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REVIEW

Effects of Artificial Sweetener Consumption on Glucose Homeostasis and Its Association with Type 2 Diabetes and Obesity

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Abstract: Artificial sweeteners (ASs) are popular for their characteristic property of providing sweetness with few or no calories. They are frequently consumed to minimize energy intake and to combat obesity and its related adverse health effects. However, since their introduction, concerns have been raised regarding their safety. Extensive research has designed a number of studies to evaluate potential adverse effects, the top among them being interference with glucose homeostasis. Numerous studies have tried to prove that AS may contribute to the development of metabolic diseases including obesity and type 2 diabetes (T2D). The matter remains controversial and a favorite topic of research. The purpose of this review was to identify and discuss the published articles that have examined the effects of AS consumption on glucose homeostasis and its association with T2D and obesity. It was observed that studies have failed to present concrete evidence to establish a link between AS consumption and glucose homeostasis, obesity, or T2D. Most studies have flaws in the study design resulting in haphazard claims with no follow-up studies to confirm reliability. It is concluded that while it is not possible to claim that ASs are metabolically inert, at the moment the haphazard evidence is not enough to link their use with glucose metabolism, obesity or T2D. There is a need to design cohort and case–control studies with reliable sample sizes to establish a cause–effect relationship or to exclude claims of safety problems.

Keywords: artificial sweeteners, glucose, diabetes, obesity

Introduction

Artificial sweeteners (ASs), or non-nutritive sweeteners, are food additives that provide a sweet flavor with zero or low calories; they are used in various products such as foodstuffs, beverages, drugs, and even toothpaste.[1] They may be derived from plant extracts or manufactured by chemical synthesis. The first AS, benzoic sulfimide, was marketed in the USA in 1879, by Constantin Fahlberg and was commercialized as saccharin.[2] Since then, the consumption of ASs has grown substantially, as reported by several studies in adults or children. A 2017 study in the USA showed that AS consumption is 41.4% among adults and 25.1% among children.[3]

Currently, six ASs have been approved by the US Food and Drug Administration (FDA): saccharin, acesulfame, aspartame, neotame, sucralose, and advantame.[4] In 2017, sucralose was the most widely AS consumed; it accounted for one-third of the global market, expected to be worth $2.8 billion by 2021.[5] Figure 1 shows the chemical structures of the approved ASs.

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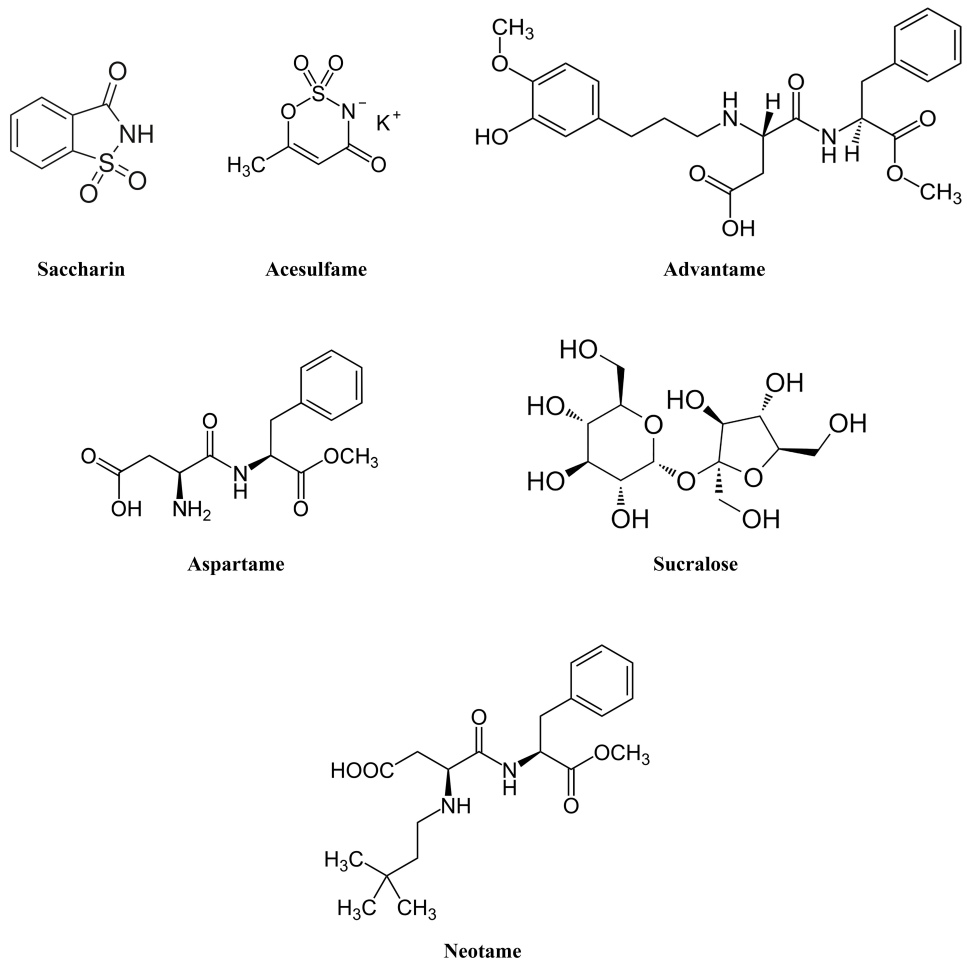

Figure 1 Chemical structures of the approved artificial sweeteners.

ASs are designed as sugar substitutes to tackle obesity and its subsequent outcomes, including metabolic syndrome, diabetes, and cardiovascular diseases. Yet several concerns have been raised about the safety of these products. In fact, the adverse health effects associated with ASs remain open to discussion among researchers. For instance, the scientific report of the Dietary Guidelines Advisory Committee in 2015 discussed that added sugars should be minimized in the diet and substituted not with ASs, but rather with more healthy choices.[6] A joint position statement from the American Heart Association and the American Diabetes Association also cautioned against AS intake and stated that there are limited data to conclude whether AS consumption to replace sugar sweeteners benefits body weight, energy balance, or metabolic risk factors.[7] Meanwhile, Diabetes UK reported that there are adequate data to support that AS consumption improves postprandial blood glucose levels if consumed instead of sugars; moderate consumption of ASs to replace sugars can be a useful strategy to manage body weight.[8] The purpose of this review is to summarize the available literature investigating the effects of AS consumption on glucose homeostasis and its association with T2D and obesity.

Glucose Homeostasis

Some clinical trials have observed the effects of ASs on glucose homeostasis. However, the results are contradictory and comparability among these trials is not feasible owing to variations in the sample size, type of AS, whether a placebo was included, exposure time, and outcomes assessed. For example, studies that evaluated the effect of sucralose consumption showed lower,[9] higher,[10] or no change in glucose levels.[11] Likewise, GLP-1 levels were increased following sucralose intake in some studies,[9,12] while other studies reported a reduction[13] or no change.[10] Aspartame consumption also showed inconsistent results, with lower[14] or no change[15] in plasma glucose levels.

Other studies investigated the levels of appetite-regulating hormones, including ghrelin, cholecystokinin, and peptide YY, following AS consumption, and showed no significant changes.[11,16]

Overall, as provided in Table 1, the vast majority of clinical trials that have investigated the effects of AS intake on glycemic response observed no significant differences between AS consumption and placebo on various measures of glycemic response, including plasma glucose, insulin, HbA_{1c}, and C-peptide. These findings are consistent with the fact that ASs provide few or no calories to the diet. Therefore, based on the available literature, the effect of ASs on glucose homeostasis cannot be established.

Type 2 Diabetes

ASs are marketed to reduce the risk of metabolic disease, including T2D. Several reports have addressed the relationship between AS consumption and the development of T2D. A dose–response meta-analysis, published in 2020, included 13 cohort studies and investigated the association between artificially sweetened beverages and the risk of T2D; the median follow-up was 8.4 years. The results revealed a linear association between AS intake and T2D risk. The risk increased by 15% for each 250 mL/day increase in AS soft drink consumption. However, the study reported considerable heterogeneity and other unmeasurable confounders cannot be excluded. Thus, the results should not be taken for granted.[17] In another systematic review, four cohorts were included from three observational studies that investigated the association between AS consumption in the form of soft drinks and risk of T2D. The review concluded that there was an increased risk of T2D when 330 mL of artificially sweetened soft drinks were consumed daily. However, the studies included were observational and significant heterogeneity was reported among the cohorts; therefore, any conclusion should be taken with caution.[18] In addition, another systematic review analyzed the data from 17 cohorts and found a positive relationship between AS consumption and T2D incidence. However, the authors of this review reported that the evidence of their findings was insufficient and potential bias as well as heterogeneity among cohort studies existed.[19]

Observational studies investigating the relationship between AS consumption and the incidence of T2D showed inconsistent results. Four cohort studies reported a positive association between AS intake and the risk of T2D. Among them, a large cohort study conducted by Fagherazzi et al[20] showed that the risk of T2D was significantly increased among women consuming ASs in the form of packets or tablets for more than 10 years compared to never or rare consumers, when adjusted for body mass index (BMI). However, adiposity cannot be excluded in this study as a confounding factor. Likewise, another study reported a significant positive association between AS intake and the incidence of T2D in women consuming over 600 mL of artificially sweetened soft drinks for 14 years, with a dose-dependent relationship. However, other independent risk factors for T2D in this study cannot be ruled out.[21] A third study, carried out for 7 years, showed a 67% greater relative risk for T2D in individuals consuming at least one diet soda per day independent of primary measures of adiposity. However, the possibility of other confounding factors cannot be eliminated from this observational study.[22] A fourth study investigated a limited number of Japanese men for 7 years and reported an increased risk of T2D among subjects who consumed one or more diet sodas daily. The results are not representative of the general population. Also, this study assessed the consumption of AS at the baseline examination and did not consider the possible changes during the 7 years of follow-up.[23]

While some cohort studies and meta-analyses observed a positive relationship between AS consumption and the risk of T2D, other studies reported no association. Bhuphatiraju et al[24] investigated the relationship between AS consumption and the incidence of T2D in 39,059 healthy professional men for 20 years. Although a positive association was observed with the development of T2D, in an age-adjusted analysis, the association was no longer significant when adjusted for BMI and total energy intake. These findings indicate that ASs were consumed to reduce weight and health conditions related to obesity, such as diabetes. Similarly, in a case cohort study of 15,384 subjects, there was no significant association between AS consumption and risk of T2D after adjustment for BMI and total energy intake.[25] A summary of observational cohort studies investigating the association between AS consumption and risk of T2D is provided in Table 2.

A possible explanation for the relationship between AS consumption and risk of T2D that has been observed in some studies might be related to reverse causality. O'Connor et al,[26] in a long-term large cohort study of 24,653 adults, concluded that the positive association between AS consumption and T2D may be an artifact of reverse causality. Subjects with higher BMI or a tendency

Table 1 Clinical Trials Investigating the Effect of AS Consumption on Glucose Homoeostasis

Authors and Year	Study Design	Population and Age	Parameters	Findings
Anton et al[14] 2010	Single-blind randomized crossover study	19 participants with normal weight and 12 obese subjects (18–49 years)	• Glucose • Insulin • Insulinogenic index	• Reduction in blood glucose and insulin levels with stevia consumption compared to sucrose • Lower blood glucose levels with aspartame consumption at 20 min compared to sucrose • Higher insulinogenic index with aspartame consumption at 1 hour
Ma et al[41] 2010	Single-blind randomized crossover study	10 healthy normal weight subjects (25–29 years)	• Glucose • GLP-1	Intraduodenal infusion of sucralose did not change glucose intestinal absorption or GLP-1 secretion compared to control infusion
Brown et al[42] 2011	Double-blind randomized crossover study	8 healthy normal weight women (19–24 years)	• Glucose • Insulin • Glucagon • Ghrelin	No significant changes were described with sucralose consumption compared to water
Ford et al[43] 2011	Single-blind randomized crossover study	8 healthy normal weight subjects (22–27 years)	• Glucose • Insulin • GLP-1 • PYY	Sucralose consumption did not change any variables compared to water
Steinert et al[44] 2011	Randomized crossover study (no blinding)	12 healthy normal weight subjects (22–24 years)	• Glucose • Insulin • GLP-1 • PYY • Ghrelin	No significant differences were observed in any of the parameters following consumption of aspartame, acesulfame-k, or sucralose compared to water
Wu et al[45] 2012	Single-blind randomized crossover study	10 healthy obese subjects (25–33 years)	• Glucose • Insulin • GLP-1 • GIP	Sucralose consumption had no effects on any parameters
Maersk et al[16] 2012	Randomized crossover study (no blinding)	24 healthy obese subjects (20–50 years)	• Glucose • Insulin • GLP-1 • GIP • Ghrelin	Aspartame consumption did not change any variables
Brown et al[11] 2012	Randomized crossover study (no blinding)	44 subjects divided into 3 groups: 25 healthy controls, 10 with T2D, and 9 with type 1 diabetes (12–25 years)	• Glucose • GLP-1 • GIP • PYY • C-peptide	• Diet soda consumption before a glucose load increased GLP-1 secretion in healthy and type 1 diabetic individuals compared to carbonated water • No changes in other parameters
Stellingwerff et al[46] 2013	Double-blind randomized crossover study	23 healthy normal weight men (22–36 years)	• Glucose • Insulin	Sucralose consumption immediately before exercise had no effects on glucose and insulin concentrations during exercise

(*Continued*)

Table 1 (Continued).

Authors and Year	Study Design	Population and Age	Parameters	Findings
Pepino et al[10] 2013	Randomized crossover study (no blinding)	17 healthy obese (34–36 years)	• Glucose • Insulin • Insulin sensitivity • Insulin clearance • glucagon • GLP-1 • GIP • C-peptide	• Sucralose consumption showed higher glucose, insulin, and C-peptide concentration, with a reduction in insulin sensitivity and insulin clearance • No differences were found in GIP, GLP-1, and glucagon
Olalde-Mendoza et al[15] 2013	Randomized study (no blinding)	80 obese individuals with T2D (40–58 years)	• Capillary glucose	Diet soda consumption had no effects on capillary glucose concentrations
Bryant et al[47] 2014	Randomized crossover study (no blinding)	10 normal weight subjects (18–24 years)	• Glucose	Consumption of saccharine, aspartame, or acesulfame-k in combination with glucose did not change blood glucose concentrations compared to glucose alone
Temizkan et al[9] 2015	Single-blind randomized crossover design	8 newly diagnosed type 2 diabetic patients (51.5±9.2 years) and 8 healthy obese subjects (45.0±4.1 years)	• Glucose • Insulin • GLP-1 • C-peptide	• Sucralose consumption was associated with lower glucose and higher GLP-1 concentrations compared to water consumption in healthy individuals • No differences in sucralose or aspartame on insulin and C-peptide
Boyle et al[48] 2016	Single-blind randomized crossover design	40 healthy normal weight and obese subjects (50–65 years)	• Capillary glucose • Interstitial glucose	Sucralose consumption had no effects on capillary or interstitial glucose concentrations
Dhillon et al[49] 2017	Single-blind randomized crossover design	64 obese subjects (18–50 years)	• Glucose • Cephalic phase insulin response	• Significant changes in blood glucose concentration with sucralose consumption compared to control • Significant cephalic phase insulin response following sucralose consumption
Tey et al[50] 2018	Single-blind randomized crossover study	32 healthy normal weight men (21–50 years)	• Postprandial glucose	• Consumption of low-calorie sweeteners was associated with a lower postprandial glucose concentration compared to high-calorie sweeteners
Crézé et al[51] 2018	Randomized crossover study (no blinding)	18 healthy normal weight subjects (age not provided)	• Glucose • Insulin • Ghrelin	• Consumption of artificial sweetened beverages was associated with lower plasma glucose and insulin concentration compared to sucrose-sweetened beverages • Plasma ghrelin showed higher values in artificially sweetened beverages compared to sucrose-sweetened beverages

(*Continued*)

Table 1 (Continued).

Authors and Year	Study Design	Population and Age	Parameters	Findings
Farhat et al[52] 2019	Single-blind randomized crossover study	30 healthy normal weight and obese subjects (16–36 years)	• Postprandial glucose	• Stevia consumption had no effect on postprandial glucose
Gómez-Arauz et al[53] 2019	Randomized placebo-controlled trial	45 participants divided into 2 groups: 20 controls (21.55±2.18 years) and 25 who ingested sucralose (22±2.99 years)	• Glucose • Insulin	• Sucralose consumption showed higher serum insulin levels at 30, 45, and 180 min following oral glucose tolerance test. • No differences were observed for blood glucose levels
Nichol et al[54] 2020	Randomized crossover study (no blinding)	10 healthy normal weight and 11 healthy obese subjects (23–33 years)	• Glucose • Insulin • C-peptide • GIP	• Sucralose consumption elevated plasma glucose by 30±10% in lean and obese subjects compared to water • Insulin levels reduced within 20–40 min of the oral glucose tolerance test in lean subjects and increased within 90–120 min in obese subjects • C-peptide and GIP did not show significant differences
Bueno-Hernández et al[55] 2020	Randomized double-blind placebo-controlled trial	137 subjects divided into 3 groups: a) subjects receiving water as controls, b) subjects receiving 48 mg sucralose, and c) subjects receiving 96 mg sucralose	• Glucose • insulin	Sucralose intake for 10 weeks resulted in: • higher insulin concentrations at 0, 30, 105 and 120 min following oral glucose tolerance test in the group receiving 48 mg sucralose • higher blood glucose at −15, 0, and 120 min in the group receiving 48 mg sucralose • higher area under the curve (AUC) of insulin in groups receiving 48 and 96 mg sucralose

for weight gain, already at risk of diabetes, consume AS products as a strategy to reduce calorie intake.

In conclusion, the reported studies assessing the risk of T2D reveal divergent results. Reverse causality and residual confounding factors such as adiposity were observed in most of the studies. Therefore, a final conclusion cannot be reached now, and further well-designed human studies, of long duration, evaluating the risk of diabetes are desperately needed.

Obesity

Various large cohort studies have described a positive dose-dependent relationship between AS consumption and increased BMI. In 2020, Qin et al,[17] in a meta-analysis including six prospective cohort studies of 26,551 subjects, found that the risk of obesity increased by 21% for each 250 mL/day increase in AS soft drink consumption. Likewise, another meta-analysis including three cohort studies of 12,987 participants showed a pooled relative risk of obesity of 1.59% (95% CI 1.22–2.08) in subjects consuming artificially sweetened beverages.[27] Azad et al[28] conducted a meta-analysis of eight cohort studies and concluded that AS consumption was associated with a slightly positive increase in BMI, weight, waist circumference, and incidence of obesity. In a cohort study of 1454 subjects with a median follow-up of 10 years, AS consumers had 0.80 kg/m^2 higher BMI, 2.5 cm greater waist circumference, and 53% higher incidence of abdominal obesity compared to non-consumers.[29]

Table 2 Observational Cohort Studies Investigating the Association Between AS Consumption and Risk of Development of T2D

Authors and Year	Number and Age of Participants	Follow-up Period	Main Outcomes
Palmer et al[56] 2008	43,960 women (21–69 years)	4 years	No association was found between diet soft drink consumption and incidence of T2D
Nettleton et al[22] 2009	5011 adults (45–84 years)	7 years	Daily diet soda intake was associated with a 67% higher risk of developing T2D
de Koning et al[19] 2011	40,389 male health professionals (40–75 years)	20 years	Relationship of artificially sweetened beverages consumption and risk of T2D was observed in the age-adjusted analysis. However, in the multivariate-adjusted analysis no relationship was found
Bhupathiraju et al[24] 2013	74,749 female nurses (30–55 years)	24 years	Significant association was observed between caffeine-free artificially sweetened soft drinks and incidence of T2D after multivariable adjustment for BMI and energy intake
Bhupathiraju et al[24] 2013	39,059 healthcare professional men (40–75 years)	22 years	No association was found between caffeinated or non-caffeinated artificially sweetened beverage intake and risk of T2D after multivariable adjustment
The InterAct Consortium[25] 2013	34,234 adults (39–69 years)	16 years	No relationship was observed between artificially sweetened beverage intake and the incidence of T2D after multivariable adjustment for BMI and energy intake
Fagherazzi et al[21] 2013	66,118 women (46–59 years)	14 years	Significant association was described between high consumption of artificially sweetened beverages (>630 mL/week) and the development of T2D
Sakurai et al[23] 2014	2037 men (35–55 years)	7 years	Daily consumption of diet soda was positively associated with increased risk of T2D after multivariable adjustment
O'Connor et al[26] 2015	24,653 adults (40–79 years)	10.8 years	Significant association was found between artificially sweetened beverage consumption and incidence of T2D. Yet, after adjusting for adiposity (BMI and waist circumference) this became insignificant
Ma et al[57] 2016	1685 adults (43–61 years)	14 years	No association was found between diet soda intake and increased prediabetes risk
Fagherazzi et al[20] 2017	61,440 women (46–59 years)	18 years	Significant association was observed between AS consumption in packets or tablets and development of T2D after adjustment for BMI
Huang et al[58] 2017	64,850 women (50–79 years)	8.4 years	Consumption of artificially sweetened beverages was associated with a 21% higher risk of developing T2D
Gardener et al[59] 2018	2019 adults (59–79 years)	11 years	Strong positive association was found between diet soda intake and the development of T2D. Yet, after adjusting for BMI this became null
Jensen et al[60] 2020	1359 adults (25–60 years)	8 years	No association was found between AS consumption and the risk of T2D

In children, most of the observational studies demonstrated that AS intake is associated with increased weight.[30] Moreover, Azad et al[31] reported that the daily maternal consumption of AS during pregnancy was associated with a higher infant BMI and a two-fold greater risk of the infant being overweight at the age of 1 year.

Several proposed mechanisms in vitro and in vivo may describe the link between AS intake and obesity. One potential explanation derives from a hypothesis that the sensation of sweetness without calorie absorption may disturb brain metabolic signaling and appetite regulation.[32] Absence of satiety can encourage more eating. Another mechanism is that AS consumption may activate intestinal and pancreatic sweet taste receptors stimulating GLP-1 and insulin release, as shown in in vitro studies.[33] Alterations in the gut microbiota have

also been described as a potential mechanism. Studies of rodent models showed that saccharin intake promotes weight gain and glucose intolerance by changing the physiology of the intestinal microbiota.[34,35] Another important mechanism that should not be ignored is related to limitations in the study design. Residual confounding and reverse causality in these observational studies may elucidate the relationship between AS intake and obesity. Overweight or obese individuals tend to consume ASs to manage their weight. Likewise, obese people presenting with prediabetes or T2D start consuming ASs to improve their blood glucose control, which causes a false association between AS consumption and the increased risk of developing T2D. This mechanism is supported by the results of several interventional studies that showed no or even a beneficial effect of AS on body weight.

In a meta-analysis of 15 randomized controlled trials (RCTs), the results revealed significant benefits of AS consumption on body weight, BMI, fat mass, and waist circumference compared with sugar intake. The authors concluded that AS consumption as a replacement option for caloric sweeteners may help individuals cope with a weight management plan.[36] Another meta-analysis of human RCTs of 4 weeks' to 40 months' duration found that AS consumption was associated with reduced body weight compared with a sugar sweetener or water consumption.[37] Toews et al[38] conducted a meta-analysis of RCTs with a study duration of 1 week or longer. The authors found no significant variations in body weight between adults consuming AS compared with those consuming caloric sweeteners or placebo. Subgroup analysis, by body weight level, reported that AS intake by obese or overweight subjects resulted in a reduction of 1.99 kg. However, no change was observed in adults of normal weight. In addition, BMI was 0.6 units lower in individuals consuming AS compared with sucrose consumers. In the meta-analysis mentioned earlier in this section by Azad et al,[28] the included RCTs did not show a significant correlation between AS consumption and BMI or body weight. The authors concluded that the results from RCTs do not support the proposed benefits of AS for weight control.

Therefore, unlike most prospective observational studies, the meta-analyses of RCT studies suggest that AS consumption has neutral or positive outcomes for weight management. However, methodological limitations in the included studies were apparent and have raised many questions about the outcomes and efficacy of ASs in weight management. Thus, no definite conclusions can be drawn about the effect on body weight of replacing natural sweeteners with ASs.

Future Studies

While the subject of ASs has generated extensive research, much about ASs has yet to be fully explored. The links between ASs and metabolic diseases remain unclear. At this stage, we are unable to ascertain whether AS consumption has beneficial or adverse effects on health outcomes. Most studies have flaws in study design, study population, sample size, control groups, managing the confounders, use of improper placebo, and interpretation of data. For example, experimental designs using sham feeding, acute exposure, and water as a placebo apparently give inconclusive results. Likewise, gas bubbles in carbonated drinks may act as a confounder in some study designs, resulting in a lack of consistent results among different groups. Thus, it is of paramount importance to design long-term cohort studies along the pattern of the Framingham Study to determine cause-and-effect relationships between AS consumption and the prevalence of different metabolic diseases. Likewise, case–control studies could be designed to establish cause-and-effect relationships in obese individuals presenting with T2D. In addition, future studies should attempt to explain the effects of different AS independently since ASs may differ in their physiological impacts. One study found that different ASs (saccharine, sucralose, and aspartame) had different effects on body weight over 3 months.[39] Thus, the type and dose of AS used should be documented clearly in all studies.

Besides investigating the effects of AS intake on healthy individuals, research should also be directed toward diseased populations and other subgroups, such as pregnant women and their infants. Exposure of babies to ASs via breast milk has been postulated to have potential adverse outcomes in adult life.[40] Further studies are needed to explore this matter in detail.

Conclusion

AS consumption is associated with obesity and T2D in observational cohort studies, but the findings are questionable since reverse causality and residual confounders cannot be excluded. A majority of interventional clinical trials observe neutral or even beneficial effects of AS when consumed in the context of a weight-loss program. Further well-designed studies that mimic real-life

consumption are needed to explore the long-term specific effects of the different ASs available.

Based on the available data, it is not possible to claim that ASs are metabolically inert; however, current evidence is not sufficient to link their use with glucose metabolism, obesity, or T2D.

Disclosure

The author reports no conflicts of interest in this work.

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