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## Fructose toxicity: is the science ready for public health actions?

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### Summary

**Purpose of review**—The assumption that fructose may be “toxic” and involved in the pathogenesis of non communicable diseases such as obesity, diabetes mellitus, dyslipidemia, and even cancer has resulted in the call for public health action, such as introducing taxes on sweetened beverages. This review evaluates the scientific basis for such action.

**Recent findings**—Although some studies hint towards some potential adverse effects of excessive fructose consumption especially when combined with excess energy intake, the results from clinical trials do not support a significant detrimental effect of fructose on metabolic health when consumed as part of a weight maintaining diet in amounts consistent with the average estimated fructose consumption in Western countries. However, definitive studies are missing.

**Summary and conclusion**—Public health policies to eliminate or limit fructose in the diet should be considered premature. Instead, efforts should be made to promote a healthy life style that includes physical activity and nutritious foods while avoiding intake of excess calories until solid evidence to support action against fructose is available. Public health is almost certainly to benefit more from policies that are aimed at promoting what is known to be good than from policies that are prohibiting what is not (yet) known to be bad.

### Keywords

Fructose; sugar; hypertriglyceridemia; insulin resistance; obesity; diabetes; non-alcoholic fatty liver disease

### Introduction

Recently, the potential adverse metabolic effects of sugars, in particular fructose have been the focus of attention. The assumption that fructose, especially when consumed with sweetened beverages, may be “toxic” and involved in the pathogenesis of non communicable diseases such as obesity, diabetes mellitus, dyslipidemia, and even cancer has been spurred by the introduction of high fructose corn syrup (HFCS) and the concomitant increase in obesity (1). This concept has been of major interest to journalistic inquisitiveness and has been promoted in the lay press (2), as well as in articles published in high impact peer-reviewed journals (3). The suspicion about specifically deleterious effects of fructose has resulted in the call for public health action, such as introducing taxes on sweetened

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beverages (4). These statements have had a wide echo and may be influential in devising public health actions in the fight against obesity and related diseases. Indeed, taxes on sweetened (with sugar or HFCS) beverages have been introduced in France at the beginning of this year, and are presently being considered in several other countries around the world. One may however question whether such action would rest on solid scientific and clinical evidence.

### Sources of fructose in our diet

An immediate difficulty one encounters when trying to evaluate the scientific literature is to identify what is the potential deleterious factor we are talking about. Based on biochemical considerations and some experimental evidence, fructose may indeed be the main target, due to the fact that it is essentially metabolized in splanchnic tissues, and that its metabolism and conversion into other intermediary substrates is not regulated by insulin or the energy status of the liver (5). However, there is no food containing pure fructose only, and fructose and glucose are always co-ingested, either as free hexoses in fruits and honey, or as free glucose-fructose mixtures in HFCS, or bound together as sucrose. In HFCS, which is produced by processing corn starch to yield glucose, and then processing the glucose to produce a syrup that contains various amounts of fructose, the most commonly used grade (and that found in soft drinks) is HFCS 55 which contains 55% fructose and 45% glucose; roughly the same as the fructose to glucose ratio in sucrose (6). Thus, fructose intake is essentially proportional to caloric sweetener intake regardless of whether the sweetener is sucrose (sugar) or HFCS. In the USA and in Europe, half of the added sugar intake results from consumption of sweetened solid food items (yogurt, cereal bars, chocolate bars, ice-creams, etc.) and half from consumption of sweetened beverages (regular sodas, fruit juices, energy drinks, sport drinks, and sweetened milk products) (7). Approximately 50% of the added sugar intake comes from sucrose and 50% from HFCS, with fructose accounting for ~ 10% of total calorie intake (7, 8). Therefore, it is difficult to dissect the effect of fructose *per se* from the effect of added sugar intake (regardless of whether it comes from beverages or other food items) in any practically meaningful way. Along the same lines, evaluating the effect of added sugar intake carries the question of whether or not to account for the extra calories or not and what calories to use as a replacement (i.e., coke vs. water, coke vs. milk, coke vs. diet coke, sugar vs. glucose? etc). Now, what have we learned so far and where does the fear of fructose coming from? Is it legitimate?

### Observations collected from epidemiological studies

Due to the fact that most nutritional tables used for epidemiological studies did not specifically include fructose data, the bulk of epidemiological studies have assessed the relationship between metabolic diseases on one hand, and either sugar intake or sweetened beverage intake on the other hand. A comprehensive review of these studies is beyond the scope of this editorial but most report that sugar/calorically sweetened beverage intake is associated with increased body weight and obesity (9). Interpretation of these results however is complicated because sweetened beverage intake is also associated with increased total energy intake and increased consumption of processed and high-fat foods (such as fried potato products and processed meats) as well as reduced consumption of fruits and vegetables and reduced physical activity (10). In fact, several studies that adjusted for total energy intake in their analysis failed to observe a direct positive relationship between sugar intake and obesity (11-13). Not surprisingly, a recent meta-analysis including 41 short-term intervention trials concluded that fructose increased body weight when included in a hypercaloric, but not when included in an energy balanced, isocaloric diet (14). In addition, although, it has been proposed that fructose may be less satiating than other carbohydrates (15), and that consumption of sugar with sweetened beverages is incompletely compensated

by a reduction of solid food intake (16), a recent systematic review of the literature on this topic concluded that there is no consistent evidence that fructose effects body weight when consumed at levels corresponding to usual, western intake (17). Associations between sugar and/or sweetened beverage intake and diabetes, dyslipidemia, non-alcoholic fatty liver disease, and markers of cardiovascular diseases have also been reported (18-20). However, these associations were not independent of body weight. The data collected from epidemiological studies therefore support the idea that sugar and sweetened beverage consumption most likely contribute quite significantly to excess energy intake and obesity, but do not demonstrate that fructose *per se* or even just sugar are responsible for increased energy intake or metabolic diseases.

## Observations collected from clinical trials

In general, the results from clinical trials do not support a significant detrimental effect of fructose on metabolic health and although some studies hint towards some potential adverse effects, the clinical relevance of these findings is unclear. Many short term studies, performed in the 1980's showed that fructose substituted for starch or sucrose, increased fasting and postprandial triglyceride concentrations in healthy subjects and in type 2 diabetes patients (21). Since then, several overfeeding studies in non-obese and overweight subjects have confirmed the hypertriglyceridemic effect of fructose (22-24). When consumed in amounts consistent with the average estimated fructose consumption by Americans and other people from Western societies, fructose did not affect plasma lipid concentrations (25, 26) but it increased the number of small dense LDL particles, which may be associated with an increased cardiovascular risk (27). Twenty four hour glucose and insulin concentrations are also not adversely affected by a diet providing as much as 25% of energy as fructose (equivalent to ~50% of dietary caloric intake as sugar or HFCS) for 10 weeks; in fact fructose lowered plasma glucose and insulin concentrations (28, 29). Even in the context of fructose overfeeding, providing about 30% excess energy via fructose, whole-body insulin-mediated glucose disposal, assessed by using the gold-standard hyperinsulinemic-euglycemic clamp technique, was unchanged (22, 23, 30) and fasting hepatic glucose production was only marginally increased by about 14% (30). Furthermore, as far as we can tell, only one study has found that consumption of 200 g of fructose per day during 2 weeks increased blood pressure (31) whereas others report no effect (22, 24) and a recent meta-analysis including 13 isocaloric and 2 hypercaloric fructose feeding intervention studies concluded that substitution of fructose for other carbohydrates did not adversely affect blood pressure in human subjects (32).

Of significant concern could be the potential of fructose to preferentially increase visceral fat deposition and stimulate ectopic fat accumulation, especially in the liver. However, so far fructose-related increases in visceral and ectopic fat accumulation have only been observed in subjects who consumed quite substantial amounts (about 150 g/d or more) of fructose for 1 week up to 6 months and either received a hypercaloric diet per design or gained significant amounts of weight during the study (23, 24, 33) so it is unclear how much of the increase in these fat depots is simply due to excess energy intake. The mechanisms responsible for increased hepatic fat deposition during fructose overfeeding studies involve a stimulation of hepatic de novo lipogenesis and an inhibition of adipose lipolysis and hepatic lipid oxidation (23, 24, 30). Furthermore, there is concern that fructose may cause hepatic inflammation and accelerate the progression of non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH). In rodent studies, fructose not only induces hepatic steatosis but also enhances hepatic TNF- $\alpha$  and PAI-1 production (34, 35), two mediators thought to be involved in liver inflammation, and stimulates the progression of NAFLD to NASH in animals fed a high saturated fat diet (36). It also impairs liver regeneration after partial hepatectomy (36). Thus, there is concern that fructose may exert a pro-inflammatory

effect on liver cells, which, when combined with other risk factors, such as excess energy or high fat intake or low physical activity, may trigger progression of NAFLD to NASH.

### **So, is there a need for public policy against fructose or rather a need for more scientific inquiry?**

There are indeed reasons to be concerned about an excessive intake of fructose and a call for limiting its consumption is in place because excess energy intake in the form of fructose (just like any other energy source) is associated with excess body weight and metabolic alterations that often accompany obesity. However, there is clearly a need for more clinically relevant research before taking drastic public health actions to specifically target fructose-containing caloric sweeteners, which may divert authorities from other, possibly more important public health actions, such as promoting an increase in physical activity, a decrease in energy consumption in general and an increase in the consumption of fresh fruit and vegetables because there is little evidence that fructose itself causes significant metabolic alterations when consumed in amounts that are consistent with current dietary habits. However, crucial studies that will provide definitive answers to the concerns of fructose toxicity and others which should guide decisions of public policy makers are still missing. What are they?

1. What are the metabolic effects of fructose when consumed in amounts consistent with that consumed on average in the general population under conditions of weight stability?
2. Are there beneficial effects to removing fructose, especially sugar/HFCS-sweetened beverages, from the diet and will it decrease obesity in the population (or simply shift the consumption of excess energy from beverages to other items)? In this regard, there is an urgent need for intervention studies. Recently the CHOICE study indicated that replacing sweetened beverages by non caloric beverages in a group of overweight adults led to a 2 % weight loss after 6 months (37). However, avoiding these beverages was a choice made with the intent to lose weight and equal amounts of weight were lost in the control subjects who reduced calorie intake through cutting down on foods of their choice. Which leads to the next question.
3. What are the consequences of “forcing” fructose, especially HFCS-sweetened beverages from the market? Will this result in an increase in the use of sugar again or an increase in artificial sweetener consumption and if so, is this safer? Or might a ban of sweetened beverages simply shift the consumption of sugar/HFCS in beverages to the consumption of sugar in other goods to satisfy ones sweet tooth?
4. Does dietary sugar/HFCS/fructose, especially when consumed in the form of beverages, impair the control of food intake and induce excessive energy intake (38)? So far, there is no compelling evidence for this, but studies have mostly been limited to single meals (39-42).
5. What are the long term effects of heavy fructose consumption? So far most studies have been limited to relative short-term interventions. However, given the fact that marked alterations of molecular events can be observed over short periods and that alterations of glucose homeostasis can be documented within a few days to weeks in animal models (43), it appears unlikely that alterations of energy metabolism or endocrine regulations independent of a body fat increase would take several years in human subjects.

6. Are there particularly susceptible populations and what are the reasons for their increased susceptibility? In rats, fructose causes adverse metabolic effects in males and in oophorectomized females, but not in non-oophorectomized females (44). In humans, short term fructose overfeeding also produced much blunted metabolic effects in pre-menopausal females (45-47). It has also been suggested that fructose causes more significant metabolic alterations in insulin resistant subjects (48). Finally, it has been proposed that the consequences of sugar consumption on hepatic fat may vary according to ethnic groups and genetic variations (49). The concept that susceptibility to fructose may be different presently rests on a small number of studies, and needs to be assessed more broadly in a public health perspective.

## Conclusion

Rather than damning fructose, efforts should be made to promote a healthy life style that includes physical activity and fresh fruits and vegetables while avoiding intake of excess calories until solid evidence to support action against fructose is available. Public health is almost certainly to benefit more from policies that are aimed at promoting what is known to be good than from policies that are prohibiting what is not (yet) known to be bad.

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**Key bullet points**

- There is some evidence that suggests excessive fructose consumption especially when combined with excess energy intake may have adverse effects on metabolic health.
- The results from clinical trials do not support a significant detrimental effect of fructose on metabolic health when consumed as part of a weight maintaining diet in amounts consistent with the average estimated fructose consumption in Western countries.
- Public health policies to eliminate or limit fructose in the diet should be considered premature.
- Crucial studies that will provide definitive answers to the concerns of fructose toxicity and others which should guide decisions of public policy makers are still missing.