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Fructose and metabolic diseases: New findings, new questions

Luc Tappy M.D.[a,b], Kim A. Lê Ph.D.[a], Christel Tran M.D.[a], Nicolas Paquot M.D.[c]

[a] *Department of Physiology, University of Lausanne, Lausanne, Switzerland*
[b] *Service of Endocrinology, Diabetes and Metabolism, CHUV, Lausanne, Switzerland*
[c] *Service of Diabetology CHU Sart Tilman, Liège, Belgium*

ABSTRACT

There has been much concern regarding the role of dietary fructose in the development of metabolic diseases. This concern arises from the continuous increase in fructose (and total added caloric sweeteners consumption) in recent decades, and from the increased use of high-fructose corn syrup (HFCS) as a sweetener. A large body of evidence shows that a high-fructose diet leads to the development of obesity, diabetes, and dyslipidemia in rodents. In humans, fructose has long been known to increase plasma triglyceride concentrations. In addition, when ingested in large amounts as part of a hypercaloric diet, it can cause hepatic insulin resistance, increased total and visceral fat mass, and accumulation of ectopic fat in the liver and skeletal muscle. These early effects may be instrumental in causing, in the long run, the development of the metabolic syndrome. There is however only limited evidence that fructose per se, when consumed in moderate amounts, has deleterious effects. Several effects of a high-fructose diet in humans can be observed with high-fat or high-glucose diets as well, suggesting that an excess caloric intake may be the main factor involved in the development of the metabolic syndrome. The major source of fructose in our diet is with sweetened beverages (and with other products in which caloric sweeteners have been added). The progressive replacement of sucrose by HFCS is however unlikely to be directly involved in the epidemy of metabolic disease, because HFCS appears to have basically the same metabolic effects as sucrose. Consumption of sweetened beverages is however clearly associated with excess calorie intake, and an increased risk of diabetes and cardiovascular diseases through an increase in body weight. This has led to the recommendation to limit the daily intake of sugar calories.

Pure, white, and deadly: the dark side of sugar was suspected many years ago, when an association between sugar consumption and coronary heart diseases was recognized and emphasized by John Yudkin [1]. Sugar, a natural sweetener obtained from either sugar cane or beets, is a disaccharide composed of one glucose molecule linked through an α1-4 glycoside bond to a fructose molecule. Fructose, besides contributing to half the total content of sugar, can also be found as a hexose in fruits and honey. More recently, sweeteners started to be produced from corn through starch isolation and hydrolysis to glucose, followed by enzymatic isomerization of part of the glucose into fructose [2,3]. The resulting mixture, known as high-fructose corn syrup (HFCS), has several industrial advantages over sugar, the most important being its low price, and has progressively replaced sugar consumption in North America over the past 30 years.

Fructose metabolism has been reviewed extensively elsewhere [4-6] and will be only briefly outlined here. In the gut, fructose is transported by specific transporters, GLUT5 [7,8]. In some subjects, fructose absorption is quantitatively limited, and some malabsorption occurs when large amounts of fructose are ingested. This can cause abdominal discomfort and diarrhea, and production of volatile fatty acids from colonic fructose fermentation [9,10]. Fructose absorbed from the gut into the portal vein is nearly completely metabolized in the liver through metabolic pathways distinct from those of glucose; furthermore, the initial steps of its metabolism are insulin-independent, and hence, fructose is largely metabolized without requiring insulin secretion and without increasing plasma glucose. This is due to the fact that 1) part of the fructose appears to be directly metabolized in enterocytes, where it is converted and into lactate and glucose, and 2) the bulk of absorbed fructose is taken up by liver cells, where it is rapidly converted into fructose 1-phosphate and triose-phosphates through the sequential actions of fructokinase and aldolase B and triokinase. Fructokinase and aldolase B are not inhibited by ADP and citrate and hence are not regulated by the cellular energy status. In that, fructose differs from glucose, because the ADP and citrate concentrations exert a negative feedback control on the initial steps of glycolysis. As a consequence of this absence of feedback inhibition, virtually all the fructose ingested with a meal (whether under its pure, unbound form, or bound to glucose in sucrose) is rapidly converted into hepatic triose-phosphates [11]. These substrates are subsequently oxidized within the liver cells or converted into glucose and lactate to be released into the bloodstream, or converted into hepatic glycogen. A small, but significant amount of trisose-phsophates is also converted into triacylglycerol in liver cells through the process of de novo lipogenesis (TG) [12]. Although quantitatively far less important than the other pathways of fructose

disposal, de novo lipogenesis appears to be closely associated with the adverse metabolic effects of fructose.

Because fructose metabolism is not dependent on insulin secretion, at least for its initial steps, and because fructose ingestion causes only a limited rise in glycemia, fructose was initially proposed as a natural substitute of sucrose for diabetic patients. It however became rapidly apparent that an increased dietary intake of fructose had serious adverse metabolic effects in both rodents and humans. Thus it was recognized that a high-fructose intake is associated with increased plasma triglyceride concentrations, hepatic steatosis, impaired glucose tolerance and insulin resistance, and even high blood pressure [4,5].

Besides these metabolic effects, fructose effects on mineral metabolism have also been considered. Fructose forms complexes with metal ions and hence may modulate the intestinal absorption and bioavailability of minerals [13]. Fructose has indeed been reported to decrease copper absorption in rats [14]. A diet containing up to 20% energy as fructose had however no adverse effect on copper balance in humans [15]. Fructose also increases iron absorption in rats [15] but does not appear to alter zinc bioavailability [16]. The effects of fructose on calcium metabolism have also been documented. The results indicated that rats receiving glucose-sweetened beverages had lower phosphate and calcium intake and increased urinary calcium excretion compared to the rats receiving fructose-sweetened beverages. These results suggest that fructose is not directly involved in the negative association that was observed between sugar intake and bone health [17]. Sweetened beverage consumption however accounts for an important portion of total fructose intake. In some populations, mainly children and teenagers, a high consumption of sweetened beverages may be associated with a lowered intake of milk, and hence, of calcium [18].

Several important questions regarding the role of fructose in the pathogenesis of metabolic diseases remain, however, only partially addressed, as follows.

What are the mechanisms responsible for fructose-induced metabolic alterations?

There is overwhelming evidence that, in rodents, a high-sucrose or a high-fructose diet will lead to the development of obesity, diabetes, and dyslipidemia, and to a substantial decrease in both liver and muscle insulin sensitivity [19]. Oxidative stress and endoplasmic reticulum stress appear to be involved in these processes [20-23]. Furthermore, the adverse metabolic effects observed with high-sucrose diets appear directly related to the fructose component of sucrose [24]. The adverse effects of fructose on glucose metabolism are closely linked to alterations of lipid metabolism. In rats, intrahepatic fat content and blood very low density lipoprotein (VLDL)-triacylglycerol concentrations increase within 6 wk of a high-fructose diet, while intramuscular fat content increases within about 3 mo. Interestingly, the development of insulin resistance follows a similar time course: hepatic insulin resistance is observed early after switching to a high-fructose diet, while the appearance of muscle insulin resistance is delayed [19]. This suggests that fructose-induced insulin resistance is closely linked to ectopic lipid deposition and tissue-specific lipotoxicity [25].

In humans, the adverse metabolic effects of fructose are less clearly documented. There is ample evidence that increasing the fructose content of the diet increases plasma triglycerides, through several mechanisms, among which are a stimulation of hepatic de novo lipogenesis [26], and a decreased VLDL-triacylglycerol clearance [27]. Based on animal experiments, an increased VLDL-triacylglycerol secretion is also likely to be involved [28]. The increase in plasma triglyceride induced by fructose is significantly blunted in females, which suggests that female sex hormones may exert a protective effect [29,30]. In humans, a high-fructose, hypercaloric diet leads to ectopic fat deposition in liver cells and skeletal muscle in humans already after a 1-wk period [31]. There is strong evidence that fructose decreases hepatic insulin sensitivity in humans [26,32,33], and that a 10-wk high-fructose diet impairs glucose homeostasis in overweight individuals [34]; however, few studies have directly evaluated the effect of a high-fructose diet on whole body insulin sensitivity. It has been reported that supplementation with various amounts of fructose for up to 4 wk failed to decrease whole body insulin sensitivity in healthy individuals [31,35]. Whether this may be different in obese insulin-resistant subjects remains to be evaluated.

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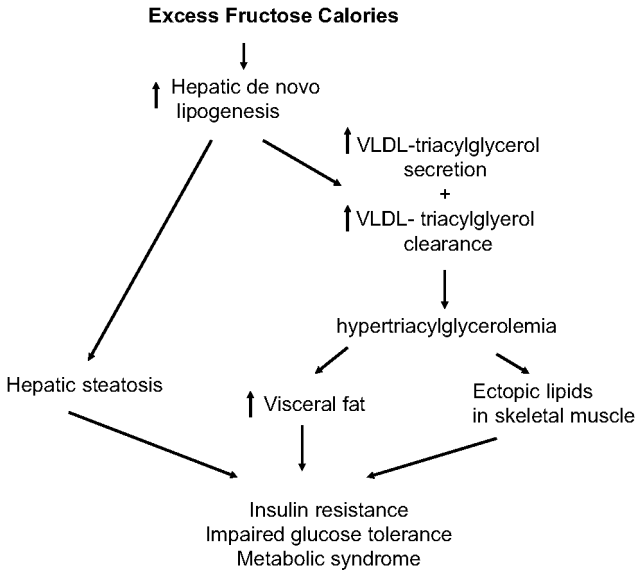
In animal models, high-fructose diets almost invariably lead to the concomitant development of excess body fat and insulin resistance; an increased body fat mass, body fat distribution, and ectopic lipid deposition in liver and muscle can all play a role in the development of the metabolic syndrome. In humans, it has been recognized for several decades that abdominal fat distribution is associated with metabolic and cardiovascular diseases [36], and that intravisceral fat contributes much more to insulin resistance than subcutaneous fat [37]. In this regard, the interrelationship between body fat distribution and intrahepatic fat content bears a special interest. Many obese patients indeed do not display significant metabolic disorders and have been coined "healthy obese" or "metabolically fit obese" [38]. When comparing these healthy obese subjects to obese subjects with metabolic complications, it appears that both intravisceral fat and intrahepatic fat content are tightly related with insulin resistance. Furthermore, intrahepatic fat content appears more specifically related to the metabolic syndrome [39,40]. In humans, a high-fructose diet has been shown to increase visceral fat [34] and intrahepatic fat [31], which raises the possibility that the effects on hepatic fat metabolism and on visceral fat deposits may be central in the adverse metabolic effects of fructose. Based on these considerations, it is tempting to speculate that a stimulation of hepatic de novo lipogenesis induced by fructose leads to intrahepatic fat deposition, increased VLDL-triacylglycerol secretion, and hepatic insulin resistance; this may also secondarily lead to visceral fat deposition through mechanisms that remain to be determined. With time, the increased plasma VLDL-TG and an inhibition of lipid oxidation induced by a high-fructose diet may favor ectopic fat deposition in muscle, muscle lipotoxicity, and whole body insulin resistance (Fig. 1).

Fructose is also known to increase plasma uric acid, and this effect may be involved in the development of insulin resistance. In rats, fructose-induced hyperuricemia results in inhibition of NO synthase. Because insulin-induced glucose utilization involves not only the stimulation of key metabolic pathways in insulin-sensitive cells but also a NO-dependent increase in muscle blood flow [41], it was proposed that inhibition of the vascular effects of insulin by uric acid was involved in fructose-induced insulin resistance. In support of this hypothesis the development of insulin resistance was prevented by lowering uric acid concentrations with an uricosuric agent in fructose-fed rats [42].

Fig. 1. *Putative mechanisms linking excess fructose consumption to the metabolic syndrome. In liver cells, fructose stimulates de novo lipogenesis, leading to increased hepatic fatty acids, which can be deposited as ectopic liver fat (hepatic steatosis) or be secreted as VLDL-triacylglycerols. In addition, fructose impairs the extrahepatic clearance of VLDL-triacylglycerols. When excess fructose calories are consumed, this leads to hepatic steatosis and to hyper-triacylglycerolemia, which in turn favors visceral fat accumulation and ectopic lipid deposition in skeletal muscle. The metabolic syndrome develops in the long run as a consequence of hepatic and muscle lipotoxicity and of visceral obesity.*



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Are the effects of fructose different from those of glucose?

In our everyday diet, naturally occurring, free fructose (essentially with fruits and honey) is a modest component of energy intake. Furthermore, there is some evidence that consumption of fructose with fruits or honey does not produce the same adverse metabolic effects as added fructose. This may be due to the presence of natural antioxidants and/or dietary fibers with fruits and honey [20,21]. The vast majority of fructose in our diet corresponds to added sugars, the two main sources being sucrose (containing 50% fructose) and HFCS (containing 42%-55% fructose). As a consequence, the intakes of fructose and glucose always vary simultaneously, and therefore, high-fructose consumers are also high-glucose consumers. Few studies have however compared the effects of high-fructose versus high-glucose diets. In rodents, a high-fructose diet was shown to increase the expression of lipogenic genes, to suppress peroxisome proliferator activated receptor-alpha (PPAR-α)-dependent lipid oxidation genes, and to cause intrahepatic fat deposition and hypertriglyceridemia. In contrast, a high-glucose diet also stimulated lipogenic gene expression, but failed to suppress lipid oxidation genes or to produce hepatic steatosis or dyslipidemia [43]. In humans, it has been shown that fructose, when substituted for starch, increases plasma triglycerides [44]. It has also been shown that, in obese hyperinsulinemic women, administration of equivalent amounts of pure fructose, sucrose, and HFCS led to identical increases in plasma triglyceride, although the intake of fructose was about 50% less with sucrose and HFCS compared to pure fructose [30]. In normal weight and obese women overfed for 4 d with 50% glucose or fructose above their energy requirement, de novo lipogenesis was found to be identical under both conditions. There was also no significant difference in plasma glucose, triacylglycerol, or insulin concentrations [45]. In healthy young normal weight subjects, a 6-d overfeeding with 3.5 g/kg fat-free mass/d (corresponding roughly to 30% energy requirements) fructose or glucose increased both VLDL-triacylglycerol concentrations and intrahepatic fat, with large interindividual variations, however [46]. In overweight subjects who received glucose or fructose drinks corresponding to 30% of their energy requirements with ad libitum food intake, body weight increased to the same extent with both sugars, while impaired glucose tolerance developed only in subjects receiving fructose. Interestingly, fructose significantly increased visceral adipose tissue as estimated by magnetic resonance imaging, while the increase with glucose was of smaller magnitude and failed to reach statistical significance [34].

Because all these experiments involved hypercaloric conditions, one might wonder whether the observed effects can be specifically attributed to sugars or are the mere consequence of hypercaloric feeding. Similar short-term overfeeding experiments were performed with a saturated fat supplementation corresponding to 30% energy requirements: they demonstrated that fat overfeeding also increased intrahepatic fat content, but failed to increase plasma VLDL-triacylglycerol. Altogether, one may conclude that excess calories, whether as simple sugars or as saturated fat, increases intrahepatic fat content, and that sugars specifically increase plasma VLDL-triglyceride. Fructose however appears to exert this latter effect more potently than glucose. Such short-term experiments remain however difficult to extrapolate to dietary alterations of longer durations, for, with time, significant changes in body composition are likely to occur.

Are the effects of free fructose different from bound fructose?

In North America, HFCS has replaced a substantial portion of sucrose over the past three decades. The concomitant increases in the HFCS intake and in the prevalence of obesity have raised concern regarding a possible causal role of HFCS [47]. In rodents, feeding a diet rich in HFCS increased body weight and body fat and caused dyslipidemia and insulin resistance. As for fructose, HFCS feeding elicited an endoplasmic reticulum stress response in hepatocytes. These effects of HFCS appear therefore very comparable to those of sucrose [48,49]. HFCS differs from sucrose by a slightly higher fructose content, and by providing glucose and fructose as monosaccharides. There is however no evidence that providing fructose as a hexose has different metabolic effects than when fructose is consumed bound to glucose in sucrose. In patients with type 2 diabetes, the glucose and insulin responses to administration of 35 g of sucrose or HFCS were quite similar [50]. Based on the fact that fructose inhibits less ghrelin and increases less leptin than glucose [51], one may have hypothesized that HFCS would have a different effect than sucrose on these hormones and hence would have a lesser satiating effect. It was however documented that it was not the case, and that HFCS and sucrose produced similar leptin increases and ghrelin suppression in healthy female volunteers [52]. Furthermore, HFCS, sucrose, or equimolar glucose-fructose mixtures elicited similar satiety responses [53] or energy intake at a subsequent meal [54]. There is therefore no hint that the effects of free fructose may differ from those of fructose bound to glucose.

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Do changes in fructose consumption explain the current epidemics of metabolic disorders?

There is compelling evidence that a hypercaloric, high-fructose diet can induce, not only in animal models, but also in humans, a whole range of metabolic alterations, the most prominent being a disturbance of hepatic lipid metabolism and of plasma lipid profile. This, together with the observation that total sugar and fructose intakes have increased significantly over the past three decades, has led to the speculation that a high-fructose intake may bear a direct, causal effect in the current epidemics of obesity and related metabolic disorders [47,55]. Several surveys, using various epidemiologic methods to assess dietary intakes, have consistently reported that total sugar consumption, added sugar intake, and fructose have indeed increased worldwide over the past three decades [56], reviewed in [6]. In the US, average fructose consumption has increased from about 37 g/d in the late 1970s [56] to 49 g/d in the 1999-2004 period [57]. Not only fructose, but also total energy intake, increased during the same period.

Consumption of sweetened beverages accounts for the major portion of total fructose consumption, the remaining being mainly added sugar. As a result, glucose intake always covaries with fructose intake, and epidemiologic studies cannot differentiate between the effects of fructose per se and those specifically attributable to glucose. In this regard, it is therefore more appropriate to evaluate the potential effect of fructose by comparing the evolutions over time of sweetened beverages and metabolic diseases. While doing so, one has however to keep in mind that sweetened beverage consumption impacts on both sugar consumption and total energy intake at the same time.

Several studies have assessed the relationships between sweetened beverages consumption and energy intake, and a meta-analysis clearly documented that sweetened beverages consumption was associated with an excess energy intake [18]. Many cross-sectional studies have shown a positive association between consumption of sweetened beverages, mainly in teenagers, and body weight [58-65] (reviewed in [66]). Interventional studies further showed that adding sweetened beverages to the usual diet led to an increase in body weight [67,68], while reducing sweetened beverages intake in overweight subjects decreased body weight [69-73]. Several large studies also reported that sweetened beverage consumption increased the risk of developing type 2 diabetes, but this effect was essentially linked to body weight changes [74-76]. A significant association was observed between sweetened beverage consumption and an increased incidence of heart disease. Here again, this was mainly explained by a higher body weight in those consuming sweetened beverages. The relationship nonetheless remained significant after adjusting for body weight and may be explained either by the high-glycemic index or by the high-fructose content of sweetened beverages [77]. Finally it was reported that the consumption of sweetened beverages was higher in patients with non-alcoholic steatohepatitis than in healthy controls [78].

Perspectives and conclusions

There is considerable evidence that a high-fructose intake can indeed produce adverse metabolic alterations, the most prominent ones being an increase in plasma triglycerides, hepatic insulin resistance, and hepatic steatosis. These effects are consistently observed in rodents fed a high-fructose diet and are generally concomitant with an increased body mass. In humans, many of these alterations (hepatic steatosis, hepatic insulin resistance) are observed when fructose is experimentally administered in amounts largely exceeding usual fructose intake, and under hypercaloric conditions. When administered as part of a weight-maintenance diet, fructose can indeed increase plasma triglyceride. A recent meta-analysis [79] concluded that a fructose intake >50 g/d was already associated with altered plasma triglyceride concentrations. Fructose consumption and sweetened beverages are closely linked, and there is overwhelming evidence that sweetened beverage intake favors weight gain and that excess body weight in turn increases the risk of diabetes and coronary heart diseases. It appears therefore sound at this stage to advise limiting consumption of sugar calories to less than 140 kcal/d for men and 100 kcal/d for women (corresponding to about one can of sweetened beverage/d), as recently proposed by the American Heart Association [80]. Several important questions remain nonetheless unaddressed, and further studies are clearly required to better delineate the potential adverse metabolic effects of fructose when included in a weight-maintenance, non-hypercaloric diet, to document the interactions between fructose and other nutrients, and to evaluate whether there exist subgroups of individuals (obese insulin-resistant patients, offsprings of patients with type 2 diabetes) in whom the adverse metabolic effects of fructose may possibly be enhanced.

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