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Understanding the metabolic and health effects of low-calorie sweeteners: methodological considerations and implications for future research

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Abstract

Consumption of foods, beverages, and packets containing low-calorie sweeteners (LCS) has increased markedly across gender, age, race/ethnicity, weight status, and socioeconomic subgroups. However, well-controlled intervention studies rigorously evaluating the health effects of LCS in humans are limited. One of the key questions is whether LCS are indeed a beneficial strategy for weight management and prevention of obesity. The current review discusses several methodological considerations in the design and interpretation of these studies. Specifically, we focus on the selection of study participants, inclusion of an appropriate control, importance of considering habitual LCS exposure, selection of specific LCS, dose and route of LCS administration, choice of study outcomes, and the context and generalizability of the study findings. These critical considerations will guide the design of future studies and thus assist in understanding the health effects of LCS.

Keywords

Diet soda; Artificial sweeteners; Low-calorie sweeteners; Obesity; Weight; Beverages; Metabolism; Study design

1 Introduction

Low-calorie sweeteners (LCS) including acesulfame-potassium, aspartame, saccharin, and sucralose provide sweet taste with no or few calories and are therefore palatable alternatives to caloric sugars. Despite the recent decline in sales of diet soda [1], consumption of LCS has increased over the past decade [2] and is particularly common among females, non-Hispanic white individuals, and those of higher socio-economic status in the United States [2, 3]. LCS use will likely continue to increase because excessive consumption of added sugars is well-recognized as detrimental [4].

Despite their widespread availability and consumption [2] and their increasing presence in the environment (e.g. including in soil, waste water, and surface water) [5, 6], the effects of LCS on metabolism, obesity and other health outcomes in humans remain controversial [7–9]. Associations between LCS consumption, weight gain, and metabolic abnormalities are reported in epidemiologic studies [10–14] and have been consistently observed in rodent models [15–19]. Meanwhile, intervention studies evaluating the effects of chronic LCS consumption in humans suggest potential benefits of LCS on body weight, when compared to caloric sweeteners [20].

Given the controversies surrounding the health effects of LCS, the objective of this review is to highlight several critical methodological considerations in the design, interpretation, and generalizability of human interventional studies. Consideration of often overlooked factors will inform the design of future studies and ultimately, promote continued progress toward better understanding of their effects. In this review, we focus on interventional studies of LCS effects on metabolism and weight.

2 Methodological considerations

2.1 Selection of study population

The majority of intervention studies evaluating prolonged LCS exposure have enrolled young and middle-aged adults, with few studying children or older adults [21–23]. In this context, we define prolonged exposure as occurring repeatedly (more than a single event). It is particularly important to study LCS in a wide range of age groups because sweet taste preference is greatest early in life [24] and sensitivity to sweet taste is considerably diminished in the elderly [25]. It is also necessary to study LCS during pregnancy and lactation, as in utero and postpartum exposure has been shown to promote preferences for sweet taste in rodents [26].

Several studies, conducted both in the United States [27, 28] and in Europe [29, 30], do not report race/ethnic characteristics of study participants, while studies that do enroll a substantial proportion of minority individuals typically do not analyze (or do not report) outcomes stratified by race/ethnicity subgroups [31]. This is an important limitation, as there is likely inter-individual variation in responses to LCS [32]. For example, a recent short-term study conducted in predominantly obese, non-Hispanic black women ($n = 17$) [32] reported that sucralose ingestion increased glucose and insulin concentrations during an oral glucose tolerance test (OGTT), compared to pre-treatment with water. However, neither glucose nor insulin was altered following sucralose in our experience studying predominantly normal weight, non-Hispanic white individuals [33]. Furthermore, in a study by Ebbeling et al. [22], effects of replacement of sugar-sweetened beverages with non-caloric beverages (water and beverages with LCS) were stronger among Hispanic male youths compared to non-Hispanic participants. These findings emphasize that racial/ethnic differences, in addition to age, gender, habitual diet, and weight status, may contribute to marked inter-individual differences in responses to LCS. Polymorphisms in sweet and bitter taste receptor genes may also explain clinically relevant individual differences [34, 35].

Most studies evaluating prolonged LCS consumption have enrolled healthy adults, who may have different susceptibility to potential LCS-induced metabolic changes, compared to overweight/obese adults and/or individuals with diabetes. Studying effects of LCS specifically in obese and/or diabetic cohorts is critical, as these are the individuals that use LCS most frequently [2] and already have metabolic complications.

This is important particularly in light of recent findings suggesting that LCS may affect the gut microbiota [15, 16, 36], which differ in individuals who are obese or have diabetes [37]. Both conditions are characterized by reduced bacterial diversity and increased inflammation [38]. In addition to the known causal role of microbial alterations in the onset of weight gain [39], metabolic syndrome [40], dysglycemia [15], and disturbance of circadian rhythms [41], it is likely that an individual's microbial composition may influence metabolic responses to LCS [42]. This dynamic interplay between the gut microbiota and the pathophysiology of metabolic disease further emphasizes the need to widen the spectrum of potential LCS effects beyond weight change (see Section 2.6. below).

2.2 Inclusion of appropriate control group

The majority of intervention studies on energy intake and weight have compared LCS (typically aspartame) to either sucrose or high-fructose corn syrup. Overall, these studies have reported neutral effects or modest benefits of LCS on energy intake [43, 44] and weight [21, 22, 27, 28, 30, 31, 45–47]. For example, de Ruyter et al. [21] reported less weight gain in children assigned to replace their daily sugar-sweetened beverage with a flavor-matched non-caloric beverage in an 18-month intervention. Similar findings were reported by Raben et al. [30], where overweight adults randomized to consume aspartame-sweetened drinks lost weight during the 10 week intervention, whereas those randomized to sucrose-sweetened beverages gained weight. Reductions in body weight following replacement of sugar-sweetened beverages with LCS, particularly when studied in the context of weight loss (see Section 2.7.), are convincing; yet, many of these studies lack a true control [21, 22, 30, 44, 45, 47–49]: that is, plain water, unsweetened seltzer, and/or calorie-matched foods without sweetness.

2.3 Habitual exposure to low-calorie sweeteners

Habitual LCS consumption at baseline must be considered in order to obtain clinically relevant data from human intervention studies. For example, in a study by Peters et al. in which diet beverages were reportedly more effective for weight loss compared to plain water, participants were regular consumers of at least three LCS sweetened beverages per day prior to entering the study [50]. This is concerning, as randomizing regular LCS users to consume only water for 12 weeks, may result in replacement of their usual LCS beverage with other sweet, palatable foods and beverages. However, no data on total energy intake were reported. It is therefore critical that these findings be replicated in obese individuals who do not regularly use LCS prior to randomization.

The ubiquity of LCS in commercially available foods and beverages also necessitates careful monitoring and reporting of dietary intake throughout intervention studies, in order to ensure

that individuals who are not assigned to consume LCS, are not inadvertently exposed to them.

2.4 Not all low-calorie sweeteners are the same

Human studies evaluating prolonged exposure to LCS often report using “diet beverages” [22, 31]. Though most diet sodas are sweetened with aspartame (at least until recently) [51], “diet beverages” represent a heterogeneous class of soft drinks containing different sweeteners, taste profiles, and a wide range of different nutrients, ingredients and additives. While all LCS are highly sweet compounds, each LCS is chemically distinct (Table 1). Importantly, some LCS such as aspartame are metabolized rapidly after ingestion [52], whereas other LCS such as saccharin are absorbed and excreted in the urine unchanged [53]. Meanwhile, the majority of sucralose is not absorbed but excreted in the feces [54]. The dissimilar chemical, physical, biological, and pharmacokinetic properties of different LCS suggest that they likely have different metabolic and health effects. While potential sweet-taste receptor mediated effects may be generalizable across LCS due to their sweet taste, other proposed mechanisms (e.g. changes in the gut microbiota, interaction with specific transporters [17, 54]) should be considered in a sweetener-specific manner.

The need to consider each LCS as a unique chemical compound is also demonstrated by acute human studies, which have tested different sweeteners. For example, a small, short-term study has suggested that sucralose may promote relative hyperglycemia when administered prior to a glucose load [32], whereas another study has suggested that stevia, but not aspartame, may reduce post-prandial glucose excursions (compared to sucrose), when administered before a test meal [55]. Importantly, the latter study did not include a water control and administered LCS prior to a meal, rather than a bolus of pure glucose. Thus, whether stevia and aspartame responses were higher or lower than what would be expected following a plain water or unsweetened control is not clear. Furthermore, given their different preloads and different study designs, it is not possible to determine whether the aspartame response was similar to the sucralose response in the prior study. Despite the inability to directly compare these findings, one likely explanation is that different LCS have diverse effects on post-prandial glycemia.

2.5 Route and vehicle of sweetener administration

Most human intervention studies evaluate exposure to LCS in diet soda or other beverages [21, 22, 31–33, 56]. Several studies have also administered LCS in capsules [57–61]. For example, in a recent meta-analysis, administration of LCS in capsules resulted in decreased short-term energy intake (e.g. at the following meal) compared to a placebo [20]. This was not the case when LCS were mixed in beverages or administered in diet soda [20]. Similarly, LCS in beverages were shown to increase subjective appetite in young adult males, while LCS did not increase appetite when administered in capsules [57]. This may be explained by the fact that encapsulated LCS bypass lingual taste receptors, which play a role in regulation of appetite and energy intake [62]. Another reason may be higher LCS concentrations in capsules compared to LCS-containing foods and beverages [58–60, 63]. Furthermore, studies in which LCS have been administered intra-duodenally [64], have also led to different results compared to studies with oral LCS administration [33]. The potential

appetite suppressing effects of encapsulated LCS have been applied to pharmaceutical and nutraceutical applications, in products such as Lovidia™, where various dietary supplements and food additives are combined in order to stimulate production of satiety hormones, such as GLP-1. However, neither ingestion of LCS in capsules nor intra-duodenal administration reflect LCS consumption in real life. LCS-containing products also contain many other ingredients, which may have independent metabolic and health effects, and/or which may interact with LCS [65]. Examples are presented in Table 2.

2.6 Selection of study outcomes

Few intervention studies have evaluated the effects of chronic LCS consumption on outcomes other than body weight [29, 48, 49, 66, 67]. Examples are clinical trials reporting on glycemia, in which no differences were observed following 6 weeks [49] or 90 days [66] treatment with aspartame compared to sucrose among adults with type 2 diabetes. Similar findings were reported with saccharin [48] and rebaudioside A [46]. In overweight and obese individuals without diabetes, consumption of aspartame-sweetened diet cola for six months led to reductions in visceral, skeletal, and liver fat and lowered triglycerides and cholesterol compared to consumption of sucrose-sweetened beverages [29]. As discussed above (see Section 2.2.), these studies compare LCS to sucrose and do not include an unsweetened control. Given that LCS have been shown to induce metabolic impairments in the absence of increased body weight in rodent models [68], it is critical that intervention studies are designed to evaluate metabolic outcomes beyond body weight.

2.7 Caloric context (eucaloric versus hypocaloric)

As mentioned in Section 2.2., most intervention studies have been conducted in the context of caloric restriction. Administration of diet beverages as part of a comprehensive weight loss plan generally results in similar [27, 31, 43, 47] or greater [50] weight reduction compared to water or unsweetened controls. For example, Kandors [47] and Blackburn [27] observed weight loss in overweight and obese adults on a calorie restricted diet with or without aspartame. Tate et al. [31] and Piernas et al. [43] also documented comparable weight loss following consumption of diet beverages versus water, while all participants (water, diet beverages, and attention control) received behavioral counseling, regular weigh-ins, and other nutritional resources. These studies support the conclusion that LCS do not interfere with weight loss in the context of caloric restriction and may actually promote compliance, especially in individuals with a history of high sweetener intake. However, without concurrent, comprehensive, and sustained dietary modifications, it is unlikely that LCS will contribute to weight loss when used in the general population.

2.8 Clinical studies versus real life

In clinical studies LCS are typically used to replace caloric sugars in foods or beverages, thus reducing the overall caloric intake. In real life, the scenario is very different: LCS are often consumed along with caloric sugars. In addition to consciously choosing LCS, e.g. in LCS packets, individuals consume them unintentionally due to their ubiquitous presence [69, 70]. The way that LCS are used today has changed considerably since their initial FDA approvals, and clinical studies have not kept up with rapid advances in product development and reformulation.

3 Summary

Whether LCS are beneficial or detrimental to human health has been a topic of much debate over the past several decades [7, 11, 71]. Given the importance of the eight methodological considerations discussed within this review, future well-designed studies are required to elucidate the health consequences of LCS consumption under real life conditions. It is essential to study LCS in diverse populations, including children and the elderly, individuals with obesity and diabetes, and to focus on health outcomes beyond body weight. Understanding how LCS work is essential especially when considering their ‘booming’ consumption in the United States [2], and even more imperative as their use continues to accelerate globally [72].

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Table 1

Chemical formulas and structure low-calorie sweeteners commonly consumed in the United States

Chemical Name	Chemical Formula	Trade Name	Structure
Aspartame	(C ₁₄ H ₁₈ N ₂ O ₅)	Nutrasweet™ Equal™	
Acesulfame-Potassium	(C ₄ H ₄ KNO ₄ S)	Sunett™ SweetOne™	
Advantame	C ₂₄ H ₃₀ N ₂ O ₇	N/A	
Saccharin	(C ₇ H ₅ NO ₃ S)	Sweet N'Low™	
Sucralose	(C ₁₂ H ₁₉ Cl ₃ O ₈)	Splenda™	
Stevioside ^a (Stevia)	(C ₃₈ H ₆₀ O ₁₈)	Truvia™	

^aWhile aspartame, acesulfame-potassium, advantame, saccharin, and sucralose are approved by the FDA as food additives, steviol glycosides including stevioside (stevia) and rebaudioside A are not approved sweeteners, but are considered Generally Recognized As Safe (GRAS).

Table 2
Ingredient composition of commonly-consumed LCS containing foods and beverages

Description	LCS	Nutritive Sweeteners	Food Additives	Other ingredients
Diet Cola	Aspartame	None	Caramel Color, Phosphoric Acid, Potassium Benzoate, Natural Flavors, Citric Acid	Carbonated Water, Caffeine
Diet Lemon-Lime Soda	Aspartame, Acesulfame-potassium	None	Citric Acid, Natural Flavors, Potassium Citrate, Potassium Benzoate	Carbonated Water
25 % lower sugar granolabar	Sucralose	Brown Sugar, Corn Syrup, Oligofructose, Polydextrose, Corn Syrup Solids, Glycerin, Invert Sugar, Molasses	Soy Lecithin, Caramel Color, Calcium Carbonate, Diacetyl Tartaric Acid Ester of Mono-Diglycerides, Natural and Artificial Flavor, BHT, Citric Acid	Granola, Whole Grain Rolled Wheat, Soybean Oil, Dried Coconut, Whole Wheat Flour, Sodium Bicarbonate, Nonfat Dry Milk, Semisweet Chocolate Chips, Brown Rice Crisp, Sunflower Oil, Contains 2 % or less of Water, Salt
Meal Replacement Bar	Sucralose	Maltitol Syrup	Artificial Color, Polydextrose, Glycerin, Soy Lecithin, Artificial Flavor, Soy Lecithin, Hydrolyzed Gelatin	Palm Kernel, Palm Oil, Fructooligosaccharides, Water, Skim Milk Powder, Butter Protein Blend, Soy Nuggets, Palm Kernel and Palm Oil, Cocoa Powder, Sunflower Oil, Vitamin Mineral Mix, Salt
Sugar Free Gelatin Snacks	Aspartame, Acesulfame Potassium	None	Adipic Acid, Sodium Citrate, Citric Acid, Salt, Red 40, Artificial Flavor	Water, Gelatin
Light Yogurt	Sucralose, Acesulfame Potassium	Fructose, Blueberry Puree	Kosher Gelatin, Natural and Artificial Flavors, Red 40, Blue 1, Malic Acid, Potassium Sorbate, Vitamin A Palmitate, Vitamin D3, Sodium Citrate.	Cultured Grade A Non Fat Milk, Water, Modified Food Starch, Modified Corn Starch
No Sugar Added Ice Cream Bars	Aspartame	Malt Extract, Maltitol	Guar Gum, Polydextrose, Monoglycerides Glycerin, Polysorbate 80, Locust Bean Gum, Citric Acid, Natural and Artificial Flavor, Caramel Color, Annatto, Cocoa Soy Lecithin, Maltodextrin, Natural and Artificial Flavor, Vitamin A Palmitate	Nonfat Milk, Milk Fat, Pectin, Vegetable Oil, Nonfat Dry Milk, Whey, Rice Flour, Salt, Rice Extract