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The not-so-sweet effects of sucralose on blood sugar control

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In recent years, the food industry has provided consumers with the choice of low-calorie versions of foods and beverages by substituting added sugars with low-calorie sweeteners (LCSs) and a growing number of "sweetener enhancers" (1). Marketing claims include how these foods and beverages can contribute to diet healthfulness by delivering a pleasant, sweet taste with fewer or no calories. Despite these claims, data from several epidemiologic studies, but not all (2), suggest that frequent consumption of LCSs is associated with the same detrimental health effects as high consumption of added sugars, including an increased risk of developing type 2 diabetes (3, 4).

Although LCSs activate the heterodimer sweet taste receptor [taste receptor type 1, subunits 2 (T1R2) and 3 (T1R3)] in the tongue and palate (1), they have otherwise been considered metabolically inert, and the association between LCS consumption and metabolic disorders has been often disregarded as an exemplary case of reverse causation. However, the discoveries that sweet taste receptors are also expressed in the gastrointestinal tract and the pancreas (among other nonoral tissues) and that they contribute to the regulation of glucose absorption and insulin secretion (5-7) provide a potential mechanism by which LCSs could have "post-oral" metabolic effects and in turn increase the risk for developing metabolic disorders. Results from preclinical studies conducted in vivo and from human cells in vitro consistently reveal that sucralose, one of the most widely used LCSs, affects glucose metabolism by activating sweet taste receptors in enteroendocrine cells and pancreatic β-cells, which trigger the secretion of incretins (5, 6) and insulin (7), respectively.

However, results from clinical studies that evaluate sucralose's effect on glucose homeostasis have been equivocal. For example, in people with obesity, screened to be nonhabitual consumers of LCSs, the acute ingestion of sucralose in a quantity equivalent to that found in 1 can of diet soda potentiated glucose-stimulated insulin secretion and reduced insulin sensitivity (8). In contrast, a single dose of sucralose in normal-weight adults, whose dietary history of LCS was not reported, did not affect glycemic or hormonal responses to the ingestion of glucose or other carbohydrates (reviewed in reference 9).

That habitual LCS consumption accelerates intestinal sugar absorption in animal models (5) and is associated with higher postprandial glucose-dependent insulinotropic polypeptide in people (10) suggests that discrepancies between findings in animal models and human research may be related, in part, to lack of control of history of LCS exposure. The research by Romo-Romo et al. (11), reported in this issue of the Journal, controlled for the potentially important factor of LCS use and took a different approach. Instead of studying the acute effects of sucralose, the authors investigated the effects of consuming sucralose regularly for 2 wk on glucose metabolism in healthy normal-weight subjects who had low habitual consumption of LCSs at baseline. The dose of sucralose used for the intervention aimed to achieve 45% of the Acceptable Daily Intake for sucralose set by the US Food and Drug Administration (5 mg/kg). Therefore, participants assigned to the experimental group ($n = 33$) were instructed to consume an average of ~130 mg sucralose/d. The authors evaluated metabolic response to glucose (acute insulin response, insulin sensitivity, glucose effectiveness, and disposition index) using a 3-h modified intravenous glucose tolerance test (IVGTT) both before and after the intervention period. A control group ($n = 33$), which received no intervention, was also evaluated at baseline and 2 wk later with the use of identical procedures.

The key finding of the study was that sucralose consumption decreased insulin sensitivity by ~18%, compared with a nonsignificant decrease in insulin sensitivity of ~3% in the control group. Sucralose did not affect acute insulin response, glucose effectiveness (i.e., the capacity of glucose to mediate its own clearance), or disposition index (i.e., the product of insulin sensitivity and acute insulin response). However, further analysis in a subgroup of participants who presumably adhered to the intervention ($n = 27$) (i.e., consumed ≥80% of the prescribed Splenda packets on ≥12 d of the intervention) showed a 16% increase in the acute insulin response to glucose.

Because increased insulin secretion compensated for the reduction in insulin sensitivity, one could interpret these data to indicate that regular consumption of sucralose for 2 wk did not affect glucose tolerance (although data on glucose responses during the IVGTT were not provided). Such an interpretation would be consistent with the findings from another trial in which healthy adults consumed 1000 mg encapsulated

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sucralose or placebo for 3 mo (dietary history of LCS was not reported) and which found no differences between sucralose and placebo groups in glycohemoglobin, plasma glucose, or insulin concentrations at fasting or during a 2-h oral-glucose-tolerance test (9). However, the lack of an effect of repeated sucralose ingestion for 3 mo on simple blood glucose and insulin concentrations (or on glycohemoglobin) should not be taken as conclusive evidence that sucralose consumption has no effect on blood glucose control. People who use LCSs often ingest them chronically, for several decades. The findings of Romo-Romo et al. underscore the importance of controlling for dietary LCS history and assessing metabolic effects of LCSs with techniques that are sensitive to determine possible alterations on reliable biomarkers of metabolic disease.

The results of Romo-Romo et al. (11) are provocative because they suggest that regular consumption of sucralose leads to insulin resistance in healthy normal-weight adults—insulin resistance is a risk factor for the development of type 2 diabetes and other metabolic diseases even in people with normal glucose tolerance. Their finding of reduced insulin sensitivity is consistent, in part, with recent findings from a similar study by Lertrit et al. (12) that evaluated the effects of consuming pills containing either 200 mg sucralose or placebo for 4 wk in healthy Thai adults who were nonhabitual users of LCS. However, Lertrit et al. found that sucralose reduced insulin sensitivity (estimated from an oral-glucose-tolerance test) but also reduced (not increased) acute insulin response to an IVGTT. The reason for the discrepancy between these 2 study findings is unknown but may relate to substantive differences between study protocols [e.g., length of intervention (2 wk compared with 4 wk), body weight status and ethnicity of study subjects (100% normal-weight Latin compared with 53% normal-weight, 7% overweight, 40% obese Thai), and sucralose administration [packets of Splenda (taste stimulation) compared with pills (bypassing taste)].

Some important strengths of the Romo-Romo et al. (11). study are also a limitation. The IVGTT allows direct and accurate measurement of acute insulin response and an estimate (by the use of minimal models) of insulin sensitivity that correlates well with clamp-derived measures (the "gold-standard" method for the measurement of insulin sensitivity). However, the IVGTT is nonphysiologic because it omits important regulators of postprandial glycemia, including oral and intestinal sweet taste receptors in the gastrointestinal tract (13) (which could likely be affected by regular consumption of sucralose). The findings in this homogeneous group of healthy, normal-weight adults, nonregular consumers of LCSs, might not extrapolate to adults with obesity or with diabetes, to children, or even to people who consume LCSs chronically, and additional studies are needed.

Clearly, much more needs to be learned about the effects of sucralose and other LCSs on metabolism to inform clinical practice and public health recommendations on the use of these food additives. LCSs are a structurally diverse group of chemicals, and although all activate the sweet taste receptor, results from 1 LCS cannot be necessarily generalized to another. Depending on their chemical structure, LCSs bind at different sites of the heterodimeric sweet taste receptor (1) and dose-dependently can affect signaling in dissimilar ways [from agonism to antagonism (14)]. In addition, other mechanisms, independent of sweet taste receptor signaling, such as LCS-induced dysbiosis (15), could also underlie their metabolic effects. The study by Romo-Romo et al. (11) is valuable because it adds to a growing body of evidence supporting the view that sucralose has "post-oral" metabolic effects, and encourages further research to better understand potential mechanisms by which LCSs affect metabolic health over time.

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