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Not-so-healthy sugar substitutes?

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Abstract

Replacing sugar-sweetened beverages with diet soft drinks containing sugar substitutes that provide few or no calories has been suggested as one strategy for promoting improved public health outcomes. However, current scientific evidence indicates that routine consumption of beverages with non-nutritive sweeteners not only fails to prevent disease, but is associated with increases in risks for the same health outcomes associated with sugar-sweetened beverages, including type 2 diabetes, cardiovascular disease, hypertension and stroke. Results from pre-clinical studies have provided plausible biological mechanisms that could promote these counterintuitive negative health effects of artificial sweeteners. Taken together, scientific studies currently indicate that public health will be improved by reducing intake of all sweeteners, both caloric and non-caloric.

Introduction

Recent dramatic increases in sugar consumption documented across the globe, particularly in the form sugar-sweetened beverages, are considered to play a significant role in elevating risks for a variety of negative health outcomes including type 2 diabetes, cardiovascular disease, hypertension and stroke, 3 of top causes of death in the United States [1]. It has been estimated that over 10 years, sugar sweetened beverage consumption could contribute to up to 2.6 million cases of type 2 diabetes in the U.S. alone [2], and up to 180,000 deaths per year worldwide [3]. Short-term and long-term evidence also indicates that reducing intake of sugar-sweetened beverages could promote a variety of healthy outcomes. In the UK, an estimated 14-25% reduction in risk of development of type 2 diabetes could be achieved by replacing one serving/day of a sugar-sweetened drink with an unsweetened beverage [4]. A growing scientific consensus indicates that public health would be improved by reducing consumption of sugar-sweetened beverages [5].

One seemingly logical approach to achieve this goal would be to switch from sugar-sweetened beverages to versions sweetened with high-intensity sweeteners (sometimes called non-caloric sweeteners, low calorie-sweeteners, or artificial sweeteners), such as

Conflict of interest
Nothing declared.

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sucralose, aspartame, acesulfame potassium or saccharin that provide the sweet taste of sugar, but with less energy. In fact, many beverages manufactured with these sweeteners are labeled “diet” soft drinks and have been assumed to promote weight loss, prevent weight gain, and to improve health. And increasing numbers of people appear to be choosing to consume beverages sweetened with high-intensity sweeteners. For example, in the U.S., 24% of adults and 12% children aged reported consuming such beverages, while a recent study in the UK reported approximately 39% of the 11-year-old children studied were daily consumers of artificially-sweetened soft drinks [6,7].

Artificially-sweetened beverages are also associated with metabolic dysfunction

Unfortunately, the evidence that these types of beverages actually convey health benefits is far from convincing [2,8,9]. In fact, an overwhelming majority of studies indicate that over the long term artificially-sweetened beverages do not promote improved health outcomes, but instead may contribute to heightened risk for negative health outcomes. For example, a recent review of prospective cohort studies published during the past 10 years illustrates how consumption of diet soft drinks (typically 1 or more servings/day) was associated with significant increases in risk for diseases like type 2 diabetes, cardiovascular disease, hypertension and stroke rather than the decreases that might be expected if diet sodas actually represent healthy options [9].

Additional cohort studies published since that review have only strengthened the concerns about potentially negative health effects of artificially-sweetened beverages. For example, results of a small study of Japanese men reported almost double the risk of type 2 diabetes among those who consumed diet sodas [10]. Another study of close to 25,000 people in the UK documented significantly elevated risk of type 2 diabetes among diet soft drink consumers compared to non-consumers and concluded that switching from sugar-sweetened beverages to artificially-sweetened beverages would not achieve decreases in diabetes risk [4]. This connection to diabetes was reinforced in a meta-analysis indicating that artificially sweetened beverages were associated with a 25% increase in the incidence of type 2 diabetes which also concluded that “artificially sweetened beverages ... were unlikely to be healthy alternatives to sugar sweetened beverages for the prevention of type 2 diabetes [2].” Another meta-analysis also reported significant elevation of the relative risk of type 2 diabetes for consumers of artificially-sweetened beverages compared to non-consumers, with the magnitude of the increase similar to that seen for consumers of sugar-sweetened soft drinks compared to non-consumers [8].

More recent work has provided additional support for the association of diet soft drink consumption with increased risk for metabolic diseases beyond type 2 diabetes. For example, a prospective study of a cohort of individuals aged 65 and older documented increases in waist circumference (a marker of abdominal fat closely linked to cardiovascular disease) that were tripled in diet soda consumers compared to non-consumers [11]. These increases in waist circumference were dose-related, with heavier consumers of diet soft drinks demonstrating greater increases in waist circumference, and they were independent of

changes in body mass index. A recent study in post-menopausal women also indicated elevated risk for cardiovascular disease events, cardiovascular disease mortality and overall mortality among women who consumed 2 or more diet soft drinks daily [12]. A recent meta-analysis indicated that artificially-sweetened beverages are associated with ~ 15% increase in the risk of hypertension [13]. And although increased risk of stroke and heart failure were linked to sweetened beverage intake in Swedish cohorts [14,15], these studies did not separate sugar-sweetened beverages and artificially-sweetened beverages; thus, the meaning of these results with regard to potential effects of artificially-sweetened soft drinks must be interpreted with even more caution.

In addition to hypertension and stroke, some studies have indicated an increased risk of chronic kidney disease associated with consumption of artificially-sweetened beverages, but a recent meta-analysis did not find this relationship to be statistically significant [16], possibly due to a very small number of published papers examining this link. A recent study also indicated that while sugar-sweetened beverage intake was associated with increased risk for fatty liver disease, diet soda intake was not [17]. However, the number of reports that have investigated relationships among artificially-sweetened beverage intake and hypertension, stroke, kidney or liver disease remains small, and additional investigation of such links is clearly warranted.

But what about weight?

Concern about weight loss or the prevention of weight gain may be a primary reason may individuals initiate intake of artificially-sweetened beverages in the first place, but the data demonstrating that diet soft drinks contribute to positive weight-related outcomes is no more convincing than the health outcome data. It is true that in studies where individuals are assigned to add relatively large quantities of sweetened beverages (e.g. ~ 1 liter/day) to their diets for periods of 6 – 10 weeks, outcomes are significantly worse when the beverages are sugar-sweetened compared to artificially-sweetened [e.g. [18]. However, data from other interventional studies indicate that weight loss outcomes are similar when sugar-sweetened beverages were replaced by either water or artificially sweetened beverages [19], and that consuming artificially-sweetened beverages in place of sugar-sweetened beverages did not lead to greater reductions in total sugar intake compared to consuming water [20]. An interventional study in children aged 4-11 indicated that substituting daily consumption of an artificially-sweetened beverage for daily consumption of a sugar-sweetened beverage did lead to lower weight gain [21]. A second study in adolescents indicated that reducing sugar-sweetened beverage intake resulted in less weight gain, but in that study replacement with unsweetened beverages was promoted over artificially-sweetened beverages, meaning the role of the “diet” soft drinks could not be determined [22].

Two recent studies have provided conflicting outcomes with regard to the effects of diet soft drinks compared to water in individuals intentionally restricting their total caloric intake. In one study, diet soft drinks appeared to produce greater weight loss while in the second, water was superior to diet soda [23,24]. In both of these studies, however, neither subjects nor experimenters appear to have been blinded to the hypotheses, suggesting that expectancy effects regarding the effects of using diet soda or water could have played significant roles in

the outcomes. Further, both studies recruited individuals who were already consuming diet soft drinks and had been weight stable for the previous 6-months. This suggests that among those who regularly consume diet sodas in the real world, weight loss is not a given.

Observational studies that have followed people over longer time periods provide little support for better weight outcomes with diet soft drinks. For example, in one study, replacing sugar-sweetened beverages with artificially-sweetened soft drinks was estimated to result in lower weight gain across time, but only in those who were already overweight or obese at baseline not in normal weight subjects [25]. In contrast, a separate study in adults indicated that both weight gain and the likelihood of becoming overweight or obese were significantly higher in individuals who consumed diet soft drinks at baseline compared to those who did not [26] and a prospective study that examined children between 7 and 11 years of age indicated that daily consumption of artificially-sweetened beverages promoted both increased BMI and increased adiposity [6]. Observational work has also indicated that diet soft drink consumption is associated with increased caloric intake from other foods, including those that are energy dense, but of low nutritional quality [27,28].

Negative effects of artificial sweeteners on body weight and health outcomes appear paradoxical. These products are designed to provide little or no energy, yet cohort studies provide consistent evidence that regular consumption of artificially-sweetened beverages is linked to increased risk for several diseases. It's important to bear in mind that these data don't actually inform us directly about cause, and it is not uncommon for individuals who consume diet soft drinks to differ from those who don't along a number of dimensions at baseline in these cohort studies. For example, diet soda consumers often have higher baseline BMIs and levels of adiposity than non-consumers e.g [11,28]. The magnitude of the observed associations, as well as the strength of the statistical significance, are typically modulated by the factors that are considered and how they are accounted for in particular models. Because some prospective cohort studies have linked diet soda consumption to increased weight gain and increased waist circumference independent of BMI (e.g. [[6,11,26]]), it might be argued that adjusting for these factors in statistical models is an example of throwing the baby out with the bathwater since negative health effects of artificial sweeteners may be partially mediated through changes in weight and/or adiposity. Nevertheless, even when baseline differences in factors such as body weight and adiposity are accounted for, disease risks remained significantly elevated among diet soda consumers in a number of studies. Further, it's important to note that none of these prospective studies have provided any evidence that diet soda consumption reduces the risk of developing diabetes, heart disease, hypertension or stroke.

Mechanisms underlying counterintuitive effects of artificial sweeteners

The link between artificial sweeteners and negative health outcomes has often been explained as an example of "reverse causation" in which individuals who are already at high risk for health problems turn to using them to avoid such outcomes. However, as with all correlational data, we are precluded from determining the direction of any causal effects. To address causal relationships, experimental studies are required, and experiments in non-human animal models have provided evidence that artificial sweeteners can cause a variety

of negative outcomes under some conditions. For example, artificial sweeteners can stimulate excess weight gain, particularly when diets high in fat and sugar are consumed along with the sweeteners [29–33]. In addition, artificial sweeteners have been demonstrated to cause deficits in glucose homeostasis even independent of effects on weight gain [34–36]. Several plausible mechanisms to explain such paradoxical effects have been supported. First, evidence suggests that artificial sweeteners can interfere with learning mechanisms that contribute to regulation of food intake and weight gain [37,38]. According to this hypothesis, animals (including humans) typically experience predictive relations between a sweet taste in the mouth, and the arrival of sugar and energy in the gut. As a result of this experience, sweet tastes come to evoke anticipatory physiological responses that promote effective and efficient metabolism of the ingested sugars and may contribute to satiety and satiation [e.g. [39–41]]. Introduction of the sweet taste cue without the anticipated consequences, such as occurs with artificial sweeteners, disrupts the predictive nature of the relationship. And based on principles of learning, disrupting the predictive relation results in a blunting of the anticipatory responses. This means that when real sugar is actually consumed, physiological responses may be slower and/or smaller. Consistent with this hypothesis, rats who have had prior experience with artificial sweetener show blunted thermic effects of food when they subsequently consume a sweet diet containing sugar [[31]]. In addition, compared to animals without artificial sweetener experience, hyperglycemia and reduced release of the incretin hormone GLP-1 are observed in animals given oral glucose tolerance tests after saccharin exposure, but not if the glucose is delivered by gavage, bypassing oral taste receptors [34].

Beyond potential effects on learned responses, artificial sweeteners may also promote dysregulation of weight and glucose homeostasis by altering the balance of bacteria that colonize the gut. Studies in both rats and mice have demonstrated increases in weight gain associated with alterations in gut bacterial populations in response to artificial sweeteners [35,42], and small studies in humans have suggested difference in bacterial populations in consumers of artificial sweeteners compared to non-consumers [35,43]. Further, both rodent and human data indicate that altered gut bacteria in response to artificial sweeteners is associated with altered glucose homeostasis [35,36].

What does this mean for people who drink diet soft drinks?

Animal studies have provided evidence for potential mechanisms that may underlie the counter-intuitive effects of artificial sweeteners, but it has been argued that the animal work does not does not mimic the use of artificially-sweetened products by people. In many ways, completely replicating the human situation is not the goal of such models. What animal models can do is provide us with the ability to rigorously and experimentally test hypotheses that might explain the outcomes actually observed in humans. Presently, data from these models support causal links between consumption of artificial sweeteners and the development of diabetes and cardiovascular diseases. And when use of artificial sweeteners by people in the real world is considered, there's minimal evidence that they are healthy options. Over the short term, sugar-sweetened beverages do appear to be worse choices than their artificially-sweetened alternatives especially if consumed in large quantities, but that doesn't mean that the "diet" versions are healthy. Over the long term, people in the real

world who consume even a single diet soft drink daily are more likely to suffer from diabetes, hypertension, stroke, and cardiovascular disease. The public health messages should be clear; drinking sweetened beverages on a daily basis is not a healthy choice. Public health is likely to be improved by reducing intake of all sweeteners, including sugar and its non-nutritive substitutes. But to be clear, excess sweetener consumption alone is not the only culprit; all dietary choices need be considered in a broad context and improving long-term health outcomes will require not only following overall recommendations on diet, such as the Dietary Guidelines for Americans [44] but also incorporating recommended levels of physical activity [45].

Acknowledgments

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Artificially-sweetened beverages are linked to increased risk for negative health outcomes in clinical cohorts

Little scientific evidence supports a role for diet soft drinks in reducing risk of overweight or obesity

Multiple biologically plausible mechanisms have been supported by experimental models in pre-clinical studies

Reduced intake of beverages sweetened with sugar or sugar-substitutes may improve public health outcomes