Artificial sweeteners as a sugar substitute: Are they really safe?

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Introduction

Artificial sweeteners are increasingly popular as an alternative to sugar. Increased incidence of obesity, diabetes, and metabolic syndrome, coupled with heightened consumer awareness, has led to a steady paradigm shift toward the use of low-calorie artificial sweeteners. These artificial sweeteners, also called nonnutritive sweeteners (NNS)/low calorie sweeteners/intense sweeteners, provide more intense sweetness and no or a few calories per gram and are used in beverages, dietary products, drugs, and even mouthwashes.\[1\]

The United States Food and Drug Administration (US-FDA) authority has approved six NNS (saccharine, aspartame, sucralose, neotame, acesulfame-K, and stevia) for use in humans and has classified them under generally recognized as safe (GRAS) category. Another two widely used agents are alitame (approved for use in South America, China, and Australia)\[2\] and cyclamate (used in 50 countries excluding the US). Siraitia grosvenorii Swingle fruit extract (SGFE; Luo Han Guo in Chinese) is an herbal-based sweetener recently approved by the FDA. However, to this date, a consensus has not been reached by the scientists regarding the safe use of these artificial sweeteners. NNSs include agents from different chemical classes and are 300–13000 times sweeter than sucrose.\[3\] The FDA has established an acceptable daily intake limit (expressed in mg/kg body weight) for each NNS, and this value is usually set at 1/100 of the no observed adverse effect level.

ABSTRACT

Nonnutritive sweeteners (NNS) have become an important part of everyday life and are increasingly used nowadays in a variety of dietary and medicinal products. They provide fewer calories and far more intense sweetness than sugar-containing products and are used by a plethora of population subsets for varying objectives. Six of these agents (aspartame, saccharine, sucralose, neotame, acesulfame-K, and stevia) have previously received a generally recognized as safe status from the United States Food and Drug Administration, and two more (Swingle fruit extract and advantame) have been added in the recent years to this ever growing list. They are claimed to promote weight loss and deemed safe for consumption by diabetics; however, there is inconclusive evidence to support most of their uses and some recent studies even hint that these earlier established benefits regarding NNS use might not be true. There is a lack of properly designed randomized controlled studies to assess their efficacy in different populations, whereas observational studies often remain confounded due to reverse causality and often yield opposite findings. Pregnant and lactating women, children, diabetics, migraine, and epilepsy patients represent the susceptible population to the adverse effects of NNS-containing products and should use these products with utmost caution. The overall use of NNS remains controversial, and consumers should be amply informed about the potential risks of using them, based on current evidence-based dietary guidelines.

KEY WORDS: Diabetes, metabolic disorder, nonnutritive sweeteners, obesity
level (maximum level at which no adverse effects were seen in animal studies). This review envisages the appropriate use, toxicity, and current guidelines for using NNS in clinical practice.

Uses of Artificial Sweeteners

Extensive marketing by the manufacturers has led to overuse, and sometimes even abuse of NNS, by the population. They are believed to suppress hunger and appetite, leading to beneficial effect on body weight and cardiometabolic profile and are consumed by both lean and obese alike. A huge number of diabetic patients too opt for these “sugar-free” sweeteners as a substitute for sugar in their diet.

Are Nonnutritive Sweeteners Effective and Totally Safe? Evidence-Based Reality

Most NNSs are not metabolized in the body and so, are generally considered safe for consumption. However, there are prevailing concerns over toxicity of “nonmetabolized” compounds in preclinical models. Cyclamate ban in 1970, due to suspicions over carcinogenicity, shocked the artificial sweetener market. In contrast, the carcinogenic concerns have not been replicated in human epidemiological studies. Further, it has been observed that only extensive NNS use (>1680 mg/day) leads to an increased risk of bladder cancer in humans. An 11–12 years follow-up study in the UK showed that consuming 2 or more servings of NNS-containing diet soft drinks increased the risk of coronary heart disease and chronic kidney disease in comparison with consuming <1 serving per month. In a 2007 study conducted during acute exercise in 14 men with type 2 diabetes, Ferland et al. observed that aspartame breakfast induced a rise in glucose and insulin levels similar to the sucrose meal suggesting that NNS consumption might be deleterious for the diabetics. In a recent study, in 17 obese, insulin sensitive subjects with no previous history of NNS use, Pepino et al. observed a greater incremental increase in glucose followed by a 20% increase in insulin secretion rate after sucralose ingestion in comparison with control (water). This effect of sucralose on glycemic and hormonal responses warranted additional studies in distinct heterogeneous populations to evaluate the effects of NNS on metabolic response following ingestion of mixed meal. The benefits of using NNS in obesity are often offset by the phenomena of compensation (ingesting calories later to compensate for energy deficit caused by NNS). Many observational studies have reported contrasting results in the past. A limiting factor in the clinical evaluation of NNS has been the fact that most people use them as diet adjuncts, whereas the majority of the studies replace sugar entirely with NNS. Some earlier studies reported a positive correlation between NNS use and weight gain; however, they were conducted in selected populations. A 2008 study analyzing the San Antonio Heart Study population (5158 adults) indicated a positive direct dose-response correlation between NNS-containing beverage consumption and incidence of obesity in individuals with body mass index (BMI) <30. Mean BMI gain in the NNS group was 1.47, whereas in the nonuser group, it was 1.01. However, given the multitude of dietary and health variables which interact with NNS intake, and the absence of large-scale interventional trials, clear cut evidence-based picture obtained solely from observational data cannot be painted. Another concern remains that the effects of NNS might be confounded by reverse causality.

Recent articles published in nature (2014) reported that NNS ingestion in mice for 11 weeks led to the development of glucose intolerance by altering the gut microbiome. 10-week old mice were fed with varying diet patterns (normal diet/high-fat diet), and their drinking water was laced with either glucose or glucose mixed with saccharin. Saccharin fed mice (in high fat fed) developed marked glucose intolerance as compared to the control group, and this intolerance was abolished by antibiotic treatment and even transferable by fecal transplantation, thereby confirming saccharin’s role in rendering the microbiome unhealthy. This has raised alarms whether NNS use in humans can exacerbate metabolic disorders due to dysbiosis and raise the risk for progression to diabetes and obesity. Hence, a reassessment of the massive and widespread use of NNS is indeed the need of the hour.

Nonnutritive Sweeteners Use: Susceptible Populations

Artificial sweeteners are widely used every day in a variety of food, cosmetic, and dietary products and so, eliminating their daily use is virtually an uphill task. However, their use should be accompanied with caution in certain high-risk individuals such as pregnant and lactating women, diabetics, migraine, and epilepsy patients, and children. Children are especially important because they have higher food and beverage intake per kilogram of their body weight. A pediatric epidemiological study has found a positive correlation between intake of NNS-containing beverage and weight gain; however, conclusive data are still lacking. The use of NNS in epileptic patients is controversial since preclinical studies show a lowering of seizure threshold, whereas some clinical studies exhibit a minor anticonvulsant activity. Nevertheless, they must be used with caution in people with low seizure threshold. A Danish study done in 59,334 pregnant women found that intake of artificially sweetened beverage was associated with an increased risk of preterm delivery. Studies done by Sedová et al., on early life exposure to sucrose-rich diet in rats resulted in higher adiposity and increased liver triglycerides in the offspring. Artificial sweetener use has been associated with triggering migraine in susceptible individuals. Another important and recently highlighted subset is that of diabetic patients routinely relying on these sweeteners to cut down on calories; however, recent evidence hints that this practice might actually be deleterious in the long run.

Guidelines for Practice

Incidence of obesity and diabetes continues to rise worldwide. Health awareness and adopting “healthier” diets in the quest to quell metabolic disorders and diseases are increasing. In addition, there is widespread marketing of NNS by the manufacturers who label them safe for consumption, despite often lacking scientific data. Thus, an evidence-based approach needs to be adopted by the prescribing physicians and dieticians when advising the use of these sweeteners to the patients.
Artificial NNS when consumed in daily acceptable limit can help in limiting carbohydrate and energy intake as a tool to manage weight or blood glucose. Energy allowance should be calculated by the dieticians for each individual consumer based on age, sex, nutritional status, and physical activity.[23] An individualized goal should be set after chalk out a diet plan that incorporates NNS and leads to incomplete compensation of energy reduction. Consumer should be encouraged to establish a holistic dietary environment to maintain weight control. The goal of calorie control by incorporating NNS into daily dietary regimen should be viewed in context of the overall diet plan. Food products with low calories and no added sugars such as fiber-rich grains, green vegetables, fruits, and low/no fat dairy products should be incorporated into the diet.[24] NNS is least useful when they are used to substitute nutrient-dense foods such as milk and fruits.[24] In addition, guided physical activity and counseling should be introduced, and positive as well as negative aspects regarding NNS use should be disclosed to the consumer. The fact that though NNS help in cutting down calories, conclusive evidence of their efficacy in weight loss is still lacking should be made clear.

Diabetes should be advised to consume NNS in minimal amounts as new evidence suggests that long-term use might be harmful in this population subset.[13.14] Carbohydrate intake should be measured by them to achieve a good glycemic control.[25] NNS as such have shown little effect on glycemic response in diabetic patients although some NNS-containing products might contain energy and carbohydrate from other sources and should be borne in mind while prescribing.[26] Stevia (rebiana) has shown minimal effects on blood glucose, and some derived compounds have even shown a therapeutic blood glucose-lowering effect; however, the antidiabetic effects remain inconclusive at present.[5,24] Stevia has also shown antihypertensive effects in preclinical rodent models as well as in a multicentric study in China and it might be beneficial in hypertensives.[24,27]

Social, behavioral, and parental influences often lead to NNS consumption in children, who demonstrate more complete calorie compensation than adults. Evidence states that NNS consumption (dietary products and snacks) between meals may offer optimal benefit in this population subset and may reduce total caloric intake, whereas consumption with meals might lead to compensation by increased intake of meal-related calories.[16] American Dietetic Association states that NNS should not be used in children age <2 years of age and minimal or totally restricted during pregnancy and lactation, even though the FDA has declared the use as not unsafe.[28] Cyclamate, saccharin, and sucrose-containing products should be avoided at best, whereas other NNS can be used in moderate amounts or better still, not used at all.[20,24,29] Due to lack of large-scale studies at present, NNS-containing products should be used in moderation or not at all used in epilepsy and migraine patients.[17,21,22]

SGF (Luo Han Guo/SGFE) was recently given the GRAS category status by the FDA and contains sweet glycoside mogroside V as the primary sweetening component.[30] Another newer agent, advantame, has been approved by the FDA in 2014 for use as a sweetener and flavor enhancer, except in meat and poultry.[31] It is a heat stable, chemical analog of aspartame that generates lesser amounts of phenylalanine and thus, unlike aspartame, does not have to bear warning label for people with phenylketonuria.[32] However, extensive and long-term clinical data on both these agents are awaited before their safety in special populations can be determined.

Conclusion

NNSs are ubiquitous and found in a variety of products around us. Their use has been controversial and riddled with many concerns regarding their safety. They are used by obese and lean, diabetics and nondiabetics, adults and children alike and extensive marketing and increased health awareness have led to their widespread use. They provide greater food choices to people looking to cut down calories and improve the palatability of food. However, many of their purported beneficial effects remain invalidated in large scale clinical studies, and some recent evidence also questions these previously established benefits. It is imperative that health-care providers judiciously assess the overall individual benefits and risks of NNS use to a consumer before recommending their use. Different population subsets incorporate NNS-containing products into their diet with different goals and the same should be borne in mind while recommending a holistic dietary plan to the consumer. It is duty of the health-care providers to be aware of the latest evidence-based dietary guidelines and to inform the consumers regarding the potential risks associated with NNS use.

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Conflicts of Interest

There are no conflicts of interest.

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