Artificial Sweeteners and Metabolic Syndrome: Paradox of Physiological Behavior or Neuroendocrine Mechanisms

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Authors’ contributions

This work was carried out in collaboration among all authors. Authors MRM and KN has taken the responsibility in the conception and idea of the study. Authors MLM and KVK contributed substantially in compiling literature sources and drafting the manuscript. Authors SD and HB has provided critical revision of the article for important intellectual content. Authors TT and NBA has checked the references. All authors have given final approval of the version to be published.

Article Information

DOI: 10.9734/JPRI/2020/v32i3330953

Editor(s):
(1) Dr. Takashi Ikeno, National Center of Neurology and Psychiatry, Japan.

Reviewers:
(1) Anthony Kodzo-Grey Venyo, North Manchester General Hospital, United Kingdom.
(2) Carem Francelys Prieto Fuenmayor, Catholic University of Cuenca, Ecuador.

Complete Peer review History: http://www.sdiarticle4.com/review-history/63220

Received 20 September 2020
Accepted 28 November 2020
Published 10 December 2020

ABSTRACT

Artificial sweeteners owing to their non-caloric nature were proposed as a healthful means with the prospective benefits. Epidemiological data indicate direct relationship between artificial sweetener intake and increase in body weight, glycemic status, and adiposity. Despite strong association, evidence is still lacking in establishing the causal relationship between artificial sweeteners and various risk factors for the development of metabolic syndrome. In vitro studies have disclosed that artificial sweeteners similar to glucose/fructose bind to sweet-taste receptors on the tongue and intestinal mucosa stimulating enhanced sugar absorption, through glucagon like peptide-1 (GLP-1) secretion. Human studies failed to recapitulate these effects, advocating that artificial sweeteners rather serve to promote food consumption rather than improving satiety. Therefore, enhanced food consumption, disallowance of caloric adjustments could in some measure explain body

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weight gain with the use of artificial sweeteners. However, the physiological behavior and neuroendocrine mechanisms by which the non-caloric sweeteners may stimulate appetite needs further scrutiny.

Keywords: Artificial sweeteners; metabolic syndrome; appetite; body weight; neuroendocrine; paradox; glycemic.

1. INTRODUCTION

1.1 Diabetes, Obesity and Metabolic Syndrome (DO & MS)

According to the latest International Diabetes Federation (IDF) Atlas, around 415 million adults have diabetes globally with type 2 diabetes mellitus is reaching epidemic proportions [1]. The incidence of type 2 diabetes mellitus has increased by 33% in the United States. In a similar manner, the world is witnessing the obesity epidemic [2]. Among the U.S. adults, obesity (BMI ≥ 30 kg/m²) incidence has increased from 15% in the early 1970s to 34% in 2009–2010 [3,4]. About 62% of Americans are classified as obese or overweight. Similar patterns of increased prevalence of obesity are seen in other countries and were shown to be comparable across different age, ethnic, educational and income groups [5]. If these trends of obesity incidence continue, by 2030 the obese population could rise to about 1.12 billion or equal 20% of the world’s adult population [6]. The prevalence of metabolic syndrome in the adult population worldwide varies from 8-24.2% in males and from 7-46.5% in females [7-10]. Data from the National Health and Nutrition Examination Survey (NHANES) reported a peak incidence of metabolic syndrome risk factors in the 2001-2002 cycle, which was ensured by declining incidence thereafter. Recent data report of metabolic syndrome of 34%, with nearly 35% of all adults and more than 50% of individuals who older than 60 years that are estimated to have the metabolic syndrome [11].

2. ASSOCIATION BETWEEN DIET (FRUCTOSE, SUCROSE, FAT INTAKE) AND RISK FOR DIABETES, OBESITY AND METABOLIC SYNDROME (DO & MS)

Excess intake of sugars, particularly liquid sugar largely contributes to caloric consumption and leads to increased body weight, given the individual’s inability to expend the excess calories [12-15]. Excess consumption of sugar-rich drinks was found to expose women to high risks of experiencing insulin-dependent diabetes and cancer, [16] obesity and metabolic syndrome [17-18]. In contrast, the Atherosclerosis Risk in Community (ARIC) prospective study failed to show a clear association between sweetened beverage intake and the incidence of metabolic syndrome, although more than 60% of the cohort either had metabolic syndrome at the beginning of the study or began to show symptoms of metabolic syndrome during the 9 year follow-up period [19]. Consumption of high-sucrose foods was shown to decrease insulin sensitivity in animal as well as human studies [15,16,20]. High sucrose intake also leads to a host of other symptoms, including lipid dysregulation, increased adiposity, hypertension, inflammation, all of which are potential risk factors for metabolic syndrome [17,20]. This worldwide pandemic of obesity, type-2 diabetes, and cardiovascular disease has increased concerns about the possible adverse effects of excessive sugar consumption [21]. As a measure to slash the obesity and cancer epidemic, modest alterations in diet were proposed to prevent weight gain in children and adolescents [22].

3. WHAT ARE ARTIFICIAL SWEETENERS?

There are two essential classes of sweeteners, nutritive and non-nutritive. Nutritive sweeteners provide calories in the diet and taste sweet due to the presence of glucose and fructose, alone or together as sucrose. Sugar alcohols also provide energy to the body and affect blood glucose levels. Non-nutritive sweeteners (NNS), also called sugar substitutes or artificial sweeteners, do not provide calories and are believed to not affect blood glucose homeostasis. However, they are 160-13,000 times sweeter than sucrose on a weight-to-weight basis, regardless of their structural differences and composition. The FDA has given the label “Generally Recognized as Safe” (GRAS), to five* NNSs: Aspartame (NutraSweet® and Equal®), Acesulfame-K (Sweet One®), Neotame, Saccharin (Sweet’N Low®), Sucralose (Splenda®).
4. AS USE AND WEIGHT GAIN

High-sugar foods and beverages have been proposed to result in weight gain attributed to lower satiety, increased food consumption and augmented fuel storage pattern aiding fat accumulation [23]. Replacing sugar with artificial sweeteners that provide very little or no calories was believed to be productive in avoiding weight gain and controlling blood glucose levels in diabetics. National surveys from the 1990s estimated that artificial sweetener sodas accounted for approximately 4-18% of total carbonated beverage intake in children [24,25]. Acceptable daily intakes of various artificial sweeteners as per the FDA guidelines is 5 mg/kg body weight of sucralose, saccharin; 15 mg/kg body weight of Acesulfame-K, 50 mg/kg body weight of Aspartame; 0-4 mg/kg Stevia glycoside or 12 mg/kg rebiana. In the Nurses’ Health Study II, decreased weight gain was reported among adults who consumed artificially sweetened beverages [16]. Diet soda consumption was positively correlated with follow-up BMI Z-score after two years in 164 elementary school-aged children [26]. Similar effect of diet soda consumption on BMI change in over 10000 children aged 9-14 years was reported in a study over the course of one year in boys, but not in girls indicating gender differences [27]. In a prospective mortality study of women aged 50-69 years, artificial sweetener use increased with relative weight, but decreased with age. This study reported that AS users were significantly more likely to gain weight compared to non-AS users, regardless of initial body weight and specific dietary habits [28].

In a recent prospective, randomized trial that examined the effect of consumption of water versus NNS beverages within the context of behavioral weight loss, it was observed that NNS beverage treatment resulted in significantly more weight loss (5.5 kg loss) than water treatment (3.8 kg loss) during the first 12 weeks of intervention in a total of 303 overweight and obese participants [29]. The increased weight loss was associated with significant decrease in weekly hunger scores with consumption of 24 ounces of NNS beverages/day (with libitum water consumption) compared to consumption of at least 24 ounces of water/day (no consumption of NNS beverages). Increased weight contributed to greater reduction in total and LDL-cholesterol with NNS consumption, although there were no differences in changes in physical activity or sedentary behavior between NNS and water treatment groups.

In the Atherosclerosis Risk in Communities Study, diet soda was positively associated with incident metabolic syndrome, with those in the highest tertile of intake at 34% greater risk than those in the lowest tertile [30]. The strength of this association, although surprising, is consistent with cross-sectional and longitudinal data from the Framingham Heart Study, which found a 56% increased risk of metabolic syndrome among those consuming ≥1 serving of diet soda per day [17]. Interestingly, the positive relationship was much larger than that obtained with consumption of regular soda (sweetened beverage). Furthermore, in another cross-sectional study, diabetics who consumed diet soda had poorer glucose control than those who consumed none [30]. In the San Antonio Heart study, a significant, positive, dose-response relationship emerged between artificial sweetener consumption and incidence of overweight/obesity, along with change in body mass index (BMI), suggesting that use of artificial sweeteners might have contributed to long-term weight gain in this prospective study. Intake of >21 non-nutritive sweetened beverages per week (diet sodas and artificially sweetened coffee and tea) was associated with about double the risk of obesity compared to non-users at follow up 7-8 years later. It was also found that the percentage of calories from total and saturated fat increased with artificial sweet beverage dosage, with fats representing 37.5% of calories in non-users, but 39.6, 40.0, 41.7 and 40.9% for Artificially Sweetened Beverage quartiles 1-4, respectively. These data strongly indicate that weight gain can be indirectly related to increased fat consumption in the ASB users [31]. Other large, prospective cohort studies in adults have shown an association between artificial sweetener intake and the incidence of the metabolic syndrome and its components, including waist circumference, BMI, blood pressure, and fasting blood glucose [32,33]. However, none of these studies established a causal relationship between ASB consumption and weight gain and do not confirm the hypothesis that the use of non-nutritive sweeteners causes increased weight gain. It also does not differentiate the interpretation from the alternative view that weight gain is the impetus for increased use of non-nutritive sweeteners. Nonetheless, an animal study suggested that consumption of artificial sweeteners impairs the ability of the body to predict the caloric content of
foods and may lead to increased food/calorie intake and gain in body weight [34].

The prospective study designs indeed provide a temporal relationship, but reverse causality or other confounding factors lead to paradoxical findings of the association between artificial sweetener consumption and body weight gain, especially because consumption of diet soda is higher among diabetics than among non-diabetics [30]. Individuals seeking to shed weight or maintain weight and control glucose levels often switch to artificial sweeteners in order to reduce their caloric intake in the form of sugars, but they tend to show increased fast-food consumption. Consistent with this later statement, several prospective studies have found no association between AS consumption and weight change. In a longitudinal study, soda consumption was associated with the greatest increase of BMI, but had also exhibited increased caloric intake [25]. Similarly, increased weight among adult New England Saccharin users was not significant after adjustment for total caloric intake [35]. If ASB use consistently results in increased caloric consumption, this would represent an over-adjustment and needs caution, as demonstrated by the Choose Health Option Consciously Everyday (CHOICE) randomized clinical trial [36]. The participants were randomly assigned to substitute caloric beverage with either water or diet beverages or an attention control. The substitution of caloric beverages by low-calorie beverages (DBs or water) resulted in average weight losses of ~2–2.5%. Subjects in intervention groups, regardless of the type of beverages they consumed, were twice as likely as control subjects to achieve a 5% weight loss at 6 months [37]. During 6 months, the macronutrient composition changes in both groups without significant differences between groups over time. The CHOICE RCT failed to prove the hypothesis that the short-term consumption of low caloric sweet beverages enhances the consumption of sweet-tasting foods and beverages [36].

Using animal models, it was found that consumption of non-nutritive sweetener foods or fluids was associated with increased food intake, weight gain, accumulation of body fat, and weaker caloric compensation, compared to consumption of glucose containing foods and fluids [38]. On the other hand, some studies have found no association between artificial sweetener use and diabetes incidence or glycemic control [39,40]. Despite limited and inconclusive scientific evidence about whether this strategy controls or worsens the risk factors of metabolic syndrome, various reviews have claimed that artificial sweeteners do not increase weight in humans [41,42]. However, determining the potential benefits or adverse effects of NNS is complicated and depends on where foods/drinks containing them fit within the context of everything eaten during the day.

Data from human and animal studies have provided insights into the role of sweet-taste receptors, including the taste receptor T1R family and α-gustducin, that respond not only to caloric sugars, such as sucrose and glucose, but also to artificial sweeteners, including sucralose, acesulfame-K [43,44]. These receptors have been observed not only in lingual taste buds, but also in glucagon-like peptide-1 (GLP-1) secreting L cells of the gut mucosa, [45-47] where they serve as critical mediators of GLP-1 secretion. In line with this, stimulation of the intestinal taste receptors with sucralose led to rapid absorption of sugars from the intestine into the bloodstream in rats [43]. Similarly, consumption of diet soda before an oral glucose challenge potentiated GLP-1 secretion, thus potentially altering both gastric emptying and insulin secretion [48]. The capacity of artificial sweeteners to mimic the sugars in inducing the GLP-1 secretion could be one of the factors affecting the postprandial glucose response and therefore the “metabolic quality” of the carbohydrates. On the contrary, denying the in vitro data that application of sucralose to L-cells stimulates GLP-1 secretion, equisweet loads of AS (aspartame, acesulfame-K and sucralose) dissolved in 250 ml of water did not affect gastrointestinal GLP-1 secretion and showed only minimal effects on appetite compared to glucose or fructose load in a placebo-controlled, double-blind, six-way, cross-over trial in healthy subjects [49]. These results suggest that both glucose and fructose increased satiety and fullness compared with water and that more than sweetness, the structural analogy of sweeteners to glucose could be important in determining the GLP-1 secretion response and glucose homeostasis. Adding credence to this notion, a randomized, single-blinded, cross-over study in eight healthy subjects revealed neither stimulatory effect of sucralose on L-cell derived GLP-1 release nor reduced appetite [50,51]. Critical piece of evidence for interactions of artificial sweeteners with taste receptors is still lacking and needs molecular modeling and rigorous assessment of in vitro and in vivo effects.
5. ALTERNATE MECHANISMS

Hormonal and neural responses triggered by sensory cues, including taste, texture, and sight of food, influence the digestion, absorption of foods and utilization of the energy and nutrients yielded from the food [52-54]. The sensory signals of different foodstuffs directly influence subsequent metabolic consequences, resulting in conditioned responses. A regulated pattern of food intake can be observed owing to the association between sensory cues and metabolic adaptations. These cephalic responses indeed contribute to the regulation of food intake, digestion and utilization. It is believed that the initial cephalic response allows consumption of a larger meal, whereas the satiation is induced by the prandial cephalic response. It is argued that lack of this neurophysiological cephalic signal also termed as ‘cephalic phase stimulatory response’ may bolster the risk of obesity, due to lack of satiation and increased tendency to consume food. Cephalic phase response can also be stimulated by consumption of any foods in general [55,56] or specific sweet items [57]. Tasting sweet food has been shown to elicit insulin release prior to increase in plasma glucose levels by some investigators, [58,59] but not by others [60-63]. Artificial sweeteners may induce insulin spike, but may not increase hunger. However, insulin spikes in brain were shown to lower food consumption in animals, but not in humans when using euglycemic clamps [64]. In the same study, it was also proven that glucose concentrations do not affect hunger sensation. However, if glucose was believed to be an appetite signal, a decline in hunger due to the stimulating effects of AS on insulin is unlikely because cephalic phase insulin response moderates glucose excursions [65,66] rather than augments swings. Further, other cephalic phase responses might counter mechanisms promoting hunger, such as the thermogenic reduced hunger [67]. As with cephalic phase insulin response, this response may not be evoked by all sweeteners, as was reported for aspartame [24,68]. Thus, there is no adequate and consistent proof for the concept that AS stimulate hunger via cephalic phase response.

A recent study reckons a compelling dimension to the diverse ramifications of consumption of artificial sweeteners. Use of saccharin, sucralose and aspartame was found to directly predispose mice to obesity and glucose intolerance [69]. These effects were shown to be arbitrated by altered composition and function of the intestinal microbiota; deleterious metabolic effects could be transmitted to germ-free mice by fecal transplantation and were negated by antibiotic treatment, clearly establishing the causal effect of artificial sweeteners on microbial population viz. a viz. the metabolic pattern. The authors further demonstrated that artificial sweeteners can induce dysbiosis and glucose intolerance in healthy human subjects, and advocate that it may be necessary to develop new nutritional strategies tailored to the individual and to suit the individual’s gut microbiota.

6. CONCLUSIONS

This review aimed to provide current and comprehensive information regarding the effects of artificial sweeteners on food intake, body weight, glycemic control, and sweet liking and craving. The majority of observational studies show a positive association between artificial sweetener use and body weight gain. The results of short-term satiety studies are intricate and yielded different outcomes based on the study design. In general, younger children seem to square up better for lower calories in artificially sweetened drinks by increasing subsequent food intake. Unlike observational studies, randomized controlled trials of artificial sweeteners in children have not shown that artificial sweeteners cause weight gain. Sugar has been shown to cause release of endogenous opioids, endorphins, and dopamine from the brain in an analogous manner to addictive drugs. More research is needed to further examine if consumption of artificial sweeteners can evoke similar brain responses that may lead to increased craving for sweet taste. It is also imperative that long term studies should be carried out in children, as metabolic and behavioral alterations that occur in response to artificial sweeteners introduced and conditioned during childhood may accumulate throughout adolescence and adulthood. Taken together, it can be argued that if NNS are used as substitutes for higher energy yielding sweeteners, rather than adding them to what is being consumed, they can be a useful adjunct in the management of various risk factors for metabolic syndrome.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not
intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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