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Artificial sweetener use among children: epidemiology, recommendations, metabolic outcomes, and future directions

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Abstract

Synopsis—This review summarizes the existing literature pertaining to the epidemiology and current recommendations for pediatric artificial sweetener use and presents the results of studies investigating metabolic responses to artificial sweeteners among children. Observational and interventional studies testing the effects of artificial sweeteners on body weight, short-term satiety, glycemia, and glucoregulatory hormones are described. In addition, this review touches on the growing body of literature about taste, craving, and addiction to sweet taste. Gaining an understanding of the research previously conducted and the gaps that remain will inform future clinical and translational research, in order to develop evidence-based recommendations for artificial sweetener use in the prevention and treatment of pediatric obesity.

Keywords

artificial sweeteners; non-nutritive sweeteners; non-caloric sweeteners; low-calorie sweeteners; sugar substitutes; obesity; overweight

Introduction: Artificial sweeteners and obesity

Childhood obesity is associated with numerous unfavorable consequences including type 2 diabetes, non-alcoholic fatty liver disease, hypertension and psychosocial problems, and often results in obesity during adulthood¹. Consumption of added sugars is positively associated with higher energy intakes, and is thought to be a significant contributor to the rapid rise in obesity worldwide². Since the majority of added sugars are obtained from consumption of soft drinks³, artificially sweetened beverages have emerged as an alternative, providing the desired sweetness and palatability without contributing to caloric intake⁴. In addition to their use in “diet” and “light” beverages, artificial sweeteners are often used to replace added sugars in various foods, including yogurts, puddings, baked goods, and ice cream, among many other items frequently consumed by children and

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adolescents⁵. Despite their widespread and increasing use⁶, the effects of artificial sweeteners in children have not been well studied.

The purpose of this review is to summarize the existing literature pertaining to the epidemiology and current recommendations for artificial sweetener use in children, and to present the results of studies investigating metabolic responses to artificial sweeteners among children. In addition, this review will touch on the growing body of literature about taste, craving, and addiction to sweet taste. Artificial sweeteners have also been studied in relation to dental cavities, fetal outcomes, and carcinogenesis, but these issues will not be addressed in this review. In presenting and analyzing the current scientific evidence on the metabolic safety of artificial sweeteners and their potential effectiveness in promoting weight loss and weight management, this review aims to provide clinicians with a comprehensive understanding of current knowledge about artificial sweetener usage in children.

Regulatory status of artificial sweeteners

FDA, ADI, EDI, aspartame, acesulfame-potassium, sucralose, stevia, neotame, saccharin

There are currently five artificial sweeteners approved by the Food and Drug Administration (FDA) for use in the United States (Table 1). These include aspartame, acesulfame-potassium, saccharin, sucralose, and neotame⁷. In addition, stevia, a natural sweetener made from extracts of the intensely sweet *S. Rebaudiana* (Bertoni) plant has been approved for limited use⁸. For each sweetener, the FDA establishes an Acceptable Daily Intake (ADI)⁹, in mg per kg body weight, which is the amount of sweetener thought to be safe to consume every day for a lifetime. The ADI is typically 100 times lower than the dose of the sweetener that caused toxicity in animal studies. To determine if a sweetener should be approved for use, the FDA then must establish that typical human intake of the sweetener (Estimated Daily Intake, or EDI) will be below the ADI. If the estimated daily intake (EDI) is below the ADI, then the sweetener is considered safe for human use. Aspartame, saccharin, sucralose, and neotame are classified as food additives by the FDA, while stevia is classified as Generally Recognized as Safe (GRAS), meaning that similar data consistent with its safety exist as for food additives.

Key points:

- There are five artificial sweeteners currently approved for use in the United States as well as stevia, a natural non-caloric sweetener
- For each sweetener, the FDA establishes an acceptable daily intake (ADI) which is the amount of sweetener thought to be safe to consume every day for a lifetime.

Artificial sweetener consumption among children

Sweetness, intake, and consumption

Apparent consumption of artificial sweeteners (based on servings of foods and beverages containing these sweeteners) has increased with time across all age groups¹⁰. Because the FDA does not require manufacturers to report the actual amounts of sweeteners contained in foods and beverages¹¹, quantification of the precise amount of sweeteners present in the food is difficult. Hence, information about the total quantity of sweeteners in use is extracted from intake information for the various foods that contain them, using food composition tables and validated food databases¹². It is important to understand that the sweetening power of the artificial sweeteners listed above is hundreds of times greater than that of sucrose (Table 1)¹³. Therefore, it takes a much smaller amount of an artificial sweetener relative to caloric sugars to produce the same level of sweetness in a product.

Due to their smaller size and relatively high intake of beverages, children consume the highest amount of artificial sweeteners relative to their body weight per day⁵. A recent systematic review estimated that between 4 and 18% of total carbonated beverage intake among children is from artificially sweetened beverages¹⁴. A second review determined that approximately 15% of the total United States population above the age of 2 years use artificial sweeteners¹⁰. A third study, comparing NHANES data from 1999–2000 to 2007–2008¹⁵ and a recent study (unpublished data, courtesy of Jean Welsh, PhD) showed that consumption of artificially sweetened beverages has increased in the general population, and has doubled among children over this time period. Artificial sweetener consumption in foods has increased to a greater extent than in beverages. Furthermore, of those who already consume artificially sweetened products, the amount of these products being consumed has increased¹⁰. Given the extent to which consumption of artificially sweetened products is rising, it is important that more intervention studies testing the effects are conducted, in order to develop evidence-based recommendations for artificial sweetener usage in the prevention and treatment of childhood obesity.

Key points:

- Artificial sweetener consumption is increasing in all age groups, particularly in children
- Because the FDA does not require manufacturers to report the actual amounts of sweeteners contained in foods and beverages¹¹, quantification of the precise amount of sweeteners in food is difficult

Current recommendations

Guidelines, American Dietetic Association (ADA), American Academy of Pediatrics (AAP), Institute of Medicine (IOM)

There are few explicit recommendations regarding consumption of artificially sweetened foods and beverages in children; however, the American Dietetic Association (ADA) states that both nutritive and artificial sweeteners may comprise part of a diet that follows the Dietary Guidelines for Americans⁵. Specifically, a position statement from the ADA stated that artificial sweeteners can allow consumers to enjoy sweetness while continuing to manage weight, diabetes, and other chronic illnesses. With regard to children specifically, the ADA stated that artificial sweeteners are safe to use within the range of the acceptable daily intake (ADI), which varies for each of the five FDA approved artificial sweeteners. Current intake levels of artificial sweeteners among children are believed to be well below the ADI, but range from around 10% of the ADI for current levels of aspartame consumption to as high as 60% of the ADI for acesulfame-potassium⁵. In contrast, the Institute of Medicine (IOM) does not support artificial sweetener use in children because artificially sweetened beverages have been shown to displace milk and 100% juice at mealtimes. In addition, the IOM stated that more research is needed on the effectiveness of artificial sweeteners for weight management and that more studies are needed on safety effects when artificial sweeteners are consumed over many years starting in childhood or adolescence. Similarly, the American Academy of Pediatrics stated that artificial sweeteners have been inadequately studied for use in children and that they should not form a significant part of a child's diet. Other medical societies have stated their positions on the use of artificial sweeteners, which are outlined in Table 2 (below). However, these statements are not sweetener specific and many do not make recommendations for the use of these sweeteners in a pediatric population.

Key points:

- There are few explicit recommendations for artificial sweetener consumption in children
- Recommendations from medical societies are conflicting

Artificial Sweeteners and the control of body weight

Calories, compensation, energy, BMI, weight

Although artificial sweeteners do not contribute significantly to energy intake, their effectiveness in promoting weight loss and weight control has been questioned¹⁶. To date, eight observational studies have explored the relationship between consumption of artificial sweeteners and weight in children^{17–22}. Of the three cross-sectional studies, including between 385 and 3311 children, the two conducted in school-age and adolescent children showed positive associations between artificial sweetener consumption and BMI^{19, 21}, while the one in 2–5 year olds did not find an association²⁰. Similarly, four of the five longitudinal cohort studies, including between 166 and 11654 children, showed positive associations between artificially sweetened beverage consumption and weight related outcomes including BMI change (in boys, but not girls)²³, BMI z-score¹⁷, energy intake (but not BMI)²⁴, and fat mass (no longer significant after adjustment for covariates)²⁵. A single study showed no association between artificially sweetened beverage intake and BMI, but an inverse correlation with incident obesity, meaning that children who consumed fewer artificially sweetened beverages were less likely to become obese²⁶. Given the observational nature of the above mentioned studies, these data cannot establish that consumption of artificially sweetened beverages was the cause of increased body weight or food intake. There are likely to be many differences, both genetic and cultural, between families that do versus do not offer their children artificially sweetened beverages. Children consuming artificial sweeteners may be those who are at risk of weight gain, thus reversing the direction of the causal relationship.

One proposed explanation for the association between artificial sweetener consumption and weight gain in epidemiologic studies is that knowledge of consuming a substance lower in energy could drive people to eat more¹⁰; this phenomenon has been best described in the context of low-fat foods, in which people overeat foods after receiving a food labeled as low-fat²⁷. In addition, studies in animals (who have no cognitive awareness of the energy content of foods) have shown that the disconnect between sweetness and caloric content from use of artificial sweeteners may impair energy regulation and lead to positive energy balance^{28, 29}. It has also been suggested that the observed paradoxical relationship between artificial sweetener intake and body weight may be due to alteration of gut microbiota³⁰. Although these hypotheses are intriguing, few data exist to support them, especially in children, and future human studies are greatly needed.

While it is expected that substituting artificially sweetened beverages in place of sugar-sweetened beverages would lead to weight loss due the lower caloric intake, experimental studies have shown that the assumed calorie deficit is not maintained^{31–34}. One reason for this is that people tend to compensate for the “missing calories” in an artificially sweetened food or drink by subsequently eating more. Compensation involves the ability to account for excess calorie consumption by reducing intake later, or in the case of an artificially sweetened beverage, to account for the “missing calories,” by subsequently consuming more. Seven studies have evaluated how children compensate for changes in calorie density due to use of caloric versus artificial sweeteners. These studies involved between 14 and 262 participants, ages two to 14 years^{32, 35–40}. The results of these studies are complex, and vary significantly based on study design. In general, younger children seemed to compensate better for missing calories in artificially sweetened foods and drinks by increasing subsequent food intake, thus raising questions about the efficacy of these products for

weight control in young children. It is important to realize, however, that this study design only provides insight into effects that occur within hours, while changes in body weight occur over much longer time frames⁴¹. In addition, these studies generally take place in laboratory settings and it may not be accurate to generalize their findings to 'real life'. It is therefore of great interest to evaluate changes in food intake and body weight that occur with chronic consumption of artificial sweeteners, over the course of weeks, months, or years.

There are very few randomized controlled trials evaluating the effects of artificial sweeteners on weight change in children. One study randomized 103 adolescents of varying BMI to either consume only non-caloric beverages (including both water and artificially sweetened beverages) or to maintain their normal beverage consumption habits. At the end of the 25-week intervention, no difference in BMI was found between groups; however, a post hoc subgroup analysis including only overweight participants did show lower BMI in the treatment group⁴². However, the effect of increased water versus artificially sweetened beverages cannot be determined. A confirmatory study enrolling only overweight adolescents is currently in progress⁴³. A second trial randomized overweight adolescent girls to a restricted 1500 kcal per day diet that either permitted sugar-sweetened soda (within the 1500 kcal limit), or permitted only water or artificially sweetened beverages⁴⁴. Both diets led to a modest amount of weight loss, but there were no significant differences between groups in this small pilot study. In a third study designed to prevent excess weight gain, children in the intervention group were assigned to replace sugar with artificial sweeteners and increase physical activity. As in other studies, the primary outcome of change in BMI z-score was not different between groups, but fewer children in the intervention group increased their BMI z-score. However, the effect of the artificial sweetener and the physical activity intervention cannot be separated⁴⁵. Finally, a study conducted shortly after the approval of aspartame randomized 55 children and young adults to consume an aspartame capsule three times daily or a placebo while on a calorie restricted diet. No significant difference in weight loss was observed at the end of the 13 week intervention⁴⁶.

Key points:

- The majority of observational studies show a positive association between artificial sweetener consumption and body weight.
- The results of short-term satiety studies are complex and vary significantly based on study design. In general, younger children seem to compensate 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. However, the current studies are not sufficient to show that these sweeteners aid in weight loss, either.

Effects artificial sweeteners on glycemia and glucoregulatory hormones

Glucose, insulin, glucagon-like peptide 1, gastric inhibitory peptide, GLUT2, metabolism

Because artificial sweeteners are frequently recommended for use by patients with diabetes, it is critical to understand their effects on glycemia. Early studies in adults with diabetes did not show acute or chronic effects artificial sweeteners on blood glucose or insulin levels^{47, 48}. However, this topic has recently been readdressed as a result of new evidence that artificial sweeteners may be biologically active in the gastrointestinal tract, via binding to sweet taste receptors located on enteroendocrine L-cells^{49, 50}. The biological relevance of intestinal sweet taste receptors in gut hormone secretion in humans has been nicely demonstrated in two recent studies. In both experiments, blockade of these receptors using the sweet taste antagonist lactisole reduced glucose-stimulated secretion of glucagon-like

peptide 1 (GLP-1) and peptide YY (PYY), both of which are made by L-cells. The effects of artificial sweeteners binding to intestinal sweet taste receptors are still being elucidated. *In vitro* studies demonstrated that artificial sweetener binding to intestinal sweet taste receptors increased secretion of the incretin hormones GLP-1 and gastric inhibitory peptide (GIP), and, in rodents *in vivo*, increased the rate of intestinal glucose absorption by upregulating the apical glucose transporter, GLUT-2⁵¹. The relevance of these findings in humans is under active investigation, and this review will focus on studies conducted in humans.

In contrast to *in vitro* data, human studies do not support an effect of artificial sweeteners in isolation on gut hormone secretion. When artificial sweeteners were delivered in 240 mL solutions by intragastric infusion to adults, none had an effect on ghrelin, PYY, glucose, GLP-1 or insulin⁵². In a similar study, no changes in insulin, glucose, GLP-1, or gastric emptying were observed following intragastric infusions of sucralose solutions⁵³. A third study provided adults with equi-sweet solutions of glucose, fructose, saccharin, or aspartame via intra-gastric infusion⁵⁴. The artificial sweeteners alone did not slow gastric emptying to a greater extent than water, though the caloric glucose and fructose solutions did. In another study, eight healthy adults orally ingested 50 mL of sucralose solution versus water, and no differences in PYY, insulin, or GLP-1 were observed⁵⁵. Finally, when aspartame was provided in a tablet form, no insulin or glucose response was observed⁵⁶.

A recent study conducted by Brown et al suggests that artificial sweeteners might affect gut hormone secretion when given in combination with caloric sugars. In this study, healthy adolescents and young adults drank 240 milliliters of diet soda, containing acesulfame potassium and sucralose prior to a 75g glucose load⁵⁷. No significant changes in glucose or insulin were observed, but the diet soda led to a higher GLP-1 response when compared to carbonated water. This study suggests that artificial sweeteners do not affect glucoregulatory hormones when delivered alone, but might have an effect when administered in conjunction with an energy containing food item. In contrast, however, in a human study where intra-duodenal infusion of glucose was accompanied by an intra-duodenal infusion of sucralose or a saline control, sucralose had no effect on either GLP-1 secretion, or the absorption of glucose from the small intestine⁵⁸.

The conflicting data from available studies might be related to differences in sweetener dose, content (acesulfame-K plus sucralose, versus sucralose alone), mode of delivery (oral versus intraduodenal, or infusion rates). Artificial sweeteners each have a different chemical structure and may affect metabolic response differently. Similarly, the physiologic response to a sweetener ingested orally may be different from a sweetener infused intra-gastrically, due to interactions with taste and reward pathways and with cephalic phase responses, in which small insulin responses are observed in response to gustatory stimulation, prior to the absorption of nutrients⁵⁹. Cephalic phase insulin response has been observed before swallowing non-sweet nutritive substances and artificially sweetened energy containing substances in humans. However, sweet non-caloric stimuli alone have not been sufficient to generate an expectatory, cephalic phase response in humans⁵⁹. Further studies are needed to determine whether artificial sweeteners can reliably elicit a gut hormone response in humans.

Key points:

- Human studies do not support an effect of artificial sweeteners in isolation on gut hormone secretion
- Recent studies suggest that artificial sweeteners might affect gut hormone secretion when given in combination with caloric sugars

Artificial sweeteners and their potential effects on taste, reward, and addiction pathways

Addiction, dependence, taste, reward, craving, dopamine, opioids

In an effort to further understand and explain the etiology behind the rising epidemic of obesity, a new research area exploring potentially addictive properties of sugar has emerged. The concept of addiction is hard to define, but is commonly characterized by compulsive and uncontrollable behaviors that are driven by cravings. Though most addiction research examines more common drugs of abuse, such as alcohol, cocaine, morphine, and nicotine, various studies have drawn parallels between drug seeking behavior and food seeking behavior. This has led some to believe that sugar and other sweet substances could become physiologically addictive⁶⁰.

Both feeding patterns and drug use involve learned habits, intense reinforcement, and reward pathways, which persist despite the likelihood of negative consequences.⁶¹ The neurobiological pathways that underlie drug addiction and proposed sugar addiction share the same neurotransmitters, the same receptors, and activate many of the same brain regions⁶². Interestingly, a recent study in children demonstrated that familial alcoholism and depressive symptoms were associated with a preference for more concentrated sucrose solutions and a greater liking of sweet foods⁶³. Specifically, sugar has been shown to cause release of endogenous opioids, endorphins, and dopamine from the brain in an analogous manner to addictive drugs⁶⁴. Furthermore, artificially sweetened solutions have, like sugar, been shown to be effective for pain reduction in infants, providing solid evidence that perception of sweet taste alters central responses⁶⁵. In fact, in rats, gene expression for dopamine receptors and opioids is altered in sugar-dependent rats in a similar manner to morphine-dependent rats⁶⁶. Sugar dependence, defined by indices of bingeing, withdrawal, and increased intake after deprivation arises when rats are maintained on a schedule of intermittent access to a sugar and chow which leads to behavioral and neurological changes^{64, 66}. However, while animals can be conditioned to follow particular eating patterns, which may evoke a drug-like response, this cannot be replicated in humans, and the observed reaction may result from the specific feeding pattern rather than a physical addiction⁶⁷.

Limited data from humans and animal models suggest that some, but not all, effects of caloric sugars on brain reward systems are recapitulated by artificial sweeteners. Although sweet-taste from either caloric or artificial sweeteners produce activation of dopaminergic reward systems in wild-type mice, rodents with an inability to sense sweet-taste only increase dopamine in response to caloric sugars, not artificial sweeteners⁶⁸. In addition, in humans, drinking a calorically versus artificially sweetened beverage led to greater activation of the amygdala in functional MRI studies⁶⁹. Both of these studies suggest that, although artificial sweeteners can stimulate reward pathways, the nutritive value of sweet foods and drinks plays a role in brain reward signaling, independent of their sweetness.

It has also been proposed that frequent exposure to highly sweet items alters food preferences, rather than promoting tolerance; hence, humans develop an expectation that foods and beverages ingested will be sweet and increase their intake of sweet items in accordingly⁶⁷. Recent animal data suggest that artificial sweeteners can be ingested during infancy through breastmilk and prenatally through amniotic fluid, exerting changes in sweetness preferences of exposed offspring⁷⁰. Further supporting this view, experimental studies in young children have shown that early and repeated exposure to sweet taste can shape preferences for sugar-rich food items⁷¹. The idea of habituation to consume a palatable, low energy substance leading to inability to compensate for higher energy variants

with similar flavor was tested by randomizing healthy adults to consume a yogurt drink of low or high energy, and then reversing the energy content after a 9 week habituation period⁷². Participants who switched from the low-energy yogurt drink to the identically flavored high-energy yogurt drink were unable to compensate for the additional calories and overate at the subsequent ad libitum meal. Meanwhile, those who were habituated to the high energy variant did not alter their energy intake when they were provided with the lower-energy yogurt⁷². Similar findings were observed in three to five year old children habituated to aspartame-sweetened versus maltodextrin-sweetened pudding³⁸. This inability for both children and adults to adequately alter their energy intake after repeated experience with a specific pairing of flavor and calories supports the idea that regular consumption of artificial sweeteners which provide sweetness without calories might lead to overconsumption when presented with a sweet energy-containing food or beverage. Key points:

- 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.

Conclusion

This review aims to provide clinicians with current and comprehensive information regarding the effects of artificial sweeteners on food intake, body weight, glycemic control, and sweet liking, craving, and addiction in children. Understanding and critically evaluating past research will assist clinicians in making informed recommendations for use of artificial sweeteners as a means of combating pediatric obesity. Taking into consideration the evidence that exists, we can cautiously conclude that there are no benefits of artificial sweetener use in young children, though it is possible that consumption of artificial sweeteners may be beneficial in limiting weight gain in overweight adolescents. In order to recommend consuming or avoiding artificially sweetened products as a weight control strategy, more studies evaluating the effect of artificial sweeteners on hormonal and metabolic response and on sweet craving must be conducted in children. It is also imperative that longer term studies 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. Continued research about the various mechanisms that underlie energy compensation, satiety, sweet craving, food intake, and weight control will contribute to the growing body of literature examining the role of artificial sweeteners in combating childhood obesity.

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Table 1
FDA approved artificial sweeteners

Table 1 describes the six sweeteners currently approved by the FDA, in terms of the approval status by the FDA, and the acceptable (ADI) and estimated (EDI) intake levels for adults of children. If ADI is greater than or equal to the EDI, the sweetener is approved for use. Aspartame has caloric value, and hence is defined as a nutritive sweetener; however, because it is so much sweeter than sucrose, its caloric value is negligible in the quantities typically consumed. NNS: Non-nutritive sweetener, NUTRS: Nutritive sweetener, GMP: Good manufacturing practices, REG: Food additives for which a petition has been filed and a regulation issued.

Sweetener	FDA Status	Acceptable Daily Intake (ADI)	Sweetness Relative to Sucrose
Acesulfame Potassium	NNS, REG	15 mg/kg (~ 30 cans of diet soda)	200X
Aspartame	NUTRS, REG, GMP	50 mg/kg (~ 18 cans of diet soda)	160–220X
Neotame	NNS, REG, GMP	2 mg/kg	7,000–13,000X
Saccharin	NNS, REG/ITEM	5 mg/kg	300X
Stevia	GRAS	5 mg/kg	300X
Sucralose	NNS, REG, GMP	5 mg/kg (~ 6 cans of diet soda)	600X

Table 2

Position statements for use of sweeteners from various scientific organizations

Scientific Organization	Year	Position statement	Population considered
American Dietetic Association	2004, 2009	Consumers can safely use artificial sweeteners when consumed in a diet guided by current federal nutrition recommendations. The wide range of artificial sweeteners available in food supply should keep artificial sweeteners intake in children well below the acceptable daily intakes.	Children and adults
American Academy of Pediatrics	2010	The use of artificial sweeteners to provide health benefits for children and adolescents has been inadequately studied. As such, they should not form a significant part of a child's diet.	Specific to children
American Heart Association	2010	People with diabetes can use artificial sweeteners, as can people on a weight loss diet	General population
American Diabetes Association	2010	Foods and drinks that contain artificial sweeteners are an option for those with diabetes to consume fewer calories and carbohydrates when replaced for a food or drink containing sugar.	General population
Institute of Medicine	2007	No recommendations are made regarding foods containing artificial sweeteners because 1) artificially sweetened beverages have been shown to displace milk and 100% juice at mealtimes 2) more research is needed on the effectiveness of artificial sweeteners in foods for weight management, and 3) more studies are needed on safety effects when artificial sweeteners are consumed over many years starting in childhood or adolescence	Specific to children