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Supplement: The State of the Science on Dietary Sweeteners Containing Fructose

The Effect of High-Fructose Corn Syrup Consumption on Triglycerides and Uric Acid[1,2]

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Abstract

Rates of overweight and obesity have been on a steady rise for decades, and the problems society faces from this and associated metabolic diseases are many. As a result, the need to understand the contributing factors is great. A very compelling case can be made that excess sugar consumption has played a significant role. In addition, fructose, as a component of the vast majority of caloric sweeteners, is seen to be particularly insidious. Evidence shows that fructose bypasses many of the body's satiating signals, thus potentially promoting overconsumption of energy, weight gain, and the development on insulin resistance. It has also been shown to increase uric acid levels, which in turn promotes many of the abnormalities seen in the metabolic syndrome including hypertriglyceridemia. However, the main source of fructose in the diet is high-fructose corn syrup (HFCS), an artificially manufactured disaccharide that is only 55% fructose. This review highlights the fact that limited data are available about the metabolic effects of HFCS compared with other caloric sweeteners. The data suggest that HFCS yields similar metabolic responses to other caloric sweeteners such as sucrose. J. Nutr. 139: 1242S–1245S, 2009.

Introduction

Obesity has escalated to epidemic proportions in the United States and around the Western Hemisphere. This increase in the prevalence of obesity has occurred at the same time sweeteners became readily available in the food supply. Of particular importance, over the past 3 decades there has been a shift in the source of sweetener used in the United States, and, as a consequence, dietary fructose consumption has increased slightly (1,2). Although the impact of caloric sweeteners remains unclear (3), the temporal association between the increase in dietary fructose and the rise of the obesity epidemic has led some to suggest a causal relation (1,4). Principally, the focus has been on the most common source of fructose, high-fructose corn syrup (HFCS),[6] which has largely replaced sucrose as the sweetener used in prepared foods and in carbonated soft drinks in the United States (4). HFCS is produced by isomerizing most of the glucose in corn syrup to fructose and then mixing this syrup with varying amounts of corn-based glucose syrup. HFCS-55, consisting of 55% fructose and 42% glucose, is used primarily in sweetened beverages, whereas HFCS-42 (42% fructose; 53% glucose) is used primarily to sweeten other products (e.g., baked foods and confectionaries).

Recently fructose-induced hyperuricemia has been suggested to mediate many of the abnormalities seen in the metabolic syndrome, including elevated triglycerides (5). This hypothesis was based on studies of consumption of pure fructose, but because this is not typically a significant contributor to dietary fructose intake, it is more meaningful to examine the effects of fructose as delivered through the most common source, HFCS. The objective of this article, therefore, is to examine the responses of triglycerides and uric acid following consumption of HFCS. A brief discussion of metabolic derangements caused

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[6] Abbreviations used: AUC, area under the curve; HFCS, high-fructose corn syrup; G20/F80, 20% glucose and 80% fructose; G35/F65, 35% glucose and 65% fructose; G50/F50, 50% glucose and 50% fructose; G80/F20, 80% glucose and 20% fructose.

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by fructose precedes the presentation of the available data on HFCS.

Fructose as a cause of metabolic derangement

Fructose has long been known to be metabolized differently than the other commonly consumed monosaccharides, and recently this has caused it to be implicated in the development of the metabolic abnormalities of the metabolic syndrome (5). Fructose, unlike glucose, does not stimulate insulin secretion from the pancreatic β-cells (6,7). In a recent study, pure fructose, consumed with mixed meals, was shown to result in decreased circulating insulin and leptin and to attenuate postprandial suppression of ghrelin in women, as compared with dietary glucose (8). These authors concluded that the differential impact of fructose on energy regulatory systems as compared with glucose might contribute to increased caloric intake and ultimately contribute to weight gain and obesity during chronic consumption of a diet high in fructose.

Fructose metabolism is also known for its lipogenic potential. On entry into the liver, it is broken down into dihydroxyacetone phosphate and glyceraldehyde-3-phosphate. The former ultimately becomes the glycerol backbone of triglycerides, and the latter produces the acetyl-CoA units required for de novo lipogenesis and the synthesis of fatty acids. Thus, hepatic fructose metabolism can produce the 2 required components for triglyceride synthesis. Importantly, this pathway is unaffected by the regulatory step of glycolysis, phosphofructokinase, meaning that when exposed to high levels of fructose, it is metabolized by the liver unabated and thus rapidly increases triglyceride synthesis. Experimental evidence has shown that fructose increases postprandial levels of triglyceride (8,9), and, although it is not consistently observed (10,11), repeated consumption of high levels of fructose over the short term (2–10 wk) has been shown to increase fasting levels of triglycerides in a variety of human populations (12–14).

Another unique characteristic of fructose metabolism is the ability to raise uric acid levels (15). Uric acid is a product of nucleotide metabolism, which is up-regulated by fructose. In addition, in a recent in vitro study, it was suggested that HFCS from carbonated soft drinks could be a significant source of reactive dicarbonyls that would by itself induce hyperuricemia (16). Despite uric acid's early designation as an antioxidant (17,18)—it is estimated to be responsible for as much as 60% of the antioxidant capacity of the plasma (19)—it is now also known to have prooxidative properties (20,21). Elevated levels are seen in a wide variety of metabolic disease states (22–25), which poses the question of whether hyperuricemia is secondary to the disease state (26,27) or whether it plays a mechanistic role in the development of metabolic disease states (5). Increasingly, the weight of evidence is in support of the latter.

A recent study by Nakagawa et al. (28) confirmed the uric acid–elevating potential of fructose ingestion. More interestingly, they demonstrated that many of the manifestations of the metabolic syndrome are mediated by the rise in uric acid. Rats fed a diet of high fructose (60% of energy) presented with elevated fasting triglycerides, blood pressure, and insulin resistance within 10 wk, but all of these abnormalities were attenuated in rats also given the uric acid–lowering agents allopurinol or benzbromarone. Additionally, it was observed that impaired nitric oxide–dependent dilation accompanied the hyperuricemia, the extent of which was related to the magnitude of the elevation in uric acid. Because an impaired nitric oxide response to insulin may play a role in the development of insulin resistance (29), a potential link has been elucidated among fructose consumption, elevated uric acid levels, and the manifestation of insulin resistance that is considered central to the development of the metabolic syndrome.

A compelling case can therefore be made that excess fructose consumption may play an active role in the pathology of the metabolic syndrome. Whether fructose consumption via the most commonly consumed form of fructose, HFCS, provides a sufficiently high fructose load to cause the same metabolic changes seen with the consumption of pure fructose is less well supported by the literature.

Effect of HFCS consumption on triglyceride levels

Despite the wealth of information available on the effects of fructose on lipid metabolism and triglycerides, little data exist on the effects of HFCS. Data in mice have shown that HFCS consumption contributes to elevated triglyceride levels (30). Tetri et al. (30) investigated whether 16 wk of a Westernized lifestyle would promote cellular and metabolic abnormalities present in nonalcoholic steatohepatitis. C57BL/6 mice that were fed nonpurified diet with added *trans* fats, had HFCS added to the drinking water, and were forced into sedentary behavior were compared with control mice who were allowed to exercise as normal and fed a normal diet. In addition, 2 intermediate conditions were tested, 1 experimental group minus the *trans* fat in the nonpurified diet and another experimental group minus the HFCS in the drinking water. After 16 wk, the triglyceride levels in the 2 HFCS groups were elevated, but the increase attained significance only compared with control in the HFCS minus *trans* fat condition. The lack of sufficiently elevated fasting triglycerides in the experimental group was proposed to be a result of *trans* fats blocking hepatic triglyceride secretion.

It is important to note that the mice in the experimental conditions became insulin resistant as early as 4 wk into the study. Because of the known affect of insulin resistance on lipid metabolism and triglyceride levels (31), it is difficult to draw strong conclusions about the specific effect of repeated HFCS consumption on fasting triglyceride levels from these data.

Teff et al. (8) previously reported the results of a delicate series of experiments comparing the short-term metabolic effects of fructose as compared with glucose in women. Using a similar study design, the same group has recently extended these observations in a group of men and women (n = 34) by comparing the effects of HFCS and sucrose (32). Their study was a crossover design that required participants to consume sweetened soft drinks as part of a mixed meal for each of the 3 meals per day for each of the treatments. The standardized diet was composed of 30% energy from complex carbohydrate, 30% from fat, 15% from protein, and the final 25% from the sweetened drinks and individualized to each participant's energy needs. While subjects rested in the metabolic unit, blood samples were obtained frequently over the course of 24 h for the analysis of triglycerides.

No differences between the 2 treatments were observed for postprandial triglyceride response or 24 h area under the curve (AUC). A small subsample of men (n = 7) repeated this procedure 2 additional times, once to complete a glucose treatment and once for a fructose treatment. Unexpectedly, the postprandial triglyceride response for fructose, which is known to be elevated, was comparable to both the sucrose and HFCS conditions. Also of note was that fasting triglycerides were elevated compared with baseline levels after all treatments, suggesting that consumption of a diet of 25% sugar may have negative short-term metabolic effects regardless of the identity of the sugar.

Effect of HFCS consumption on uric acid levels

There is even less information available about the specific effect of HFCS on uric acid levels; in fact, there are no published data that compare such effects with those of other caloric sweeteners.

The closest that can be found is an intricate study by Akhavan and Anderson (33) that was designed to test whether solutions containing different ratios of glucose and fructose affected food intake and signals controlling food intake.

A small sample of men fasted overnight before eating a standardized breakfast in the morning. Four hours later, a 300-kcal (1.26-MJ) drink was provided that had to be consumed within 3 min. Participants then rested for the duration of the study period and had blood sampled every 15 min for 75 min. The solutions were sweetened with either disaccharides, HFCS (HFCS-55), sucrose, or the monosaccharide forms of glucose and fructose in specific ratios. Unfortunately, for those of us interested in HFCS, the part of the study that measured uric acid did not use HFCS. Instead, comparisons were made between solutions of 80% glucose/20% fructose (G80/F20), sucrose, G50/F50, G35/F65, and G20/F80.

The data showed that the 75-min AUC for uric acid was affected by the fructose ratio. Although the effect of G20/F80 was statistically greater than those of all treatments except G35/F65, the data are complicated by the G35/F65, G50/F50, and sucrose conditions not being significantly different from each other. Despite there being no difference in AUC of uric acid between the G35/F65and G20/F80 conditions, there was a significant difference in the value after 75 min. Importantly, at that time no differences among the G35/F65, G50/F50, or sucrose conditions were observed (although G35/F65, but not sucrose or G50/F50, had a greater effect than the G80/F20 condition).

The implication for HFCS from these results is far from clear. The G35/F65 treatment provided an addition 30 kcal (126 kJ) from fructose compared with what would have been contained in a solution of HFCS. The observation that uric acid levels in this treatment were indistinguishable from those of sucrose and G50/F50 suggests the fructose load in HFCS may not be sufficiently greater than that of sucrose to affect uric acid levels differently. However, the observation that the AUC of the G20/F80 and G35/F65 were not different may suggest otherwise. Whether the additional 30 kcal (126 kJ) from fructose made a difference compared with what would have been used with HFCS is impossible to tell, but it is also of note that the sample size for this portion of the study was very small (n = 7).

The only thing that is clear from these observations about the effect of HFCS on uric acid levels is that more work needs to be done. However, observations from our laboratory may provide some clarity. Using the same study design as described previously (34), we showed that in women, HFCS did not affect uric levels any differently than did sucrose (35).

Summary

There is considerable evidence of a detrimental effect on metabolic health of excess fructose consumption. However, the common source of fructose in the diet is HFCS, and there is currently a paucity of information on the effects on HFCS compared with other sweeteners. What little is available suggests that HFCS does not seem to be any more insidious than other caloric sweeteners, but clearly more short-term studies are needed to further substantiate this view. In addition, despite the difficulty in performing such work, longer-term human studies that test the effects of sustained HFCS consumption at high levels (20–30% of energy) are also needed.

Other articles in this supplement include references (36–45).

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