COMMENTARY

Protecting the Liver: Should We Substitute Fruit Juices for Sugar-Sweetened Beverages?

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With an overall prevalence of 25.2%, nonalcoholic fatty liver disease (NAFLD) is the world's leading cause of chronic liver disease. NAFLD is defined as the detection of hepatic steatosis by either imaging or histology in the absence of any other cause of secondary accumulation of intrahepatic lipids (IHLs), such as alcohol, viral infection, or drugs. The spectrum of NAFLD includes steatosis, nonalcoholic steatohepatitis (NASH) and associated fibrosis, and cirrhosis, and it is associated with an increased risk of hepatocellular carcinoma (1). Although NAFLD is generally considered benign, 30% of affected patients present with NASH, which has a high probability of progression to later stages of disease (2). Thus, even if the risk of progression to cirrhosis and hepatocellular carcinoma is much lower for NAFLD than for chronic hepatitis B, its high prevalence makes it the second leading etiology of liver disease among adults awaiting liver transplantation in the U.S. (3), and the number of liver transplants performed for NASH is increasing (4,5). Therefore, NAFLD is a public health issue.

Clinically, NAFLD is frequently associated with components of the metabolic syndrome, such as obesity, hyperlipidemia, hypertension, and type 2 diabetes, with type 2 diabetes being the main risk factor for NAFLD (6). In their 2016 meta-analysis, Younossi et al. (2) reported a type 2 diabetes prevalence of 22.51% in patients with NAFLD and 43.63% in patients with histologically proven NASH. In a 2019 meta-analysis, the same authors (7) found an overall NAFLD prevalence of 55.5% in patients with type 2 diabetes, reaching 68% in Europe. The overall prevalence of NASH was 37.3% in patients with type 2 diabetes. These data support the bidirectional relationship between type 2 diabetes and NAFLD/NASH, which share several pathophysiological mechanisms (8). Notably, the long-term prognosis of patients with NAFLD is negatively affected by the presence of type 2 diabetes, with an increased risk of progression to NASH, liver fibrosis, hepatocellular carcinoma, and mortality (9–11).

The involvement of nutritional factors in the development and progression of NAFLD is now well established, with calorie overload appearing to be a major player, whereas the roles of specific nutrients remain more controversial (12). In this regard, fructose, a simple sugar naturally present in fruits, fruit juices, and honey, is given special attention. Currently, the main source of fructose consumption is as sucrose (glucose and fructose disaccharide) and high-fructose corn syrup (mixture of fructose and glucose monosaccharides), which are present in large quantities in sugar-sweetened beverages (SSBs). The increase in sugar consumption, in the form of SSBs abundantly consumed by children and adolescents (13), during the second half of the 20th century is correlated with the epidemic spread of obesity and the prevalence of cardiometabolic diseases, including NAFLD and NASH (14).

Experimental data provide many arguments in favor of the involvement of fructose in the pathophysiology of various components of metabolic syndrome and NAFLD. In animals, including humans, fructose intake stimulates de novo hepatic lipogenesis (DNL) and blocks hepatic β-oxidation of fatty acids (15,16). Taskinen et al. (17) recently showed that 75 g of fructose administered as three 330-mL bottles per day for 12 weeks in men with obesity decreases fatty acid oxidation and increases DNL and IHLs without any change in visceral and subcutaneous fat. Stanhope et al. (18) previously showed that consumption of a fructose-sweetened beverage over 10 weeks by adults with overweight or obesity increases DNL as well as visceral adiposity and insulin resistance, effects that were not found with an isocaloric drink sweetened with glucose. Sigala et al. (19) have shown more recently that the consumption of drinks sweetened with sucrose or high-fructose corn syrup induces similar changes in the accumulation of IHLs and insulin sensitivity after only 2 weeks. In addition to increased DNL, fructose consumption is quickly followed by increased liver production of uric acid, which fosters mitochondrial oxidative stress (20). Finally, fructose consumption alters the gut microbiota and its bacterial metabolites, promoting an increase in gut permeability and allowing toxic bacterial metabolites to

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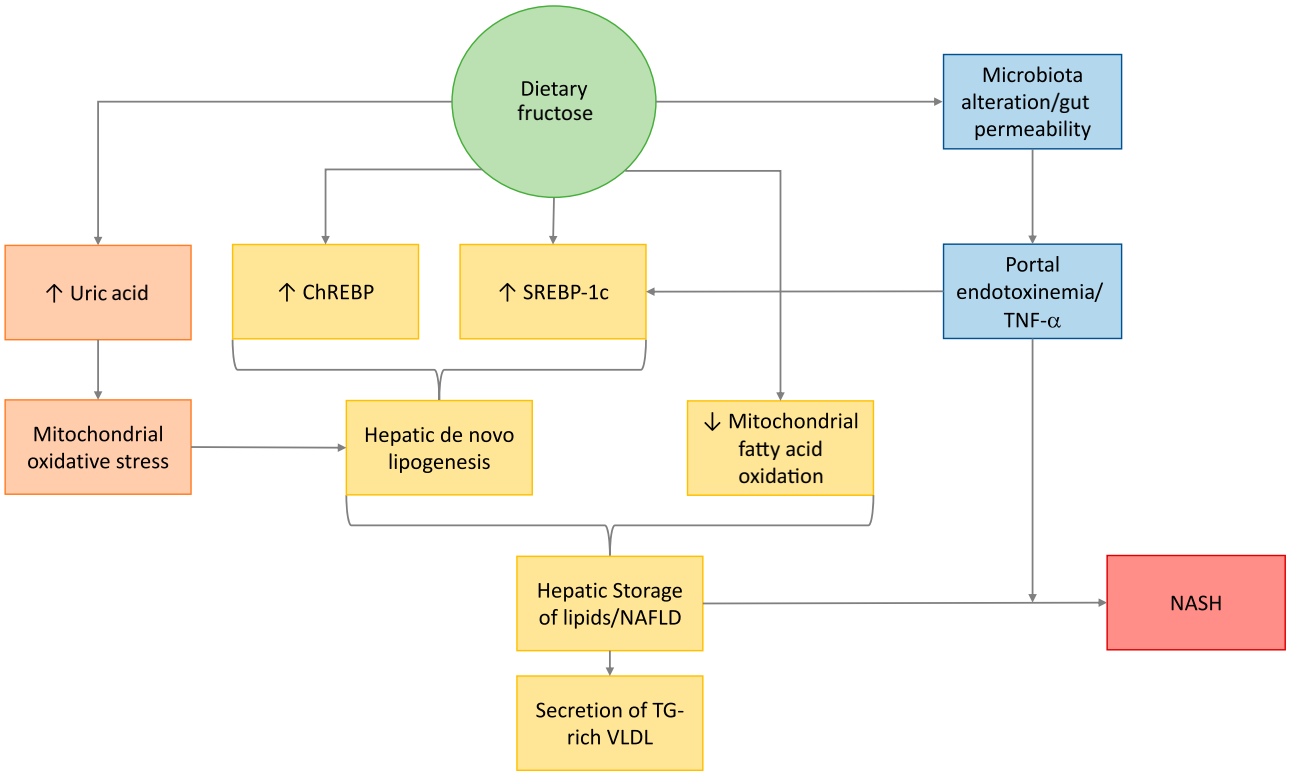

Figure 1—Mechanisms involved in fructose-induced NAFLD and NASH. In the liver, fructose is rapidly phosphorylated to fructose 1-P, stimulating ATP hydrolysis, with a subsequent increase in AMP leading to increased uric acid synthesis and the generation of mitochondrial oxidants. Fructose-derived metabolites activate carbohydrate response element-binding protein (ChREBP) and sterol regulatory element-binding protein 1 (SREBP-1c), which regulate enzymes involved in lipogenesis, and very-low-density lipoprotein (VLDL) export. Fructose-dependent alterations in the intestinal microbiota may lead to the progression of NAFLD due to increased intestinal permeability and secondary increase in tumor necrosis factor alpha (TNF-α) and endotoxin in the portal blood. TG, triglycerides.

reach the liver, promoting evolution to NASH (Fig. 1) (21).

Despite many experimental arguments, data from observational studies evaluating the links between fructose consumption and NAFLD show divergent results. This could be related to variability in the methods used for the quantification of IHLs, which are not always based on reference methods, or to the insufficient adjustment for possible confounding factors. Studies have also rarely considered the different sources of fructose by differentiating fruits, fruit juices, and SSBs. This is important, because although fruit juices have an equivalent or even higher fructose content than SSBs (13), they contain polyphenols and vitamins that could counterbalance or limit the cardiometabolic consequences of fructose through their antioxidant effects (22).

In this issue of *Diabetes Care*, Buziau et al. (23) cross-sectionally analyze data from 3,981 individuals (60 ± 9 years old, 50% women) from The Maastricht Study, an extensive phenotyping study that focuses on the etiology of type 2 diabetes and its complications (24), to evaluate the links between the amount of IHLs quantified by 3T Dixon MRI and the consumption of total fructose and fructose from fruits, fruit juices, or SSBs, assessed by a food frequency questionnaire. The total amount of fructose consumed inversely correlated with IHLs, even after correcting for age, sex, type 2 diabetes, and extensive lifestyle data. This association was lost after correcting for the nutritional factors known to be associated with IHLs (alcohol, saturated fats, proteins, and vitamin E). By considering the different sources of fructose separately, the authors also found an inverse association between the consumption of fructose from fruit and IHLs. Although weaker, this association persisted after adjusting for nutritional factors and disappeared when fibers were introduced into the model. On the other hand, consumption of either fruit juice or SSB was positively associated with IHLs in the fully adjusted models. Strikingly, the associations between total fructose, fructose from fruit, fructose from fruit juice, and IHLs were more pronounced in people with type 2 diabetes.

The study is subject to several limitations. The evaluation of food intake by a frequency questionnaire is, like any food collection, subject to errors, and the questionnaire that was used has not been validated for the consumption of fruit juice and SSBs. The authors also did not differentiate between fresh and packed fruit juice. Furthermore, the study was carried out in a European population that is rather old and has relatively low fructose consumption. Therefore, these data could not be extrapolated to other populations in which fructose consumption is much higher, such as young American adults or adolescents. Finally, this is a cross-sectional study that does not allow causal attribution. However, as stressed by the authors, reverse causality (i.e., high IHLs leading to more intake of fructose from fruit juice and SSBs) seems very unlikely.

Until now, the various nutritional recommendations have not established a place for fruit juices (2). By providing arguments for the differences in the hepatic effects of fruits and fruit juices, using a reference method on a well-characterized cohort, Buziau et al. (23) unquestionably provide important elements to consider in the establishment of future nutritional recommendations, even though more randomized controlled trials evaluating the metabolic effects of fruit juice are warranted, especially among adolescents and young adults who are the main consumers.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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