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Review Article

COUNTERPOINT: Artificial Sweeteners for Obesity—Better than Sugary Alternatives; Potentially a Solution

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ABSTRACT

Objective: Nonnutritive (NNSs) are used in place of sugars to reduce caloric and glycemic intake while providing desired sweetness, commonly replacing sugar-sweetened beverages (SSBs) with "diet" (zero-calorie) alternatives. Concern has developed due to observational data associating NNSs with obesity and adiposity-based chronic disease. This counterpoint argues that, in general, NNSs used in place of added or excess sugars in the diet are likely beneficial.
Methods: A literature review was conducted on interventional trials investigating NNSs and obesity or type 2 diabetes mellitus. Key words used in the search included artificial sweeteners, nonnutritive sweeteners, saccharin, sucralose, aspartame, stevia/steviol, acesulfame potassium, meal replacements, type 2 diabetes mellitus, obesity, and weight.
Results: Interventional data and indirect interventional data consistently showed beneficial effects on weight and cardiometabolic health, including glycemia, when SSBs or other energy-dense foods were replaced by artificially sweetened beverages or artificially sweetened meal replacements.
Conclusion: Although NNSs correlate with obesity and adiposity-based chronic disease, those data are fraught with confounding and error. Plausibility has been suggested on the basis of preclinical research on neuroendocrine control of appetite, satiety, and cravings plus the gut microbiome. However, interventional data reveal that replacing caloric/glycemic energy intake via NNSs creates an energy deficit resulting in weight loss and improvement in disease—especially dysglycemic disease. Intensive dietary intervention using artificially sweetened meal replacements shows a marked clinical benefit without detriment from their NNSs. Furthermore, beverages sweetened with NNSs rather than SSBs have been noted to be a critical component for those succeeding in maintaining weight loss. Although individual responses to the effects of NNSs are always warranted just like in any clinical situation, patients should not be advised to avoid NNSs in the context of dietary intervention to improve quality and energy deficit.

Introduction

Obesity is a complex disease of abnormal and/or excess adipose tissue that results in adiposity-based chronic disease (ABCD), including type 2 diabetes mellitus (T2DM) and increased cardiovascular risk.[1-3] The diagnostic term ABCD reflects disease pathophysiology and specific complications causing morbidity and mortality. The pathology of obesity and ABCD fundamentally involves perturbations of energy homeostasis resulting in the accumulation of adipose tissue confounded by individual factors ranging from genetics to environmental, including dietary habits and food availability.[4] Sugar-sweetened beverages (SSBs) have been known to substantially contribute toward excess dietary energy consumption associated with obesity and cardiometabolic disease, which calls to reduce or replace as described in a previous point-counterpoint publication regarding health hazards of sugar, high-fructose corn syrup, and fructose in the context of SSBs.[5] Nonnutritive or artificial sweeteners (NNSs) have been historically incorporated in beverages and sometimes in processed food in place of added sugar to avoid or reduce caloric and glycemic intake without sacrificing the desired sweetness. Most commonly, this practice has typically been used to replace SSBs with "diet" or zero-calorie alternatives, but it has been fraught with controversy over its potential harms rather than benefits. The most used NNSs include

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Abbreviations: ABCD, adiposity-based chronic disease; ASB, artificially sweetened beverage; BMI, body mass index; CGM, continuous glucose monitoring; EI, Energy intake; NNS, nonnutritive or artificial sweetener; SSB, sugar-sweetened beverage; T2DM, type 2 diabetes mellitus.
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saccharin, aspartame, sucralose, steviol glycosides (stevia), acesulfame potassium, and luo han guo (or "monk fruit"), and data for each must be considered independently to some degree. Although obesity and energy intake or expenditure plus partitioning has turned out to be extraordinarily complex, simple principles of energy balance ultimately boil down to the energy intake versus energy expenditure. This physiology is undoubtedly influenced by genetic heritability along with innumerable external factors which may or may not be in one's control. Dietary intervention is the primary first-line therapy for obesity and ABCD, with related clinical practice guidelines and consensus generally suggesting NNSs as substitutes for SSBs to improve and reduce energy intake.[6,7] Could artificial sweeteners play a role, and if so, for better or for worse? They do not provide energy (ie, calories), so they cannot contribute directly to the intake per se. A tightly-controlled inpatient metabolic ward feeding trial has confirmed this principle of energy balance but within the context of complex mechanisms governing body weight regulation.[8]

The apprehension in using NNSs has materialized in the scientific, medical, and nutritional communities due to observational data that suggest an association of NNSs with obesity and adiposity-based disease like T2DM, cardiovascular outcomes including stroke, and cancer.[9-12] Observational nutrition data are generally fraught with methodological limitations, including confounded baseline analyses, resulting in possibly biased associations of behavior clustering improved by repeated measures and substitution analyses.[13] For example, a recently published analysis of 3 large population cohorts (Nurses' Health study, Nurses' Health study II, and the Health Professionals' follow-up study) concluded that increasing the consumption of both SSBs and artificially sweetened beverages (ASBs) was associated with a higher risk of obesity and T2DM, and there was a positive association between high intake of ASBs and mortality in women; however, possible reverse causation and surveillance bias in the ASB correlations were noted.[14,15] Biologic plausibility and mechanisms, ranging from altered subjective hunger and satiety to driving sweet-seeking behavior and energy intake, must also be considered. Neuroimaging studies have shown neuronal responsivity to NNSs in reward and satiation areas of the brain similar to sugar-based sweeteners; however, the physiologic response was affected heterogeneously.[16]

Although observational data and some preclinical data on biologic mechanisms raise concerns, correlation does not equal causation, and interventional trial data, including randomized placebo-controlled trials, are more appropriate to test these hypothesis-generating data. This counterpoint in response to the accompanying point by Christofedes[17] is to provide contrary evidence to suggest that, in general, NNSs used in place of added or excess sugars in the diet are likely beneficial and generally not counter-productive for intensive weight loss efforts and adiposity-based health (Fig. 1).

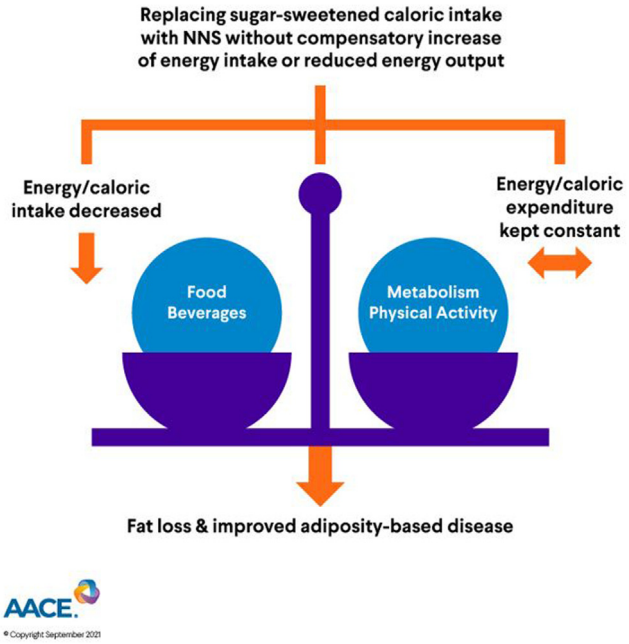

Fig. 1. Central illustration showing that the replacement of sugar-sweetened caloric intake with nonnutritive sweetened alternatives without compensatory energy intake or reduced energy output results in fat loss and improved adiposity-based health.

Interventional Trials

A 2014 meta-analysis identified 15 randomized controlled trials to evaluate the replacement of caloric sweeteners with NNSs, resultant body weight changes, and composition.[18] While the analysis of 9 observational studies showed no association (other than a slight positive association with body mass index [BMI]), findings from the randomized controlled trials indicate that substituting NNSs for their regular calorie versions resulted in a statistically significant modest decrease in weight by 0.8 kg, in fat mass by 1.1 kg, and in waist circumference by 0.83 cm.[18]

In 2016, Rogers et al[19] published a systematic review and meta-analysis of animal and human trials, dividing the human trials into 43 short-term ($\leq$1 day) and 12 sustained interventions (>1 day) to decipher the effects of NNSs and energy intake plus body weight. The short-term trial data were further divided into 5 types of comparisons: NNSs versus sugar, NNSs versus unsweetened products, NNSs versus water, NNSs versus nothing, and NNSs in capsules versus placebo capsules. Further, they derived estimates of "compensation index" scores for the NNSs versus sugar trials, which describe the adjustment in test meal intake to "compensate" for the difference in energy contribution of sugar preload compared with the NNSs. Energy intake (EI) was lower for the NNSs versus sugar with partial compensation, no difference of EI between NNSs or "unsweetened" or water preloads, and a tendency for reduced EI for NNSs capsules (predominantly aspartame) compared with the placebo. The sustained interventions varied greatly in design and quality but consistently revealed a lower EI for NNSs versus sugar and NNSs versus water comparisons. In trials ranging from $\geq$4 weeks to >3 years, this EI difference translated into either the smallest weight gain or a loss in body weight. Overall, they broadly concluded that the use of NNSs in place of sugar results in beneficial effects for reducing ones' EI and adiposity compared to sugar, and possibly even compared to water.

The possible benefits compared to water are intriguing and certainly against the common perception. For example, a 12-week randomized trial of 303 men and women who were involved in a 12-week behavioral weight loss program as a part of a 1-year trial compared those asked to drink water and to avoid NNSs in beverages with those who consumed more than 24 ounces of daily beverages with NNSs. Results showed that the group consuming NNS beverages showed 5.95 kg weight loss, whereas the group consuming water only showed 4.09 kg weight loss ($P < .0001$), and better hunger scores were noted.[20] At the end of 1 year, subjects consuming water had maintained a loss of 2.45 ± 5.59 kg, whereas those consuming NNS beverages maintained a loss of 6.21 ± 7.65 kg ($P < .001$). On the other hand, an analysis of females in a 24-week weight loss program that randomized participants to replacement of "diet" beverages (NNS) with water after the main meal revealed that water led to slightly greater weight reduction than NNS

beverages (−8.8 kg vs −7.6 kg, respectively; $P = .015$) along with possible clinical benefits improving insulin resistance; however, a similar reduction in waist circumference, lipids, and hemoglobin A1C was observed.[21]

As noted earlier, we must consider the effects of individual NNSs as they encompass different chemicals with potentially different biologic effects. One recent example published by Higgins et al[22] includes a 1-week trial with 100 "lean" healthy participants randomly assigned to consume aspartame (0 mg vs 350 mg vs 1050 mg) via daily beverages. The 0-mg group also consumed 680-mg dextrose capsules + 80-mg para-amino benzoic acid, the 350-mg aspartame group consumed aspartame only, and the 1050-mg aspartame group consumed the 350-mg aspartame beverage + 680-mg dextrose capsules and 700-mg aspartame capsules. There were no changes in body weight or body composition, no changes in appetite, and no differences in oral glucose tolerance test, insulin, leptin, and glucagon-like peptide/glucose-dependent insulinotropic polypeptide based on aspartame ingestion. Further, they delineated different sweeteners using a parallel-arm design, with 154 participants randomly assigned to consume 1.25 to 1.75 L of daily beverage sweetened with sucrose ($n = 39$), aspartame ($n = 30$), saccharin ($n = 29$), sucralose ($n = 28$), or steviol glycoside rebaudioside A ($n = 28$) for 12 weeks.[23] The beverages contained 400 to 560 kcal daily (sucrose treatments) or <5 kcal daily (NNS groups). Sucrose consumption significantly increased body weight ($+1.85 \pm 0.36$ kg; $P \leq .02$) as expected from the additional energy consumption. Moreover, saccharine consumption was also associated with weight gain ($+1.18 \pm 0.36$ kg; $P \leq .02$), whereas aspartame and rebaudioside A did not result in a significant change. Somewhat surprisingly, weight change was directionally negative and lower for sucralose than for saccharin, aspartame, and rebaudioside A consumption (-1.37 ± 0.52 kg, $P \leq .008$).

Glycemic Considerations

Of great importance when considering the potential benefits and risks of NNS consumption in the context of obesity and ABCD is the effect on dysglycemia. Several of the studies cited earlier noted a lack of concerning effect on glycemia in addition to the adiposity-based foundation of dysglycemia. In 2016, Romo-Romo et al[24] performed a systematic review of 14 observational and 28 clinical trials evaluating the association and effects, respectively, of NNS consumption on the development of dysglycemic metabolic disease and appetite-regulating hormones.[24] They concluded that although some observational studies suggest an association between NNSs and dysglycemic disease, adiposity remained a frequent confounder when the results of the clinical trials were contradictory and overall unclear. One randomized control trial tested the effects of daily sucralose and placebo over several months in subjects with obesity complicated by T2DM.[25] This multicenter, double-blinded, placebo-controlled randomized control trail consisted of a 6-week screening phase, a 13-week test phase, and a 4-week follow-up phase. It included 128 subjects with T2DM who were randomized to placebo or 667-mg sucralose capsules daily (dosing based on 7.5 mg/kg per day = 3 × maximum intake) for 13 weeks. Placebo capsules were given to all subjects for 4 weeks before and after the 13-week test phase. There was no effect on glucose homeostasis or intolerances noted in this trial, including on hemoglobin A1C, fasting blood glucose, and C-peptide levels, which were measured every 2 weeks. A similar study investigating normoglycemic healthy males supplemented with 333-mg sucralose 3 times a day with meals revealed no effect on glycemic control; moreover, the investigators performed a systematic review and suggested that this is a constant finding for sucralose.[26] Although these data on sucralose seem reassuring, controversy remains in the context of real-world use, with an "uncoupling" of sweet taste from EI driving sugar-seeking behavior. To test this hypothesis, Dallenburg et al[27] randomly assigned 45 healthy participants to consume the following: (1) beverages sweetened with sucralose (sweet uncoupled from calories [NNS]), (2) beverages sweetened with sucrose (sweet coupled with calories [sugar]), or (3) beverages sweetened with sucralose plus maltodextrin (combination). They used oral glucose tolerance testing, taste perception testing, and functional magnetic resonance imaging to assess metabolic and central neural responses. It was found that sucralose consumption in combination with maltodextrin, but not by itself, results in diminished response, which may negatively impact adiposity-based metabolic health.[27]

A meta-analysis of 29 studies including 741 participants looking at short-term glycemic impact of NNSs, including aspartame, saccharin, stevia, and sucralose, revealed no hyperglycemic excursion without a difference between type, and had less impact on participants of older age, higher BMI, and with T2DM.[28] Another meta-analysis looked at trials for both post-prandial glucose and insulin responses and concluded that even in combination with a nutrient-containing preload, there are no acute effects of NNSs and not even a slight beneficial effect on post-prandial glucose in those with T2DM not differing by type or dose of NNSs.[29] A recent small trial used continuous glucose monitoring (CGM) to examine the glycemic effects of aspartame and acesulfame potassium in 39 subjects without T2DM who had a BMI ranging from "normal" weight (18-25 kg/m^2) to obese (30-45 kg/m^2).[30] The subjects were randomly assigned to consume either 0.6 L/d of artificially sweetened soft drinks or mineral water for 2 weeks. Each group was underwent a 4-week washout period without beverage consumption. A 75-g oral glucose tolerance test was performed at the beginning and the end of each intervention and did not have altered results for glucose or insulin; the CGM data revealed no significant differences between the NNS beverages and mineral water groups.

Stevia extract (steviol glycoside) has recently risen in popularity due to its "natural" origins and potentially metabolic benefits. In 2019, Farhat et al[31] published a small, 3-arm crossover trial of 30 participants (20 women and 10 men) without obesity that investigated the effect of stevia on post-prandial glucose levels, appetite, and food intake.[31] The participants were randomized to different days of water, 60-g sugar, or 1-g stevia followed by ad libitum pizza lunch, preceded by standardized breakfast. While EI did not differ between any of the preloads, the hunger and "desire to eat" scores were lower following stevia preloads. A subsequent small randomized controlled, double-blinded, crossover study of healthy participants consuming 5 different beverages (water, water with glucose, water with sucrose, maltodextrin, or stevia) on 5 separate days resulted in similar beneficial appetite ratings, with stevia leading to reduced intake of ad libitum lunch along with much higher post-prandial glycemia following the caloric beverages.[32] A meta-analysis of placebo-controlled trials showed nonsignificant trends in reduced BMI and fasting glucose with stevia and a significant reduction in systolic blood pressure.[33]

Indirect Interventional Data From Meal Replacements

A surprisingly absent aspect to the debate on NNSs and adiposity-based disease is regarding the wealth of data looking at the safety and efficacy of meal replacement strategies for weight loss and glycemic control, specifically, meal replacement shakes. Meal replacement shakes have been a longtime popular dietary strategy to impose intensive energy-restriction for weight loss and T2DM, often replacing at least 1 to 2 meals daily. Although these shakes are generally high in protein, usually some form of milk

protein (ie, whey or casein), and are low in carbohydrates/sugars and fats, they are designed to be sweet and palatable for enjoyment. To avoid caloric and glycemic load, meal replacement shakes use a variety of NNSs, ranging from the older aspartame and acesulfame potassium to the more recent sucralose or stevia. Meta-analyses of meal replacement shake strategy trials have shown around 2.5% more weight loss than the reduced-calorie plan groups, showing benefits regardless of meeting caloric goals and irrespective of T2DM status.[34,35] The DROPLET trial randomized patients with obesity to total meal replacement plans for 8 weeks, followed by 4 weeks of food reintroduction and behavioral support or usual care including frequent nurse practitioner visits for behavioral weight management advice.[36] The meal replacement shakes used were sweetened with aspartame and acesulfame potassium. After 12 weeks, the meal replacement group reported a 10.7-kg weight loss, whereas the usual care group reported a 3.1-kg weight loss.

The acute glycemic impact of sucralose and acesulfame potassium sweetened shakes in people with obesity complicated by T2DM was evaluated in a recent randomized parallel trial using CGM.[37] This trial had 81 participants continue their habitual dietary intake for days 1 to 6 and compared those replacing 2 daily meals with shakes to those receiving none. The CGM data showed an improved overall glycemic excursion with use of the shakes in place of meals and improved glycemic variability along with "increased confidence in choosing foods to control their diabetes."

The Look ahead trial, well known for resulting in a plethora of data supporting weight loss benefits via intensive lifestyle intervention in obesity and T2DM, encouraged to replace 2 meals (typically breakfast and lunch) with a liquid shake and 1 snack with a bar during weeks 3 to 19.[38,39] Participants were able to choose from 4 meal replacements: Slim-Fast (aspartame and acesulfame potassium, manufactured by Glanbia), Glucerna (sugar and acesulfame potassium, manufactured by Abbott), OPTIFAST (sugar and sucralose, manufactured by Nestle), and HMR (saccharin, manufactured by Providence St. Joseph Health), which obviously had no detriment on the expected and actual outcomes of this successful trial and support the inclusion of NNSs in a weight loss and diabetes prevention meal plan.

Meal replacement shake strategies have recently been studied as part of intensive dietary plans to put prediabetes and T2DM into remission through weight loss. Meal replacement liquid protein formulas, including sucralose as the sweetener, were used in the PREVIEW and DIRECT trials and resulted in weight loss and remission of prediabetes and early T2DM.[40,41] PREVIEW was a noncontrolled trial of over 2000 participants with a BMI $\geq$25 kg/m^2 + prediabetes, and all participants were prescribed an 8-week low-energy diet, including protein shakes sweetened by sucralose and acesulfame potassium, and permitted to consume ASBs with any NNS. This intervention resulted in a mean weight loss of 10.3% in women and 11.8% in men; 35% of all participants reverting to normoglycemia. The DiRECT trial randomized 49 primary care sites with over 300 patients diagnosed with obesity and T2DM to an intensive meal replacement plan including protein shakes again sweetened with sucralose and acesulfame potassium or "usual care" as the control group. All subjects were taken off their antihyperglycemic pharmacologic agents (patients using insulin were excluded), and the intensive dietary plan was continued for 3 to 5 months followed by food reintroduction between 2 and 8 weeks and a maintenance phase, all totaling to 52 weeks. Mean weight loss was 10% in the meal replacement group and 1% in the control group. Results revealed that 24% of patients in the meal replacement group achieved a 15% weight loss at 12 months and 46% achieved remission from T2DM compared with 0% and 4%, respectively, for the control group.

Table
Summary of the Effects of Nonnutritive Sweeteners on Obesity/Adiposity and Dysglycemia Based on the Cumulative Body of Interventional Trial Evidence

Summary of Effects of NNS on Adiposity & Dysglycemia		
NNS	Adiposity (compared to water / sugar-sweetened alternative)	Dysglycemia (compared to water / sugar-sweetened alternative)
Saccharin	⇔/⇓	⇔/⇓
Aspartame	⇔/⇓	⇔/⇓
Sucralose*	⇔/⇓	⇔/⇓
Steviol	⇔/⇓	⇔/⇓
Overall	⇔/⇓	⇔/⇓

* Some data suggest that sucralose may have better effects on weight and adiposity compared with other NNSs but can be potentially worse when combined with caloric companion. *NNS* = nonnutritive sweetener.

In addition to these interventional trials summarized in the Table, it should be noted that beverages sweetened with NNSs have been noted to be critical for weight maintenance after weight loss. The National Weight Control Registry survey of those who had lost 13.6 kg and maintained this loss for >1 year revealed that <10% of participants ever consumed SSBs and 53% consumed NNS beverages regularly, with 78% believing that it helped control total calorie intake; however, it was also revealed that increasing water intake was the most common strategy. Regular consumption of artificially sweetened or low-calorie beverages is common in successful weight loss maintainers for various reasons, including helping individuals to limit total EI. Changing beverage consumption patterns was believed to be very important for weight loss and maintenance by a substantial percentage of successful weight loss maintainers in the National Weight Control Registry.[42]

Conclusion

Observational data that correlate NNSs with obesity and ABCD are hypothesis-generating, and preclinical research has elucidated some potential biologic plausibility, including alterations in appetite-regulating hormones, gut microbiome, and neurogastrointestinal hormones. Consumption of NNSs is not encouraged, per se, for those who consume unsweetened beverages as it is, and consumption of sweet-tasting processed foods, in general, is not promoted. On the contrary, the body of evidence from interventional trials on varying NNSs on weight and adiposity, in addition to very convincing indirect trial data on artificially sweetened meal replacements, convincingly shows superiority over SSBs without safety concerns.[43] Dietary intervention for obesity and ABCD includes reducing caloric and glycemic intake by restricting SSBs. This is an obvious priority and often the "low-hanging fruit." Patients should be encouraged to replace high caloric/glycemic loads such as soda-pop, sweet tea, and juice with any noncaloric beverages as personally preferred, including those sweetened with NNS, with individually-responsive nuance and without compensation by ingesting other energy-rich food. Pragmatically, energy balance ultimately matters, as does the context of the overall dietary pattern quality. Replacing SSBs with ASBs while personalizing an individual's dietary plan to reduce processed/refined calorically dense foods in favor of whole foods or using artificially sweetened meal replacements is certainly favorable based on the most relevant data we have available (Fig. 2).

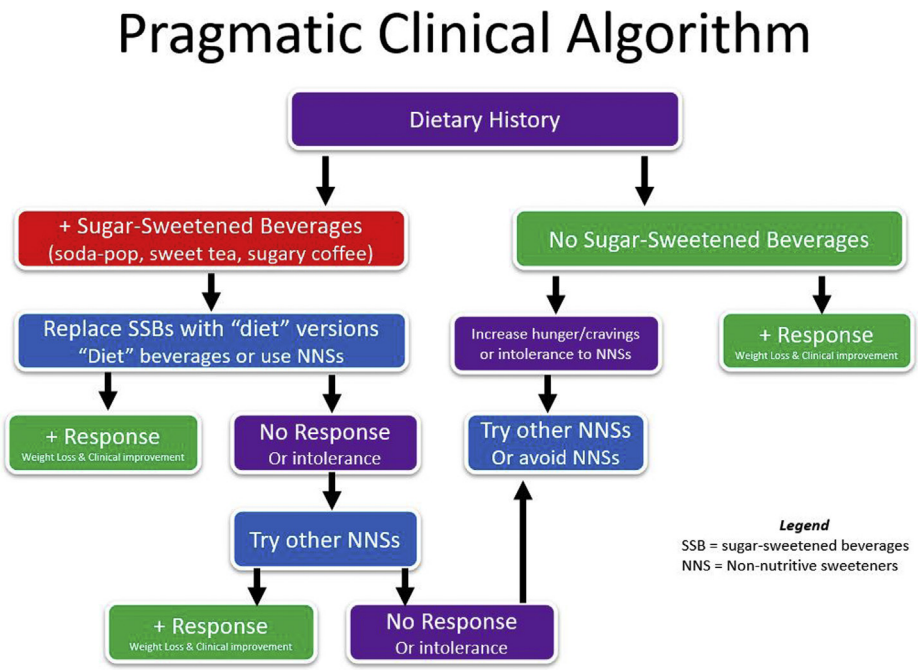

Fig. 2. Pragmatic algorithm to clinically guide patient education on reducing sugar-sweetened caloric intake through replacement with nonnutritive sweetener alternatives.

Disclosure

The author has no multiplicity of interest to disclose.

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