See corresponding article on page 1002.

Low-energy sweeteners and cardiometabolic health: is there method in the madness?

Tauseef A Khan[1,2] *and John L Sievenpiper*[1,2,3,4,5]

[1]Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [2]Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St Michael's Hospital, Toronto, ON, Canada; [3]Division of Endocrinology and Metabolism, Department of Medicine, St Michael's Hospital, Toronto, ON, Canada; [4]Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, ON, Canada; and [5]Department of Medicine, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Excess intake of sugars has been singled out as a primary driver in the dual epidemics of obesity and diabetes and its downstream cardiometabolic complications (1). Low-energy sweeteners (LESs) provide an alternate strategy for displacing excess calories from sugars in the diet while maintaining sweet taste. Despite safety approvals by major health and regulatory bodies (FDA, the Joint FAO/WHO Expert Committee on Food Additives, the European Food Safety Authority, and Health Canada) (2–5) from the standpoint of toxicology, there has been emerging concern that LESs might not have the intended benefits and could even increase the risk of the cardiometabolic diseases that they are intended to reduce. These concerns are largely driven by adverse signals for obesity, metabolic syndrome, diabetes, and coronary heart disease in prospective cohort studies (6, 7), signals that are well understood to be at high risk of reverse causality (8, 9).

Several acute mechanisms provide biological plausibility to support the signals of harm seen in the prospective cohort studies. Much of the attention has focused on the acute metabolic and endocrine responses to LESs, by which LESs act upon intestinal sweet taste receptors leading to impaired postprandial release of glucagon-like peptide 1 and insulin (10, 11). Other mechanisms include the uncoupling of sweet taste and delivery of calories (12), alterations in gut microbiota (13), and adaptive changes in taste preference (14). Whether these mechanisms are operational under real-world intakes across different food matrices and contribute to increased risk of cardiometabolic complications is unclear. Many of these mechanisms have been questioned for their veracity in humans (15) and clinical relevance (16).

Important Methodological and Design Issues

Addressing these mechanisms requires careful consideration of key methodological and design issues. One consideration is the food matrix and pattern of intake. Is the LES consumed without any other sources of calories (e.g., an LES-sweetened beverage consumed alone for hydration between meals) or in combination with calories (e.g., an LES-sweetened beverage consumed along with a snack or meal, or LESs consumed as part of a food matrix such as cereal, yogurt, or confectionery)? The first pattern of intake allows one to test directly the effect of LESs on metabolic and endocrine responses, whereas the second pattern allows one to test whether LESs modify the metabolic and endocrine response to other coingested macronutrients and/or the food matrices in which they are contained. A second consideration is the type of LES. Because LESs represent a heterogeneous group of compounds with distinct absorption, distribution, metabolism, and excretion kinetics (3), it is important to know which LESs [e.g., aspartame, sucralose, or acesulfame potassium (Ace-K)] or, most commonly, LES blends (e.g., sucralose and Ace-K) and doses were used. A third consideration is the nature of the comparator, and the calories and carbohydrate available to be displaced. Is it a caloric or noncaloric comparator and, in the case of a caloric comparator, are the calories and carbohydrate unmatched [e.g., a zero-calorie LES-sweetened beverage in substitution for the equivalent sugar-sweetened beverage (SSB)] or matched (e.g., LESs added to a caloric carbohydrate preload compared with the same preload alone, as can happen as part of sugars-reduction reformulation strategies in which milligram amounts of LESs replace gram amounts of sugars in a solid food matrix such that the other components of the food, often refined starches, make up the difference by weight resulting in a reduction in sugars but a trivial reduction or no difference in the amount of calories or glycemic carbohydrate)? A fourth consideration is the mode of delivery. Does the LES bypass the cephalic phase (e.g., a non–"real-world" scenario in which LESs are delivered via capsules or intragastric infusion to blind the

TAK was funded by a Toronto 3D Postdoctoral Fellowship Award. JLS was funded by a Diabetes Canada Clinician Scientist award.

Supplemental Table 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

TAK and JLS contributed equally to this work.

Address correspondence to JLS (e-mail: john.sievenpiper@utoronto.ca).

Abbreviations used: Ace-K, acesulfame potassium; LES, low-energy sweetener; SSB, sugar-sweetened beverage.

First published online September 16, 2020; doi: https://doi.org/10.1093/ajcn/nqaa260.

intervention or test the effect of LESs independent of sweetness and stimulation of the oral sweet receptor)?

Article in the Present Issue of the Journal

In this issue of the Journal, the systematic review and meta-analysis of acute randomized controlled trials by Greyling and coworkers (17) of the effect of LESs on acute postprandial blood glucose and insulin responses makes an important contribution by recognizing the importance of the pattern of intake and type of LES. A strength of the analysis is that the authors prespecified subgroup analyses by the pattern of intake to assess effect modification by LESs alone compared with LESs in combination with a caloric preload. The authors showed no evidence of effect modification or interaction by the pattern of intake. Total LESs neither elicited a postprandial glycemic or insulinemic response themselves nor affected the postprandial glycemic or insulinemic responses to coingested caloric preloads. There was also no evidence of a dose–response gradient.

Another strength is that the authors, in acknowledging that LESs are a heterogenous group of compounds that might not share the same effects, undertook network meta-analyses to compare the different LESs (although this analysis was not prespecified). Network meta-analyses have the advantage of being able to simultaneously compare multiple interventions in a single analysis, by combining direct and indirect comparisons with a common comparator, allowing one to compare LESs that have never been compared head-to-head and yielding more precise estimates than a traditional pairwise analysis. The network meta-analysis did not show any differences by type of LES, confirming the findings of the pairwise meta-analyses.

Unfortunately, the present systematic review and meta-analysis did not differentiate by the mode of delivery, pooling trials that delivered LESs orally via foods and beverages with trials that delivered LESs using capsules or intragastric infusions thereby bypassing the cephalic phase. A subgroup analysis would have been useful to answer the question of whether LESs affect glucose and insulin responses via the cephalic sweet taste response. Although a formal subgroup analysis was not undertaken, the 95% CIs for these trials appear to overlap with those of the overall pooled estimate, suggesting that the cephalic phase might not be an important modifier of any effect of LESs on glucose and insulin responses.

What Are the Implications?

In establishing that acute administration of LESs does not elicit glucose or insulin responses or modify the glucose and insulin responses to coingested caloric preloads, the question shifts to the long-term clinical and public health implications of the systematic review and meta-analysis by Greyling and coworkers (17). Do these findings translate to a sustained lack of effect or even benefit (through displacement of sugars and calories) of LESs over the longer term?

The interpretation of the systematic reviews and meta-analyses of longer-term randomized controlled trials has been less clear. Whereas an earlier systematic review and meta-analysis of randomized controlled trials showed no harm and even benefit of LESs over the longer term (18), 2 subsequent highly influential systematic reviews and meta-analyses of randomized controlled trials concluded that harm could not be excluded (6, 7). A series of letters to the editor, editorials, commentaries, and consensus statements (8, 9, 19, 20) have questioned these differences in interpretation on the basis of the same methodological and design issues affecting the acute evidence. One of the most important considerations identified for the longer-term randomized controlled trials is the nature of the comparator. The 2 syntheses that could not exclude harm (6, 7) failed to account for the calories and glycemic carbohydrate available to be displaced by LESs. Pooling caloric comparators (e.g., LES-sweetened beverages in substitution for SSBs with displacement of calories and sugars) with noncaloric comparators (e.g., LESs in substitution for water, placebo, or weight-loss diets without caloric displacement of calories or sugars) and even using noncaloric comparators as the sole comparator for some outcomes likely contributed to an underestimation of the true effect of LESs in their intended displacement of calories and sugars, and severely limited the usefulness of these syntheses (8, 9, 19).

The syntheses of the prospective cohort studies, which have been a source of much of the concern, have been equally sensitive to methodological and design issues. Although prospective cohort studies represent the highest quality evidence among observational studies with the advantage of long longitudinal follow-up, adjustment for multiple confounders, and ascertainment of clinical cardiometabolic outcomes rather than intermediate risk factors, these studies are at high risk of residual confounding from behavioral clustering and reverse causality in assessing the association between LES exposures and clinical cardiometabolic outcomes. The reverse causality is a point readily acknowledged by the authors of prospective cohort studies (21, 22), the systematic reviews and meta-analyses that include these studies (6), and guidelines committees that use the systematic reviews and meta-analyses (23, 24) because higher consumers of LESs could be consuming LES-containing beverages and foods as a weight-loss strategy because of their higher risk of obesity and adverse and cardiometabolic outcomes rather than the other way around. Letters to the editor, editorials, commentaries, and consensus statements (8, 9, 19, 20, 25) have again called for strategies to address these issues including adjustments for adiposity in primary analyses, assessment of exposures using repeated measures of change in exposures (as opposed to prevalent or baseline exposures), and substitution analyses that model the intended replacement strategy (i.e., the substitution of LESs for caloric sugars such as the substitution of LES-sweetened beverages for SSBs), approaches that have yielded the opposite associations: weight loss (21) and lower diabetes incidence (22) and cardiovascular mortality (26).

What Are the Next Steps?

There is a need to apply the same careful consideration of the methodological and design issues highlighted by the systematic review and meta-analysis by Greyling and coworkers (17) to updated systematic reviews and meta-analyses of the longer-term randomized controlled trials of intermediate cardiometabolic risk factors and prospective cohort studies of clinical cardiometabolic outcomes. In this regard, we await several important ongoing systematic reviews and meta-analyses of the randomized controlled trials (1 that includes a network meta-analysis) with prespecified

analyses that account for the nature of the comparator and the type and dose of LESs (PROSPERO 2019 CRD42019135483; clinicaltrials.gov identifier: NCT02879500) and of the prospective cohort studies with prespecified repeated measures change analyses and substitution analyses that model the intended replacement strategy of LESs for caloric sugars (clinicaltrials.gov identifier: NCT04245826). More longer-term pragmatic, "real world" high-quality randomized controlled trials of the most commonly consumed beverage/food sources of LES blends and doses on the market (e.g., LES-sweetened beverages containing sucralose and Ace-K, aspartame and Ace-K, or all 3) using caloric comparators (e.g., SSBs as the target of the intended replacement strategy) and/or noncaloric comparators as an active control (e.g., water as the "standard of care") will also be important for informing future systematic reviews and meta-analyses, with several trials currently in progress (clinicaltrials.gov identifiers: NCT01295671, NCT03543644, NCT03259685, NCT03944616, NCT02591134). The epistemological approaches to the question of LESs and cardiometabolic health will continue to evolve and improve, and, as Polonius says to Hamlet, "Though this be madness, yet there is method in 't" [Hamlet, 2.2.223–224 (27)].

The authors' responsibilities were as follows—TAK: wrote the first draft; JLS: revised and updated the draft; and both authors: read and approved the final manuscript.

TAK has received research support from the International Life Sciences Institute (ILSI) and National Honey Board and an honorarium from the Calorie Control Council. JLS has received research funding, honoraria, and/or reimbursement of travel expenses from various food, beverage, and ingredient companies, trade organizations, and other commercial and nonprofit entities with an interest in energy and low-energy sweeteners. A full list of potential conflicts of interest is shown for both authors in **Supplemental Table 1**.

References

1. Lustig RH, Schmidt LA, Brindis CD. Public health: the toxic truth about sugar. Nature 2012;482:27–9.
2. Mortensen A. Sweeteners permitted in the European Union: safety aspects. Scand J Food Nutr 2006;50:104–16.
3. Magnuson BA, Carakostas MC, Moore NH, Poulos SP, Renwick AG. Biological fate of low-calorie sweeteners. Nutr Rev 2016;74:670–89.
4. Health Canada. Sugar substitutes [Internet]. Health Canada; 2004 [cited July 15, 2020]. Available from: https://www.canada.ca/en/health-canada/services/food-nutrition/food-safety/food-additives/sugar-substitutes.html.
5. Center for Food Safety and Applied Nutrition. High-intensity sweeteners [Internet]. FDA; 2020 [cited July 15, 2020]. Available from: https://www.fda.gov/food/food-additives-petitions/high-intensity-sweeteners.
6. Toews I, Lohner S, Kullenberg de Gaudry D, Sommer H, Meerpohl JJ. Association between intake of non-sugar sweeteners and health outcomes: systematic review and meta-analyses of randomised and non-randomised controlled trials and observational studies. BMJ [Internet] 2019;364:k4718. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30602577.
7. Azad MB, Abou-Setta AM, Chauhan BF, Rabbani R, Lys J, Copstein L, Mann A, Jeyaraman MM, Reid AE, Fiander M, et al. Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies. CMAJ [Internet] 2017;189:E929–39. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28716847.
8. Sievenpiper JL, Khan TA, Ha V, Viguiliouk E, Auyeung R. The importance of study design in the assessment of nonnutritive sweeteners and cardiometabolic health. CMAJ [Internet] 2017;189:E1424–5. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29158457.
9. Malik VS. Non-sugar sweeteners and health. BMJ [Internet] 2019;364:k5005. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30606710.
10. Sylvetsky AC, Brown RJ, Blau JE, Walter M, Rother KI. Hormonal responses to non-nutritive sweeteners in water and diet soda. Nutr Metab (Lond) [Internet] 2016;13:71. Available from: https://doi.org/10.1186/s12986-016-0129-3.
11. Brown RJ, Rother KI. Non-nutritive sweeteners and their role in the gastrointestinal tract. J Clin Endocrinol Metab 2012;97:2597–605.
12. Swithers SE. Artificial sweeteners produce the counterintuitive effect of inducing metabolic derangements. Trends Endocrinol Metab 2013;24:431–41.
13. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, Israeli D, Zmora N, Gilad S, Weinberger A, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 2014;514:181–6.
14. Piernas C, Tate DF, Wang X, Popkin BM. Does diet-beverage intake affect dietary consumption patterns? Results from the Choose Healthy Options Consciously Everyday (CHOICE) randomized clinical trial. Am J Clin Nutr 2013;97:604–11.
15. Dalenberg JR, Patel BP, Denis R, Veldhuizen MG, Nakamura Y, Vinke PC, Luquet S, Small DM. Short-term consumption of sucralose with, but not without, carbohydrate impairs neural and metabolic sensitivity to sugar in humans. Cell Metab [Internet] 2020;31:493–502.e7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1550413120300577.
16. Sylvetsky AC, Rother KI. Nonnutritive sweeteners in weight management and chronic disease: a review. Obesity (Silver Spring) 2018;26:635–40.
17. Greyling A, Appleton KM, Raben A, Mela DJ. Acute glycemic and insulinemic effects of low-energy sweeteners: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2020;112(4):1002–14.
18. Rogers PJ, Hogenkamp PS, de Graaf C, Higgs S, Lluch A, Ness AR, Penfold C, Perry R, Putz P, Yeomans MR, et al. Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies. Int J Obes (Lond) 2016;40:381–94.
19. Mela DJ, McLaughlin J, Rogers PJ. Perspective: standards for research and reporting on low-energy ("artificial") sweeteners. Adv Nutr 2020;11:484–91.
20. Ashwell M, Gibson S, Bellisle F, Buttriss J, Drewnowski A, Fantino M, Gallagher AM, de G K, Goscinny S, Hardman CA, et al. Expert consensus on low-calorie sweeteners: facts, research gaps and suggested actions. Nutr Res Rev 2020;33:1–10.
21. Smith JD, Hou T, Hu FB, Rimm EB, Spiegelman D, Willett WC, Mozaffarian D. A comparison of different methods for evaluating diet, physical activity, and long-term weight gain in 3 prospective cohort studies. J Nutr 2015;145:2527–34.
22. Pan A, Malik VS, Schulze MB, Manson JE, Willett WC, Hu FB. Plain-water intake and risk of type 2 diabetes in young and middle-aged women. Am J Clin Nutr 2012;95:1454–60.
23. Dietary Guidelines Advisory Committee. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. Washington, DC: USDA and US Department of Health and Human Services; 2015.
24. Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C, Williams SL. Nutrition therapy. Can J Diabetes 2018;42:S64–79.
25. Khan TA, Malik VS, Sievenpiper JL. Letter by Khan et al regarding article, "Artificially sweetened beverages and stroke, coronary heart disease, and all-cause mortality in the Women's Health Initiative." Stroke 2019;50:e167–8.
26. Malik VS, Li Y, Pan A, De Koning L, Schernhammer E, Willett WC, Hu FB. Long-term consumption of sugar-sweetened and artificially sweetened beverages and risk of mortality in US adults. Circulation 2019;139:2113–25.
27. Shakespeare W. Hamlet. Simon and Schuster; 2014. 309 p.