Nonnutritive Sweeteners in Weight Management and Chronic Disease: A Review

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Objective: The objective of this review was to critically review findings from recent studies evaluating the effects of nonnutritive sweeteners (NNSs) on metabolism, weight, and obesity-related chronic diseases. Biologic mechanisms that may explain NNS effects will also be addressed.

Methods: A comprehensive review of the relevant scientific literature was conducted.

Results: Most cross-sectional and prospective cohort studies report positive associations between NNS consumption, body weight, and health conditions, including type 2 diabetes, cardiovascular disease, and nonalcoholic fatty liver disease. Although findings in cellular and rodent models suggest that NNSs have harmful effects on metabolic health, most randomized controlled trials in humans demonstrate marginal benefits of NNS use on body weight, with little data available on other metabolic outcomes.

Conclusions: NNS consumption is associated with higher body weight and metabolic disease in observational studies. In contrast, randomized controlled trials demonstrate that NNSs may support weight loss, particularly when used alongside behavioral weight loss support. Additional long-term, well-controlled intervention studies in humans are needed to determine the effects of NNSs on weight, adiposity, and chronic disease under free-living conditions.

Introduction

Obesity is an urgent public health challenge in the United States and worldwide (1). As obesity and its comorbidities have become unprecedentedly common, emphasis has been placed on lowering calorie intake and specifically on reducing added sugars. Given the well-established associations among added sugars, obesity (2), type 2 diabetes (3), cardiovascular disease (4), nonalcoholic fatty liver disease (5), and cancer (6), the 2015 Dietary Guidelines for Americans recommend limiting added sugar to less than 10% of total energy intake (7), and similar guidance has been put forth by the World Health Organization (8). As such, considerable pressure has been placed on the food industry to reformulate its products to lower sugar content and provide reduced-calorie alternatives. One strategy is to substitute nonnutritive sweeteners (NNSs) for added sugars, as NNSs are highly sweet and palatable but contain no or few calories.

Until recently, NNSs were found primarily in beverages (e.g., diet sodas) and in sweetener packets (e.g., Equal, Sweet’N Low, Splenda), but they are now widespread in the food supply, including in condiments, reduced-calorie desserts and yogurts, cereals, snack foods, medications, and hygiene products (9,10). We recently demonstrated that consumption of NNSs increased by approximately 200% among children and adolescents from 1999 to 2000 (11), yet whether NNSs are helpful or harmful for weight management and chronic disease remains a topic of controversy (12,13). The purpose of this review is to summarize evidence from the recent literature investigating NNS consumption in relation to appetite, metabolism, weight, and health and to discuss physiologic mechanisms that may explain these findings.

Recommendations

Despite widespread and increasing consumption of NNSs, dietary recommendations for their consumption are inconsistent across different health organizations and are often inconclusive (14). For example, the 2015 Dietary Guidelines Advisory Committee scientific report (15) stated, “added sugars should be reduced in the diet and not replaced with low-calorie [nonnutritive] sweeteners, but rather with healthy options, such as water in place of sugar-sweetened beverages.” A joint position statement from the American Diabetes Association and American Heart Association also urged caution in the use of NNSs, stating that “at this time, there are insufficient data to determine conclusively whether the use of NNS to displace caloric sweeteners in beverages and foods reduces added sugars or carbohydrate intakes, or benefits appetite, energy balance, body weight, or cardiometabolic...
risk factors” (16). Much of this uncertainty results from a growing body of observational literature linking NNSs (mainly in the form of diet soda) to a variety of health concerns (17).

**Observational Studies**

Associations linking NNSs with unfavorable health outcomes (e.g., obesity, diabetes, nonalcoholic fatty liver disease) have been reported in prospective cohort studies (17-19) and, in some cases, remained statistically significant after adjustment for BMI and other relevant covariates (20,21). Although observational studies are limited by their inability to establish causality, the dose-response relationships reported, along with the fact that several plausible mechanisms may explain these findings, support a role of NNSs beyond simply reverse causality.

In 2008, Fowler et al. reported a dose-response relationship between baseline consumption of NNS-containing diet beverages and weight gain 7 to 8 years later (22). Compared with nonconsumers, participants who reported drinking diet beverages were more likely to gain weight over time, even after adjustment for baseline BMI. Interestingly, total daily energy intakes were lower among diet beverage consumers, despite increased weight gain. This phenomenon has been observed in several other studies (21,23), suggesting that NNSs may influence body weight via mechanisms independent of increasing energy intake (see Proposed Mechanisms Linking NNSs to Weight and Health Outcomes). The same group reported that NNS use in the form of diet beverages was associated with greater visceral adiposity after 9 to 10 years of follow-up, independent of baseline BMI and with minimal changes in body weight (24).

Results of epidemiologic studies evaluating whether NNS use is associated with a healthier or less healthy overall dietary pattern have been mixed (25-27). Inconsistent findings are likely due to differences in the way that NNS consumers are classified and with whom they are compared. For example, Leahy et al. (27) recently reported that NNS consumers had improved diets compared with water consumers, yet water consumers also included individuals consuming sugar-sweetened and NNS-sweetened beverages, as the groups were not mutually exclusive.

Positive associations between NNS use, type 2 diabetes (20,28), metabolic syndrome (30,31), cardiovascular disease (32), and nonalcoholic fatty liver disease (33) have also been observed in longitudinal analyses among adults. O’Connor et al. reported a 22% higher incidence of diabetes among NNS consumers (20). Although attenuated after adjustment for adiposity, substitution models also indicated that replacement of sugar-sweetened beverages with diet beverages did not lower diabetes incidence (20). In a similar study, Ma et al. (33) demonstrated that diet beverage consumption was predictive of nonalcoholic fatty liver disease, but this association was no longer statistically significant after adjustment for BMI. It is important to point out that if NNSs directly contribute to weight gain and increased adiposity, adjustment for BMI in these analyses may not be appropriate (34). Most recently, Pase and colleagues reported similar findings linking NNS use with stroke and dementia incidence (21). Positive associations between NNSs and other unfavorable health outcomes in longitudinal analyses have been further detailed in recent systematic reviews (17,35).

While well established in adults, limited data on the associations among NNSs, weight, and chronic disease are available in children (36). However, an emerging body of observational literature suggests that maternal ingestion of diet beverages during pregnancy may increase obesity risk in children (37). Associations between maternal NNS consumption and infant weight have been recently reported by two independent groups (38,39) and remained statistically significant after adjustment for confounders, including maternal body weight, calorie intake, diet quality, physical activity, and sociodemographic characteristics. A third group conducted a similar analysis but did not observe differences in child weight at 7 years of age based on maternal NNS consumption (40). Although the biologic mechanisms connecting infant overweight to in utero NNS exposure have yet to be elucidated, these studies raise questions as to whether ingestion of NNSs during pregnancy may contribute to childhood obesity.

**Proposed Mechanisms Linking NNSs to Weight and Health Outcomes**

Reverse causality and residual confounding may in part explain associations among NNS use, weight, and metabolic disease (41). For example, individuals who are already overweight or at risk for diabetes or related diseases may use NNSs to manage their weight or delay disease onset. Even after adjustment for relevant covariates, findings may be biased by residual confounding.

Several biologic mechanisms tested in vitro and in vivo may explain these associations (42,43). While the potential mechanisms discussed here are not exhaustive, it is important to recognize that some mechanisms may be generalizable across NNSs (e.g., sweet taste receptors), whereas others may be compound specific (e.g., only relevant for sucralose and not for aspartame) (43). Furthermore, these mechanisms may not be mutually exclusive.

**Sweet taste receptors**

Sweet tasting compounds, including caloric sugars (e.g., sucrose, fructose), NNSs (e.g., sucralose, aspartame), and sweet proteins (e.g., thau-matin), activate the heterodimeric sweet taste receptor T1R2/T1R3 (44). Although once believed to be present exclusively in the oral cavity (45), sweet taste receptors have recently been located throughout the body. Whereas sweet taste receptor activation on taste buds triggers the release of neurotransmitters to convey sweetness to the brain, activation of sweet taste receptors extra-orally exerts different downstream effects, only some of which are currently understood (46).

Activation of pancreatic or intestinal sweet taste receptors leads to insulin or glucagon-like peptide 1 release, respectively, as has been shown in response to NNSs in in vitro studies (45,47,48). In human studies, augmentation of insulin and/or glucagon-like peptide 1 has been shown by our group (49-51) and others (52) when administered in combination with oral glucose, although the clinical impact of the observed hormonal responses remains to be elucidated (51,53). However, when NNSs were administered without glucose, the majority of human studies have not reported changes in hormonal responses (54,55).

**Disturbance of relationship between sweetness and calories**

Evolutionarily, sweet taste was indicative of calories and nutrients (e.g., fruit), yet this is not the case for NNSs. It has therefore been
hypothesized that the sensation of sweetness without the delivery of calories may result in a disturbance of appetite regulation and impaired metabolic signaling (13). This concept is supported by several rodent studies involving intermittent access to either glucose (nutritive) or saccharin (nonnutritive) (56,57). In one set of experiments (57), rodents were given standard chow ad libitum and plain yogurt on 3 days of the week. Yogurt sweetened with either sucrose or saccharin was provided three other days of the week. Using this and similar paradigms (e.g., intermittent access to sweetened solutions instead of yogurt, ad libitum access to a high-fat/high-sugar diet instead of standard chow, longer or shorter duration of study), Swithers and colleagues have repeatedly shown that rodents have higher energy intake, gain more weight, and have relative hyperglycemia following intermittent access to saccharin, compared with glucose. Similar findings have been reported following prolonged exposure to aspartame and saccharin (58), yet no differences in weight were reported by Boakes et al. (59) after repeated saccharin exposure in an analogous design (57).

Several challenges exist in generalizing the Swithers paradigm (56) to human NNS consumption (60). Whereas rodents were exposed to sweetness intermittently and received sweetness only from NNSs or glucose-sweetened yogurt (or solutions) (57), humans are continually exposed to a plethora of sweet foods and beverages with varying nutrient profiles. It is therefore unclear whether the same potential disturbance in conditioning between sweet taste and calories would be expected in humans. This has not been investigated in clinical studies and warrants further investigation.

Alterations in gut microbiota
NNSs influence the microbial composition of the oral mucosa, and they are viewed positively by the dental community (61). In vitro studies (62) have demonstrated that NNSs, including aspartame, saccharin, and sucralose, have antimicrobial activity against common periodontal pathogens. It is therefore not surprising that NNSs have recently been shown to alter the gut microbiota, primarily in rodent models (63-65).

Suez et al. demonstrated that treating mice with NNSs for 11 weeks resulted in glucose intolerance (63), and transplantation of microbiota from saccharin-exposed mice to germ-free mice induced glucose intolerance among the recipients (63). Although results following saccharin exposure were the most robust, the authors reported that similar findings were observed after exposure to aspartame and sucralose. Alterations in the gut microbiota and glucose intolerance among saccharin-exposed mice were observed in comparison to glucose-exposed mice, as well as relative to mice administered unsweetened water. While the increased volumes of caloric liquid and subsequent reduction in solid food calories and accompanying nutrients may explain differences in microbiota between saccharin- and water-exposed mice, this difference would not explain differences in comparison to mice consuming glucose, as liquid volumes and solid food intakes were similar between saccharin- and glucose-exposed mice. Notably, despite the observed microbial alterations and relative glucose intolerance, weight gain among the NNS-exposed mice was similar to that observed among the nutritive sweetener or water controls.

Another rodent study demonstrated that 8 weeks of aspartame exposure altered gut bacterial composition, leading to elevated fasting glucose and impaired insulin-stimulated glucose disposal (64). Both studies showed increases in short chain fatty acid concentrations, specifically propionate, in the stool (63) and serum (64). Propionate is a substrate for gluconeogenesis and lipogenesis (66), and thus, increases in propionate may promote greater nutrient efficiency/energy harvest (67). However, the role of propionate in human health is controversial (67), and whether fecal short chain fatty acid concentrations accurately reflect the intestinal content is unclear (68).

Experimental evidence for NNS-induced alterations in gut microbiota in humans is limited (63). NNS exposure for 1 week was associated with changes in the microbiome and glucose metabolism in a small human sample (63), but the lack of a control group makes these findings less interpretable. Nevertheless, further study in this area is warranted, as such findings may have important implications given the emerging role of the gut microbiome in health and disease (69,70).

Changes in taste preferences
NNSs are potently sweet at low concentrations (71), and relative to caloric sugars, they are hundreds or thousands of times sweeter by weight, depending on the specific compound. Aspartame, for example, is 200 times more potent than sucrose, and sucralose is 600 times sweeter, yet advantame, the most recently approved NNS in the United States (72), is approximately 20,000 times sweeter than sucrose by weight (73). Thus, NNSs can be used in small amounts to achieve comparable sweetness to caloric sugars. Some NNSs also activate bitter taste receptors (e.g., saccharin, acesulfame-potassium), and thus, multiple NNSs are often present in food and beverage products in order to maximize their palatability.

Given the innate liking for sweetness (74), it has been hypothesized that exposure to sweet compounds, particularly early in life, may promote a higher preference for sweet taste. Many highly sweet foods and beverages are also high in calories (e.g., brownies, cookies), and thus, enhanced sweetness preference may promote poor dietary patterns, positive energy balance, and ultimately obesity. However, as previously discussed, cross-sectional findings linking NNSs to dietary patterns have been mixed (25-27).

Greater sweetness preference as a result of early-life exposure is also supported by findings in rodents but has not been well studied in humans. When pregnant rats were exposed to aspartame, their offspring ingested larger quantities of sweet foods at 60 days of life (75). Similar results were reported in offspring following exposure to acesulfame-potassium, whether exposure occurred in utero or during lactation (76). Analogous results were found in children who were given sugar-sweetened water in infancy (77). Epidemiologic findings linking NNS consumption to overall dietary patterns in adults are mixed (25,26,78,79) and have not been investigated in children. Gaining a better understanding of the influence of NNSs on the development of taste preferences is particularly important, as infants are exposed to NNSs via human breast milk (80) and exhibit a higher sweetness preference compared with older children and adults (81).

Human Intervention Studies
In contrast to the epidemiologic literature, the majority of human intervention studies suggest neutral or beneficial effects of low-calorie sweetener use for weight management (35,82-86). This is particularly the case when NNSs are compared with caloric sweeteners (87,88) or when NNSs are used as part of comprehensive dietary and behavioral

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weight loss interventions (82,83). While recent meta-analyses and systematic reviews have disagreed as to whether NNSs are truly beneficial (17,35,87), the replacement of sugar-sweetened beverages with NNSs appears to be helpful for weight management, especially among individuals who are cognitively engaged in weight loss (87).

Findings are less conclusive when NNSs are compared with water or unsweetened controls (87). As discussed in detail (88), randomized controlled trials showing the benefits of NNSs on body weight have often compared NNSs with sugar-sweetened beverages and have lacked a plain, unsweetened control. However, several recent trials have indeed compared NNSs with water (82-84), two of which (82,83) have reported that there are benefits to diet beverages. The administration of diet beverages led to both significantly greater weight loss during the intervention as well as to less subsequent weight regain during the maintenance period (83). Both studies were conducted in the context of behavioral weight loss support, which may not reflect typical NNS use in the general population. The Peters et al. trial (83) exclusively enrolled individuals who were already habitual consumers of NNSs. Thus, those assigned to the water intervention underwent a more drastic behavior change in having to adhere to the caloric restriction, discontinue diet beverages, and start drinking water.

While these trials have supported the utility of NNSs in weight loss programs, there are additional factors to consider in interpreting study findings (88). These include participant characteristics (e.g., age, race/ethnicity, genetics) and metabolic health (e.g., obesity vs. leanness, diabetes vs. no diabetes, overall dietary pattern), length of the intervention, specific NNS used, and the extent to which administration of NNSs reflects their use in real life. Importantly, most trials have provided NNSs in diet beverages, yet NNSs are found in numerous applications and are often ingested inadvertently (9,10).

Beyond assessing body weight, few intervention studies have investigated the effects of prolonged NNS exposure on glucose homeostasis and other metabolic outcomes. Maersk et al. (84) compared consumption of aspartame-sweetened beverages with sugar-sweetened beverages, isocaloric milk, and water. Aspartame-sweetened beverages, milk, and water all lowered liver fat, visceral adiposity, triglycerides, fasting glucose, fasting insulin, and the homeostatic model assessment of insulin resistance relative to sugar-sweetened beverages, with similar reductions in the aspartame and water groups. Grotz et al. (89) and Baird et al. (90) reported no differences in glucose homeostasis after high-dose encapsulated sucralose (94). Colagiuri et al. (95) administered aspartame to nine subjects with well-controlled type 2 diabetes at clinically relevant concentrations. While no adverse effects were reported, aspartame did not improve glycemia compared with equally sweet quantities (9% total energy) of sucrose.

Several studies have administered high doses of encapsulated aspartame to individuals with diabetes, with no adverse effects on glycemia (91-93). Similar findings were reported in individuals with diabetes after high-dose encapsulated sucralose (94). Colagiuri et al. (95) administered aspartame to nine subjects with well-controlled type 2 diabetes at clinically relevant concentrations. While no adverse effects were reported, aspartame did not improve glycemia compared with equally sweet quantities (9% total energy) of sucrose.

Discussion

Epidemiologic studies report positive associations among NNS consumption, obesity, and metabolic impairments and are supported by intervention studies in rodent models. In contrast, human randomized controlled trials suggest that NNSs may be a useful, or at least neutral, tool for weight management, particularly when used by individuals cognitively engaged in weight loss and who habitually consume NNSs. Given the discrepancies in the available evidence, the extent to which NNSs are helpful or harmful for weight management and chronic disease prevention warrants further study.

The discrepant findings of observational and interventional studies may be explained by several factors. Although randomized trials are the gold standard, they are limited by highly controlled environments that do not reflect consumption patterns in free-living individuals. They also have relatively small sample sizes and short follow-up periods compared with cohort studies. Intervention studies also involve replacement of sugar-sweetened beverages with NNSs, yet it is likely that NNSs are used not only as a substitute but also in addition to caloric sugars. In this case, their use would be unlikely to lower total energy intake.

Meanwhile, observational studies are unable to establish cause and effect, are subject to inherently flawed dietary assessments (96), and can be biased by reverse causality and residual confounding. It is also difficult to discern the context in which subjects use NNSs in epidemiologic analyses (e.g., whether they are cognitively engaged in behavioral weight loss or consumption of NNSs in an effort to adhere to a specific dietary plan). Despite these inherent limitations, findings from well-conducted epidemiologic analyses better capture free-living consumption patterns and provide important insight into biomarker and health outcomes yet to be systematically tested in randomized trials.

Priorities for further research include determining whether NNSs are helpful for weight loss and maintenance in a manner that closely reflects their consumption and whether NNSs impact glucose homeostasis in individuals with and without diabetes (97). In the design and interpretation of these studies, it is critical to consider the characteristics of the individuals enrolled, including habitual NNS consumption, as well as the reasons for and patterns of NNS use, among other factors.

While it is nearly impossible to replicate “real-life” consumption in randomized controlled trials, investigators can meaningfully expand upon the existing body of literature by broadening the route of NNS administration to include foods and condiments. Additional emphasis should also be placed on studying the effects of beverages sweetened with NNSs other than aspartame. For example, of the seven randomized controlled trials evaluating NNS use and cardiometabolic health (17), only in one were NNSs administered in foods or packets, whereas the other six administered NNSs in capsules or beverages. In one study in which aspartame was administered via packets and foods, this administration was in addition to aspartame-sweetened beverages (86). Given that NNSs are widespread in the food supply and are often consumed unknowingly (9), trials testing covert incorporation of NNSs into a variety of foods, beverages, and condiments would better represent use in the general population (11).

There is also an urgent need to understand whether early-life NNS exposure, including in utero and via breast milk, has long-term
implications for diet, metabolism, and health (98). Particularly relevant to children, the widespread presence of NNSs in foods and beverages, as well as in breast milk (80,98), leads to inadvertent exposure and reflects addition of NNSs to the diet, rather than replacement. It is also important to determine whether the intense sweetness contributed by adding NNSs to foods and beverages (especially to those that are not typically sweet) leads to heightened expectations for sweetness throughout the diet. Addressing these and other questions (97) using longer-term, well-controlled trials conducted in a manner that best reflects real-life consumption is critical to inform conclusive recommendations regarding NNS use.

Conclusion

Consumption of NNSs is associated with a variety of unfavorable metabolic and health outcomes in observational studies, yet intervention trials demonstrate that NNSs may benefit weight management, specifically when used in the context of calorie restriction and intentional weight loss. Additional human studies are needed to determine NNS effects on weight, metabolism, and chronic disease in a manner that closely reflects their use in real life. It is also critical to investigate NNS effects in other populations, such as infants and young children, pregnant and lactating women, and those with metabolic disease. Addressing key research questions related to NNS effects in a variety of populations and using different sweeteners (e.g., aspartame, sucralose, saccharin) and routes of administration (e.g., foods, beverages, packets) will inform us about the role of NNSs in weight management and chronic disease and will contribute to public health recommendations promoting or discouraging their use.

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