

# Added Fructose: A Principal Driver of Type 2 Diabetes Mellitus and Its Consequences

James J. DiNicolantonio, PharmD; James H. O'Keefe, MD;  
and Sean C. Lucan, MD, MPH, MS

## Abstract

Data from animal experiments and human studies implicate added sugars (eg, sucrose and high-fructose corn syrup) in the development of diabetes mellitus and related metabolic derangements that raise cardiovascular (CV) risk. Added fructose in particular (eg, as a constituent of added sucrose or as the main component of high-fructose sweeteners) may pose the greatest problem for incident diabetes, diabetes-related metabolic abnormalities, and CV risk. Conversely, whole foods that contain fructose (eg, fruits and vegetables) pose no problem for health and are likely protective against diabetes and adverse CV outcomes. Several dietary guidelines appropriately recommend consuming whole foods over foods with added sugars, but some (eg, recommendations from the American Diabetes Association) do not recommend restricting fructose-containing added sugars to any specific level. Other guidelines (such as from the Institute of Medicine) allow up to 25% of calories as fructose-containing added sugars. Intake of added fructose at such high levels would undoubtedly worsen rates of diabetes and its complications. There is no need for added fructose or any added sugars in the diet; reducing intake to 5% of total calories (the level now suggested by the World Health Organization) has been shown to improve glucose tolerance in humans and decrease the prevalence of diabetes and the metabolic derangements that often precede and accompany it. Reducing the intake of added sugars could translate to reduced diabetes-related morbidity and premature mortality for populations.

© 2015 Mayo Foundation for Medical Education and Research ■ Mayo Clin Proc. 2015;90(3):372-381



From the Department of Preventive Cardiology at Saint Luke's Mid America Heart Institute, Kansas City, MO (J.J.D., J.H.O.), and Department of Family and Social Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY (S.C.L.).

Worldwide, approximately 1 in 10 adults has type 2 diabetes mellitus, with the number of individuals diagnosed as having the disease more than doubling from 153 million in 1980 to 347 million in 2008.<sup>1</sup> In the United States, 29 million adults (1 in 11) have type 2 diabetes and another 86 million (more than 1 in 3) have prediabetes.<sup>2</sup> In other terms, approximately 40% of US adults already have some degree of insulin resistance, with projections that nearly the same percentage will eventually develop frank diabetes.<sup>3</sup>

Insulin resistance is associated with hyperinsulinemia, a condition that may promote abdominal-fat storage, increased triglyceride levels, and other metabolic disturbances<sup>4</sup>—all part of a broader metabolic syndrome<sup>5</sup> that is sometimes referred to as insulin-resistance syndrome. Markers of insulin resistance predict future cardiovascular (CV) risk,<sup>6,7</sup> with hyperinsulinemia being an independent risk factor for coronary heart disease.<sup>8,9</sup> Individuals with insulin-resistant (ie, type 2) diabetes have a life

expectancy 5 to 10 years shorter than those unaffected by the disease, with much of the difference due to CV causes.<sup>4</sup>

Given substantial risks in terms of morbidity and mortality, there is great interest in diabetes prevention and treatment. Key to both of these issues is dietary intake, specifically the consumption of added sugars—one of the most fundamental determinants of glucose metabolism. Of the added sugars, fructose appears to be particularly pernicious with regard to glucose metabolism.<sup>10-12</sup> There is a considerable body of basic science evidence, observational data, and clinical trial findings to suggest added fructose—even relative to other sugars—is a primary driver of diabetes development and consequences.

## BASIC SCIENCE DATA

From an evolutionary standpoint, the body's response to fructose may have conferred a survival advantage.<sup>13</sup> Fructose stimulates epigenetic changes<sup>14</sup> and metabolic alterations that

shunt calories into storage depots in abdominal fat cells.<sup>4</sup> Such effects were desirable for early humans who may have needed to endure long periods of food scarcity. Whereas fructose in Paleolithic times was likely encountered only rarely and seasonally (at least in populations living in nontropical climates) in low concentrations as ripened fruit, fructose today is ubiquitous in all seasons and encountered in high concentrations in processed foods.<sup>11</sup>

At a molecular level, fructose is a monosaccharide that when combined with the monosaccharide glucose forms the disaccharide sucrose, otherwise known as table sugar or simply “sugar”. Sucrose is commonly used in processed foods and beverages; however, its predominance in processed items has gradually been surpassed by another sweetener—high-fructose corn syrup (HFCS).<sup>15</sup> Whereas sucrose contains 50% fructose (and 50% glucose), HFCS (particularly as found in soft drinks) commonly contains up to 65% fructose.<sup>10,16,17</sup> The fructose in HFCS represents nearly 50% of the sweetener’s weight.<sup>18</sup> By comparison, the fructose in a fresh peach represents only about 1% of the sweet fruit’s weight.<sup>19</sup>

In both human<sup>20</sup> and animal studies,<sup>21,22</sup> concentrated fructose loads have been found to decrease adenosine triphosphate content in the liver. This effect may contribute to decreased cellular binding of insulin, possible reduction in the number of insulin receptors, and subsequent insulin resistance.<sup>23,24</sup> Fructose also increases hepatic de novo lipogenesis and reduces hepatic fatty acid oxidation, both of which can lead to increased accumulation of fat in the liver, which subsequently triggers inflammation and hepatic insulin resistance.<sup>25,26</sup> Increased hepatic insulin resistance promotes increased insulin secretion from pancreatic  $\beta$ -cells, which can result in progressive  $\beta$ -cell dysfunction.<sup>27</sup> Over time, deterioration in  $\beta$ -cell function can lead to inadequate insulin secretion, compounding fructose-induced inflammation and oxidative stress, and making hepatic insulin resistance worse.<sup>28-32</sup>

Fructose may also induce peripheral (skeletal muscle) insulin resistance by prompting excessive hepatic free fatty acid production, increased free fatty acid release from very-low density lipoproteins, and intramyocellular lipid accumulation.<sup>28,33</sup> In addition, fructose can increase hepatic gluconeogenesis, raising

serum glucose levels and placing further stress on the pancreatic  $\beta$ -cells.<sup>28</sup>

The net result of excess consumption of added fructose is derangement of both hepatic and systemic metabolism and global insulin resistance. Other dietary sugars not containing fructose have been found to be less detrimental in these respects. For example, in a 6-month randomized trial in overweight individuals, compared with isocaloric milk, diet soda, and water, sucrose-sweetened sodas alone increased ectopic fat accumulation and lipids.<sup>34</sup> This finding suggests that sucrose is more harmful compared to lactose and sugar-substitutes.

Sucrose—the combination of fructose with glucose—has also been found to induce insulin resistance, hyperinsulinemia, hypertriglyceridemia, and hypertension when consumed in large quantities, just as fructose does alone.<sup>25,35-52</sup> However, comparing the effects of isolated glucose vs isolated fructose, the negative effect of fructose administration on insulin sensitivity is more pronounced. In fact, decreased insulin binding to monocytes and a 25% reduction in insulin sensitivity have been found in healthy volunteers fed isolated fructose vs glucose.<sup>23</sup> Isolated fructose also induces greater detrimental effects on glucose, insulin, and triglyceride concentrations compared with glucose, and isolated fructose has been found to promote greater food intake, body weight, and liver weight in rodents.<sup>53</sup>

Replacing starch (an all-glucose polymer) with sucrose (glucose and fructose) increases fasting insulin, reduces insulin sensitivity, and leads to increased glucose concentrations.<sup>54-60</sup> The change also leads to a variety of other undesirable metabolic effects, including increased cholesterol, apolipoprotein B, triglycerides, adipose storage, and blood pressure.<sup>54-60</sup> Trials looking at isolated fructose (vs starch or glucose) reveal the same derangements, supporting the notion that fructose is the likely component of sucrose that causes the adverse metabolic effects.<sup>42,52,61-63</sup> Animal data are corroborated by experimental trials in humans, indicating that isolated fructose promotes impaired glucose tolerance vs other types of carbohydrates even when matched for total caloric intake.<sup>23,25,64</sup>

Fructose consumption—as from sucrose or HFCS—has been linked not only to diabetes-related metabolic abnormalities but also to end-organ damage and diabetic complications.

Isolated fructose causes renal injury in animals,<sup>65-67</sup> and fructose consumption from soft drinks (ie, HFCS) is associated with kidney disease in humans.<sup>68</sup> Chronic isolated fructose feeding in rodents is associated with diffuse glomerulosclerosis,<sup>69</sup> whereas sibling rodents fed starch do not develop this renal abnormality or diabetic microangiopathy as fructose-fed rodents do. Sucrose feeding in rodents causes intercapillary glomerulosclerosis,<sup>70</sup> and fructose alone promotes other diabetes-related microvascular complications, such as impaired motor nerve conduction velocity (ie, neuropathy).<sup>71</sup> Postprandial fructose levels are associated with retinopathy in patients with type 2 diabetes,<sup>72</sup> and animal data have revealed that fructose is the component of sucrose that leads to retinopathy.<sup>73</sup> Isolated fructose feeding in rats also causes arterial atherogenesis.<sup>74</sup>

Overall, the evidence in the literature suggests that added fructose—from sucrose or HFCS—is associated with a variety of undesirable biological effects in both humans and animals. These effects may include epigenetic regulation of intestinal fructose transporters during early development, making absorption of future ingested fructose more efficient from the gastrointestinal tract and thereby inducing further harm.<sup>14</sup> Nonetheless, many of the adverse biological effects (eg, insulin resistance, hyperinsulinemia, hypertriglyceridemia, and hypertension) can be reversed by reducing sources of added fructose in the diet.<sup>41,75,76</sup>

### OBSERVATIONAL DATA

Although fructose is found naturally in some whole foods, such as fruits and vegetables, consumption of these foods poses no problem for human health and indeed may be protective against diabetes and broader cardiometabolic dysfunction.<sup>77,78</sup> Moreover, consumption of whole fruits and vegetables is associated with reduced premature mortality.<sup>79</sup> The difference may be a matter of dose and context; fructose in natural foods exists in lower concentrations (eg, the peach example from earlier) and is accompanied by water, fiber, antioxidants, and other whole-food constituents. In this way, whole foods are very much unlike the predominant sources of fructose in the American diet: processed products, with their high amounts of added sugars, high proportions of fructose,

and low amounts of natural compounds that might slow absorption or buffer the sugar load.

Processed foods (including beverages), created in industrial manufacturing plants, bear little resemblance to whole foods grown on living botanical plants. The consumption of processed foods and beverages is associated with markedly poor health outcomes.<sup>80,81</sup> A recent meta-analysis of human studies revealed that increasing consumption of fructose from processed foods and beverages is associated with higher fasting blood glucose levels.<sup>82</sup> Sugar-sweetened beverages (which are most often actually HFCS-sweetened) may be of particular concern. These products provide the greatest quantities of added fructose in the diet,<sup>83</sup> and their consumption is notably high in individuals with diabetes, particularly those whose condition is undiagnosed.<sup>84</sup> Observational studies have found that sugar-sweetened beverages are associated with type 2 diabetes, abdominal obesity, and the metabolic syndrome.<sup>85-89</sup> Stronger associations are noted in larger studies of longer duration,<sup>90,91</sup> and systematic reviews and meta-analyses corroborate these adverse effects.<sup>85,92-94</sup>

Even 100% fruit juice (although technically not a sugar-sweetened beverage) provides high concentrations of fructose, removed from its usual biological context (eg, whole fruit). The consumption of fruit juice is associated with both increased body weight and risk of diabetes<sup>95-97</sup>; associations that are also seen with the consumption of artificially sugared beverages<sup>98</sup> but not with the consumption of whole fruits (examples of fructose content per 100 g: peach [1 g], raspberries [2g], strawberries [2 g], blackberries [3 g], cranberries [3 g], apple [6 g], grapes [7 g]).<sup>19,99</sup>

Carbohydrate intake, particularly intake of sucrose (glucose and fructose), has been directly correlated with fasting insulin levels and insulin concentrations 2 hours after a glucose load.<sup>100</sup> But correlations were not as strong when looking solely at starch. The observational study that produced these findings used a 7-day weighed-food assessment, which provides a relatively robust method to estimate nutrient intake, giving more credence and relevance to the findings.

Other observational studies have found that insulin levels directly correlate with dietary sucrose intake,<sup>101</sup> and higher total sugar intake is independently and significantly associated

with lower  $\beta$ -cell function.<sup>102</sup> In particular, in one study, sugar-sweetened beverage consumption was associated with lower insulin secretion in overweight children, suggesting that consuming these beverages for an extended period can place added stress on  $\beta$ -cells and promote insulin deficiency.<sup>102</sup> The authors of the study concluded that “modest reductions in sugar intake could potentially preserve  $\beta$ -cell function and prevent metabolic disorders.”

Additional ecologic data suggest that the availability of sugars is independently associated with an increased prevalence of diabetes, even after adjustment for other covariates.<sup>26,103</sup> Each extra year of exposure to high sugar availability has been associated with an increased prevalence of diabetes.<sup>26</sup> Moreover, the risk of diabetes was 11-fold higher with each 150-kcal per person per day increase in sugar vs 150-kcal per person per day increase in total calorie availability.<sup>26</sup> Because no other food types have yielded significant associations with diabetes prevalence after controlling for obesity, calorie intake, and other confounders, the implication is that sugar—compared with other food types—is particularly harmful for inducing diabetes.

Among the sugars, HFCS availability has independently predicted greater diabetes prevalence, even when adjusting for obesity and total sugar and calorie availability.<sup>10</sup> Because HFCS may have as much as 50% more fructose in it than glucose, the suggestion is that added fructose is particularly detrimental for promoting diabetes.<sup>17</sup>

## CLINICAL TRIALS

One human trial investigated the isocaloric exchange of sucrose for starch among individuals with normal glucose tolerance. When sucrose was provided in a “nibbling pattern” (small doses at frequent intervals throughout the day), no statistically significant increase in insulin levels was found,<sup>104</sup> suggesting (as with the difference between processed foods and natural fruit) that dose and context are important. However, even lower doses buffered by other dietary constituents resulted in increased fasting glucose levels in the trial.<sup>104</sup>

Moreover, in another trial—this time among adults who were already likely insulin resistant (having an exaggerated insulin response to a sucrose load)—substitution of sucrose for wheat

starch produced more obvious detriment.<sup>40</sup> In the trial, sucrose of 5%, 18%, or 33% of total daily calories replaced an isocaloric amount of wheat starch, but the overall carbohydrate level was held constant in all groups. Men receiving 18% sucrose had significantly higher mean fasting serum insulin levels at 6 weeks vs those receiving 5% sucrose. In women, the 33% sucrose diet caused a significantly higher fasting insulin level vs the 18% sucrose diet. In addition, the 6-week mean glucose levels, the serum insulin response to a sucrose load, and the glucose response to a sucrose load were all higher for men and women when comparing the 18% and 33% sucrose diets vs the 5% sucrose diet.

Similar findings were reported from another trial in which sucrose was substituted for wheat starch in glucose-intolerant individuals. Sucrose, compared with wheat starch, produced increases in fasting serum insulin, insulin to glucose ratio, and insulin response to a given sucrose load.<sup>64</sup>

Taken together, the trials above suggest (1) that replacing glucose-only starch with fructose-containing sucrose results in significant adverse metabolic effects, (2) that adverse effects are broader with increasing baseline insulin resistance, and (3) that adverse metabolic effects are more profound with greater proportions of added fructose in the diet.

One of the trials suggests that consuming a diet low in sucrose (5%) may normalize fasting insulin levels. Indeed, the prevalence of individuals being classified as having diabetes or borderline diabetes was more than 50% lower on the 5% sucrose diet vs the 18% and 33% sucrose diets.<sup>40</sup>

Conversely, a recent meta-analysis of controlled feeding trials in individuals with diabetes indicated that isocaloric exchange of isolated fructose for other carbohydrates actually improved glycemic control.<sup>105</sup> However, most of the included trials had major limitations, including short duration and a study population of patients who already had diabetes and often were using hypoglycemic agents or insulin-sensitizing medications. The conclusions from this meta-analysis may not apply to individuals without insulin resistance or to insulin-resistant individuals who are not using antidiabetic medications. More important, almost all of the included studies in this meta-analysis were funded by the food industry, which raises serious

concerns about financial conflicts of interest and bias. Indeed, another recent meta-analysis found that among trials with financial conflicts to the food industry, 83.3% found insufficient support of a positive association between sugar-sweetened beverage consumption and weight gain, whereas among trials without any reported conflicts, the same percentage (83.3%) found that sugar-sweetened beverage consumption was a potential risk factor for weight gain.<sup>106</sup>

In a trial of men with both normal and elevated insulin levels, replacing starch with moderate amounts of isolated fructose (7.5%-15% of total caloric intake) for just 5 weeks caused elevations in fasting glucose and insulin levels and also led to elevations in insulin and glucose responses to a sucrose load.<sup>107</sup> Replacing starch with sucrose or isolated fructose was found in another trial to increase fasting blood glucose in patients with type 2 diabetes.<sup>108</sup>

Nonetheless, all these dietary-replacement trials likely have low applicability to the real world, where isocaloric exchanges are unlikely and sugar may be consumed in addition to, rather than in place of, starch and other dietary constituents. Overall overconsumption may result because sugar stimulates increased food intake<sup>109,110</sup> and additional intake of other sugary foods in particular<sup>111</sup> or because it fails to induce satiety, particularly if ingested in liquid form.<sup>112</sup> Trials that restrict total calories may miss effects related to postprandial hyperglycemia, hyperinsulinemia, compensatory hypoglycemia, and increased hunger due to sugar intake.<sup>113-115</sup>

Widespread metabolic derangements are seen when sucrose is consumed. A randomized trial that consisted of 14 young men following either a high-sugar diet (260 g of sucrose) or a moderate-sugar diet (115 g of sucrose) found lower high-density lipoprotein cholesterol levels and increases in *N*-acetyl-glucosaminidase—an early indicator of kidney damage—among the high-sugar group.<sup>116</sup> Detriment occurred after just 3 weeks, and markers did not improve after 2 weeks of reverting back to a diet lower (albeit still rather high) in sugar. Another randomized trial tested a diet high in isolated fructose (200 g/d), specifically in 74 adult men, and found increases in fasting insulin level and homeostatic model assessment index (a measure of insulin resistance and  $\beta$ -cell function).<sup>46</sup>

Human trials also suggest that protection from diabetes and its consequences can be achieved by limiting added-fructose consumption. A study randomizing 131 patients to 2 different diets low in added fructose found significant and comparable improvements in serum glucose and insulin resistance vs baseline.<sup>76</sup> Lowering fructose intake from 59 to 12 g/d has been shown to lower fasting insulin levels in patients with chronic kidney disease.<sup>75</sup> A low-fructose diet has also been shown to lower blood pressure and inflammation and improve renal function.<sup>75</sup>

## DISCUSSION

From 1776 to 1994, the estimated consumption of added sugar by Americans increased from 4 lb per person per year to 120 lb per person per year.<sup>80</sup> Approximately 75% of all packaged foods and beverages in the United States today have sugars added to them,<sup>117</sup> and 13% of the US population consumes at least 25% of their total calories as added sugars.<sup>118</sup> Estimated consumption of sugar-sweetened beverages has increased from 10.8 gallons per person per year in 1950 to 49.3 gallons in 2000.<sup>80</sup> The proportion of total sugar consumed in the form of beverages has also increased, from one-third of the total added sugar intake in the 1960s and 1970s to two-thirds in 2000.<sup>80</sup> The mean daily consumption of fructose is now 83.1 g per person in the United States,<sup>118</sup> which is likely an underestimation<sup>10</sup> because fructose is not required to be disclosed on nutrition labels and amounts that actually occur in processed foods are higher than once thought.<sup>17</sup> More worrisome, up to 20% of the population exceeds 100 g/d of fructose consumption.<sup>66</sup>

At current levels, sugar consumption and fructose consumption in particular—in concentrations and contexts not seen in natural whole foods—are fueling a worsening epidemic of type 2 diabetes.<sup>25,64,107,119</sup> Even without existing data for the duration of diabetes' 20-year incubation period,<sup>4,120</sup> shorter-term basic science evidence, observational data, and clinical trial findings present compelling evidence to suggest that added sugar and especially added fructose (provided from HFCS and sucrose) present a serious and increasing public health problem.

Several dietary guidelines appropriately recommend consuming whole foods rather

than foods with added sugars. However, the American Diabetes Association and the 2010 Dietary Guidelines for Americans do not recommend restricting fructose-containing added sugars to any specific level. More worrisome, is that the 2010 Dietary Guidelines for Americans allow up to 19% of total caloric intake as added sugars (depending on total caloric intake),<sup>121</sup> and the Institute of Medicine allows up to 25% of calories as added sugars in its recommendation statements (regardless of total calorie intake).<sup>122</sup> Encouragingly, the World Health Organization recommends that added sugars should make up no more than 10% of an entire day's caloric intake, with a proposal to lower this level to 5% or less for optimal health.<sup>123</sup> Such levels would be similarly restrictive to the existing American Heart Association recommendation to consume no more than 6 tsp (24g, providing 100 calories) of sugar per day for women and 9 tsp (36 g, providing 150 calories) of sugar per day for men.<sup>124</sup> Whereas less restrictive guidelines place individuals at risk for development or worsening of diabetes, more restrictive recommendations have the potential to help protect populations from diabetes and its CV and other consequences. Essential points regarding added sugars and fructose promoting type 2 diabetes are summarized in Table 1 and Table 2.<sup>124,125</sup>

**CONCLUSION**

There is no biological need for any added sugars in the diet, particularly those containing fructose (eg, sucrose and HFCS). Although biological response to fructose consumption may have been adaptive for early human ancestors, this response evolved from fructose encountered rarely (at least in populations not living in tropical regions) and in low concentrations in nature. The same biological response is maladaptive when the fructose is encountered frequently and in high concentrations in processed foods. Indeed, what once conferred a survival advantage in the context of scarcity may be a decided disadvantage in the context of overabundance. Avoiding processed foods altogether would be ideal, although this end seems unlikely given the current prominence—indeed predominance—of processed foods in the US diet. Dietary guidelines should encourage

**TABLE 1. Essential Points Regarding Added Sugars and Fructose**

Added sugar and high-fructose corn syrup elevate diabetes risk independent of their effect on weight. <sup>10,26</sup>
High-fructose corn syrup elevates diabetes risk even when adjusted for overall sugar availability and caloric intake. <sup>10</sup>
Fructose is the likely moiety of sucrose and high-fructose corn syrup that induces insulin resistance. <sup>25</sup>
In animals and humans, isocaloric replacement of starch (chains of glucose) with sucrose (glucose and fructose) or fructose has been found to do the following: <ol style="list-style-type: none"> <li>1. Increase fasting insulin levels.<sup>64,119</sup></li> <li>2. Reduce insulin sensitivity.<sup>23,56,58</sup></li> <li>3. Increase fasting glucose concentrations<sup>104</sup></li> <li>4. Increase glucose and insulin responses to a sucrose load.<sup>64,119</sup></li> <li>5. Reduce cellular insulin binding.<sup>23</sup></li> </ol>
Biological response to fructose consumption may have been adaptive for early human ancestors who encountered fructose rarely and in low concentrations in the form of ripened fruit. <sup>11,13</sup> The same biological response is maladaptive when the fructose is encountered frequently and in high concentrations as added sugar in processed foods.
Approximately 75% of all foods and beverages in the United States contain added sugars. <sup>117</sup>
The Institute of Medicine and 2010 Dietary Guidelines for Americans allow for an added sugar intake, which—if consumed at the upper recommended limit—could reasonably induce type 2 diabetes mellitus.
By limiting sugar to 5% to 10% of total caloric intake, the harmful effects of sugar, particularly fructose, on insulin resistance could be minimized.
Reducing fructose consumption may protect against diabetes and its complications, <sup>40,76</sup> including early mortality from cardiovascular causes. <sup>125</sup>

individuals to replace processed foods with whole foods, such as fruits and vegetables, and should incentivize industry to add less sugar, especially fructose-containing varieties, to food and beverage products. Most existing guidelines fall short of this mark at the potential cost of worsening rates of diabetes and related CV and other consequences. The existing basic science evidence, observational data, and clinic trial findings suggest that reducing consumption of added sugars, particularly added fructose, could translate to reduced diabetes-related morbidity and potentially premature mortality. At an individual level,

**TABLE 2. How Sucrose and High-Fructose Corn Syrup Cause Type 2 Diabetes Mellitus**

Increased liver fat accumulation and subsequent hepatic insulin resistance <sup>28</sup>
Increased free fatty acid release from very-low density lipoprotein, resulting in intramyocellular lipid accumulation and skeletal muscle insulin resistance <sup>28</sup>
Decreased cellular adenosine triphosphate, leading to reduced cellular binding of insulin and a possible reduction in the number of insulin receptors <sup>23</sup>
Increased inflammation and oxidative stress, leading to β-cell damage and reduced insulin secretion <sup>28</sup>

limiting consumption of foods and beverages that contain added sugars, particularly added fructose, may be one of the most effective strategies for ensuring one's robust future health.

**Abbreviations and Acronyms:** CV = cardiovascular; HFCS = high-fructose corn syrup

**Correspondence:** Address to James J. DiNicolantonio, PhamD, Saint Luke's Mid America Heart Institute, 4321 Washington St, Ste 2100, Kansas City, MO 64111 (jjdicolantonio@gmail.com).

## REFERENCES

- Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet*. 2011;378(9785):31-40.
- CDC News Room Press Release. Atlanta, GA: Centers for Disease Control and Prevention; June 10, 2014. <http://www.cdc.gov/media/releases/2014/p0610-diabetes-report.html>. Accessed October 4, 2014.
- Gregg EW, Zhuo X, Cheng YJ, Albright AL, Narayan KM, Thompson TJ. Trends in lifetime risk and years of life lost due to diabetes in the USA, 1985-2011: a modelling study. *Lancet Diabetes Endocrinol*. 2014;2(11):867-874.
- Taubes G. *Good Calories, Bad Calories*. New York, NY: Knopf; 2007.
- Reaven GM. Role of insulin resistance in human disease (syndrome X): an expanded definition. *Annu Rev Med*. 1993;44:121-131.
- Venkataraman K, Khoo CM, Leow MK, et al. New measure of insulin sensitivity predicts cardiovascular disease better than HOMA estimated insulin resistance. *PLoS One*. 2013;8(9):e74410.
- Gast KB, Tjeerdema N, Stijnen T, Smit JW, Dekkers OM. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. *PLoS One*. 2012;7(12):e52036.
- Pyorala K. Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. *Diabetes Care*. 1979;2(2):131-141.
- Welborn TA, Weame K. Coronary heart disease incidence and cardiovascular mortality in Busselton with reference to glucose and insulin concentrations. *Diabetes Care*. 1979;2(2):154-160.
- Goran MI, Uliaszek SJ, Ventura EE. High fructose corn syrup and diabetes prevalence: a global perspective. *Glob Public Health*. 2013;8(1):55-64.
- Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr*. 2005;81(2):341-354.
- Ahrens EH Jr, Boucher CA. The composition of a simulated American diet: comparison of chemical analyses and estimates from food composition tables. *J Am Diet Assoc*. 1978;73(6):613-620.
- Johnson RJ, Andrews P, Benner SA, Oliver W, Theodore E. Woodward Award: the evolution of obesity: insights from the mid-Miocene. *Trans Am Clin Climatol Assoc*. 2010;121:295-308.
- Suzuki T, Douard V, Mochizuki K, Goda T, Ferraris RP. Diet-induced epigenetic regulation in vivo of the intestinal fructose transporter Glut5 during development of rat small intestine. *Biochem J*. 2011;435(1):43-53.
- Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr*. 2004;79(4):537-543.
- Ventura EE, Davis JN, Goran MI. Sugar content of popular sweetened beverages based on objective laboratory analysis: focus on fructose content. *Obesity (Silver Spring)*. 2011;19(4):868-874.
- Walker RW DK, Goran MI. Fructose content in popular beverages made with and without high fructose corn syrup. *Nutrition*. 2014;30(7-8):928-935.
- US Department of Agriculture, Agricultural Research Service. National Nutrient Database for Standard Reference Release 27. <http://ndb.nal.usda.gov/ndb/foods/show/6278?fg=&man=&facet=&format=&count=&max=25&offset=&sort=&qlookup=high-fructose+com+syrup>. Accessed October 10, 2014.
- Food Intolerance Diagnostics. <http://www.foodintolerances.org/fructose-food-table.aspx>. Accessed October 10, 2014.
- Bode C, Schumacher H, Goebell H, Zelder O, Pelzel H. Fructose induced depletion of liver adenine nucleotides in man. *Horm Metab Res*. 1971;3(4):289-290.
- Woods HF, Eggleston LV, Krebs HA. The cause of hepatic accumulation of fructose 1-phosphate on fructose loading. *Biochem J*. 1970;119(3):501-510.
- Burch HB, Lowry OH, Meinhardt L, Max P Jr, Chyu K. Effect of fructose, dihydroxyacetone, glycerol, and glucose on metabolites and related compounds in liver and kidney. *J Biol Chem*. 1970;245(8):2092-2102.
- Beck-Nielsen H, Pedersen O, Lindskov HO. Impaired cellular insulin binding and insulin sensitivity induced by high-fructose feeding in normal subjects. *Am J Clin Nutr*. 1980;33(2):273-278.
- Thomopoulos P, Kosmakos FC, Pastan I, Lovelace E. Cyclic AMP increases the concentration of insulin receptors in cultured fibroblasts and lymphocytes. *Biochem Biophys Res Commun*. 1977;75(2):246-252.
- Stanhope KL, Schwarz JM, Keim NL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest*. 2009;119(5):1322-1334.
- Basu S, Yoffe P, Hills N, Lustig RH. The relationship of sugar to population-level diabetes prevalence: an econometric analysis of repeated cross-sectional data. *PLoS One*. 2013;8(2):e57873.
- Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes*. 2002;51(9):2796-2803.
- Lustig RH. Fructose: metabolic, hedonic, and societal parallels with ethanol. *J Am Diet Assoc*. 2010;110(9):1307-1321.
- Schalkwijk CG, Stehouwer CD, van Hinsbergh VW. Fructose-mediated non-enzymatic glycation: sweet coupling or bad modification. *Diabetes Metab Res Rev*. 2004;20(5):369-382.
- Dills WL Jr. Protein fructosylation: fructose and the Maillard reaction. *Am J Clin Nutr*. 1993;58(5 suppl):779s-787s.
- Santos CX, Tanaka LY, Wosniak J, Laurindo FR. Mechanisms and implications of reactive oxygen species generation during the unfolded protein response: roles of endoplasmic reticulum oxidoreductases, mitochondrial electron transport, and NADPH oxidase. *Antioxid Redox Signal*. 2009;11(10):2409-2427.
- Hummasti S, Hotamisligil GS. Endoplasmic reticulum stress and inflammation in obesity and diabetes. *Circ Res*. 2010;107(5):579-591.
- Krassak M, Falk Petersen K, Dresner A, et al. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a <sup>1</sup>H NMR spectroscopy study. *Diabetologia*. 1999;42(1):113-116.
- Maersk M, Belza A, Stodkilde-Jorgensen H, et al. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. *Am J Clin Nutr*. 2012;95(2):283-289.

35. Lee MK, Miles PD, Khourshed M, Gao KM, Moossa AR, Olefsky JM. Metabolic effects of troglitazone on fructose-induced insulin resistance in the rat. *Diabetes*. 1994;43(12):1435-1439.
36. Bhanot S, McNeill JH, Bryer-Ash M. Vanadyl sulfate prevents fructose-induced hyperinsulinemia and hypertension in rats. *Hypertension*. 1994;23(3):308-312.
37. Hwang IS, Ho H, Hoffman BB, Reaven GM. Fructose-induced insulin resistance and hypertension in rats. *Hypertension*. 1987;10(5):512-516.
38. Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities: the role of insulin resistance and the sympathoadrenal system. *N Engl J Med*. 1996;334(6):374-381.
39. Szanto S, Yudkin J. Dietary sucrose and the behaviour of blood platelets. *Proc Nutr Soc*. 1970;29(1 suppl):3A.
40. Reiser S, Bohn E, Hallfrisch J, Michaelis OE, Keeney M, Prather ES. Serum insulin and glucose in hyperinsulinemic subjects fed three different levels of sucrose. *Am J Clin Nutr*. 1981;34(1):2348-2358.
41. Szanto S, Yudkin J. Insulin and atheroma. *Lancet*. 1969;1(7607):1211-1212.
42. Zavaroni I, Sander S, Scott S, Reaven GM. Effect of fructose feeding on insulin secretion and insulin action in the rat. *Metabolism*. 1980;29(10):970-973.
43. Tobey TA, Mondon CE, Zavaroni I, Reaven GM. Mechanism of insulin resistance in fructose-fed rats. *Metabolism*. 1982;31(6):608-612.
44. Thorburn AW, Storlien LH, Jenkins AB, Khouri S, Kraegen EW. Fructose-induced in vivo insulin resistance and elevated plasma triglyceride levels in rats. *Am J Clin Nutr*. 1989;49(6):1155-1163.
45. Raben A, Vasilaras TH, Moller AC, Astrup A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. *Am J Clin Nutr*. 2002;76(4):721-729.
46. Perez-Pozo SE, Schold J, Nakagawa T, Sanchez-Lozada LG, Johnson RJ, Lillo JL. Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. *Int J Obes (Lond)*. 2010;34(3):454-461.
47. Te Morenga LA, Howatson AJ, Jones RM, Mann J. Dietary sugars and cardiometabolic risk: systematic review and meta-analyses of randomized controlled trials of the effects on blood pressure and lipids. *Am J Clin Nutr*. 2014;100(1):65-79.
48. Dai S, McNeill JH. Fructose-induced hypertension in rats is concentration- and duration-dependent. *J Pharmacol Toxicol Methods*. 1995;33(2):101-107.
49. Dai S, McNeill JH. Effects of fructose loading in streptozotocin-diabetic and nondiabetic rats. *Can J Physiol Pharmacol*. 1992;70(12):1583-1589.
50. Yoshino G, Iwai M, Kazumi T, et al. Effect of dietary fructose on triglyceride turnover in streptozotocin-diabetic rats. *Atherosclerosis*. 1989;79(1):41-46.
51. Kazumi T, Vranic M, Steiner G. Triglyceride kinetics: effects of dietary glucose, sucrose, or fructose alone or with hyperinsulinemia. *Am J Physiol*. 1986;250(3, pt 1):E325-E330.
52. Martinez FJ, Rizza RA, Romero JC. High-fructose feeding elicits insulin resistance, hyperinsulinism, and hypertension in normal mongrel dogs. *Hypertension*. 1994;23(4):456-463.
53. Rawana S, Clark K, Zhong S, Buisson A, Chackunkal S, Jen KL. Low dose fructose ingestion during gestation and lactation affects carbohydrate metabolism in rat dams and their offspring. *J Nutr*. 1993;123(12):2158-2165.
54. Storlien LH, Kraegen EW, Jenkins AB, Chisholm DJ. Effects of sucrose vs starch diets on in vivo insulin action, thermogenesis, and obesity in rats. *Am J Clin Nutr*. 1988;47(3):420-427.
55. Hulman S, Falkner B. The effect of excess dietary sucrose on growth, blood pressure, and metabolism in developing Sprague-Dawley rats. *Pediatr Res*. 1994;36(1, pt 1):95-101.
56. Pagliassotti MJ, Shahrokhi KA, Moscarello M. Involvement of liver and skeletal muscle in sucrose-induced insulin resistance: dose-response studies. *Am J Physiol*. 1994;266(5, pt 2):R1637-R1644.
57. Pugazhenthis S, Angel JF, Khandelwal RL. Effects of high sucrose diet on insulin-like effects of vanadate in diabetic rats. *Mol Cell Biochem*. 1993;122(1):77-84.
58. Gutman RA, Basilio MZ, Bernal CA, Chicco A, Lombardo YB. Long-term hypertriglyceridemia and glucose intolerance in rats fed chronically an isocaloric sucrose-rich diet. *Metabolism*. 1987;36(11):1013-1020.
59. Reiser S, Hallfrisch J. Insulin sensitivity and adipose tissue weight of rats fed starch or sucrose diets ad libitum or in meals. *J Nutr*. 1977;107(1):147-155.
60. Wright DW, Hansen RI, Mondon CE, Reaven GM. Sucrose-induced insulin resistance in the rat: modulation by exercise and diet. *Am J Clin Nutr*. 1983;38(6):879-883.
61. Sleder J, Chen YD, Cully MD, Reaven GM. Hyperinsulinemia in fructose-induced hypertriglyceridemia in the rat. *Metabolism*. 1980;29(4):303-305.
62. Pamiés-Andreu E, Fiksen-Olsen M, Rizza RA, Romero JC. High-fructose feeding elicits insulin resistance without hypertension in normal mongrel dogs. *Am J Hypertens*. 1995;8(7):732-738.
63. Storlien LH, Oakes ND, Pan DA, Kusunoki M, Jenkins AB. Syndromes of insulin resistance in the rat. Inducement by diet and amelioration with benfluorex. *Diabetes*. 1993;42(3):457-462.
64. Reiser S, Handler HB, Gardner LB, Hallfrisch JG, Michaelis OE IV, Prather ES. Isocaloric exchange of dietary starch and sucrose in humans. II: effect on fasting blood insulin, glucose, and glucagon and on insulin and glucose response to a sucrose load. *Am J Clin Nutr*. 1979;32(11):2206-2216.
65. Nakayama T, Kosugi T, Gersch M, et al. Dietary fructose causes tubulointerstitial injury in the normal rat kidney. *Am J Physiol Renal Physiol*. 2010;298(3):F712-F720.
66. Glushakova O, Kosugi T, Roncal C, et al. Fructose induces the inflammatory molecule ICAM-1 in endothelial cells. *J Am Soc Nephrol*. 2008;19(9):1712-1720.
67. Gersch MS, Mu W, Cirillo P, et al. Fructose, but not dextrose, accelerates the progression of chronic kidney disease. *Am J Physiol Renal Physiol*. 2007;293(4):F1256-F1261.
68. Shoham DA, Durazo-Arvizu R, Kramer H, et al. Sugary soda consumption and albuminuria: results from the National Health and Nutrition Examination Survey, 1999-2004. *PLoS One*. 2008;3(10):e3431.
69. Cohen AM, Teitelbaum A, Rosenman E. Diabetes induced by a high fructose diet. *Metabolism*. 1977;26(1):17-24.
70. Cohen AM, Rosenmann E. Diffuse intercapillary glomerulosclerosis in sucrose-fed rats. *Diabetologia*. 1971;7(1):25-28.
71. Hotta N, Kakuta H, Fukasawa H, et al. Effects of a fructose-rich diet and the aldose reductase inhibitor, ONO-2235, on the development of diabetic neuropathy in streptozotocin-treated rats. *Diabetologia*. 1985;28(3):176-180.
72. Kawasaki T, Ogata N, Akanuma H, et al. Postprandial plasma fructose level is associated with retinopathy in patients with type 2 diabetes. *Metabolism*. 2004;53(5):583-588.
73. Boot-Handford R, Heath H. Identification of fructose as the retinopathic agent associated with the ingestion of sucrose-rich diets in the rat. *Metabolism*. 1980;29(12):1247-1252.
74. Dai S, Todd ME, Lee S, McNeill JH. Fructose loading induces cardiovascular and metabolic changes in nondiabetic and diabetic rats. *Can J Physiol Pharmacol*. 1994;72(7):771-781.
75. Brymora A, Flisinski M, Johnson RJ, Goszka G, Stefanska A, Manitius J. Low-fructose diet lowers blood pressure and inflammation in patients with chronic kidney disease. *Nephrol Dial Transplant*. 2012;27(2):608-612.
76. Madero M, Arriaga JC, Jalal D, et al. The effect of two energy-restricted diets, a low-fructose diet versus a moderate natural



- fructose diet, on weight loss and metabolic syndrome parameters: a randomized controlled trial. *Metabolism*. 2011;60(11):1551-1559.
77. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet*. 2006;367(9507):320-326.
  78. Carter P, Gray LJ, Troughton J, Khunti K, Davies MJ. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. *BMJ*. 2010;341:c4229.
  79. Bellavia A, Larsson SC, Bottai M, Wolk A, Orsini N. Fruit and vegetable consumption and all-cause mortality: a dose-response analysis. *Am J Clin Nutr*. 2013;98(2):454-459.
  80. Bray GA, Popkin BM. Dietary sugar and body weight: have we reached a crisis in the epidemic of obesity and diabetes?: health be damned! pour on the sugar. *Diabetes Care*. 2014;37(4):950-956.
  81. Wolf A, Bray GA, Popkin BM. A short history of beverages and how our body treats them. *Obes Rev*. 2008;9(2):151-164.
  82. Kelishadi R, Mansourian M, Heidari-Beni M. Association of fructose consumption and components of metabolic syndrome in human studies: a systematic review and meta-analysis. *Nutrition*. 2014;30(5):503-510.
  83. Block G. Foods contributing to energy intake in the US: data from NHANES III and NHANES 1999-2000. *J Food Compos Anal*. 2004;17(3-4):439-447.
  84. Bleich SN, Wang YC. Consumption of sugar-sweetened beverages among adults with type 2 diabetes. *Diabetes Care*. 2011;34(3):551-555.
  85. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care*. 2010;33(11):2477-2483.
  86. Malik VS, Willett WC, Hu FB. Sugar-sweetened beverages and BMI in children and adolescents: reanalyses of a meta-analysis. *Am J Clin Nutr*. 2009;89(1):438-440.
  87. Schulze MB, Manson JE, Ludwig DS, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA*. 2004;292(8):927-934.
  88. Chan TF, Lin WT, Huang HL, et al. Consumption of sugar-sweetened beverages is associated with components of the metabolic syndrome in adolescents. *Nutrients*. 2014;6(5):2088-2103.
  89. Basu S, McKee M, Galea G, Stuckler D. Relationship of soft drink consumption to global overweight, obesity, and diabetes: a cross-national analysis of 75 countries. *Am J Public Health*. 2013;103(11):2071-2077.
  90. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet*. 2001;357(9255):505-508.
  91. Berkey CS, Rockett HR, Field AE, Gillman MW, Colditz GA. Sugar-added beverages and adolescent weight change. *Obes Res*. 2004;12(5):778-788.
  92. Olsen NJ, Heitmann BL. Intake of calorically sweetened beverages and obesity. *Obes Rev*. 2009;10(1):68-75.
  93. Greenwood DC, Threapleton DE, Evans CE, et al. Association between sugar-sweetened and artificially sweetened soft drinks and type 2 diabetes: systematic review and dose-response meta-analysis of prospective studies. *Br J Nutr*. 2014;112(5):725-734.
  94. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health*. 2007;97(4):667-675.
  95. Bazzano LA, Li TY, Joshipura KJ, Hu FB. Intake of fruit, vegetables, and fruit juices and risk of diabetes in women. *Diabetes Care*. 2008;31(7):1311-1317.
  96. Flood-Obbagy JE, Rolls BJ. The effect of fruit in different forms on energy intake and satiety at a meal. *Appetite*. 2009;52(2):416-422.
  97. Odegaard AO, Koh WP, Arakawa K, et al. Soft drink and juice consumption and risk of physician-diagnosed incident type 2 diabetes: the Singapore Chinese Health Study. *Am J Epidemiol*. 2010;171(6):701-708.
  98. Suez J, Korem T, Zeevi D, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature*. 2014;514(7521):181-186.
  99. Meyer BJ, de Bruin EJ, Du Plessis DG, van der Merwe M, Meyer AC. Some biochemical effects of a mainly fruit diet in man. *S Afr Med J*. 1971;45(10):253-261.
  100. Sevak L, McKeigue PM, Marmot MG. Relationship of hyperinsulinemia to dietary intake in south Asian and European men. *Am J Clin Nutr*. 1994;59(5):1069-1074.
  101. Manolio TA, Savage PJ, Burke GL, et al. Correlates of fasting insulin levels in young adults: the CARDIA study. *J Clin Epidemiol*. 1991;44(6):571-578.
  102. Davis JN, Ventura EE, Weigensberg MJ, et al. The relation of sugar intake to beta cell function in overweight Latino children. *Am J Clin Nutr*. 2005;82(5):1004-1010.
  103. Gross LS, Li L, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *Am J Clin Nutr*. 2004;79(5):774-779.
  104. Dunnigan MG, Fyfe T, McKiddie MT, Crosbie SM. The effects of isocaloric exchange of dietary starch and sucrose on glucose tolerance, plasma insulin and serum lipids in man. *Clin Sci*. 1970;38(1):1-9.
  105. Cozma AI, Sievenpiper JL, de Souza RJ, et al. Effect of fructose on glycemic control in diabetes: a systematic review and meta-analysis of controlled feeding trials. *Diabetes Care*. 2012;35(7):1611-1620.
  106. Bes-Rastrollo M, Schulze MB, Ruiz-Canela M, Martinez-Gonzalez MA. Financial conflicts of interest and reporting bias regarding the association between sugar-sweetened beverages and weight gain: a systematic review of systematic reviews. *PLoS Med*. 2013;10(12):e1001578.
  107. Hallfrisch J, Ellwood KC, Michaelis OE IV, Reiser S, O'Dorisio TM, Prather ES. Effects of dietary fructose on plasma glucose and hormone responses in normal and hyperinsulinemic men. *J Nutr*. 1983;113(9):1819-1826.
  108. NikKilla EA. Influence of dietary fructose and sucrose on serum triglycerides in hypertriglyceridemias and diabetics. In: Sipple H, McNutt K, eds. *Sugars in Nutrition*. New York, NY: Academic Press; 1974:439-448.
  109. DiMaggio DP, Mattes RD. Liquid versus solid carbohydrate: effects on food intake and body weight. *Int J Obes Relat Metab Disord*. 2000;24(6):794-800.
  110. Mattes RD. Dietary compensation by humans for supplemental energy provided as ethanol or carbohydrate in fluids. *Physiol Behav*. 1996;59(1):179-187.
  111. Lucan SC, DiNicolantonio JJ. How calorie-focused thinking about obesity and related diseases may mislead and harm public health: an alternative [published ahead of print November 24, 2014]. *Public Health Nutr*. <http://dx.doi.org/10.1017/S1368980014002559>.
  112. Tordoff MG, Alleva AM. Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight. *Am J Clin Nutr*. 1990;51(6):963-969.
  113. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA*. 2002;287(18):2414-2423.
  114. Janssens JP, Shapira N, Debeuf P, et al. Effects of soft drink and table beer consumption on insulin response in normal teenagers and carbohydrate drink in youngsters. *Eur J Cancer Prev*. 1999;8(4):289-295.
  115. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. *Diabetes Care*. 1990;13(6):610-630.
  116. Yudkin J, Kang SS, Bruckdorfer KR. Effects of high dietary sugar. *Br Med J*. 1980;281(6252):1396.

117. Ng SW, Slining MM, Popkin BM. Use of caloric and noncaloric sweeteners in US consumer packaged foods, 2005-2009. *J Acad Nutr Diet*. 2012;112(11):1828-1834.e1821-1826.
118. Mariott BP, Olsho L, Hadden L, Connor P. Intake of added sugars and selected nutrients in the United States, National Health and Nutrition Examination Survey (NHANES) 2003-2006. *Crit Rev Food Sci Nutr*. 2010;50(3):228-258.
119. Reiser S, Michaelis OE IV, Cataland S, O'Doniso TM. Effect of isocaloric exchange of dietary starch and sucrose in humans on the gastric inhibitory polypeptide response to a sucrose load. *Am J Clin Nutr*. 1980;33(9):1907-1911.
120. Yudkin J. Sugar and disease. *Nature*. 1972;239(5369):197-199.
121. US Department of Health and Human Services, US Department of Agriculture, US Dietary Guidelines Advisory Committee. *Dietary Guidelines for Americans, 2010*. 7th ed. Washington, DC: US Dept of Health and Human Services; 2010.
122. Trumbo P, Schlicker S, Yates AA, Poos M. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. *J Am Diet Assoc*. 2002;102(11):1621-1630.
123. Malnik E. World Health Organisation advises halving sugar intake. *The Telegraph*. March 2014.
124. Johnson RK, Appel LJ, Brands M, et al. Dietary sugars intake and cardiovascular health: a scientific statement from the American Heart Association. *Circulation*. 2009;120(11):1011-1020.
125. Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among US adults. *JAMA Intern Med*. 2014;174(4):516-524.