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Non-nutritive Sweeteners in Weight Management and Chronic Disease: a review

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Abstract

Objectives—To critically review findings from recent studies evaluating effects of non-nutritive sweeteners (NNS) on metabolism, weight, and obesity-related chronic diseases. Biologic mechanisms that may explain NNS effects will also be addressed.

Methods—We conducted a comprehensive review of the relevant scientific literature.

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 non-alcoholic fatty liver disease. While findings in cellular and rodent models suggest harmful effects of NNS on metabolic health, most human randomized controlled trials in humans demonstrate marginal benefits of NNS use on body weight, with little data available on other metabolic outcomes.

Conclusion—NNS consumption is associated with higher body weight and metabolic disease in observational studies. In contrast, randomized controlled trials demonstrate that NNS 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 NNS effects on weight, adiposity and chronic disease under free-living conditions.

Keywords

low-calorie sweetener; diet beverages; artificial sweeteners; metabolism; sugar; obesity; diabetes

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Introduction

Obesity is an urgent public health challenge in the US 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 well-established associations between added sugars, obesity[2], type 2 diabetes[3], cardiovascular disease[4], non-alcoholic 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 their products to lower sugar content and provide reduced calorie alternatives. One strategy is to substitute non-nutritive sweeteners (NNS) for added sugars, as NNS are highly sweet and palatable, but contain no or few calories.

Until recently, NNS were found primarily in beverages (e.g. diet sodas) and in sweetener packets (e.g. Equal™, Sweet N Low™, Splenda™), but 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 NNS has increased by approximately 200% among children and adolescents since 1999–2000[11], yet whether NNS 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 which may explain these findings.

Recommendations

Despite widespread and increasing consumption of NNS, 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 [non-nutritive] 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 NNS, in 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 intake, or benefits appetite, energy balance, body weight, or cardio-metabolic risk factors[16].’ Much of this uncertainty results from a growing body of observational literature linking NNS (mainly in the form of diet soda) to a variety of health concerns[17].

Observational Studies

Associations linking NNS with unfavorable health outcomes (e.g. obesity, diabetes, non-alcoholic fatty liver disease) are reported in prospective cohort studies[17–19], and in some cases, remain 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 NNS 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 7–8 years later[22]. Compared to non-consumers, participants who reported drinking diet beverages were more likely to gain weight over time, even after adjustment for baseline body mass index (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 NNS may influence body weight via mechanisms independent of increasing energy intake (see Proposed Mechanisms section below). The same group reported that NNS use in form of diet beverages was associated with greater visceral adiposity after 9–10 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 are 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 have improved diets compared to 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[28,29], metabolic syndrome[30,31], cardiovascular disease[32], and non-alcoholic 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[28]. Although attenuated after adjustment for adiposity, substitution models also indicated that replacement of sugar-sweetened beverages with diet beverages did not lower diabetes incidence[28]. In a similar study, Ma et al.[33] demonstrated that diet beverage consumption was predictive of NAFLD, but this association was no longer statistically significant after adjustment for BMI. It is important to point out that if NNS directly contribute to weight gain and increased adiposity, adjustment for BMI in these analyses may not be appropriate[34]. Most recently, Pase and colleagues reporting similar findings linking NNS use with stroke and dementia incidence[21]. Positive associations between NNS 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 between NNS, 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 their children[37]. Associations between maternal NNS consumption and infant weight were recently reported by two independent groups[38,39], and remained statistically significant after adjustment for confounders including maternal body weight, calorie intake, diet quality, and physical activity, and socio-demographic characteristics. A third group conducted a similar analysis but did not observe differences in child weight at seven 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 NNS during pregnancy may contribute to childhood obesity.

Proposed Mechanisms Linking NNS To Weight and Health Outcomes

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

Several biological mechanisms tested *in vitro* and *in vivo* may explain these associations[42,43]. While the potential mechanisms discussed below are not exhaustive, it is important to recognize that some mechanisms may be generalizable across NNS (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), NNS (e.g. sucralose, aspartame), and sweet proteins (e.g. thaumatin), 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 presently understood[46].

Activation of pancreatic or intestinal sweet-taste receptors leads to insulin or glucagon-like-peptide 1 (GLP-1) release, respectively, as has been shown in response to NNS in *in vitro* studies[45,47,48]. In human studies, augmentation of insulin and/or GLP-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 NNS are administered without glucose, the majority of human studies do not report 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 NNS. 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 (non-nutritive)[56,57]. In one set of experiments[57], rodents were given standard chow ad libitum and plain yogurt on three 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 to 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 NNS 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

NNS influence the microbial composition of the oral mucosa and are viewed positively by the dental community[61]. *In vitro* studies[62] demonstrate that NNS including aspartame, saccharin, and sucralose have anti-microbial activity against common periodontal pathogens. It is therefore not surprising that NNS were recently shown to alter the gut microbiota, primarily in rodent models[63–65].

Suez et al. demonstrated that treating mice with NNS 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 (SCFA) 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 SCFA 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 one 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

NNS are potently sweet at low concentrations[71], and relative to caloric sugars, 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, NNS can be used in small amounts to achieve comparable sweetness to caloric sugars. Some NNS also activate bitter taste receptors (e.g. saccharin and acesulfame-potassium), and thus, multiple NNS 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 discussed above, cross-sectional findings linking NNS 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 NNS on the development of taste preferences is particularly important, as infants are exposed to NNS via human breast milk[80] and exhibit a higher sweetness preference compared to 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 LCS use for weight management[35,82–86]. This is particularly the case when NNS are compared to caloric sweeteners[87,88] or when NNS are used as part of comprehensive dietary and behavioral weight loss interventions[82,83]. While recent meta-analyses and systematic reviews disagree as to whether NNS are truly beneficial[17,35,87], replacement of sugar-sweetened beverages with NNS appear to be helpful for weight management, especially among individuals who are cognitively engaged in weight loss[87].

Findings are less conclusive when NNS are compared to water or unsweetened controls[87]. As discussed in detail[88], randomized controlled trials showing benefits of NNS on body weight often compare NNS with sugar-sweetened beverages and lack a plain, unsweetened, control. However, several recent trials have indeed compared NNS to water[82–84], two of which[82,83] have reported benefits of diet beverages. Administration of diet beverages led to both significantly greater weight loss during the intervention as well as to less subsequent weight re-gain 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 NNS. 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 support utility of NNS 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. obese vs. lean, diabetes vs. no diabetes, overall dietary pattern etc.), length of the intervention, specific NNS used, and the extent to which administration of NNS reflects their use in real life. Importantly, most trials provide NNS as diet beverages, yet NNS are found in numerous applications and are often ingested inadvertently[9,10].

Beyond assessing body weight, few intervention studies have investigated 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 HOMA-IR 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 sucralose exposure compared to placebo. However, the latter study was designed for toxicological safety assessment and both trials administered encapsulated sucralose to healthy, normo-glycemic volunteers. In contrast, a recent same-subject crossover study, also in healthy volunteers, reported decreased insulin sensitivity following exposure to 200 mg encapsulated sucralose (equivalent of ~three sucralose-containing diet sodas per day) compared to placebo (unpublished; abstract SUN-580 presented at the Endocrine Society Annual Meeting 2017).

Several studies have administered high doses of encapsulated aspartame to individuals with diabetes, with no adverse effects on glycemia[91–93]. Similar findings have been 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 to equi-sweet quantities (9% total energy) of sucrose.

Discussion

Epidemiologic studies report positive associations between NNS consumption, obesity, and metabolic impairments and are supported by intervention studies in rodent models. In contrast, human randomized controlled trials suggest that NNS 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 NNS. Given the discrepancies in the available evidence, the extent to which NNS 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 to cohort studies. Intervention studies also involve replacement of sugar-sweetened beverages with NNS, yet it is likely that NNS 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 NNS in epidemiologic analyses (e.g. whether they are cognitively engaged in behavioral weight loss or consumption NNS 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 provide important insight into biomarker and health outcomes yet to be systematically tested in randomized trials.

Priorities for further research[97] include determining whether NNS are helpful for weight loss and maintenance in a manner that closely reflects their consumption, and to determine whether NNS impact glucose homeostasis in individuals with and without diabetes. 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 effects of beverages sweetened with NNS other than aspartame. For example, of the seven randomized controlled trials evaluating NNS use and cardiometabolic health[17], only in one were NNS administered in foods or packets, whereas the other six administered NNS in capsules or beverages. In one study in which aspartame was administered via packets and foods, this was in addition to aspartame-sweetened beverages[86]. Given that NNS are widespread in the food supply and are often consumed unknowingly[9], trials testing covert incorporation of NNS 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 NNS in foods and beverages, as well as in breast milk[80,98], leads to inadvertent exposure and reflects addition of NNS to the diet, rather than replacement. It is also important to determine if the intense sweetness contributed by adding NNS 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, and conducted in a manner that best reflects real-life consumption, is critical to inform conclusive recommendations regarding NNS use.

Conclusion

Consumption of NNS is associated with a variety of unfavorable metabolic and health outcomes in observational studies, yet intervention trials demonstrate that NNS 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. food, beverage, packets), will inform the role of NNS in weight management and chronic disease, and will contribute to public health recommendations promoting or discouraging their use.

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What is already known?

- Non-nutritive sweeteners are widely consumed by children and adults and are found in numerous foods, beverages, and personal care products.
- Non-nutritive sweetener use is associated with higher body weight and metabolic abnormalities in epidemiologic studies.
- Replacing sugar-sweetened beverages with beverages containing non-nutritive sweeteners may be beneficial for weight loss when used as part of comprehensive lifestyle interventions.

What does this review add?

- This review highlights discrepancies between the observational and interventional literature in humans and discusses potential factors which may explain these discordant findings.
- Potential mechanisms linking non-nutritive sweeteners to obesity and chronic disease are discussed and their relevance is examined in the context of human consumption.
- Key future research needs related to non-nutritive sweeteners and their effects are highlighted.