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Is the fructose index more relevant with regards to cardiovascular disease than the glycemic index?

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Abstract The glycemic index (G.I.) is a means for categorizing carbohydrates based on their ability to raise blood glucose, subsequently this index has been popularized as a way for selecting foods to reduce the risk for obesity, diabetes, and cardiovascular disease. We suggest that the G.I. is better aimed at identifying foods that stimulate insulin secretion rather than foods that stimulate insulin resistance. In this regard, fructose has a low G.I. but may be causally linked with the obesity and cardiovascular disease epidemic. The reported association of high G.I. with cardiovascular disease may be due to the association of sugar intake which contains fructose, but which has a high G.I. due to its glucose content. We propose the use of a fructose index to categorize foods and propose studies to determine the effect of low fructose diets as a means to prevent obesity, diabetes, and cardiovascular disease in the population.

Key words cardiovascular disease – fructose – metabolic syndrome – obesity – uric acid

The glycemic index (G.I.) was introduced by Jenkins et al. in 1981 as a means to rank carbohydrate-containing foods according to their effects on glycemia. The G.I. is based on the physiological measurement of the blood glucose response to the carbohydrate content of food. Specifically, a set amount (usually 50 g) of carbohydrate is administered in the fasting state and serial blood glucose measurements are made over 2 h. The G.I. is calculated as the percentage of the area under the curve relative to the same amount of carbohydrate taken in the form of glucose [63]. Using this index, foods can be categorized as having a relatively high glycemic index, such as observed with watermelon, ice cream, and jelly beans (G.I. of approximately 70%) or as having a relatively low glycemic index, such as observed with milk, oatmeal, and chick peas (G.I. approximately 32–36%) [63]. In addition, the concept of glycemic load (G.L.) was also developed, defined as the product of the G.I. value of a food and its carbohydrate content, to factor for the varying amounts of carbohydrate that are contained in various foods [85].

The original intent of the G.I., as proposed by the authors [63], was to aid the diabetic in the selection of foods, as foods with a low G.I. would result in less glucose elevation for the same energy load. In turn, a less severe rise in blood sugar could result in tighter blood sugar control and less formation of advanced glycation endproducts (AGEs), both of which have been shown to result in reduced diabetic complications [151, 154].

The categorization of carbohydrate-containing foods according to their G.I. and G.L. has since become popular, and diets promoting foods with low G.I. have been proposed to be healthier and less likely to lead to obesity or diabetes [3]. Foods with low G.I.

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are commonly advocated for diabetic subjects [99] as well as for the general population [123]. Support for these recommendations comes from an extensive literature that has documented a significant positive relationship between the ingestion of foods having high G.I. or G.L. with the development of cardiovascular disease [5, 87, 109]. A high G.L. has also been associated with features of the metabolic syndrome, including elevated triglycerides and low HDL cholesterol [86] and obesity [88, 124]; furthermore, there is evidence that consumption of low G.I. foods may be associated with increased satiety [124]. Some epidemiological studies also found that foods high in G.I. and G.L. increase the risk for type 2 diabetes (reviewed in [165]). Other studies could not confirm an association of G.I. or G.L with insulin sensitivity or obesity ([83] and reviewed in [114]) and this has led to skepticism as to the utility of these measures for predicting cardiovascular health (reviewed in [114]).

While we believe the G.I. and G.L. may have particular utility in the management of diabetic subjects, as proposed by Jenkins [63], we would like to propose a different index, which we term the Fructose Index (F.I.), that we hypothesize may be an improved method to assess whether certain carbohydrates carry increased risk for obesity and cardiovascular disease. We define F.I. as the percentage of energy of a food item derived from fructose, and the fructose load (F.L.) is the amount of fructose present in a single serving. The underlying concept is based on the principle that it is the ingestion of foods that induce insulin resistance that carries the increased risk for obesity and cardiovascular disease and not eating foods that stimulate insulin secretion. In the following sections we present evidence for this concept based on animal and human studies. We recognize the need to conduct evidence-based trials to directly test our hypothesis.

Fructose and its relation to the G.I.

The G.I. and G.L. are based on the rise in blood sugar following ingestion of a carbohydrate and hence are strongly linked with the content of glucose or starch (a polymer of glucose) in the carbohydrate. Fifty grams of pure glucose (dextrose), by definition, has a G.I. of 100, 50 g of available carbohydrate in rice or a baked potato has a G.I. of 64 and 85, respectively, and cornstarch has a G.I. of 70 [41]. According to the paradigm, eating foods with high G.I. indices should increase cardiovascular risk [85].

Fructose is a simple sugar that does not acutely raise blood glucose, nor stimulate insulin secretion [132]. Indeed, small catalytic doses may actually lower blood glucose [100] acutely by enhancing its uptake by the liver [139] due to the ability of fructose to stimulate hepatic glucokinase activity [140]. As such, fructose has a low G.I. of 23 [41, 63]. Thus, it is not surprising that studies in diabetic subjects have suggested that fructose may help in glycemic control [100, 110], and perhaps as a consequence, fructose is sold in many health food stores as a nutritional supplement.

The major sources of fructose include table sugar (sucrose, a disaccharide composed of glucose and fructose), high fructose corn syrup (HFCS, a sweetener that contains 42% or 55% fructose with the remaining component as glucose), fruits, and honey.

The sources of fructose vary from country to country. In countries where production of HFCS is high, HFCS can be major source ranging from almost 50% of sweetener consumed in the United States to over 25% in Japan, in most other countries sucrose is the primary source [1, 43, 51]. However both sucrose and HFCS, have approximately equal portions of glucose and fructose. Due to the glucose content, it is not surprising that sucrose has a relatively high G.I. of 65 and HFCS has a G.I. of 73 [41, 59]. In turn, the ingestion of sucrose, HFCS, and other sugars currently accounts for 25% of total energy consumed in the United States [56], accounting for a large portion of total carbohydrate intake. Based on both consumption and disappearance data, certain groups, such as children and adolescents [30, 76], African Americans [27] [73], Hispanics [73], and individuals at below-poverty level [27] are likely eating more. Much of this intake of sugar and HFCS is attributed to soft drink consumption [107].

Interestingly, recent studies have linked soft drink consumption with increased risk for weight gain [16, 88, 135], hypertension [166], type 2 diabetes [49, 135] and preeclampsia [21]. This raises the question of whether the association of high G.I. foods with obesity and cardiovascular disease may be due to the association of sugar-containing foods with cardiovascular disease as opposed to all foods containing a high G.I. Furthermore, it raises the possibility that the relationship of sugar-containing beverages with obesity and cardiovascular disease is due to its fructose content as opposed to glucose content.

How is fructose different from glucose: lessons from physiology

Fructose is distinct from glucose as it is initially metabolized by 3 different enzymes before it converges with the pathways of glucose metabolism. The initial enzymatic step involves phosphorylation of fructose to fructose-1-phosphate by fructokinase (ketohexokinase) using the substrate, ATP. Unlike

glucokinase [54], the phosphorylation of fructose by fructokinase is not regulated and ATP depletion may occur with a transient arrest of mRNA and protein synthesis and with lactic acid generation [90]. Studies in humans have shown that as little as 50 g of fructose intravenously can cause ATP depletion in the liver [14, 103]. The major sites of fructokinase are in the liver, kidney, intestines and adipocytes and these cells are the most vulnerable to the effects of fructose [7, 54]. We have found that incubation of cultured tubular epithelial cells with 1 mM of fructose (equivalent to postprandial levels in the blood) results in the induction of stress responses and falling ATP levels (Cirillo P and Sautin YY, et al. unpublished). Likewise, incubation of endothelial cells with postprandial levels of fructose reduces endothelial cell ATP and induces a proinflammatory response (Glushakova O, Nakagawa T, et al., unpublished). Thus fructose is distinct from glucose in having an initial rapid phase of ATP consumption (rapid burn), transient arrest of mRNA and protein synthesis (cell shock), followed by recovery.

Besides causing transient ischemia, fructose-induced ATP depletion leads to local AMP accumulation with activation of AMP deaminase and the generation of uric acid [101]. Uric acid levels rise rapidly in the blood and are a direct reflection of intracellular ATP depletion [42, 101, 112]. Doses as low as 0.5 g fructose/kg body mass can activate this pathway, especially in children [39, 112, 145]. While initially the increase in uric acid is observed primarily following ingestion of fructose, diets high in fructose or sucrose also result in an increase in fasting uric acid within weeks [62, 121], and chronic intake of sugars and sugar-sweetened drinks is correlated with uric acid levels [47]. In contrast, glucose (or starch) does not cause ATP depletion [14], nor does it cause either acute or chronic elevations in uric acid [62, 121].

One unique aspect of fructose is that it upregulates its own pathways. Incubation of liver cells, adipocytes, or kidney tubular cells with fructose results in increasing fructokinase levels and of their respective transporters (Glut2 and Glut5) (Sautin YY, unpublished). Feeding fructose to rats increases Glut5 expression in the intestines [162] and fructokinase activity in liver and intestines [17, 75]. Humans on either a high fructose diet [145] or high sucrose diet (18% or 33% total caloric intake vs. 5% intake) [62] show an increased uric acid elevation in response to a standard dose of fructose (or sucrose), consistent with upregulated fructokinase activity. Subjects with metabolic syndrome and fatty liver have a history of drinking two to three-fold more soft drinks and also have two-fold higher levels of fructokinase mRNA in liver biopsies compared to controls with other types of liver disease (Abdelmalak M, et al., manuscript in preparation). Hypertensive subjects and subjects with chronic kidney disease also demonstrate an increased uric acid level in response to fructose strongly suggesting a history of high fructose intake [92, 128]. The implication of these findings is that fructose will cause more ATP depletion and a more severe uric acid response in individuals chronically exposed to high fructose diets.

Fructose and the metabolic syndrome: animal studies

The administration of diets high in fructose (typically 50–60% of total energy intake) is a common way to induce features of the metabolic syndrome in rodents. Fructose intake causes endothelial dysfunction within 2 weeks [72] with activation of both the sympathetic nervous system [36, 156] and renin angiotensin system [97] and with stimulation of oxidative stress [142]. This is associated with a rise in blood pressure, the development of insulin resistance, and hypertriglyceridemia [104]. These changes are not observed in animals fed the same amount of glucose [104].

Fructose can also cause weight gain [120, 167] and increased abdominal fat [9] in rodents. Some studies suggest that weight gain is independent of total energy intake, suggesting an effect on basal metabolic rate [69, 84]. One possible mechanism is that fructose may cause leptin resistance; rats chronically fed high fructose diets have higher plasma leptin levels than control animals [58]. In turn, leptin resistance may increase the risk for obesity [134].

Recently a key role for uric acid has been shown in the pathogenesis of fructose-induced metabolic syndrome in rats [104]. Specifically, lowering uric acid significantly improved insulin resistance, blood pressure and dyslipidemia associated with fructose; furthermore, if administered prophylactically, it could also prevent weight gain [104]. The mechanism may relate to the ability of uric acid to reduce endothelial nitric oxide (NO) levels [38, 70, 74, 105], as NO is required for insulin's action [127]. Mice lacking endothelial NO synthase develop features of metabolic syndrome [29]. Uric acid also induces oxidative stress in adipocytes [133]. Both endothelial dysfunction [29, 115] and oxidative stress within adipocytes [44] are strongly associated with the development of insulin resistance. While uric acid appears to have a role in causing insulin resistance, fructose, by virtue of increasing body mass, may also increase circulating levels of non-esterified fatty acids [64], which increases intramyocellular lipid content and can itself cause insulin resistance [158].

The observation that high doses (50–60% of total energy intake) of fructose are typically used to induce

metabolic syndrome in rodents has been used as an argument that these studies are non-physiologic and of little relevance to human disease. However, doses as low as 35% fructose content also induce features of metabolic syndrome within 4–6 weeks (including insulin resistance, increased triglycerides and elevated tail cuff blood pressure) [130, 152]. These latter diets still contain higher amounts of fructose than that observed in the typical American diet. Nevertheless, it must be remembered that the use of high doses is a frequently used technique for any model system for inducing disease conditions in a short period of time. Indeed, low doses of fructose (15% of total caloric intake) induces insulin resistance in rats after 15 months whereas this was not observed in control animals fed the same amount of starch [13]. This compares well with the mean intake of 12% of total energy attributed to fructose in the US population today, and which rises to 15% or more in certain populations [54].

Furthermore, the rat is likely resistant to fructose because fructose-induced hyperuricemia is blunted due to the presence of uricase [143]. Indeed, hyperinsulinemia develops within 6 weeks when 20% fructose diets is administered to rats in which uricase is inhibited [129]. Rats also make vitamin C, which blocks fructose-induced insulin resistance [155]. We have found that vitamin C also blocks the reaction of uric acid with various oxidants [133] and neutralizes the effect of fructose or uric acid to induce oxidative stress in adipocytes [133].

Many experts have also argued that fructose does not cause hypertension. Fructose-fed rats have high blood pressure by tail cuff [2, 98, 155], by intra-arterial measurement obtained under anesthesia [130], and by externalized arterial catheters under unrestrained conditions [71, 72, 142]. However, two studies reported that blood pressure is normal by intra-aortic telemetry [15, 23], which is considered the gold standard for BP measurement [78]. The reason for this discrepancy appears to be that fructose activates the sympathetic nervous system [36, 156], resulting in increased blood pressure response when the rat is stressed such as being placed in a holder for tail cuff measurement. Sympathectomy can lower blood pressure and attenuate hypertriglyceridemia and insulin resistance [57, 156]. Indeed, when fructose-fed rats are exposed to a strong puff of air, they show a greater and more prolonged increase in blood pressure (by intra-arterial catheter) than control rats (C. Baylis and R. Johnson, unpublished data). Fructose-fed mice also show elevated blood pressure by intra-arterial telemetry, but only at night when the mice are awake and feeding, consistent with activation of the sympathetic nervous system [22, 36]. This same phenomenon of elevated tail cuff blood pressure yet normal telemetry blood pressure is observed with angiotensin II. Indeed, the famed low pressor model in which physiological concentrations of angiotensin II are administered for 14 days results in increased tail cuff blood pressure due to increased sympathetic activity, yet telemetry blood pressure remains normal [111].

These studies suggest that fructose ingestion may actually be a model for white coat or stress-induced hypertension as opposed to sustained hypertension. However, white coat hypertension is the greatest risk factor for persistent hypertension, and nearly 75% of such patients develop essential hypertension within 5 years [12]. White coat hypertension also increases the risk for cardiovascular and all cause mortality [91]. We have identified a potential mechanism, and that is the induction of intrarenal arteriolosclerosis and interstitial inflammation, which then causes salt-sensitive hypertension [66]. We and others have shown engagement of this pathway with hyperuricemia [161], catecholamine exposure [65], NO blockade [116], with angiotensin II infusion [125], in models of low nephron number [144], and in genetic models of hypertension [126]. Since fructose also causes renal microvascular lesions and interstitial inflammation [130], we predict that fructose also engages this pathway. At least one study has reported that high salt diet augments fructose induced hypertension [108]. Thus, while fructose itself may cause a white coat effect, over time it is expected to cause sustained salt-sensitive hypertension.

Fructose and the metabolic syndrome: human studies

Studies in humans also suggest that fructose, and not glucose, causes the metabolic syndrome (for excellent reviews, see [34, 45, 54, 82]). While some studies have reported conflicting results, these can largely be explained by the physiology that we described above.

Fructose can cause *insulin resistance* in humans. In studies comparing the effects of fructose to starch in healthy young men, the administration of 250 g (4,200 kJ) fructose per day resulted in insulin resistance within 1 week [10]; if lower doses (216 ± 12 g or 3,600 ± 200 kJ/day for 28 days) are administered, insulin resistance is confined to the liver and adipocyte [35]; and with even lower doses of fructose (100 g, 1,700 kJ/d for 4 weeks), no insulin resistance occurs at all [81]. Control subjects receiving starch (which has a higher G.I.) had no insulin resistance in any of the studies.

The observation that insulin resistance can be induced in just 1 week with high dose of fructose in humans suggests the human is quite sensitive to the effects of fructose, as the rat requires 4–8 weeks be-

fore an effect is observed [71, 104]. The hierarchal observation that the highest dose of fructose caused insulin resistance systemically, whereas medium doses preferentially affected sites with the highest intrinsic fructokinase activity, and the lowest doses had no effect at all is also consistent with the physiology of fructose. This, of course, does not mean that lower doses of fructose do not cause insulin resistance, as the time course was very short. As mentioned earlier, rats fed 15% of their total energy as fructose do not develop insulin resistance until 15 months [13].

Furthermore, Hallfrisch et al. reported that older (mean age 39) males, of which half had underlying insulin resistance, are more sensitive to the effects of fructose. Indeed, when fructose (equating to 15% of total energy intake) was administered for 5 weeks, both fasting and sucrose-stimulated glucose and insulin levels were higher than that observed in starch-fed control subjects [52]. This observation is particularly concerning as certain segments of our population are ingesting this amount of fructose daily; for example, in one study of eighth graders, the mean fructose intake corresponded to 14–16% of total energy intake [30]. Furthermore, the increased sensitivity to fructose in this population could reflect higher fructokinase activity that was either dietary or genetically based, as reflected in our study documenting higher soft drink intake and hepatic fructokinase mRNA in subjects with metabolic syndrome and fatty liver disease (Abdelmalak M et al., unpublished).

Fructose also causes *lipid abnormalities*. Fructose, even when administered at 17–20% of total energy intake, raises triglycerides in men [8, 35, 121]. Fructose but not glucose also raises triglycerides in postmenopausal but not premenopausal women [89], which could relate to the fact that premenopausal women have better endothelial function [157] and lower uric acid levels [67]. However, some studies show younger women still have an elevated triglyceride response [150]. Fructose supplements constituting 15% of total caloric intake (as opposed to starch) ingested for 5 weeks also increased total and LDL cholesterol in hyperinsulinemic and control males and increased triglycerides in hyperinsulinemic men [53]. In contrast, in another study young healthy men given fructose supplements (20% vs. starch) for 4 weeks did not increase their fasting triglycerides although postprandial triglycerides and fasting LDL and total cholesterol were higher [147].

These studies emphasize that the proper interpretation of clinical studies with fructose requires consideration of many aspects. For example, a young athlete with great endothelial function and low fructokinase levels may be relatively immune to a short trial of fructose, whereas it may cause marked problems in an obese, soda drinking individual who already has insulin resistance and markedly upregulated fructokinase levels. Also one must consider dose, speed of ingestion (such as guzzling), and duration of exposure. Short-term studies limited to few weeks may be too short to observe an effect.

The administration of sucrose can mimic many of the effects of fructose in humans, but in addition have also been reported to increase *blood pressure* and *weight gain* (e.g., 33% caloric intake for 6 weeks [62] or 28% sucrose (2,500 kJ) for 10 weeks [119]). Reducing soft drink ingestion also results in significant weight loss in very obese adolescents [32]. The likelihood that this is due to the fructose component is supported by a study of healthy women and post-obese women who were placed on ad libitum high starch, high sucrose (23%), or high fat diet. The high starch group lost weight and fat mass whereas this was not observed with the other diets; furthermore, while there was also increased energy expenditure for subjects on the sucrose diet, 24 h energy intake was 20% greater in the post-obese and 7% greater in the healthy adults on the sucrose diet compared to respective starch controls, and postprandial catecholamine levels were also higher in subjects on the sucrose diet [118]. Nevertheless, it is also possible that the effects observed with sucrose are due to both the presence of glucose and fructose acting in concert.

It is likely that physiological, behavioral, and economic factors may all be involved in how sucrose and other fructose-containing sweeteners may cause weight gain [6, 28]. Most evidence suggests that the primary mechanism relates to an increase in total energy intake by making food more palatable [168] or suppressing the satiety response due to inadequate stimulation of leptin [150]. Teff et al. reported that subjects given a limited amount of food with fructose-rich beverages were hungrier and consumed a higher total energy intake on the following days ad libitum diet compared to individuals who were given glucose-rich beverages [150]. There is also suggestive evidence that fructose may slow basal metabolic rate. One study of children, demonstrated an increased risk of obesity was associated with a higher intake of fruit juices and soft drinks, despite similar total energy intake [24]. In addition, if fructose causes insulin resistance, then leptin resistance is also likely, and this is also associated with impaired satiety and increased weight gain in animal studies [134].

Uric acid and the oxidant-antioxidant paradox

A central tenet in our studies is that uric acid has a causal role in hypertension and the metabolic syn-

drome. Hyperuricemia has been shown to be an independent predictor of hypertension in 15 of 16 studies [4, 31, 40, 60, 61, 68, 77, 93, 95, 102, 106, 113, 136, 138, 146, 149], to predict insulin resistance [105, 106], and to predict the development of diabetes [106] and obesity [93]. A key role for xanthine oxidoreductase (the enzyme that generates uric acid) has also been shown in adipogenesis [20].

We have also found that raising uric acid in animals causes hypertension [94] and older studies using two different uricase inhibitors reported that over time uricase-inhibited rats develop hypertension, hypertriglyceridemia, and diabetes [163, 164]. Studies in humans are largely ongoing. However, allopurinol was found to improve endothelial function in 7 controlled trials [18, 19, 26, 33, 37, 48, 50, 96] with the benefit correlating with lowering of uric acid levels [25]. In the study by Siu et al., allopurinol treatment of patients with chronic kidney disease and hyperuricemia resulted in an 11 mm Hg fall in systolic BP whereas no change was observed in the placebo-treated control group [141].

Nevertheless, the possibility that uric acid may have a causal role in the cardiovascular epidemic has also been challenged, since uric acid is a known antioxidant that can scavenge peroxynitrite and other oxidants [122]. Administering uric acid can acutely improve plasma antioxidant capacity and endothelial function in humans [159, 160] and can reverse peroxynitrite mediated oxidative stress in endothelial cells [79]. The beneficial effect of allopurinol in clinical studies has been attributed to blocking xanthine oxidase-generated oxidants as opposed to uric acid [18, 19, 26, 33, 37, 48, 50, 96]. However, allopurinol substitutes for xanthine, so while blocking uric acid synthesis it does not prevent oxidant generation (unlike its metabolite, oxypurinol) [46]. One study also reported that probenecid was unable to improve endothelial function in heart failure despite lowering uric acid levels [48].

While the exact reasons for these discrepancies remain unclear, it may have to do with the ability of uric acid to react with oxidants (generating allantoin), with peroxynitrite (generating triuret), or with nitric oxide (generating 6-aminouracil). We have documented these pathways in both rats and humans. We believe the allantoin pathway is protective and is the primary pathway engaged by acute infusions of uric acid whereas the triuret pathway [131] and the aminouracil pathway (Gersch C, Palii S, et al. submitted) may be injurious. The reason probenecid may not work as well as allopurinol is likely because the latter will be more effective at blocking uric acid synthesis within the cell, which is important in heart failure given the increased xanthine oxidase levels in the endothelium in that condition [80]. Indeed, probenecid can block urate transport in and out of cells and might actually lead to increased intracellular urate concentrations and increased production of the injurious triuret and aminouracil.

Conclusions

As a dietary tool, the G.I. remains controversial [114] and its use for weight loss is not supported [117]. We believe the reason is that the association of high G.I. with cardiovascular disease is that sugar and HFCS-containing foods also have a high F.I. and it is the latter that is responsible for initiating pathways that lead to the metabolic syndrome and obesity.

Americans are currently eating 70–100 g fructose per day, and this contrasts with levels of 15–40 g per day that comprised the average diet in the early 19th century [168]. We hypothesize that the key to break this cycle is the initiation of a diet that begins with a 2 week period in which fructose intake is severely restricted to less than 5 g a day. In rats, complete cessation of fructose can result in normalized fructokinase levels after 1 week [137]. In addition, studies in humans have also shown that reducing fructose intake for 2 weeks can result in a reduced uric acid response to a fructose load [39]. The concept here is to reduce fructokinase and Glut5 levels back to baseline before returning to the historic 15–40 g of fructose per day diet. Since if fructokinase levels remain high even low doses of fructose (15–40 g) may continue to engage the pathway, causing insulin resistance and continued obesity. One might hypothesize that this may be one reason obese individuals have so much trouble losing weight; small amounts of fructose (in the form of HFCS) are in many foods so even a small amount ingested will continue to lead to acute increases in uric acid leading to insulin resistance. In this regard, the development of a F.I. or F.L. for foods based on the percentage of calories derived from fructose might be a useful way to alert individuals who are trying to lose weight. It is also important that such a diet limits other components known to have a role in cardiovascular disease, including saturated fats and trans fats. One might also limit high purine foods, as they can also raise uric acid.

While the G.I. may be useful in the diabetic population in predicting the glucose responses and insulin needs within a given patient, there are a number of reasons to question the efficacy of more than small (potentially catalytic) amounts of dietary fructose, even for the diabetic population. First, fructose can result in production of advanced glycosylation end products [148, 153]; second in diabetic animals fructose ingestion speeds the development of cataracts [11, 55, 169, 170]; third, if fructose can accelerate insulin resistance, hypertension, vascular

disease, and dyslipidemia in nondiabetic subjects, then it is reasonable that it should be avoided in the diabetic population that already suffers from these complications and in the non-diabetic public to promote cardiovascular health.

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