Fructose Ingestion: Dose-Dependent Responses in Health Research $^{1,2}$

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Abstract

Many hypotheses of disease risk and prevention depend on inferences about the metabolic effects of fructose; however, there is inadequate attention to dose dependency. Fructose is proving to have bidirectional effects. At moderate or high doses, an effect on any one marker may be absent or even the opposite of that observed at very high or excessive doses; examples include fasting plasma triglyceride, insulin sensitivity, and the putative marker uric acid. Among markers, changes can be beneficial for some (e.g., glycated hemoglobin at moderate to high fructose intake) but adverse for others (e.g., plasma triglycerides at very high or excessive fructose intake). Evidence on body weight indicates no effect of moderate to high fructose intakes, but information is scarce for high or excessive intakes. The overall balance of such beneficial and adverse effects of fructose is difficult to assess but has important implications for the strength and direction of hypotheses about public health, the relevance of some animal studies, and the interpretation of both interventional and epidemiological studies. By focusing on the adverse effects of very high and excessive doses, we risk not noticing the potential benefits of moderate to higher doses, which might moderate the advent and progress of type-2 diabetes, cardiovascular disease, and might even contribute to longevity. A salutary rather than hyperbolic examination of the evidence base needs to be undertaken. J. Nutr. 139: 1246S–1252S, 2009.

Introduction

Intervention studies have identified both potential benefits and risks of fructose consumption, and overdose focus on one rather than the other can influence beliefs about the role of fructose in the prevention or causation of disease. Researchers often use effects on markers of risk as a basis of hypotheses of clinical harm (1–7), but to date (2008) there is little evidence of such harm effects on markers of risk as a basis of hypotheses of clinical harm (1–7), but to date (2008) there is little evidence of such harm. Discussion of risk is prevalent and often takes place in the absence of consideration of benefits, a situation actually arising. Discussion of risk is prevalent and often takes place in the absence of consideration of benefits, a situation recognized to bias the literature (8,9). Often too, discussion ignores that the dose of fructose consumed is critically important.

Fructose intakes

Estimates of fructose intake made from a national representative USDA Continuing Survey of Food Intake by Individuals indicated that >95% of persons aged >19 y consume <100 g/d from all sources (10). Similar intakes have been observed in studies of health professionals in men (11), women (12), young women (13) [see also Taylor and Curhan (14)], and female adolescents (10). Such intakes are argued to be applicable to these population subgroups as recently as 2005 (10). From such data, it can be inferred that intervention studies using >100 g/d fructose (from all sources) would be of minor relevance to adult and adolescent female public health issues, although they could be of importance for some adolescent males.

More than 80% of adolescent males consume ≤100 g/d total fructose, and the remainder consume upward of 150 g/d (10). The interpretation of epidemiological studies on fructose is proving difficult. Very high fructose consumption may coincide with a high intake of high-glycemic glucose or larger than usual amounts of carbohydrate or energy or soft drink or a salty food or high-energy-density salty food such as chips (crisps) or a poor diet in general. Hence, it is especially important with fructose to validate or reject findings from epidemiology by conducting intervention studies. Another problem in epidemiology is that results are relative to some referent intake, and so there is difficulty in distinguishing 1) benefits of low dose rising toward an adverse effect of high dose from 2) increasing adverse effect with increasing intake at all dose levels.

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This amount of total fructose corresponds to an even more remarkable amount of total sugars (upward of 300 g/d).

A classification of fructose intakes

Authors may refer to intakes imprecisely, for example: low, medium, moderate, high, very high, and excessive. Unfortunately, for fructose, different authors use such terms inconsistently, which contributes to reporting bias. Such terms are used here as defined previously for adults and adolescents (10). The full range of intakes falls from near zero in persons with fructose intolerance to 150 g/d for some few adolescent males. The full range neatly falls into 3 bands: 0 to 50, >50 to 100, and >100 to 150 g/d (or more) deemed to be “moderate,” “high,” and “very high or excessive,” respectively.

Among these, “low” is undefined because it is reserved for special health needs in food-labeling regulations. The very high band also has been called excessive; the dual naming of this band reflects the fact that some persons within it could be consuming >25% energy from total fructose, which exceeds the current Institute of Medicine’s maximum intake level for all sugars combined, above which there may be inadequate intake of certain micronutrients (15). These intake ranges apply to total fructose (free and bound in sugars). The units are grams/d rather than as a percentage of energy. Fasting plasma triglycerides (FPTG), for example, respond to oral fructose in grams/d similarly in male and female subjects (10), although this may not be so when intake is expressed in kilojoules/100 kJ intake.

The 50 g/d cut point is 10% of metabolizable energy intake for a 2000 kcal/d diet (1 kcal = 4.184 kJ) and so generally corresponds to the level of fructose intake thought acceptable in people with diabetes. In persons in the United States, this level also corresponds to the approximate population median intake for total fructose.

Below 100 g/d includes amounts eaten by educated persons (health professionals), adults, and adolescent females. Above 100 g/d, the amount of glucose coingested when fructose is from sucrose or high-fructose corn syrup (HFCS) would alone constitute a health risk due to a high glycemic load (GL) (see below).

As with all such nutrient banding, the cut points are modifiable, for example, as more information becomes available about novel markers of disease or as new applications are considered, such as those for infants and children rather than adolescents and adults.

Attributes related to fructose intakes of 100 g/d

Without reference to metabolic effects of fructose per se, what might 100 g/d fructose in a diet imply? This amount corresponds to ~400 kcal/d or ~20% of energy intake for a sedentary person of energy requirement 2000 kcal/d. Persons consuming >100 g/d of sugars are potentially eating in excess of their energy requirement or may be at risk of certain micronutrient deficiencies (15). This issue then stops being a fructose issue and becomes a whole-diet issue.

The fructose:glucose ratio for sugars in the United States has been close to 0.43 for some years, so that 100 g/d total fructose also corresponds to ~232 g/d (900 kcal/d) total sugars, i.e., ~45% of energy intake for a sedentary person of energy requirement 2000 kcal/d. Persons with such intake, if not micronutrient deficient (15), would likely be taking micronutrient supplements or would be eating more food to supply micronutrients toward requirements. In the last scenario, overweight and obesity could result. In none of these scenarios is the metabolic effect of fructose per se causative other than due to its energy content.

Because of the composition of added sugars in the U.S. diet, 100 g/d fructose in the supply as 232 g/d sugars would contribute 132 g/d of free or bound glucose, so adding to the GL. For adult men and women, an increase in GL above ~100 to 120 g/d increases the risk of diabetes, coronary heart disease (CHD), and possibly certain cancers (16–18). Again, this is not a problem developing from the metabolic effects of the low-glycemic fructose (19) component of the diet.

Glycated proteins

Glycated hemoglobin (HbA1c) rises as a result of nonenzymatic modification of hemoglobin by glucose and is a strong risk factor for diabetic complications (especially retinopathy, peripheral vascular disease, and death) (20) and for CHD in nondiabetics (21). Several intervention studies in diabetics and nondiabetics show fructose to markedly lower HbA1c (22–27). Metaanalysis confirms this as a fructose dose-dependent effect (10) (10A). Neither energy nor micronutrient intakes were confounding factors, but there is still need for studies on the progression of disease over very long durations.

A fall in HbA1c caused by moderate to high fructose intake is not entirely expected. A rise in HbA1c would occur should insulin sensitivity be impaired. On the other hand, glycemic control more reflects a relative impairment of pancreatic function; meanwhile, fructose, which is low glycemics, makes little demand on the pancreas.

Insulin sensitivity

No evidence was uncovered via PubMed that <100 g/d fructose in exchange for other carbohydrate would impair insulin sensitivity in humans. Indeed, consistent with a lowering of HbA1, insulin sensitivity was improved (24) (Fig. 1B). By contrast, an excessive intake (250 g/d) is reported to cause insulin resistance (28) (Fig. 2), and intermediate but still very high or excessive doses (>100 g/d) can be without important effect (29,30). This provides weak evidence of possible dose dependency (Fig. 2) and strong reason to caution against extrapolating from excessive to moderate or high fructose intakes seen in the general population.

Plasma triglycerides

Meta-analysis of >40 human intervention studies show <100 g/d fructose is either without effect or may lower FPTG (Fig. 1C) (10). FPTG was elevated significantly only by excessive fructose intake, dose-dependently (10). Energy and micronutrient intakes were not confounding, and studies of longer duration had smaller effects; however, no studies were ad libitum. Curiously, when the postulate is that fructose is harmful, only those studies with excessive intakes get cited, which is indicative of reporting bias.

Postprandial triglycerides (PPTG) also rise in response to fructose, ~50% more than for glucose when the daily equivalent intake is >50 g/d (10). However, although a PPTG response to
dietary fat is associated with heart disease, it is unclear whether this would be so for fructose-induced PPTG. Certainly, fructose gives rise to VLDL small enough to penetrate arterial endothelia, but unlike cholesterol, which accumulates, triglyceride digests readily and is lost. Any risk from fructose-induced PPTG, if real, can be balanced against a lowering of HbA1c, a strong predictor of CHD (see below).

Uric acid
Plasma urate is an important antioxidant; its concentration is positively related to longevity in mammals and primates (31). In contrast, there is belief that urate is damaging, promoting CHD. Contributing to the latter has been evidence that allopurinol, which inhibits urate production, also reduces oxidative stress. But this has since been reported to be caused by a powerful antioxidant property of allopurinol itself (32). A role for urate in disease causation remains widely debated.

Approximately 90% of variation in plasma urate concentration is related to variation in its excretion (33). Renal absorption is higher in hyperinsulinemic states such as type-2 diabetes (T2DM) (34), lower in type-1 diabetes with inadequate insulin administration (35), and elevated again by exogenous insulin (33). An elevated urate concentration in CHD is in large part secondary to hyperinsulinemia (36).

Evidence from chronic studies (37,38) points toward fructose intakes, 100 g/d having no significant effect on fasting plasma urate in normal healthy adults. Otherwise, both acute (39,40) and chronic (41) studies find plasma urate to be elevated 6 to 24% at fructose doses of >200 g/d (or >200 g equivalents/3 meals when lower amounts are taken at a single meal). Although fructose intakes relevant to public health in adults (<100 g/d) have negligible or insignificant effects on plasma urate (Figs. 1 D and 3), offspring of persons suffering from gout are susceptible (40).

Oxidative stress
Fructose is reported not to induce oxidative or inflammatory stress even at excessive dosage, 75 g in drinks (225 g g equivalents/d) (42). Meanwhile, a contribution to antioxidant activity by fructose is evident in hereditary fructose intolerance, potentially a result of residual urate formation. A frequent side effect of a fructose-free diet in this condition is vitamin C deficiency (43), possibly from ascorbate being used as antioxidant in place of urate.
been considered causative of obesity in young persons. However, temporal association within a lifetime. overactive and obesity (55). A similar argument has also been other macronutrient intakes, and intakes may follow the rise in HFCS in the United States (54). However, there is also a rise in overweight and obesity approximately paralleled the supply of total sugars (10) and may, therefore, be subject to the balance of risk between marginally higher FPTG and potential lower HbA1c (Fig. 1). Moreover, as noted above, obesity in adolescent males may arise independently of specific metabolic effects of excess fructose through either its caloric content or a higher food intake to ensure that requirements of certain micronutrients are met.

Body weight
A very long-term intervention study on the influence of fructose versus glucose on body weight has not been uncovered or published. Short- and intermediate-duration studies (~<3 mo) show moderate and high fructose intakes in normal and diabetic subjects to have no practical or statistically significant effect on body weight (23,24,27,37,38,44–49). There is, however, some weak evidence (a few studies of short duration) that >200 g/d fructose might elevate body weight (44,50,51). A limitation to these studies is that intakes were not ad libitum. Nevertheless, the studies provide evidence for no significant partitioning or energy in humans by fructose to an extent favoring body weight gain when intake is <100 g/d. Careful energy balance studies in healthy human adults also show no significant difference between fructose and glucose despite fructose being associated with an initially higher respiratory quotient (52,53). The consequences of a high respiratory quotient for de novo lipogenesis in fatty liver disease among the obese is, however, a topic of rising interest.

Body mass index and obesity
Baseline information from 3 cohort studies indicates no association between the dose of fructose ingested and BMI (Fig. 4). This finding is consistent with the result of meta-analysis of intervention studies on <100 g/d fructose; i.e., there was no significant impact on body weight (10). Neither the intervention nor these epidemiological studies therefore support an earlier view (54) that fructose may be causal of obesity in the general population. The earlier view arose because a rise in overweight and obesity approximately paralleled the supply of HFCS in the United States (54). However, there is also a rise in other macronutrient intakes, and intakes may follow the rise in overweight and obesity (55). A similar argument has also been advanced for a temporal relation between obesity and sucrose intakes (3). However, the present author’s analysis indicates obesity to lag behind the rise in fructose supply via sucrose by ~110 years, making this an implausible reason for claiming a temporal association within a lifetime.

Sugary soft drinks, and the fructose they contain, have also been considered causative of obesity in young persons. However, a recently conducted meta-analysis of change in BMI with change in sugary soft drink consumption (including fructose as sucrose or HFCS) in longitudinal studies concluded there was no significant effect (56). Dose effects were not considered, and few studies had examined obese children or adolescents (57,58). However, effects if seen initially are not necessarily sustained (59).

Metabolic syndrome
Hyperglycemia, insulin resistance, hypertriglyceridemia, and overweight or obesity (among others) generally characterize this syndrome. The evidence for each of these does not support a role for <100 g/d fructose in causation among the adult, and female adolescent, populations. Approximately 20% of adolescent males consume very high or excessive amounts of fructose (>100 g/d) from total sugars (10) and may, therefore, be subject to the balance of risk between marginally higher FPTG and potential lower HbA1c (Fig. 1). Moreover, as noted above, obesity in adolescent males may arise independently of specific metabolic effects of excess fructose through either its caloric content or a higher food intake to ensure that requirements of certain micronutrients are met.

T2DM
The prevalence of T2DM at baseline in 3 large well-known cohort studies is strongly associated inversely with total fructose intake. The inverse association became stronger with increasing age, consistent with low fructose (or higher glycemia) being causal of T2DM (Fig. 5). Although epidemiological evidence cannot indicate causality, the associations are consistent with fructose having a low glycemic index (19), lowering protein glycation (strongly evident), and improving insulin sensitivity (weakly evident) at doses <100 g/d (Fig. 1, A and B). Likewise, low-glycemic-index/GL carbohydrates lower HbA1c and fructosamine (glycated albumin) in similar intervention studies (strongly evident) (18,60). Further, prospective studies combined show a lower incidence of T2DM when GL is reduced (author’s unpublished metaregression analysis).

Curiously, by contrast, prospective cohort studies associate T2DM positively with fructose intake (61,62). Confounding is
possible in multivariate analysis to an extent that may invert a slope used to assess cohort data. This is a recognized danger of multivariate analysis (63). Collinearity between glucose and fructose intake (which certainly exists) may explain such an association with T2DM, as advanced previously (61) and elsewhere (10). If correct, then cohort studies finding positive associations between fructose and disease would need to be reevaluated or held in abeyance until validity (or invalidity) is established via intervention studies, which offer a higher level of evidence (8,9).

**CHD**

Although oral fructose makes a low demand for insulin, studies on the potential therapeutic value of 150 g/d fructose in hyperinsulinemic conditions such as atherosclerosis and coronary artery disease found adverse influences, primarily a rise in FPTG (64) and an earlier discovered rise in total cholesterol, which is less adversely affected (65). CHD management and prevention, therefore, do not include doses of fructose exceeding those eaten in the general population.

By contrast, evidence is emerging for fructose intakes of relevance to public health, showing an impact on FPTG that is either modest or absent or even the opposite of that seen at excessive doses attempted initially for the treatment of CHD (Fig. 1 C). Also, urate generated from fructose, which had been hypothesized to be causal of CHD (see above), is hardly affected by fructose at doses ingested by adults in the general population (Fig. 1 D). Meanwhile, moderate to higher fructose intakes lower protein glycation (Fig. 1 A) (10); and lower protein glycation would predict a lower prevalence of CHD in both nondiabetics (Fig. 6) (21) and T2DM (20). Significant lowering of any level of protein glycation could be beneficial because there is no threshold (Fig. 6) (21).

**Longevity**

Factors controlling T2DM and CHD could help with longevity. Among primates and mammals, longevity is positively associated with the plasma urate concentration (31). High protein plus fructose ingestion might then be responsible for promoting such longevity in modern man. However, as noted, regular intakes of fructose rather than glucose-based carbohydrate has minimal effect on plasma urate in normal healthy adults (Fig. 1 D).

**Gout**

Unless there is either an abnormality of fructose metabolism (40,66) or surgical stress or tissue necrosis or high intake of animal tissue (33), then too high insulinization is involved in the elevation of uric acid concentrations sufficiently for gout to arise (33). However, normally for adults, fructose intake is too low for marked elevation of insulin or significant elevation of plasma uric acid (Fig. 1). Fiber, which improves insulin sensitivity and lowers the glycemic response, together with fruit (a source of fructose) and vegetables (which are usually low glycermic) are reported to protect against gout (67).

**Key points**

1. Moderate doses of fructose have neutral or diametrically opposite effects to those expected for very high or excessive fructose intakes and show evidence of improved glycemic control.
2. There is reason to believe that moderate fructose ingestion could be beneficial for public health, whereas excess intake would be a risk to health. Practical applications will depend on further research on a wider range of health risk factors than those mentioned here.
3. There is no international consensus on what is moderate and what is excessive fructose intake, although quantitative description from elsewhere (10) is discussed.
4. Epidemiological studies are difficult to interpret. The roles of GL and other factors collinear with fructose intake need to be examined.
5. Intervention studies in humans often use fructose at doses that are excessive compared with amounts generally eaten by adults; such are not interpretable for purposes of public health policy in adult nutrition.
6. There is scant information on the role of fructose dose in the health of young persons.
7. Animal studies often use doses of fructose in excess of what humans would normally consume and so have a high potential to mislead about the public health aspects of fructose.

**Other articles in this supplement include reference (69–78).**

**Literature Cited**


78. Murphy SP. The state of the science on dietary sweeteners containing fructose: summary and issues to be resolved. J Nutr. 2009;139:1269S–70S.