinks and water [15].

As suggested by the study of Ma *et al.,* overweight and obese persons may be at increased risk of fructose-related liver injury than healthy adults. In an exploratory, randomized, single-blinded, intervention trial, neither fructose nor glucose (150 g/day for four weeks) increased hepatic triglyceride concentrations in healthy adults, although both increased serum triglycerides [16]. Likewise, children fed fructose as 33% of calories for one day had increase serum triglycerides; however, the effect was greater in children with NAFLD compared with children without NAFLD. When lean healthy children of diabetic parents were fed a high fructose diet, they were also more likely to increase liver fat than controls suggesting a genetic predisposition to fructose-related metabolic and hepatic consequences. Whether genetic (i.e. polymorphisms in PNPLA3, lysophosphatidic acid acyltransferase (LPAAP, AGPAT2), or fructokinase [17]) or epigenetic risk factors [18,19] are associated with fructose-related liver injury remains unknown.

While the results reported by Ma *et al.* provide further support for dietary recommendations to limit and/or avoid SSB in patients with pre-existing metabolic syndrome, obesity and/or NAFLD, the cross-sectional and observational design limits the ability to infer temporality and/or causality between increased sugar intake and NAFLD. Part of the inability of existing studies to clearly define the health implications of fructose may be explained by the fact that intake of sucrose, fructose, fruit juices, and/or sweetened beverages was not recorded separately, thus precluding an accurate assessment of total fructose intake from various sources isolated from that of glucose. Controversy is fueled by extreme designs of animal studies bearing little resemblance in the amount or pattern to human fructose intake, emphasis on statistical rather than clinical significance, small sample sizes, confounding from excess energy intake, and the lack of long-term randomized prospective studies which isolate fructose as the primary predictor of clinical outcomes. To understand better the role of fructose in NAFLD, there is a need for larger, longer, high-quality prospective trials of the effect of "real-world" intake patterns, as well as dose thresholds for the effect of fructose on histopathological changes associated with NAFLD. There is currently no evidence to suggest the moderate intake of natural fructose as would be consumed with fruits, vegetable or honey is unsafe.

In the heat of vigorous debate regarding the role of dietary sugar consumption on health and liver disease, government taxation schemes [20] have arisen as one intervention strategy to curb the increasing public health concerns over increase SSB consumption. The potential danger of SSB, and in particular fructose, and its link with various metabolic disorders including NAFLD has been widely documented and counseling patients, particularly those with pre-existing metabolic syndrome and NAFLD, is prudent from a public health standpoint. Pending further investigation to support or refute the rising concerns, a call to action for health care providers to counsel patients at risk of or with diagnosed NAFLD on avoidance of SSB as a modifiable risk factor for NAFLD acquisition and progression, is warranted.

Conflict of interest

Authors report no conflict of interest.

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