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

To the Editor: We are concerned that the article by DiNicolantonio et al[1] published in the March 2015 issue of *Mayo Clinic Proceedings* that implicated added fructose as a driver of type 2 diabetes misrepresented the data by placing undue emphasis on low-quality evidence from ecological observations, animal models of fructose overfeeding, and selected human studies assessed in isolation. It also ignored important biological mechanisms by which fructose may assist in the metabolic handling of glucose. If one considers the totality of the highest-quality evidence from controlled feeding trials and prospective cohorts, then different conclusions are reached.

A series of carefully conducted systematic reviews and meta-analyses[2-9] of more than 50 controlled trials that included over 1000 participants of the effect of fructose across a wide dose range have failed to document a signal for harm of fructose in isocaloric substitution for other carbohydrates likely to replace it (Figure 1). Contrary to the hypothesis put forward by DiNicolantonio et al,[1] pooled analyses of the totality of the evidence from these trials show that fructose in isocaloric exchange for other sources of carbohydrate leads to clinically meaningful improvements in glycemic control as assessed by glycated blood proteins (equivalent to a 0.57% reduction in hemoglobin A_{1c}, which exceeds the US Food and Drug Administration threshold of 0.3% for the development of new oral antihyperglycemic agents) in individuals with and without diabetes.[2,3] Favorable results are also seen in blood pressure, without any adverse effects on other cardiometabolic risk factors including insulin sensitivity, body weight, fasting lipid levels, postprandial lipid levels, uric acid concentration, and markers of nonalcoholic fatty liver disease in individuals with varying metabolic phenotypes.[2-9] DiNicolantonio et al implied that bias from industry funding might explain these favorable results among the available controlled trials, but very few of these trials were funded exclusively by industry. The majority were funded by a combination of agency and industry or agency alone, and there was no evidence of publication bias across the end points.[2-9]

Prospective cohort studies, which provide the greatest protection against bias among observational studies because of their long longitudinal follow-up and the ability to adjust for multiple confounding factors, have also failed to document a direct relationship between fructose and diabetes. Although pooled analyses of the available cohorts have revealed that sugar-sweetened beverages (SSBs) as a source of free fructose are associated with an increased risk of diabetes when the highest and lowest levels of exposure are compared,[10,11] pooled analyses involving many of the same cohorts have not found the same relationship for total sugars, total sucrose, total fructose,[12] or other sources of free fructose such as 100% fruit juice[11] and cakes and cookies[13] (Figure 2). The opposite relationship (benefit) has also been reported for fruit as a source of bound fructose.[14]

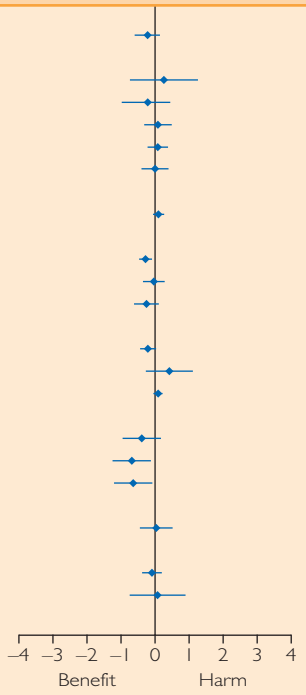
Setting aside these discrepant findings, if one wants to invoke the evidence for SSBs as a proxy for all added fructose-containing sugars, then one has to ask how important a risk factor is the intake of SSBs. A recent comparative risk assessment revealed that the burden of disease and mortality attributable to SSBs (that is, population-attributable fraction) is still much less than that of other established risk factors measured among the cohort studies, ranking 32nd among 57 risk factors globally.[15] Even among the dietary and physical inactivity risk factors, SSBs ranked 12th of 15 for both burden of disease and mortality, and no other sources of added fructose-containing sugars were identified as risk factors.[15]

The question becomes why the higher-level evidence disagrees with the current hypothesis from DiNicolantonio et al.[1] One reason may be that the mechanisms being invoked are not as relevant in humans as in the animal models used to support them. For example, although de novo lipogenesis is extremely high (estimated at $\geq$50%) with excessive fructose feeding (typically 60% of total energy intake) in rodents, a careful review of stable isotope tracer studies reveals that de novo lipogenesis from fructose (as indeed from all carbohydrate) is a minor pathway for fructose disposal in humans (estimated to range from 0%-1% at moderate intake to up to 5% with overfeeding in humans).[16]

Another reason for the differences may lie in biologically plausible pathways that offset any harm and even explain some benefits. Fructose has a very low glycemic index (15), a factor that led to an early interest in fructose in diabetes management. Emerging evidence also shows that low-dose fructose ($\leq$10 g per meal) may benefit glycemic control through its metabolite fructose-1-phosphate by inducing glucokinase activity. This catalytic effect of fructose on hepatic glucose metabolism has been reported to coincide with (1) a decrease in hepatic glucose production under hyperglycemic clamp conditions in patients with type 2 diabetes and (2) an increase in glycogen synthesis by carbon 13 nuclear magnetic resonance spectroscopy under euglycemic clamp conditions in participants without diabetes.[17,18] These mechanisms appear to be sustainable over the long term. A systematic review and meta-analysis of controlled trials of the effect of small "catalytic" fructose doses ($\leq$36 g/d) in exchange for starch reproduced the favorable glycemic effects seen at

Isocaloric substitution trials

Cardiometabolic end point		Comparisons	No.	Standardized mean difference (SMD) with 95% CI	I^2
Body weight[4]		31	637	−0.22 (−0.58, 0.13)	37%*
Fasting lipids[5]	LDL-C	26	327	0.36 (−0.27, 0.50)	11%
	Apo-B	8	176	−0.21 (−0.96, 0.43)	62%*
	Non-HDL-C	26	457	0.09 (−0.30, 0.47)	92%*
	TG	49	815	0.08 (−0.20, 0.36)	62%*
	HDL-C	27	525	0.00 (−0.38, 0.38)	49%*
Postprandial TG[6]		14	290	0.14 (−0.02, 0.30)	54%*
Glycemic control[3]	GBP	19	277	−0.28 (−0.45, −0.11)	56%*
	FBG	47	881	−0.04 (−0.34, 0.26)	78%*
	FBI	34	622	−0.25 (−0.60, 0.09)	70%*
Insulin sensitivity[3]	Whole body	16	265	−0.21 (−0.42, 0.01)	66%*
	Hepatic	3	25	0.42 (−0.25, 1.09)	51%
	HOMA-IR	39	806	0.09 (−0.03, 0.20)	66%*
Blood pressure[7]	SBP	13	352	−0.39 (−0.93, 0.16)	31%
	DBP	13	352	−0.68 (−1.23, −0.14)	47%*
	MAP	13	352	−0.64 (−1.19, −0.10)	97%*
Uric acid[8]		18	390	0.04 (−0.43, 0.50)	0%
NAFLD[9]	IHCL	4	95	−0.09 (−0.36, 0.18)	0%
	ALT	6	164	0.07 (−0.73, 0.87)	0%



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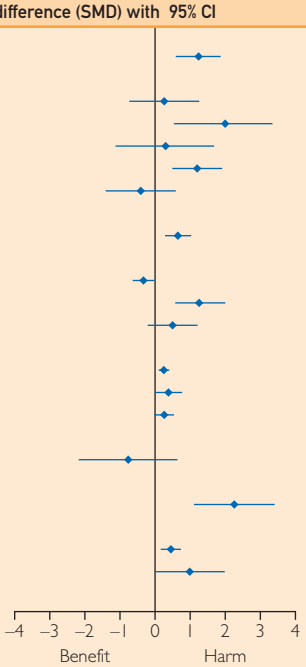
Hypercaloric addition trials

Cardiometabolic end point		Comparisons	No.	Standardized mean difference (SMD) with 95% CI	I^2
Body weight[4]		10	119	1.24 (0.61, 1.85)	30%
Fasting lipids[5]	LDL-C	4	79	0.14 (−0.39, 1.57)	77%*
	Apo-B	2	48	2.00 (0.55, 3.33)	0%
	Non-HDL-C	2	43	0.30 (−1.11, 1.66)	93%*
	TG	8	125	1.20 (0.51, 1.89)	66%*
	HDL-C	4	79	−0.41 (−1.39, 0.57)	0%
Postprandial TG[6]		2	32	0.65 (0.30, 1.01)	22%
Glycemic control[3]	GBP	2	31	−0.33 (−0.62, −0.04)	0%
	FBG	8	98	1.25 (0.59, 1.98)	59%*
	FBI	8	98	0.50 (−0.19, 1.19)	41%
Insulin sensitivity[3]	Whole body	7	74	0.25 (0.12, 0.39)	0%
	Hepatic	3	31	0.38 (0.01, 0.75)	0%
	HOMA-IR	9	113	0.26 (−0.01, 0.52)	77%*
Blood pressure[7]	MAP	2	24	−0.76 (−2.15, 0.62)	24%
Uric acid[8]		3	35	2.26 (1.13, 3.39)	0%
NAFLD[9]	IHCL	5	60	0.45 (0.18, 0.72)	51%*
	ALT	4	59	0.99 (0.01, 1.97)	28%



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