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Perspectives

Substituting Low-Calorie Sweetened Beverages for Sugar-Sweetened Beverages to Prevent Obesity and Cardiometabolic Diseases: Still a Good Idea?

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ABSTRACT

Low-calorie sweeteners (LCSs) and LCS-containing beverages have been proposed as appropriate substitutes for caloric sugars in recent years. In this Perspective, we highlight the recent findings from observational and interventional studies, focusing on obesity, gut microbiome, and cardiometabolic health. We provide public health actors and health care professionals with an insightful overview of recent evidence to bridge the gap between research and practice.

Keywords: low-calorie sweeteners, nonnutritive sweeteners, sugar, sugar-sweetened beverages, low-calorie sweetened beverages, artificially sweetened beverages, microbiome, cardiometabolic health, glycemic control, insulin resistance

Increased sugar intake, especially sugar-sweetened beverages (SSBs), has been identified as an important contributor to overweight/obesity [1,2], type 2 diabetes (T2D) [3], and cardiovascular disease (CVD) [4,5], as well as dental caries [6,7]. Facing this wide scientific consensus, the WHO recommends free sugar intake <10% of total energy intake throughout the life course (ideally 5%) [8]. This corresponds to a maximum of 50 g of free sugars per day for an adult requiring 2000 kcal (ideally <25 g/d). There is no international recommendation for maximal SSB intake. However, one 12-oz can (355 mL) of a standard SSB with 10 g total sugar per 100 mL provides ~70% (35.5 g/50 g) of the maximal total free sugar intake recommended by the WHO. This suggests that consuming a SSB daily is hardly compatible with the WHO guideline on free sugars, considering that other sweet products are often consumed during the day.

Replacing free sugars and SSBs with low-calorie sweeteners (LCSs) and LCS-containing beverages, also called diet, sugar-free, or artificially sweetened beverages, provides a simple strategy to reduce sugar and energy intake. However, in May 2023, the WHO released a new guideline recommending not to use LCS to control body weight or reduce the risk of cardiometabolic diseases [9]. In this Perspective, we provide an insightful overview of the recent evidence on LCSs and LCS-containing beverages with concrete suggestions for public health actors and health care professionals.

LCSs

The 2 main sources of LCSs in the Western diet are LCS-containing beverages and tabletop sweeteners [10,11]. A list of widely used LCSs is provided in Table 1 [12–15]. In this Perspective, we do not include sugar alcohols, which have about half the kilocalories of sugars. Sales and consumption of LCSs and LCS-containing beverages have increased globally since the

Abbreviations: ADI, acceptable daily intake; CVD, cardiovascular disease; LCS, low-calorie sweetener; RCT, randomized controlled trial; SSB, sugar-sweetened beverage; T2D, type 2 diabetes; WC, waist circumference.

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TABLE 1
Description and examples of caloric and low-calorie sweeteners, sugar-sweetened beverages, and diet beverages.

	Food additive codes	Examples of LCS-containing foods[1]	ADI: acceptable daily intake (mg per kg of body weight)[2]
Caloric sweeteners (= sugars)			
Sucrose, glucose, fructose, high-fructose corn syrup, etc.	NA	Sugar-sweetened beverages (e.g., regular Coke), fruit juices	NA
Artificial low-calorie sweeteners			
Acesulfame-K	E-950	Sunett, Sweet One, Swiss Sweet, Diet Coke, Coke Zero	9–15
Aspartame	E-951	Nutrasweet, Equal, and Sugar Twin, Canderel, Diet Coke, Coke Zero	40–50
Cyclamate	E-952	Coke Zero (in Europe)	7–11 (US: not approved)
Saccharin	E-954	Necta Sweet, Sugar Twin, Sweet'N'Low, Sweetex	5–15
Sucralose	E-955	Splenda, Diet Coke	5–15
Natural low-calorie sweeteners			
Steviol glycosides	E-960	Coke Life	4

Abbreviation: NA, not applicable.
[1] Based on food manufacturers' websites. Recipes may vary across countries.
[2] According to the Joint FAO of the United Nations/WHO Expert Committee on Food Additives (JECFA), European Food Safety Authority (EFSA) [15], and US FDA.

1990s [16–19], with some signs of a reduction in Europe [20, 21]. In the United States, 48% of adults reported consuming at least one food or beverage containing LCSs in 2-d dietary assessments performed from 2007 to 2012 [22]. LCSs are marketed as low-calorie alternatives to free sugars and as an aid for weight loss or maintenance of health or a means of controlling blood glucose, especially for patients with T2D. In addition to beverages containing only LCSs, more and more beverages nowadays contain both free sugars and LCSs [18]. This is partly a side effect of the public health interventions aiming at reducing free sugar consumption, such as taxing SSBs. In some jurisdictions, the tax includes several tiers, with higher sugar content beverages being taxed more than lower sugar content ones. To avoid taxation, soft drink manufacturers generally replace caloric sweeteners (free sugars) with LCSs to maintain the sweet taste expected by consumers [23]. Thus, an increasing number of people, including children, are exposed to LCSs, although the intake usually remains below unsafe levels fixed by the international food safety authorities (acceptable daily intake [ADI], Table 1) [16,24,25].

LCSs and Health

The first systematic reviews of experimental studies on animals and humans suggested that LCSs could facilitate weight loss and did not impair cardiometabolic markers [26,27]. Yet, new data from observational studies have pointed in the opposite direction since the 2020s. For example, the NutriNet-Santé cohort study found that high consumers of LCSs had a higher risk of developing CVD 9 y later than nonconsumers (hazard ratio: 1.09; 95% confidence interval: 1.01, 1.18; $P = 0.03$), with aspartame intake being associated with increased risk of cerebrovascular events and acesulfame potassium and sucralose with increased coronary artery disease [11]. Similarly, recent systematic reviews and meta-analyses of observational studies reported a positive association between a high intake of LCS-containing beverages (such as 1 serving/d) and the risk of obesity [28], T2D [28,29], CVD [28,29], and all-cause mortality [28–30]. However, these associations need to be interpreted with caution because they could be prone to several biases. Biases include notably the following: *1*) residual confounding (other causes of the studied disease are associated with both LCS consumption and disease, e.g., socioeconomic position and other dietary factors); and *2*) reverse causation (people with a predisposition for a cardiometabolic disease, e.g., people with obesity or family history of CVD, take LCSs hoping to prevent cardiometabolic diseases).

In 2022, the WHO published a large systematic review and meta-analysis on the health effects of LCSs. It indicated that in short-term randomized controlled trials (RCTs, often <3 mo), participants consuming LCSs had lower body weight and BMI than those consuming free sugars (no effect if the comparison group took nothing/placebo or water) [31]. The WHO review also concluded that prospective cohort studies suggest the possibility of an increased risk of obesity, T2D, CVD, and mortality in the long term [31]. This led the WHO to advise against the use of LCSs to control body weight or reduce the risk of cardiometabolic diseases in May 2023 [9].

However, the findings of the WHO review have raised some concerns recently [32]. Critics concluded that too much attention was given to the evidence from observational studies compared with RCTs, which have a higher priority in the established hierarchy of evidence and can infer causality better than observational cohort studies. In addition, similar to the majority of the published systematic reviews and meta-analyses, the WHO review also considered the association between baseline LCS intake and risk of chronic diseases, which might be prone to bias because LCS intake may change over time. Thus, frequent exposure assessment is needed to consider the changes in LCS intake over time. Some advances in methodologic analysis to account for changes in the exposure status or substitutions of food for other foods have been defined for this purpose [33]. In a

2022 meta-analysis, including 14 prospective cohort studies and assessing changes in LCS-containing beverages, an increase in LCS-containing beverage intake over time was associated with lower body weight and waist circumference (WC) and no increased risk of T2D [34]. This study also showed that substituting LCS-containing beverages for SSBs was associated with lower body weight, WC, and lower risk of obesity, coronary artery disease, and total and cardiovascular mortality [34].

These observational findings taking changes and substitutions into account are consistent with the findings of 3 recent meta-analyses of RCTs [35–37] showing moderate but favorable effects of LCS-containing beverages on weight reduction. Laviada-Molina et al. [35] included only interventions of 4 wk or more in their meta-analysis and also found that the effect was more pronounced in people with overweight/obesity. McGlynn et al. [37] also concluded that substituting LCS-containing beverages for SSBs promoted beneficial improvements, similar to water substitution, in body weight and cardiometabolic risk factors. As for patients with diabetes (type 1 or 2), a Cochrane Collaboration review of RCTs showed no clinically relevant benefit or harm to body weight or glycosylated hemoglobin A1c regarding the effects of LCS consumption compared with either sugars or placebo (very low certainty) [38].

LCSs and Gut Microbiome

LCSs do not contain sugars and do not influence glycemia directly after consumption [39]. However, recent studies have linked saccharin, sucralose, and steviol glycosides with glucose intolerance in mice as well as humans [40–43]. One of the mechanisms by which LCS could affect glucose homeostasis may involve the alteration of the gut microbiome.

In 2014, a small and short-duration trial by Suez et al. [43] found that 4 out of 7 healthy adults developed significantly poorer glycemic response after taking 360 mg saccharin daily for 1 wk (a dose close to the ADI). Moreover, the microbiome composition varied between the 4 responders and the 3 non-responders, both before and after the consumption of saccharin [43]. In 2022, the same team published the results of an RCT encompassing 120 healthy adults for 2 wk [42]. In each group, 20 nonusual consumers of LCSs received supplementation with 50 mg aspartame, 180 mg saccharin, 102 mg sucralose, and 4 mg stevia (8%, 20%, 34%, and 75% of the ADI, respectively), 5 g of glucose, or nothing (6 parallel arms). Participants receiving saccharin and sucralose had impaired glucose response measured by oral glucose tolerance test already 1 wk after LCS supplementation, and glucose tolerance improved after stopping LCS supplementation. The 4 LCS-supplemented groups of volunteers also had functionally altered gut microbiomes, which was not the case in the glucose and control groups. Finally, the authors documented a causal and individualized link between LCS-altered microbiomes and glucose intolerance developing in recipient germ-free mice after having performed fecal transplantation of human microbiomes from those responding the most and the least to LCS supplementation [42]. Thus, it seems that consuming 1 can of LCS-containing beverages (e.g., 187 mg aspartame in 12 oz or 355 mL of Diet Coke [44]) could impair gut microbiota, and low doses of saccharin and sucralose could induce elevated glycemia in the short term (~1 wk).

Conclusions

All in all, there is conflicting evidence on whether LCSs have beneficial, neutral, or harmful effects on obesity and cardiometabolic diseases. Similarly, scholarly associations do not provide consistent recommendations, as shown in Table 2, where we extracted the recent position of 4 associations. For instance, Diabetes UK stated in 2018 that patients with diabetes can benefit from substituting LCS-containing beverages for SSBs for weight and glucose management [45]. In contrast, the American Diabetes Association informs on its website that "[..] there is no clear evidence to suggest that using sugar substitutes will help manage blood sugar or weight or improve cardiometabolic health in the long run" [46].

In this context, long-term RCTs of sufficient sample size and/or duration and well-designed cohort studies are needed to adequately document the effect of LCSs on weight management, cardiometabolic health, and gut microbiota in the general

TABLE 2
Overview of recommendations by a selection of scholarly institutions

Institution	Type and year of publication	Target population(s)	Summary of recommendations regarding LCSs
WHO	Guideline, 2023 [9]	General population	• LCSs should not be used as a means of achieving weight control or reducing the risk of cardiometabolic diseases.
American Heart Association	Advisory paper, 2018 [47]	General population and patients with diabetes	• LCS-containing beverages can be a useful replacement strategy to reduce sugar for adults who are habitually high consumers of sugars. • LCS-containing beverages can help people with diabetes manage blood glucose levels. • Prolonged consumption of LCS-containing beverages is not advised for children.
Diabetes UK	Position statement, 2018 [45]	Patients with diabetes	• Substituting LCSs for sugars may be a useful, relatively simple strategy to assist with weight management, especially for people who regularly consume sweet foods and drinks and prefer sweet taste. • Replacing sugars with LCSs can be a helpful strategy to aid glucose management in children and adults with diabetes.
American Diabetes Association	Information on website, 2024 [46]	Patients with diabetes	• LCSs may not help manage blood sugar or weight or improve cardiometabolic health in the long term.

Abbreviation: LCS, low-calorie sweetener.

population but also in patients with obesity and T2D. In the meantime, what guidance should public health actors provide to the general population and what advice should healthcare professionals offer to their patients?

It seems prudent to advise the general population against the large consumption of LCSs and LCS-containing beverages, especially healthy children [9,47]. The preferred beverage should be water (tap or mineral). LCSs and LCS-containing beverages may, however, serve as useful substitutes to free sugars and SSBs for those (mainly adults) *1*) willing to lose weight, *2*) who habitually consume large quantities of free sugars and SSBs, *3*) who have a strong sweet taste preference, and *4*) who consider unsweetened beverages as undesirable [10,45,47].

As for patients with diabetes, it seems important to rely on health care professionals, such as registered dietitians. They can assess the intake of free sugars and LCSs and the patient acceptability of substituting water for SSBs as well as the overall diet and treatments for glycemic control. Based on this assessment, they can provide tailored advice balancing the individual benefits/risks of switching from SSBs to LCS-containing beverages, water, or beverages having a limited amount of sugar per 100 mL (e.g., flavored water or fruit tea) [45].

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Author contributions

The authors' responsibilities were as follows – AC: conceptualization; AC, HR: writing original draft; ASA: review and editing; and all authors: read and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

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