In reply—Fructose as a Driver of Diabetes: An Incomplete View of the Evidence

We appreciate the response to our article from Dr Sievenpiper and colleagues, who argue that the highest-level evidence fails to implicate fructose as an independent driver of type 2 diabetes. We respectfully counter that the meta-analyses and systematic reviews the authors present may be misleading and that the totality of data supports our original contention.

As a bottom line, Sievenpiper et al dismiss attributed harms of fructose as the effect of any added calories, noting detriments of fructose consumption in hypercaloric addition trials but not in isocaloric substitution trials. One problem with the logic is that isocaloric substitution is an artificial condition. Free-living individuals do not substitute fructose for other carbohydrates or macronutrients in a calorie-neutral way. When free-living individuals consume more fructose, they tend to consume more calories overall. Such overconsumption may result partly from fructose being less satiating (even when compared with glucose). Furthermore, fructose incites insulin resistance and leptin resistance, which may drive hunger and delay satiety. Thus, hypercaloric addition trials may be more representative of the effects of fructose consumption in the real world. As we stated in our article, and as the forest plot provided by Sievenpiper et al corroborates, there seems to be no question that hypercaloric fructose is associated with a variety of adverse metabolic effects.

Another problem with the cited isocaloric substitution trials may be industry involvement. Sievenpiper et al note favorable effects on hemoglobin A1c and blood pressure in trials substituting fructose for other carbohydrates, explaining that the majority of trials were not funded exclusively by industry but by a combination of industry and agency. This fact should not be at all reassuring because trials that involve industry collaboration in design, analysis, or reporting use less rigorous methods and are more likely to report pro-industry conclusions. A recent meta-analysis found a direct effect of higher sugar intake on systolic blood pressure when industry-funded trials were included but documented an even greater increase in blood pressure when industry-funded trials were excluded (an effect about twice as strong as what might be seen with high-sodium intake). Another systematic review revealed a striking dichotomy: more than 80% of industry-funded studies reported no relationship between sugar-sweetened beverage consumption and weight gain, whereas more than 80% of non—industry-funded studies found a positive correlation between intake of sugar-sweetened beverages and weight gain.

There are also measurement issues to consider in the trials cited by Sievenpiper et al. For instance, with regard to blood pressure, the hypertensive effect of sugar might have been missed in trials employing random blood pressure readings because sugar has been found to predominantly elevate blood pressure postprandially. Also, 24-hour ambulatory monitoring is more accurate and reliable for measuring blood pressure than single clinic readings. When ambulatory monitoring is used, evidence suggests that blood pressure is significantly increased after just a few weeks of high sugar intake.

Measurement is also an issue for Sievenpiper and colleagues’ cited prospective cohort studies. The authors note that such studies have failed to document a direct relationship between fructose and diabetes. Yet, these studies almost inevitably rely on self-reported intake data, which are notoriously problematic. In fact, some experts contend that self-reported intake data are wholly inadequate and unacceptable, at least with regard to energy intake. More specifically with regard to sugar, a recent prospective cohort study found that sucrose measured by objective biomarkers was directly associated with body mass index, whereas sucrose measured by self-report was inversely associated with body mass index. Thus, the assertion by Sievenpiper et al that studies employing self-reported...
dietary intakes represent the “highest-level evidence” is untenable.

As for other trial evidence, there are also “restriction trials” to consider. On average, Americans derive about 15% of their total calorie intake from added sugars, and roughly 13% of the US population consumes 25% or more of their calories as added sugars.21,22

With a background of such high sugar consumption, even a substantial reduction of fructose may not yield benefit, especially if that fructose is replaced by other sugar. However, an overall reduction in sugar consumption might have benefit, and, indeed, evidence indicates that when overall sugar is restricted, reductions in weight, blood pressure, and inflammation are observed.23,24

“Restriction trials” actually end up being “substitution trials” when calories are held constant (even though exact dietary replacements are not generally specified, measured, or reported). In trials specifically restricting intake of added sugar by substituting sugar (glucose plus fructose) with starch (all glucose), there were substantial benefits of such intervention, including lower levels of insulin and glucose, reductions in the diagnosis of diabetes or prediabetes, and improvements in fatty liver.25–27 Importantly, these beneficial effects conferred by sugar restriction were independent of calories.

Adverse effects of high sugar intake (such as worsening levels of total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol) have also been reported.28–31 Additionally, the meta-analysis reporting these associations found that the effects were independent of body weight.31

To assert that fructose is not harmful compared with other calories does not fit with the totality of data we reviewed in our article or with the considerations discussed in our reply here. Added fructose is indeed a principal driver of type 2 diabetes and related metabolic disease.14,28

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LETTERS TO THE EDITOR


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Cutaneous and Uterine Leiomyomas

To the Editor: We read with great interest the medical image feature by Seranno and Ruiz-Villaverde on a woman with cutaneous and uterine leiomyomas published in the March 2015 issue of Mayo Clinic Proceedings.1 As the authors correctly point out, the molecular defect in this syndrome is a mutation of one allele of the fumarate hydratase gene. However, this syndrome is now classified as hereditary leiomyomatosis and renal cell cancer syndrome (Online Mendelian Inheritance in Man #150800) rather than Reed syndrome. The authors indicate that this syndrome is associated with cutaneous cutaneous leiomyomas.2

In reply—Cutaneous and Uterine Leiomyomas

We appreciate the comments from Drs Stewart and Morton regarding our medical image feature on a woman with cutaneous and uterine leiomyomas published in the March 2015 issue of Mayo Clinic Proceedings.1 We recognize that this syndrome is now classified as hereditary leiomyomatosis and renal cell cancer syndrome (Online Mendelian Inheritance in Man #150800). Some authors have described it as a distinct entity altogether when multiple cutaneous uterine leiomyomas are associated with aggressive renal cancer, also known as hereditary leiomyomatosis and renal cell carcinoma (OMIM #605839).2,3 Although more than 18 mutations in the fumarate hydratase (FH) gene have been described,6 the mechanisms by which FH mutations cause tumor predisposition is unknown. Fumarate hydratase is an enzyme of the Krebs cycle and plays an important role in intermediary metabolism.

As Stewart and Morton pointed out, the patients who present with uterine myomomas usually do so at a younger age, with the myomomas being larger and more numerous than those diagnosed in the general population. This was the reason that led to an early hysterectomy before the age of 30 years in the patient in our report.5 Histopathologic study of extirpated myomomas did not reveal any sign of malignancy, but we were unable to review whether high cellularity and hyaline necrosis were present because the hysterectomy was performed in another hospital 30 years previously. We performed abdominal ultrasonography to examine for renal cell cancer, and it showed a simple cyst of 6 to 7 cm in the upper pole of the right kidney. Genetic study was not available, so we could not determine whether 1p deletion was present. These 2 characteristics would have helped us to clarify if this patient was at risk of development of a uterine sarcoma.5,6

In addition, genetic counseling was also provided to our patient, and her family was studied. She has only one child, a son who has no evidence of cutaneous leiomyomas.

It is unclear which patients should be screened for renal cancer, at what age, by what means, and how frequently. Some type 2 papillary or collecting duct renal cell carcinomas cannot be identified by ultrasonography and may therefore require computed tomography or magnetic resonance

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