Mitigating factors and metabolic mechanisms in fructose-induced nonalcoholic fatty liver disease: the next challenge

Marc K Hellerstein

One of the most remarkable medical developments over the past 3 decades is the emergence of nonalcoholic fatty liver disease (NAFLD) as a public health problem in the United States and internationally (1, 2). When I was a medical resident in the early 1980s, chronic liver disease was almost always due to alcohol intake, viral infection, or hepatobiliary conditions. Now, the leading cause of chronic elevations in liver enzymes in the serum is NAFLD. Moreover, there is some evidence that hepatic fat rather than visceral fat represents the risk factor for metabolic syndrome (3). NAFLD has surely become a major problem.

The causes of NAFLD remain uncertain. Dietary macronutrients, behaviors such as lack of exercise, and common comorbid conditions such as insulin resistance have naturally received considerable attention.

On the basis of both epidemiologic “guilt by association” observations and metabolic considerations, the leading dietary suspects have been simple sugars, particularly fructose. Simple sugar intake in the United States has increased from 20 pounds (lb)/y per person in the mid-1800s to 120 lb/y per person in 1996 and stands at 160 lb/y per person today (4). Fructose represents ~50% of simple sugar intake, or ~10% of total caloric intake in the average US diet—the largest macronutrient change over the past generation. This is not from eating apples. The consumption of sweetened beverages constitutes the major change in fructose intake and represents, on average, a 16-oz soft drink per person per day in the United States.

The biochemistry of fructose utilization has also fascinated metabolic researchers. Fructose homes in like a laser beam on the liver and its glycolytic pathways, with ~90% of fructose uptake by the liver. Fructose intake results in hepatic release of lactate, storage of glycogen, and stimulation of de novo fatty acid synthesis. Fructose shares this liver tropism with galactose, but perhaps a better analogy is ethanol. Like ethanol, fructose in the experiment phase of the study. Importantly, IHCL content was measured by magnetic resonance spectroscopy in each phase.

Theytaz et al report that EAA supplementation blunted the IHCL increase (16% lower IHCL than with fructose alone) without an effect on plasma triglycerides or hepatic glucose production. They also observed increased VLDL-triglyceride production, consistent with improved secretion of intrahepatic lipid. Interestingly, they report no effect of EAA on the stimulation of DNL by fructose.

Thus, under controlled, short-term conditions of fructose overfeeding, dietary amino acids mitigate the increase in IHCLs by metabolic mechanisms that remain uncertain but may involve improved export of lipids from the liver. The latter mechanism would be interesting by analogy to ethanol, which is believed to impair VLDL particle assembly.

The identification of modifying factors for fructose-induced NAFLD is potentially very useful, as can be seen in an analogous diet-induced metabolic condition: carbohydrate-induced HPTG. A number of factors have been shown to reproducibly modulate carbohydrate-induced HPTG (7, 8). These include the following: the percentage of carbohydrate in the diet (dose-responsive effect on HPTG), the ratio of simple sugars to complex carbohydrate (very sensitive effects on HPTG), concurrent weight loss (mitigates HPTG), addition of exercise (prevents HPTG), and presence of obesity and insulin resistance (worsens HPTG). The mechanistic
role of DNL is also of interest (may play a role in carbohydrate-induced HPTG, but reduced triglyceride clearance in plasma is as important). These interactions discovered through human research have led to solid therapeutic approaches and rational clinical advice.

Although well-conceived and executed, Theytaz et al’s study has important limitations, as noted by the authors. The fundamental gap in the fructose-cardiometabolic hypothesis is the link between acute high-dose fructose intake studies and the longer-term, lower-dose fructose intake of daily life (4). The current study does not bridge this gap. It is also not clear that modest changes in IHCL content (to ~2–3% of liver volume) in healthy subjects reflect pathologic increases in NAFLD (>10% of volume). Nor does the study definitively rule out other metabolic effects on the liver. The method used for measuring DNL was not ideal, in that hepatic precursor pool enrichments were not measured, although this is routinely possible (9), and these are dramatically affected by fructose in humans (C Beysen, S Turner, and MK Hellerstein, unpublished observations, 2011). An effect on hepatic insulin sensitivity may also not be apparent after a fructose exposure of only 6 d.

Nevertheless, this work by Theytaz et al represents a significant step in the right direction. It will be difficult to think about preventing, reversing, or mitigating the epidemic of NAFLD until we understand the interacting factors and underlying mechanisms. Some other studies in recent years have also advanced the field in this regard (10, 11).

Seen from a broader perspective, this work leaves us with 2 larger messages. First, NAFLD can now really be studied in people—with the availability of magnetic resonance spectroscopy and modern stable-isotope metabolic techniques, much like carbohydrate-induced HPTG was amenable to human investigation. And, second, the real-life interactions, metabolic mechanisms, and disease implications of fructose-induced NAFLD remain poorly understood and are the next big challenge for this important area of public health nutrition.

The author had no conflicts of interest to disclose.

REFERENCES