Nutrition 29 (2013) 1293–1299

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Non-nutritive sweeteners: Review and update

Padmini Shankar Ph.D., R.D. [a,*], Suman Ahuja Ph.D. [b], Krishnan Sriram M.B.B.S., F.R.C.S(C), F.A.C.S. [c]

[a] Department of Health and Kinesiology, Georgia Southern University, Statesboro, GA, USA
[b] Department of Cooperative Research, Human Nutrition/Obesity Research, Lincoln University, Jefferson City, MO, USA
[c] Division of Surgical Critical Care, Surgical Nutrition Section and Nutrition Support Team, Stroger Hospital of Cook County, Chicago, IL, USA

ARTICLE INFO

Article history:
Received 19 November 2012
Accepted 31 March 2013

Keywords:
Non-nutritive sweeteners
Obesity
Artificial sweeteners
Non-caloric sweeteners
Sugar substitutes

ABSTRACT

Obesity has become an epidemic, not just in the United States, but also across the globe. Obesity is a result of many factors including poor dietary habits, inadequate physical activity, hormonal issues, and sedentary lifestyle, as well as many psychological issues. Direct and indirect costs associated with obesity-related morbidity and mortality have been estimated to be in the billions of dollars. Of the many avenues for treatment, dietary interventions are the most common. Numerous diets have been popularized in the media, with most being fads having little to no scientific evidence to validate their effectiveness. Amidst this rise of weight loss diets, there has been a surge of individual products advertised as assuring quick weight loss; one such product group is non-nutritive sweeteners (NNS). Sugar, a common component of our diet, is also a major contributing factor to a number of health problems, including obesity and increased dental diseases both in adults and children. Most foods marketed towards children are sugar-laden. Obesity-related health issues, such as type 2 diabetes mellitus, cardiovascular diseases, and hypertension, once only commonly seen in older adults, are increasing in youth. Manufacturers of NNS are using this as an opportunity to promote their products, and are marketing them as safe for all ages. A systematic review of several databases and reliable websites on the internet was conducted to identify literature related to NNS. Keywords that were used individually or in combination included, but were not limited to, artificial sweeteners, non-nutritive sweeteners, non-caloric sweeteners, obesity, sugar substitutes, diabetes, and cardiometabolic indicators. The clinical and epidemiologic data available at present are insufficient to make definitive conclusions regarding the benefits of NNS in displacing caloric sweeteners as related to energy balance, maintenance or decrease in body weight, and other cardiometabolic risk factors. Although the FDA and most published (especially industry-funded) studies endorse the safety of these additives, there is a lack of conclusive evidence-based research to discourage or to encourage their use on a regular basis. While moderate use of NNS may be useful as a dietary aid for someone with diabetes or on a weight loss regimen, for optimal health it is recommended that only minimal amounts of both sugar and NNS be consumed.

Introduction

In recent years, increased obesity related mortality has resulted in a surge of weight loss diets and products, and various fitness routines. It is widely understood that of the many contributing factors, a high sugar/high fat diet is partly to be blamed for the increasing obesity and related health issues such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), hypertension, and certain cancers [1,2]. As a result of the many negative health conditions associated with the intake of excessive sugar, there has been an upsurge in the consumption of NNS as an alternative [3]. Consumption of NNS-containing foods has increased among people of all ages, with 28% of the total population reporting intake. This trend is highly prevalent among children, especially when it comes to beverage intake. Analysis of National Health and Nutrition Examination Survey data collected from 1999 to 2008 shows that NNS-containing beverage use increased from 6.1% to 12.5% among children and from 18.7% to 24.1% among adults [4]. A large variety of NNS are available, and they are differentiated based on whether they are high-intensity, low-calorie, high-potency, and/or non-nutritive [3]. NNS are known to be at least 30 to 13,000 times sweeter in taste compared with their natural counterpart, sugar (sucrose).

* Corresponding author: Tel.: 912-478-5785; fax: 912-478-0381.
E-mail address: pshankar@georgiasouthern.edu (P. Shankar).

0899-9007/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nut.2013.03.024

This intense sweetness allows for smaller portions to yield sugar like sweetness in food products, thus enabling the manufacturer to label them as virtually "sugar free" or "non-caloric" [3].

The increased incidences of obesity and related health issues, mainly T2DM and CVD, have resulted in an increased production and consumption of foods made with NNS. The fundamental principle behind this upsurge in use of NNS is that individuals struggling with obesity can enjoy foods and beverages without the risk of consuming additional calories contributed by normal sugar-based products. NNS can be found in almost any food product such as beverages, ice cream, chewing gum, chocolate, jams/jellies, yogurt, and salad dressings. Overzealous use of these NNS brings to light the issue of safety, mainly with respect to the maximum amounts of said NNS considered safe for human consumption and whether there are any associated health issues with the use of these laboratory-created sweeteners.

Since their discovery and introduction into the public market, there has been much debate regarding the health advantages and disadvantages of artificial sweeteners. The very first evidence of artificial sweetener–related health issues was observed by the FDA before it banned a commonly used sugar substitute known as cyclamate, which was deemed inappropriate for consumption due to its carcinogenic effects evidenced through many animal studies [5]. Since then, the NNS industry has come a long way and consumers now have products safe for consumption, even for kids. However, irrespective of advancements in technology, it appears that scientific information regarding these sweeteners and the established amounts considered safe for consumption seem to be scarce. Hence, through this review, we aim to establish scientific information about the most commonly used artificial sweeteners in the food industry. In reviewing these NNS, we will discuss issues involving the sweetness factor compared with sucrose, FDA-recommended safety guidelines, health implications of consuming these sweeteners, threat of a carcinogenic and/or teratogenic effect, energy restriction, and other common issues such as sweeteners acting as laxatives when consumed in excess.

Methods

Based on these factors, we decided to review the pros and cons of consuming NNS, and to outline salient properties of some of the most commonly used NNS to help clinicians counsel their patients accordingly. A systematic review of several databases including MEDLINE and PubMed, and reliable websites on the internet was conducted from 1987 to 2012 to identify literature related to NNS. The keywords used individually or in combination, artificial sweeteners, non-nutritive sweeteners, non-caloric sweeteners, obesity, sugar substitutes, diabetes, and *cardiometabolic indicators*, were variously combined in the search list.

Role of non-nutritive sweeteners on glucose homeostasis

Non-nutritive sweeteners have been in use for decades for both weight loss and in diabetic diets. In fact, the Academy of Nutrition and Dietetics [6] suggests NNS may be used to enhance the palatability of foods to help consumers increase their consumption of certain foods to be included in their respective dietary routines. However, the understanding thus far was that NNS did not affect fasting glucose and insulin responses in patients with TD2M supplemented with NNS, particularly sucralose, to assist these patients in increasing compliance with their dietary needs [7]. To better understand the effects of NNS on glucose homeostasis, a recent study investigated the short-term effects of sucralose on glucose homeostasis and hunger compared with water, sucrose, and sucrose combined with sucralose in the liquid form [8]. Additionally, the study also examined the effects of consuming the aforementioned treatment beverages before consumption of a standardized breakfast to determine the physiological responses elucidated by the body in response to specific meals. The amount of sucralose used in the study approximated that of what is in a regular soft drink. Blood samples were collected at fasting, post-treatment, and after breakfast; the study found no differences in subjective responses, circulating triglycerides, or glucagon concentrations among treatment groups over time. However, the study reported significant differences in insulin, glucose, and ghrelin concentrations over time between the sucrose and non-sucrose treatments regardless of their sucralose consumption. Thus, the study concluded that sucralose may in fact be a relatively inert NNS as far as evoking hunger signals and short-term glucose homeostasis.

Non-nutritive sweeteners and their influence on weight control

Because NNS are alternatives to table sugar and its calories, theoretically, NNS would only aid in weight loss if compensatory sugar intake does not occur. Of concern is the appetite-promoting effect of NNS. Rats administered liquids containing saccharin consumed more food and gained more weight compared with rats given liquids containing glucose. The common perception that NNS may promote weight loss by reducing calories is misguided because consumption of saccharin-sweetened liquids increased overall food intake [9]. Furthermore, positive correlations between NNS consumption and increased body mass index in children and adolescents have been reported in several observational studies [10–12]. However, there is a lack of conclusive evidence to state that NNS may be the cause of weight gain in children [13]. A second study found no evidence to link NNS use to weight gain in adults either [14]. Management of obesity is multifactorial, and no adequate evidence exists to target NNS use as an effective strategy in weight management. Other factors associated with modern lifestyle behaviors and genetics may be confounding influences that promote weight gain.

A Western diet and sedentary lifestyle encouraging energy-dense foods have resulted in a surge of chronic diseases that have led to an interest in gene–diet interactions within the clinical and scientific community. Understanding this gene–diet interaction can help promote diet modifications and reduction of obesity-related health disorders based on genetic makeup. Of all the energy-dense foods, it appears that consumption of sugar-sweetened foods and beverages may have the most effect on gene–diet-related patterns of obesity [15].

Saccharin

Saccharin has been on the market for more than 100 y and is the oldest NNS. It was discovered by Remsen and Fahlberg at John Hopkins University in 1879. This non-caloric sweetener is 200 to 700 times sweeter than sugar. It is marketed under the brand names Sweet'N Low®, Sugar Twin®, and Necta Sweet®. In the food industry, it is commonly used in soft drinks, baked goods, jams, canned fruit, candy, salad dressing, dessert toppings, and chewing gum, in addition to being used as a tabletop sweetener. It also is used in other household products such as toothpaste, lip gloss, mouthwash, vitamins, and pharmaceuticals. An important characteristic of saccharin is that its sweetening power is not reduced when heated, which makes it an excellent

candidate as an additive in low-calorie and sugar-free products. Saccharin is not metabolized in the gastrointestinal (GI) tract and therefore does not affect blood insulin levels [16], which makes saccharin a viable sugar substitute for patients with diabetes.

The Adequate Dietary Intake (ADI) for saccharin is set at 5 mg/kg body weight per day for adults and children. As per a 2010 report in *Current Oncology* [17], one would have to drink about 800 twelve-ounce diet sodas containing saccharin to reach doses that can induce carcinogenesis. The ADI also means that one can "safely consume 8.5 tabletop sweetener packets nearly every day over his or her lifetime." It seems highly unlikely that any population would exceed the ADI for such intense sweeteners, considering the average user of saccharin ingests less than 1ounce of the sweetener each year. In a Belgian study, no risk for exceeding the ADIs established for saccharin and other similar sweeteners was found among individuals older than age 15 y [18].

However, a survey of the usage pattern of saccharin in edible products in India found that in all age groups consumption exceeds the ADI, with the most susceptible group being the 6- to 10-y age group, who exceeded the ADI by 54% through the consumption of ice candy and crushed ice. Intake of foods containing saccharin is high in India, as it is the cheapest and most widely used NNS product. Furthermore, a habitual intake of pan masala and pan betel products resulted in an excessive consumption of saccharin with an estimated maximum daily intake that exceeded the ADI by 137% [19]. Thus, overconsumption is possible in some settings warranting further study.

Since its introduction into the market, saccharin has been researched extensively to determine its carcinogenic potential. Studies in the 1970s and 1980s reported bladder cancer in rats given high doses of saccharin, which prompted the FDA in 1981 to pass a mandate that products containing saccharin carry a label warning about its potential as a human carcinogen [20]. However, it was later found that the cancer-causing mechanisms in rodents are not applicable to humans. Furthermore, clinical studies conducted since then have shown no association between saccharin consumption and cancer in humans [21]. As a result, in 2000, saccharin was delisted from the National Toxicology Report on Carcinogens and labels no longer have to display such warning [22].

A case–control study in Italy examined the association between saccharin and other NNS and gastric, pancreatic, and endometrial cancers between 1991 and 2004. The results of this study indicate that consumption of NNS products such as saccharin and aspartame are not associated with the risk for neoplasms in the population studied [23].

In a recent study, rats that consumed saccharin-sweetened liquids had an increased food intake and gained more body weight than rats that consumed glucose-sweetened liquids [9]. The findings of this study have major implications on public health, given that people are consuming foods containing NNS in an effort to lose weight. This study, although not done on humans, challenges the popular notion that use of intense NNS help in weight loss due to the calorie deficit. In another study, the same authors reported that in addition to increased energy intake and weight gain, use of NNS also caused accumulation of body fat and weaker caloric compensation [24].

Saccharin is the oldest and most researched of all NNS. It bears the FDA stamp of approval in suggested quantities by being a food additive on the Generally Recognized as Safe (GRAS) list [25]. GRAS is a term designated to any substance added to food as an additive that is considered to be generally safe for human consumption. Despite its questionable carcinogenic history, currently there is not enough evidence that identifies it as a carcinogenic agent and it appears to be safe for consumption among children and adults, including pregnant women and patients with diabetes when quantities consumed are within the ADI recommendations.

Aspartame

Aspartame was originally discovered by James Schalatter, a chemist, who was working on an anti-ulcer drug. It is the methyl ester of the two amino acids, aspartic acid and phenylalanine. Although discovered in 1965, aspartame was not approved by the FDA until 1981 [26]. It is sold under the brand names Equal®, NutraSweet®, and Natra Taste®. Because it is made from amino acids, it provides 4 kcal/g. Aspartame is 200 times sweeter than sucrose and therefore very small amounts are required for sweetening foods, thus making its caloric contribution insignificant. According to the FDA, the acceptable daily intake of aspartame for humans is 50 mg/kg body weight, for both adults and children [27]. Aspartame is used as a sweetener in many products including chewing gum, diet soda, dry drink mixtures, yogurt and pudding, and instant tea and coffee. The flavor profile of aspartame is found to be highly acceptable. In a study on the effects of artificial sweeteners on food intake and satiety, aspartame was found by participants to have a more pleasant taste compared with stevia or sucrose [28]. Furthermore, aspartame does not elicit the same response as sugar does in the brain or the pancreas. A magnetic resonance imaging study showed a decline in activity of the hypothalamus part of the brain after ingestion of sucrose, whereas aspartame does not show similar response. It is suggested that for a hypothalamic reaction to occur there should be the combined stimuli of sweet taste and energy content, as found in sweetened caloric beverages. In the pancreas, aspartame does not stimulate an insulin response as sugar does [29].

Aspartame is metabolized to phenylalanine, aspartic acid, and methanol in the GI tract. People with the genetic disorder, phenylketonuria, must exercise caution because they cannot break down phenylalanine to tyrosine, and therefore must avoid aspartame [26]. Because of aspartame's effects on these patients, the FDA requires all aspartame products to have a label stating the containment of phenylalanine [6]. Common side effects reported from aspartame consumption include dizziness, headaches, GI issues, and mood changes [30].

There are mixed reports about the safety of aspartame. All of the studies funded by the industry vouch for its safety, whereas 92% of independently funded studies report that aspartame can cause adverse health effects [31]. Several studies have reported aspartame to be a trigger in causing headaches, with some people being more susceptible to this malady [32–34]. There are still many claims that a number of health problems are associated with consumption of aspartame including, but not limited to: Alzheimer's disease, attention-deficit disorders, birth defects, cancer, diabetes, Gulf War syndrome, and lupus [27]. Aspartame can promote seizures in susceptible animal models by increasing phenylalanine levels in the brain. A similar effect is probable in human beings with seizures caused by increased phenylalanine [35]. In pregnant rats, aspartame proved to be nephrotoxic by causing alterations in the morphology of renal structures in the fetus and by causing decreased fetal body weight [36]. No association was found between aspartame consumption and the risk for common neoplasms such as gastric, pancreatic, and endometrial cancers among Italian people [23]. Aspartame intake during pregnancy and lactation was not found to increase risk for brain tumors among children [37]. Aspartame remains

one of the most controversial and widely used artificial sweeteners today.

Acesulfame-K

Acesulfame-K was discovered in 1967 by the pharmaceutical company, Hoechst. This high-intensity sweetener is about 200 times sweeter than the table sugar sucrose [38]. It is used in more than 100 countries in more than 5000 products [39]. In the United States, acesulfame-K was initially permitted only in foods such as sugar-free baked goods, chewing gum, and gelatin desserts. In July 1998, this non-caloric sweetener was approved for use in soft drinks by the FDA [40]. Acesulfame-K is sold under the brand names Sunette®, Sweet One®, and Swiss Sweet® [41]. Acesulfame-K is heat stable and can be used in cooking and baking.

The ADI for acesulfame-K is 15 mg/kg body weight. In the United States, actual consumption is about 20% of the ADI over a lifetime [42]. As such, typical amounts of acesulfame-K and other artificial sweeteners consumed by the average population are quite low that toxicity is highly unlikely. In Portuguese teenagers, the highest estimated daily intake of acesulfame-K and aspartame was from soft drinks. However, the amount consumed was well below the ADI and this population was noted to be at low risk for any adverse effects arising from use of these artificial sweeteners [43].

Being a blended product comprising of an organic acid and potassium, acesulfame-K typically is found in food products in combination with other artificial sweeteners, which helps in developing an optimal flavor profile [44]. It is usually combined with aspartame or sucralose to provide a synergistic sweetening effect. Such combinations not only provide a “more sugar-like taste” but also decrease the total amount of sweetener used [41]. Concerns about the safety profile of blends of artificial sweeteners are addressed in a study that found no synergistic genotoxic effects when acesulfame-K was used in combination with aspartame in mice [45].

Acesulfame-K is excreted by the kidneys after it passes through the body unchanged [44]. One of the byproducts of acesulfame-K’s breakdown in the body is acetoacetamide, which is toxic at high doses. However, the amount of acesulfame-K used to sweeten a beverage is very small and as such does not pose a safety hazard [46].

Widespread concerns exist about the safety of acesulfame-K, since it was tested in the 1970s when “the standard criteria for the design of animal carcinogenesis bioassays were still under development” [47]. The FDA approved acesulfame-K despite inadequate and poor-quality toxicity tests. Although acesulfame-K was nominated twice for testing in 1996 and 2006 in the National Toxicology Program (NTP) bioassay program, the motion was rejected by NTP and the product has not been subjected to such testing.

Sucralose

Sucralose, an artificial sweetener discovered in 1976, was granted FDA approval in 1998 for use as a sugar substitute in 15 food and beverage categories. Marketed under the brand name Splenda®, sucralose has a taste profile very similar to sugar and has no unpleasant aftertaste, an undesirable trait found in many other NNS. Extensive testing has established an excellent safety profile for sucralose, allowing it to be used among all population groups, including pregnant and nursing mothers [48].

Sucralose is a highly intense sweetener that is 600 times sweeter than table sugar. It is made by selective substitution of chlorine for hydroxyl groups on a sucrose core. This compound is not recognized by the body as a carbohydrate due to being poorly absorbed during the digestion process. It passes through the body relatively unchanged with insignificant amounts being absorbed in the GI tract. Eventually, it is eliminated in the feces unchanged [44]. Sucralose is exceptionally stable and is able to retain its sweetness when subjected to high heat and acidity [49]. In the food industry, it is widely used as a NNS and is found in more than 4000 products in the United States [50]. Sucralose is also used as a sweetener in more than 80 countries today [51].

In a study comparing the sensory profile of several sweeteners, it was found that sucralose is most similar to table sugar [52], but unlike table sugar, sucralose does not promote tooth decay. In 2006, the FDA approved the use of a health claim regarding sucralose and the non-promotion of dental caries [53].

The safety profile of sucralose has been extensively reviewed and has been reported to be non-carcinogenic and non-genotoxic. Furthermore, due to its lack of bioreactivity and bioaccumulation in humans and animal models, sucralose is considered to be safe for long-term use [54].

There have been some claims that sucralose may negatively affect health. One controversial study found it to cause adverse effects in the GI tract [55]. Rats that consumed Splenda® for 12 wk had a significant decrease in beneficial gut bacteria with resulting weight gain, increased fecal pH due to decreased production of short-chain fatty acids by colonic bacteria, and enhanced expression of cytochromes in the body that can potentially affect bioavailability of nutrients and drugs. Furthermore, the stated changes in the GI tract occurred even when the rats were fed sucralose at low doses approved by the FDA for human consumption [55]. However, these results were widely criticized, with an expert panel report citing that the study is “deficient in several critical areas” and that the conclusions from the study are not “scientifically valid” [56].

Sucralose has been deemed safe for consumption by patients with diabetes because it has no effect on carbohydrate metabolism [57]. This NNS does not change the rate of glucose absorption from the small intestine; nor does it increase glycemic response or levels of incretin hormones such as glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in healthy humans given an intraduodenal/intragastric infusion [58,59]. Furthermore, sucralose did not stimulate insulin release or slow gastric emptying, thereby maintaining glucose homeostasis in the study population [59]. Other study findings indicate that sucralose had no effect on appetite in healthy, normal-weight adults [60]. NNS have been purported to increase insulin resistance, which could lead to weight gain. However, in a study comparing the body’s response to sucrose and sucralose, sucralose did not raise blood sugar levels or increase insulin resistance [61].

Because NNS are widely used by the public including women of childbearing potential, concern exists about its possible teratogenic effects. No adverse effect on normal fetal development was observed in pregnant rats and rabbits when fed sucralose during organogenesis [62]. However, some potential adverse health effects are reported from sucralose use. Case studies have identified sucralose to be a causative agent in triggering migraine headaches [63,64]. In a hypothetical report, sucralose is suggested to be the most likely cause in the increased incidence of inflammatory bowel disease among Canadians due to its inhibiting action on gut bacteria, gut barrier function, and digestive protease enzymes [65].

Sucralose is one of the most researched and reviewed food additives today. Based on its strong safety background, it is even promoted for use among children. It is recommended that it be used in children's foods to reduce sugar calories, which could be an effective strategy to combat childhood obesity [50], which is one of the most challenging public health concerns today.

Tagatose

Over the last few years, numerous NNS have been added to the list, one of them being a ketohexose also known as D-tagatose. Tagatose is a fructose isomer that is commonly found in milk and milk products. In comparison with sucrose and other sugars, it has been reported that tagatose produces a lower glycemic response and virtually zero calories [66]. This sweetener has been examined for its safety and functional properties as a bulk sweetener [8,67]. For an artificial sweetener to be considered a staple in commercial food products, the two qualities that render it useful for consumption are safety and taste. A study investigating D-tagatose as a bulk sweetener reported that this sweetener not only has physical attributes identical to that of sucrose, but, the sweetness was comparable to sucrose as well. In fact, this study reported that trace amounts of D-tagatose are commonly found in certain milk products [8]. Another study reported that per FDA laws and policies, D-tagatose was found to contain no toxic, carcinogenic, or teratogenic compounds or effects upon consumption [8]. A common problem associated with consumption of most artificial sweeteners is the fact that they can act as laxatives and although the FDA does not label a laxative effect as toxic, it does require that food manufacturers using sugar substitutes in their products label cautionary information regarding the possibilities of a laxative effect and subsequently print amounts/serving sizes safe for consumption to avoid such health issues [8]. In an experimental study, rats were fed a diet comprising of 20% (wt:wt) D-tagatose. The researchers evaluated both a stool-softening as well as a laxative effect induced by the sweetener. The results revealed that a laxative effect was observed only upon inducing higher doses. However, with the doses administered, the rats had normal stools and it appears that the D-tagatose was well tolerated over a period of 3 d [67]. Similar tests, when performed on humans, revealed that the mean laxative threshold value when consuming D-tagatose was approximately 40 g per meal over a single meal. However, additional studies are required to attest to these findings [67]. Another study reported that humans can easily tolerate up to 75 g of D-tagatose as long as it is equally distributed over three meals [8]. It also was reported that after carefully controlled experimental studies, D-tagatose could be used safely in products to assist with weight loss as well as diabetes because this sweetener effectively had a zero energy value as revealed via metabolic experimental studies [8,67]. One study even reported possible anti-aging properties induced by D-tagatose by way of animal subjects (rats) on D-tagatose, demonstrating consistently low plasma glucose and insulin levels compared with those fed a regular glucose diet [68]. Of course, extensive human studies would be required to justify the anti-aging properties of this sugar substitute. Finally, it has been reported that tagatose might have pharmaceutical capabilities, especially in treating patients with diabetes. A Phase III clinical trial is in place to investigate the mechanisms and efficacy of tagatose in reducing hemoglobin A_{1c} levels. Although, the trials are still under way, human studies have suggested that tagatose could be the new potential antidiabetic drug because of its effects on postprandial hyperinsulinemia and hyperglycemia in individuals with T2DM [69]. Nonetheless, it appears that at this time D-tagatose has been successfully used in chocolate and chewing gum, however, whether it may be approved as a sugar substitute safe for consumption on a regular basis and an appropriate replacement for table top sugar will depend on approvals from the FDA and other such entities.

Sugar alcohols

Sugar alcohols are saccharide derivatives obtained by replacing an aldehyde group with a hydroxyl group. Additionally, sugar alcohols also are classified as hydrogenated monosaccharides most commonly known as sorbitol, mannitol, and xylitol; hydrogenated disaccharides such as isomalt, maltitol, and lactitol; and as mixtures of hydrogenated mono-di- and/or oligosaccharides such as hydrogenated starch hydrolysates [70]. It is the limited digestion and absorption associated with sugar alcohols that make them a primary choice of ingredients in sugar- and energy-restricted foods [70]. Several factors affect the digestion and absorption of sugar alcohols, one being gastric transit time and the fact that sugar alcohols might get fermented by gut bacteria, thus allowing limited absorption and to a certain extent, some sugar alcohols may escape the process of absorption completely [70]. However, unlike other NNS, it is important to note that with sugar alcohols that make it as far as the distal intestine, they will be subjected to some amount of fermentation thus leading to production of hydrogen, methane, carbon dioxide, and small amounts of short-chain fatty acids. Of all the gaseous matter produced, likelihood of short-chain fatty acids being converted to small amounts of energy are very plausible. Although the energy available from sugar alcohols is 15% to 25% lower than glucose, the conversion of energy to adenosine triphosphate is almost as efficient as that of glucose [70]. Thus, for these reasons, the 1990 European Council Directives established an energy value for sugar alcohols for the purpose of food labeling [71].

Although sugar alcohols are widely used in foods, limited research is available to determine the metabolic effects of these sweeteners in humans [72]. A recent study investigated the metabolic effects of lactitol and xylitol in comparison with glucose on plasma insulin, glucose, and C-peptide in eight healthy, non-obese men. It was observed that upon ingestion of 25 g of lactitol or xylitol, plasma insulin, glucose, and C-peptide concentrations were not affected as dramatically as with ingestion of glucose [72]. In fact, this study also reported that glycemic indices of lactitol and xylitol were found to be –1 and 7 compared with 100 g of glucose. Finally, the effects of consumption of these sugar alcohols on carbohydrate and lipid oxidation is very minimal compared with glucose [72]. Hence, it might be worth exploring use of these sugar alcohols in food products marketed to patients with diabetes and individuals considering energy-restricted diets.

Stevia

Stevia, a natural NNS, is a glycoside isolated from the plant *Stevia Rebaudiana Bertoni* and has been widely used in Japan for more than 20 y [73,74]. Recently, stevia has been marketed as a no-calorie sweetener in baked goods and soft drinks. Studies have indicated possible hypotensive roles performed by stevia [74], in addition to some suggesting stevia increases insulin sensitivity and glucose tolerance in humans [28]. As far as safety issues concerning stevia, no negative side effects have been reported thus far. In fact, very recently stevia was approved for use

as a sweetener by the Joint Food and Agriculture Organization/World Organization Expert Committee on Food Additives [28]. A recent study evaluated the taste responses of rodents (mice and rats) to both stevia and saccharin. It was reported that both mice and rats responded strongly to stevia compared with other non-caloric sweeteners, mainly aspartame and cyclamate [73]. Such experiments provide a new understanding of the effectiveness of these products. Of course, animal data would have to be tested in humans before any conclusions on the safety and efficacy of these products are to be claimed. The very first study [28] that investigated the effects of stevia on food intake, satiety, and postprandial glucose and insulin responses in humans reported that participants who consumed products made with stevia had a lower total caloric intake compared with those consuming sucrose. Furthermore, consumption of stevia significantly lowered insulin levels compared with both aspartame and sucrose, thus suggesting that using stevia in place of sucrose might be an effective way of managing food intake and satiation concerns. This study also reported that individuals consuming stevia had significantly lower postprandial glucose responses compared with those on aspartame and sucrose [28]. These findings suggest promising avenues for both manufacturers and individuals turning to products made with artificial sweeteners to combat the twin epidemics of obesity and T2DM.

Conclusion

Consumers often do not have adequate information about NNS. The pieces of information they are provided often are contradictory depending on the motive and investment of the body, industry, or agency providing the information. Although the FDA and most published (especially industry-funded) studies endorse the safety of these additives, there is a lack of conclusive evidence-based research to discourage or to encourage their use. However, consumers should be advised to employ a cautious attitude when using artificial sweeteners. When using any new product, it is important to monitor for symptoms related to allergies or intolerance, which may occur even when very small amounts are consumed. It is highly unlikely that U.S. consumers will exceed the ADI established for NNS. As these products have been on the market for decades, with consumption patterns on the rise and no reported adverse health problems affecting large numbers of people, their continued popularity and increased use are to be expected.

The clinical and epidemiologic data available at present are insufficient to make firm conclusions regarding the benefits of NNS displacing caloric sweeteners in energy balance maintenance or decrease of body weight or cardiometabolic risk factors. As a result of scarce epidemiologic and clinical data on the pros and cons of consuming NNS, very few recommendations regarding consumption of artificial sweeteners are made available. However, the Academy of Nutrition and Dietetics recommends using artificial sweeteners in moderation, in conjunction with a healthy diet based on the recommendations provided in the Dietary Guidelines for Americans [6]. Given the sudden rise in obesity and related health issues, it is crucial that clinicians and scientists pursue research involving use of artificial sweeteners to understand their effects on energy consumption, appetite, satiety, body mass index, weight management, biochemical parameters such as insulin, glucose, leptin, cortisol, and finally the effects of artificial sweeteners on food cravings.

A recent scientific statement issued jointly by the American Heart Association and the American Diabetes Association adds credibility to this assertion [75]. A more recent publication emphasizes that obesity is not related to sugar consumption [76]. Weight management depends more on total calorie restriction rather than avoidance of caloric sweeteners. However, the use of NNS as an adjunct to dietary management in diabetes, in an attempt to optimize glycemic control, is more acceptable and practiced more frequently.

For optimal health it is recommended that only minimal amounts of both sugar and NNS be consumed. Today, there is renewed emphasis on eating fresh, local, and natural foods to maintain good health and promote sustainability. This calls for a balanced diet that includes whole grains, vegetables, fruits, legumes, nuts and seeds, low-fat dairy and lean meats, and avoidance or minimal inclusion of processed foods and additives. If these general principles of lifestyle are followed, artificial sweeteners, like the sugars they replace, will have an insignificant role in our diet and our lives.

Acknowledgments

We would like to thank Alexandra Tracchio and Shannon Cearley for their help in preparation of the manuscript.

References

[1] Mendendez de la Granda MB, Sinclair AJ. Fatty acids and obesity. Curr Pharm Des 2009;15:4117–25.
[2] Tandel KR. Sugar substitutes: health controversy over perceived benefits. J Pharmacol Pharmacother 2011;2:236–43.
[3] Zygler A, Wasik A, Wasik AK, Namiesnik J. Determination of nine high-intensity sweeteners in various foods by high-performance liquid chromatography with mass spectrometric detection. Anal Bioanal Chem 2011;400:2159–72.
[4] Sylvetsky AC, Welsh JA, Brown RJ, Vos MB. Low-calorie sweetener consumption is increasing in the United States. Am J Clin Nutr 2012;96(3):640–6.
[5] Weihrauch MR, Diehl V. Artificial sweeteners–do they bear a carcinogenic risk? Ann Oncol 2004;15:1460–5.
[6] Position of the Academy of Nutrition and Dietetics. Use of nutritive and nonnutritive sweeteners. J Acad Nutr Diet 2012;112:739–58.
[7] Grotz LV, Henry RR, McGill JB, Prince MJ, Shamoon H, Trout JR, et al. Lack of effect of sucralose on glucose homeostasis in subjects with type 2 diabetes. J Am Diet Assn 2003;103:1607–12.
[8] Livesey G, Brown JC. D-tagatose is a bulk sweetener with zero energy determined in rats. J Nutr 1996;126:1601–9.
[9] Swithers S, Martin A, Clark K, Laboy A, Davidson TL. Body weight gain in rats consuming sweetened liquids: effects of caffeine and diet composition. Appetite 2010;55:528–33.
[10] Giammattei J, Blix G, Marshak HH, Wollitzer AO, Pettitt DJ. Television watching and soft drink consumption: association with obesity in 11- to 13-year old school children. Arch Pediatr Adolesc Med 2003;157:882–6.
[11] Forshee RA, Storey ML. Total beverage consumption and beverage choices among children and adolescents. Int J Food Sci Nutr 2003;54:297–307.
[12] Blum JW, Jacobsen DJ, Donnelly JE. Beverage consumption patterns in elementary school aged children across a two-year period. J Am Coll Nutr 2005;24:93–8.
[13] Foreyt J, Kleinman R, Brown RJ, Lindstrom R. The use of low-calorie sweeteners by children: Implications for weight management. J Nutr 2012;142:S1155–62.
[14] Anderson GH, Foreyt J, Sigman-Grant M, Allison DB. The use of low-calorie sweeteners by adults: Impact on weight management. J Nutr 2012;142:S1163–9.
[15] Qi L. Gene-diet interactions in complex diseases: current findings and relevance for public health. Curr Nutr Rep 2012;1:222–7.
[16] Mukherjee M, Sarkar A. Sugar content in artificial sweetener. Adv Appl Sci Res 2011;2:407–9.
[17] Editor. Saccharin deemed “not hazardous” in United States and abroad. Curr Oncol 2010;18:213–4.
[18] Huvaere K, Vandevijvere S, Hasni M, Vinkx C, Van Loco J. Dietary intake of artificial sweeteners by the Belgian population. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2012;29:54–65.
[19] Tripathi M, Khanna SK, Das M. Usage of saccharin in food products and its intake by the population of Lucknow, India. Food Addit Contam 2006;23:1265–75.
[20] Artificial sweeteners and cancer. National Cancer Institute. Available at m.cancer.gov/topics/factsheets/artificial-sweeteners. Accessed February 19, 2013.

[21] Gallus S, Scotti L, Negri E, Talamini R, Franceschi S, Montella M, et al. Artificial sweeteners and cancer risk in a network of case–control studies. Ann Oncol 2007;18:40–4.
[22] News and views—No longer too sweet to be wholesome. Diabetes Obes Metab 2000;2:327.
[23] Bosetti C, Gallus S, Talamini R, Montella M, Franceschi S, Negri E, et al. Artificial sweeteners and the risk of gastric, pancreatic, and endometrial cancers in Italy. Cancer Epidemiol Biomarkers Prev 2009;18:2235–8.
[24] Swithers SE, Martin AA, Davidson TL. High intensity sweeteners and energy balance. Physiol Behav 2012;100:55–62.
[25] U.S. Department of Health and Human Services. Food guidance for industry: frequently asked questions about GRAS. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Food Safety and Applied Nutrition. Available at http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments. Accessed February 19, 2013.
[26] FDA statement on European aspartame study. CFSAN/Office of Food Additive Safety. Available at www.fda.gov/Food/FoodingredientsPackaging/FoodAdditives/ucm208580. Accessed February 19, 2013.
[27] Learn about cancer. Aspartame. Available at http://www.cancer.org/Cancer/CancerCauses/OtherCarcinogens/AtHome/aspartame. Accessed October 4, 2012.
[28] Anton SD, Martin CK, Han H, Coulon S, Cefalu WT, Geiselman P, et al. Effects of stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels. Appetite 2010;55:37–43.
[29] Smeets PAM, de Graaf C, Stafleu A, van Osch MJP, van der Grond J. Functional magnetic resonance imaging of human hypothalamic responses to sweet taste and calories 1'2'3. Am J Clin Nutr 2005;82:1011–6.
[30] Whitehouse CR, Boullata J, McCauley LA. The potential toxicity of artificial sweeteners. AAOHN J 2008;56:251–9.
[31] Walton RG. Survey of aspartame studies: correlation of outcome and funding sources. Available at www.dorway.com/peerrev.html. Accessed October 4, 2012.
[32] Van Den Eeden SK, Koepsell TD, Longstreth WT Jr, Van Belle G, Daling JR, McKnight B. Aspartame ingestion and headaches. AAA 1994;44:1787–93.
[33] Lipton RB, Newman LC, Cohen JS, Solomon S. Aspartame as a dietary trigger of headache. Headache 1989;29:90–2.
[34] Newman LC, Lipton RB. Migraine MLT-down: an unusual presentation of migraine in patients with aspartame-triggered headaches. Headache 2001;41:899–901.
[35] Maher TJ, Wurtman RJ. Possible neurologic effects of aspartame, a widely used food additive. Environ Health Perspect 1987;75:53–7.
[36] Martins M, Azoubel R. Effects of aspartame on fetal kidney: a morphometric and stereological study. Int J Morphol 2007;25:689–94.
[37] Gurney JG, Pogoda JM, Holly EA, Hecht SS, Preston-Martin S. Aspartame consumption in relation to childhood brain tumor risk: results from a case–control study. J Natl Cancer Inst 1997;89:1072–4.
[38] Acesulfame K. Calorie Control Council. 2012. Available at www.caloriecontrol.org/sweeteners-and-lite/sugar-substitutes/acesulfame-K. Accessed October 2, 2012.
[39] Sweet facts about acesulfame potassium. Calorie Control Council. 2010. Available at www.acesulfamek.org/faq.html#. Accessed October 2, 2012.
[40] Chemical Cuisine – Learn about food additives. Center for Science in the Public Interest. 2012. Available at http://www.cspinet.org/reports/chemcuisine.htm. Accessed October 4, 2012.
[41] The lowdown on low-calorie sweeteners. The Coca-Cola Company.
[42] IFIC Review: Low-Calorie Sweeteners and Health. Food Insight – Your nutrition and food safety resource. 2009. Available at http://www.foodinsight.org/Resources/Detail.aspx?topic=IFIC_Review_Low_Calorie_Sweeteners_and_Health. Accessed October 2, 2012.
[43] Lino CM, Costa IM, Pena A, Ferreira R, Cardoso SM. Estimated intake of the sweeteners, acesulfame-K and aspartame, from soft drinks, soft drinks based on mineral waters and nectars for a group of Portuguese teenage students. Food Addit Contam 2008;25:1291–6.
[44] Facts about low-calorie sweeteners. International Food Information Council Foundation. 2009. Available at www.foodinsight.org. Accessed October 2, 2012.
[45] Mukhopadhyay M, Mukherjee A, Chakrabarti J. In vivo cytogenetic studies on blends of aspartame and acesulfame-K. Food Chem Toxicol 2000;38:75–7.
[46] Kroger M, Meister K, Kava R. Low-calorie sweeteners and other sugar substitutes: A review of the safety issues. Compr Rev Food Sci Food Saf 2006;5:35–47.
[47] Woods D. US scientists challenge approval of sweetener. BMJ 1996;313:386.
[48] Sucralose. Calorie Control Council. 2012. Available at http://www.caloriecontrol.org/sweeteners-and-lite/sugar-substitutes/sucralose. Accessed October 3, 2012.
[49] Knight I. The development and applications of sucralose, a new high-intensity sweetener. Can J Physiol Pharmacol 1994;72:435–9.
[50] International Food Information Council Foundation. 2010. Everything you need to know about sucralose. Washington DC. IFIC. Available at http://www.foodinsight.org/Resources/Detail.aspx?topic=Everything_You_Need_to_Know_About_Sucralose. Accessed October 4, 2012.
[51] All about Sucralose. Calorie Control Council. 2012. Available at http://www.sucralose.org/. Accessed October 2, 2012.
[52] Cardoso JMP, Bolini HMA. Descriptive profile of peach nectar sweetened with sucrose and different sweeteners. J Sens Stud 2008;23:804–16.
[53] Food and Drug Administration, HHS. Food labeling: health claims;dietary non cariogenic carbohydrate sweeteners and dental caries. Final rule. Fed Regist 2006;71:15559–64.
[54] Brusick D, Grotz VL, Slesinski R, Kruger CL, Hayes AW. The absence of genotoxicity of sucralose. Food Chem Toxicol 2010;48:3067–72.
[55] Abou-Donia MB, El-Masry EM, Abdel-Rahman AA, McLendon RE, Schiffman SS. Splenda alters gut microflora and increases intestinal P-glycoprotein and cytochrome P-450 in male rats. J Toxicol Environ Health 2008;71:1415–29.
[56] Brusick D, Borzelleca JF, Gallo M, Williams G, Kille J, Hayes AW, et al. Expert panel report on a study of Splenda in male rats. Regul Toxicol Pharm 2009;55:6–12.
[57] Calorie Control Council. Sucralose—The Facts 2009. Available at www.caloriecontrol.org. Accessed October 3, 2012.
[58] Ma J, Chang J, Checklin HL, Young RL, Jones KL, Horowitz M, et al. Effect of the artificial sweetener, sucralose, on small intestinal glucose absorption in healthy human subjects. Br J Nutr 2010;104:803–6.
[59] Ma J, Bellon M, Wishart JM, Young R, Blackshaw LA, Jones KL, et al. Effect of the artificial sweetener, sucralose, on gastric emptying and incretin hormone release in healthy subjects. Am J Physiol Gastrointest Liver Physiol 2009;296:G735–9.
[60] Ford HE, Peters V, Martin NM, Sleeth ML, Ghatei MA, Frost GS, et al. Effects of oral ingestion of sucralose on gut hormone response and appetite in healthy normal-weight subjects. Eur J Clin Nutr 2011;65:508–13.
[61] Brown AW, Brown MMB, Onken KL, Beitz DC. Short-term consumption of sucralose, a non-nutritive sweetener, is similar to water with regard to select markers of hunger signaling and short-term glucose homeostasis in women. Nutr Res 2011;31:882–8.
[62] Killie JW, Tesh JM, McAnulty PA, Ross FW, Willoughby CR, Bailey GP, et al. Sucralose: Assessment of teratogenic potential in the rat and the rabbit. Food Chem Toxicol 2000;38:S43–52.
[63] Bigal ME, Krymchantowski AV. Migraine triggered by sucralose: A case report. Headache 2006;46:515–7.
[64] Patel RM, Sarma R, Grimsley E. Popular sweetener sucralose as a migraine trigger. Headache 2006;46:1303–8.
[65] Qin X. What made Canada become a country with the highest incidence of inflammatory bowel disease: Could sucralose be the culprit? Can J Gastroenterol 2011;25:511.
[66] Patra F, Tomar SK, Arora S. Technological and functional applications of low-calorie sweeteners from lactic acid bacteria. J Food Sci 2009;74:R16–23.
[67] Levin GV, Zehner LR, Saunders JP, Beadle JR. Sugar substitutes: their energy values, bulk characteristics, and potential health benefits. Am J Clin Nutr 1995;62:S1161–8.
[68] Cerami A, Vlassara H, Brownlee M. Glucose and aging. Sci Am 1987;256:90–6.
[69] Lu Y, Levin GV, Donner TW. Tagatose, a new antidiabetic and obesity control drug. Diabetes Obes Metab 2008;10:109–34.
[70] Ellwood KC. Methods available to estimate the energy values of sugar alcohols. Am J Clin Nutr 1995;62:S1169–74.
[71] EC. European Parliament and Council Directive No. 95/2/EC of February 1995 on food additives other than colours and sweeteners. Off. J. Eur. Communities L061.
[72] Natah SS, Hussien K, Tuominen JA, Koivisto V. Metabolic response to lactitol and xylitol in healthy men. Am J Clin Nutr 1997;65:947–50.
[73] Sclafani A, Bahrani M, Zukerman S, Achroff K. Stevia and saccharin preferences in rats and mice. Chem Senses 2010;35:433–43.
[74] Chan P, Tomlinson B, Chen Y, Liu J, Hsieh M, Cheng J. A double-blind placebo-controlled study of the effectiveness and tolerability of oral stevioside in human hypertension. Br J Clin Pharmacol 2000;50:215–20.
[75] Gardner C, Wylie-Rosett J, Gidding S, Steffen L, Johnson R, Reader D, et al. Non-nutritive sweeteners: current use and health perspectives: A scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2012;126:509–19.
[76] Song WO, Wang Y, Chung CE, Song B, Lee W, Chun OK. Is obesity development associated with dietary sugar intake in the U.S.? Nutrition; 2012. http://dx.doi.org/10.1016/j.nut.2012.03.008.