AMERICAN JOURNAL OF LIFESTYLE MEDICINE OnlineFirst, published on August 19, 2010 as doi:10.1177/1559827610378960

STATE OF THE ART
REVIEWS

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High-Fructose Corn Syrup: Controversies and Common Sense

Abstract: *High-fructose corn syrup is often mischaracterized and misunderstood. This sweetener was introduced into the food supply in the United States in the late 1960s as a liquid sweetener alternative to sucrose and existed in relative obscurity for many years. It carries the designations "Generally Recognized As Safe" (GRAS) and "natural" from the US Food and Drug Administration. In 2004, several investigators suggested that high-fructose corn syrup might be linked to the increased prevalence of obesity in the United States. Subsequent human studies have shown no unique link between high-fructose corn syrup and obesity. In composition, high-fructose corn syrup, sucrose, honey, invert sugar, and concentrated fruit juices are essentially interchangeable, and human studies to date have shown no significant differences in metabolic, endocrine, hormonal, or appetitive responses to these caloric sweeteners. This review explores the metabolic and nutritional effects of high-fructose corn syrup with a particular emphasis on its relationship to sucrose, the sweetener it replaced in many food products.*

Keywords: high-fructose corn syrup; HFCS; metabolism; obesity; sucrose; sweeteners; sugars

High-fructose corn syrup is one of the most misunderstood food ingredients in all of nutrition. High-fructose corn syrup (HFCS) was first developed in the mid-1960s and, because of its unique physical and functional properties, was widely embraced by food formulators. The use of high-fructose corn syrup has had rapid growth over the past 30 years principally as a replacement for sucrose (table sugar). Its use reached a peak in 1999 but has been in decline since then. Having existed as a benign and noncontroversial product for more than 30 years, high-fructose corn syrup has recently been caught up in a series of controversies that started in 2004 when Bray et al[1] suggested that there might be a link between high-fructose corn syrup consumption and obesity.

In their 2004 article published in the *American Journal of Clinical Nutrition*, Bray and colleagues[1] argued that the dramatic increase in the prevalence of obesity in the United States over the past 30 years occurred during the same timeframe as a corresponding increase in the consumption of high-fructose corn syrup. Even though a temporal association does not establish cause and effect and high-fructose corn syrup and sucrose are virtually the same from a composition and biochemical point of view, a number of researchers began to investigate whether there was something unique about high-fructose corn syrup when compared to

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Table 1.

Carbohydrate Composition of Common Nutritive Sweeteners

Component	HFCS-42, %	HFCS-55, %	Corn Syrup, %	Fructose, %	Sucrose, %	Invert Sugar, %[a]	Honey, %
Fructose	42	55	0	100	50	45	49
Glucose	53	42	100	0	50	45	43
Others	5[b]	3[b]	0	0	0	10[c]	5[d]
Moisture	29	23	20	5	5	25	18

From White J. Straight talk about high fructose corn syrup: what it is and what it ain't. *Am J Clin Nutr*. 2008;88(suppl):1716S. Used with permission of author.
HFCS, high-fructose corn syrup.
[a]Sucrose-based sweetener in which the bond between glucose and fructose is partially or fully hydrolyzed (inverted) by acid or enzyme (invertase).
[b]Readily hydrolyzable polymers of glucose.
[c]Unhydrolyzed sucrose.
[d]Sucrose and minor amounts of other carbohydrates.

sucrose, which might create a unique hazard for obesity or other metabolic problems. This was particularly important because many of the hypotheses to date had been based on comparisons of pure fructose to pure glucose, which are not common in the food supply.[2-4]

There is now abundant research demonstrating no short-term differences between high-fructose corn syrup and sucrose in any parameter yet measured in human beings.[2,4-10] This includes work in both lean[5,8-10] and obese[6,7] individuals. In addition, the published proceedings from several different conferences that brought together leading researchers in the field of nutritive sweeteners have provided uniform scientific opinion that, from a metabolic standpoint, there is nothing unique linking high-fructose corn syrup to obesity or other metabolic problems when compared to other nutritive sweeteners, including sucrose, honey, and fruit juice concentrates.[3,8,11-15] Both the American Medical Association,[16] which explored whether there was a unique link between high-fructose corn syrup and obesity, and the American Dietetic Association have concluded that high-fructose corn syrup is not a unique cause of obesity.[17]

The purpose of the current review is to provide practicing physicians and allied health care workers with a summary of the modern scientific understandings of high-fructose corn syrup, with particular emphasis on the comparison of high-fructose corn syrup to sucrose, the substance it was designed to replace in certain foods and beverages.

Discussion of the Scientific Evidence

We address issues related to high-fructose corn syrup by posing and answering a series of commonly asked questions about this sweetener. In our discussion, we draw on published research and published proceedings from 2 important, contemporary symposia on sweeteners.

What Is High-Fructose Corn Syrup?

High-fructose corn syrup is a liquid sweetener developed as a liquid alternative to sucrose (table sugar).[18] It is used in many foods and beverages to enhance flavors or sweetness. In baked goods, it enhances moisture retention and browning. Early developmental work on high-fructose corn syrup started in the 1960s, and commercial applications began in the late 1960s and early 1970s. Because of a variety of properties such as ease of handling (high-fructose corn syrup is supplied in liquid form rather than the solid form of sucrose) and other beneficial physical and functional properties, the use of high-fructose corn syrup achieved substantial growth over the next 30 years.

High-fructose corn syrup served industry in relative obscurity for many years. This is not surprising, given that it is virtually identical to sucrose: both consist of roughly equal amounts of glucose and fructose (see Table 1), have equal sweetness, have equal calories per gram, and are metabolized virtually identically. During this time, multiple expert scientific panels concluded that sucrose, high-fructose corn syrup, and their components, fructose and glucose, did not pose any significant health risk with the sole exception of promoting dental caries.[4,19-22] Added sugars have since been categorized as "discretionary calories," and moderate intake is recommended.[17,23,24] The question addressed in this article is whether any one caloric sweetener, specifically high-fructose corn syrup, is metabolically or nutritionally unique.

Glucose, fructose, and sucrose from fruit or honey have been part of the human diet for millennia. Sucrose has been produced commercially from sugarcane and sugar beets for hundreds of years and continues to serve as the benchmark against which other sweeteners are

measured. Worldwide, 9 times as much sucrose is consumed as high-fructose corn syrup. It would likely surprise many to learn that even in the United States, more sucrose is consumed per capita than high-fructose corn syrup.[15,23,25] The fact that obesity is as prevalent in countries that use little or no high-fructose corn syrup as in the United States substantially weakens the Bray hypothesis[1] of a unique link between high-fructose corn syrup and obesity.

High-fructose corn syrup proved to be an attractive alternative to sucrose because of its stability in acidic foods and beverages (eg, soft drinks). It is also an ingredient derived from corn, a dependable and renewable agricultural material grown abundantly in the midwestern region of the United States. In a sense, high-fructose corn syrup should be viewed as "corn sugar." From this perspective, it could properly be viewed as a reasonable agricultural alternative to sugar (sucrose) produced from sugarcane and sugar beets.

How Does the Composition of High-Fructose Corn Syrup Compare With Other Nutritive Sweeteners?

It is important to understand that essentially all nutritive sweeteners in common use in the American diet are similar combinations of glucose and fructose. Two main forms of high-fructose corn syrup are in common use. HFCS-55, which is composed of 55% fructose, 42% glucose, and 3% glucose polymers, is the form of high-fructose corn syrup commonly used in soft drinks. HFCS-42, consisting of 42% fructose, 53% glucose, and 5% glucose polymers, is the common form of high-fructose corn syrup used in baked goods.

Table 1 provides the carbohydrate composition of common nutritive sweeteners. As can be observed from the data in this table, HFCS-55 and HFCS-42 are very similar in composition to sucrose, invert sugar, and honey. From a practical standpoint, all 4 of these nutritive sweeteners are essentially interchangeable in many foods and beverages. High-fructose corn syrup and sucrose are both very different from "regular" corn syrup and pure fructose: corn syrup is glucose based with no fructose and low sweetness, whereas the latter contains no glucose and is used only in specialty applications. The name *high-fructose corn syrup* does not mean the fructose content is much higher than other sweeteners, but that name was given because its fructose content is higher than the corn syrup from which it was derived. These distinctions are particularly important because considerable confusion has risen in both the medical literature and lay literature, where improper references and comparisons between regular corn syrup, pure fructose, and high-fructose corn syrup are frequently made. The proper comparison is between high-fructose corn syrup and sucrose.

Is Consumption of High-Fructose Corn Syrup Linked to Obesity?

As indicated earlier, Bray et al[1] suggested in 2004 that there might be a link between increased consumption of high-fructose corn syrup and dramatic increases in obesity in the United States. These authors subsequently acknowledged that their opinion piece was intended to be provocative and stir a scientific debate. Indeed it did. Multiple studies from a variety of research laboratories,[2,5-10] as well as proceedings from 2 major symposia on nutritive sweeteners[3,8,11-15] have all uniformly concluded that, based on current science, there is no unique association between high-fructose corn syrup and obesity. Furthermore, the American Medical Association studied this issue for over a year and concluded that high-fructose corn syrup "does not appear to contribute more to obesity than other caloric sweeteners."[16] Finally, the American Dietetic Association[17] stated, "No persuasive evidence supports the claim that the high fructose corn syrup is a unique contributor to obesity."

Perhaps the most succinct synopsis of this issue came from G. Harvey Anderson[26] in an editorial for the *American Journal of Clinical Nutrition*, where he wrote:

> The hypothesis that the replacement of sucrose by HFCS in beverages plays a positive role in obesity is not supported on the basis of its composition, biologic actions, or short-term effects on food intake. Had the hypothesis been phrased in the converse, namely that replacing HFCS with sucrose in beverages would be seen as a solution to the obesity epidemic, its merit would have been seen more clearly. Put simply, a proposal that a return to sucrose containing beverages would be a credible solution to the obesity epidemic would have been met with outright dismissal.

What Are the Findings of Current Research on High-Fructose Corn Syrup and Sucrose?

The original Bray hypothesis[1] received additional traction from research performed by Teff et al,[27] who employed a model in which individuals consumed 25% of calories either as pure fructose or pure glucose in the context of mixed-nutrient meals over 1 day. Individuals who consumed 25% of calories from glucose experienced a spike in blood glucose and insulin when compared to individuals who consumed 25% of calories from pure fructose. The reduction in meal-dependent insulin secretion in individuals who consumed 25% of calories from pure fructose resulted in suppressed circulating levels of leptin and less ghrelin suppression. It was argued on the basis of this experiment that consumption of fructose could lead to overconsumption of calories by attenuating insulin and leptin concentrations, as well as ghrelin suppression.[27] When these experiments were repeated using real-world diets comparing 25% of calories from high-fructose corn syrup to 25% of calories from sucrose in the context of mixed-nutrient meals over the course of a day, all of the differences in short-term energy regulating hormone levels disappeared.[5] The contrast between these 2 sets of experiments carried out with virtually identical research procedures but

different sugar comparisons (pure glucose and pure fructose[27] [not commonly found in the diet] or high-fructose corn syrup and sucrose[5] [commonly found in the diet]) underscores the danger of extrapolating data from pure fructose and pure glucose into the real-world situation of high-fructose corn syrup and sucrose. In addition, in neither experiment did the participants express differences in appetite either during testing or the day after.

A comparison between high-fructose corn syrup and sucrose has also been made on appetite and caloric consumption at subsequent meals.[5] Recent research has shown no difference between high-fructose corn syrup and sucrose on appetite or caloric consumption at the next meal.[9,10]

It has also been argued that high-fructose corn syrup consumption may increase levels of uric acid.[28] If this were true, it would be cause for concern because there is a purported link between elevated levels of uric acid and some underlying components of the metabolic syndrome.[28] Evidence for a linkage between pure fructose consumption at high levels and increased uric acid levels comes from animal experiments performed by Johnson et al,[28] in which laboratory rats were fed more than 60% of calories from pure fructose. In this model, it was demonstrated that uric acid increases. However, research using high-fructose corn syrup and sucrose at 25% of calories (far above typical human consumption levels) over the course of 1 day did not show any differences or abnormal elevations in uric acid levels.[6]

It has been suggested that high levels of fructose consumption may also cause lipid abnormalities, particularly to postprandial elevations in triglycerides.[10] Once again, data supporting this assertion come from experiments that use high levels of pure fructose (typically 25% of calories). Recent experiments comparing mixed-nutrient meals with 25% of calories from either high-fructose corn syrup or sucrose in both lean and obese women again showed no short-term differences in triglycerides, nor were there any significant elevations in postprandial triglycerides.[7]

A few animal studies have compared effects of high-fructose corn syrup and sucrose over longer terms and have raised questions about risks of obesity and metabolic syndrome with high-fructose corn syrup.[29] However, the doses used far exceed any that would be consumed by humans. Longer-term human research is currently under way comparing the effects of common sweeteners at typical intake levels in a broad range of test participants.

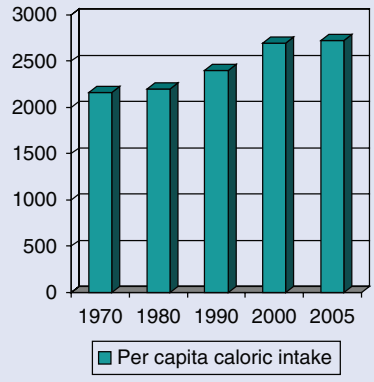
It must be recognized that most experimentation in support of a unique metabolic role for high-fructose corn syrup in obesity and related diseases relies on test diets featuring exaggerated amounts of pure fructose at levels never encountered in the human diet. Marriott et al[30] recently estimated mean and 95th percentile intakes at 9% and <18% of total calories, respectively. Experimental diets featuring 25% to 40% or 60+% of calories as fructose are commonly used in human and animal studies, respectively. Although exaggerated levels generate reportable differences between fructose and controls, they are not physiologically relevant to humans and should not be used to judge risk or guide public health decisions.

If High-Fructose Corn Syrup Is Not Causing the Obesity Epidemic, What Is?

Numerous studies, including those providing the basis for the *Dietary Guidelines for Americans 2005*[24] and the Surgeon General's report on obesity,[31] have provided compelling evidence that the obesity epidemic in the United States (and other industrialized countries) is multifactorial in origin and can be largely attributed to the significant increases in per capita calorie intake and decreases in physical activity, which have occurred in the United States and other industrialized countries over the past 30 years. As can be seen in Figure 1, average caloric consumption in the United States increased 25% between 1970 and 2005.[32] Couple this increase in caloric consumption with declines in levels of physical activity, and an environment is set up to promote weight gain. Today, added sugars account for approximately 17% of daily caloric intake. And although added sugar consumption increased during this period—*along with all other macronutrients*—it should be noted that as a percentage of total calories consumed, added sugars actually declined slightly, whereas added fats and flours/cereals modestly increased.[32] Thus, Americans are eating more of *everything* than in 1970, when high-fructose corn syrup was introduced to the food and beverage industry.[15]

Figure 1.

Per capita daily caloric intake (US Department of Agriculture Economic Research Service loss-adjusted availability), 1970-2005.



What Should the Lifestyle Physician and Practitioners Know About High-Fructose Corn Syrup in Sports Drinks?

High-fructose corn syrup and other sweeteners are commonly found in sports performance drinks, where they have been proven to maintain glucose homeostasis and provide energy substrates to maintain or improve exercise performance over long durations. Of particular importance, it has been shown that consumption of the combination of glucose and fructose results in greater exogenous carbohydrate oxidation and better athletic performance than when either monosaccharide is consumed alone.[33,34] The added calories from high-fructose corn syrup or other carbohydrates in these settings are probably less

important than the performance benefits that come from the addition of these carbohydrates.

Summary

With this background on high-fructose corn syrup, what should lifestyle physicians and practitioners understand as key messages to impart to their patients?

We suggest that the following key factors be emphasized:

1. From a compositional standpoint, high-fructose corn syrup, sucrose, invert sugar, honey, and concentrated fruit juices are all virtually interchangeable. All of these nutritive sweeteners are composed of approximately 50% glucose and 50% fructose. All are absorbed similarly, have similar sweetness, and have the same number of calories per gram.
2. From a metabolic standpoint, high-fructose corn syrup and sucrose are virtually identical by all endpoints measured to date. These include serum glucose and insulin, leptin and ghrelin, triglycerides, and uric acid.
3. There is now overwhelming scientific agreement that high-fructose corn syrup is not a unique cause of obesity when compared to other nutritive sweeteners at typical intake levels. The original hypothesis that high-fructose corn syrup was uniquely related to obesity was based on a temporal association and did not establish cause and effect. Numerous subsequent short-term metabolic trials and appetite studies now suggest that there is no unique link between high-fructose corn syrup and obesity.
4. Americans are eating more of everything than they did 30 years ago—and compared with 3 decades ago, added sugars now make up less of the diet as a percentage of total calories than fats and cereals.
5. All nutritive sweeteners should be used in moderation, as should caloric foods and ingredients from all macronutrient sources. Many strategies have been developed to promote moderation, most notably the *Dietary Guidelines for Americans 2005*.[24]
6. High-fructose corn syrup should not be confused with pure fructose or regular corn syrup. Research conducted using a pure fructose model should not be extrapolated to high-fructose corn syrup. In retrospect, high-fructose corn syrup was probably poorly named because the name implies that it must contain a preponderance of fructose, but this is not the case. The more proper comparison is between high-fructose corn syrup and sucrose, both of which contain approximately 50% glucose and 50% fructose.
7. The addition of carbohydrates to sports drinks may provide a benefit by maintaining glucose homeostasis, providing substrates for sustained energy release and increased rates of exogenous carbohydrate oxidation, which may be particularly valuable for endurance events.
8. Longer-term research is currently under way comparing the effects of common sweeteners at typical intake levels in a broad range of test participants.

As sources of authority, it is important that physicians and other health care professionals recognize that controversies arise and are perpetuated in nonrefereed venues such as the Internet. Now that abundant science exists in the area of high-fructose corn syrup in general and its comparison to sucrose in particular, lifestyle physicians can serve as a trusted source of commonsense advice in this important area. AJLM

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