REVIEW ARTICLE

Artificial Sweeteners

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Introduction

In recent years there has been a steady and significant increase in consumer demand for low calorie products in the forms of food & drinks. As a result there is growing interest among healthcare professionals and the general public to learn more about low calorie sweeteners.

Artificial sweeteners / low calorie sweeteners are synthetic sugar substitutes but may be derived from naturally occurring substances, including herbs or sugar itself (1). Artificial sweeteners are also known as intense sweeteners because they are many times sweeter than regular sugar. Artificial sweeteners currently approved by the Food and Drug Administration (FDA) are (1,2):*Table 1*

Possible Health Benefits of Artificial Sweeteners

Weight Control

One of the most appealing aspects of artificial sweeteners is that they are non-caloric. Although they are not a 'silver bullet', low calorie sweeteners can help people reduce their calorie intakes. Long-term trials consistently indicate that the use of low calorie sweeteners results in slightly lower energy intakes and that if low calorie sweeteners are used as substitutes for higher energy-yielding sweeteners, they have the potential to aid in weight management (3,4).

Diabetes

People with diabetes have difficulty in regulating their blood sugar levels. Low calorie sweeteners offer people with diabetes broader food choices by providing the pleasure of the sweet taste without raising blood glucose. As low calorie sweeteners have no impact on insulin and blood sugar levels and do not provide calories, they can also have a role in weight loss and weight control for people with type II diabetes (5,6).

Dental Cavities

When sugar-sweetened foods and drinks are consumed, the bacteria present in the mouth converts the sugar to acid. If this acid is not removed by teeth cleaning, it can wear away the surface enamel, eventually causing cavities to form. Low calorie sweeteners are not fermentable and do not contribute to tooth decay. By improving palatability, low calorie sweeteners can also encourage the use of toothpastes, mouthwashes and fluoride supplements that assist dental hygiene (7).

Possible Health Concerns of Artificial Sweeteners

Cancer

Since their introduction, the role of artificial sweeteners on cancer risk has been widely debated. They have been the subject of intense scrutiny for decades. That's largely because of studies dating to the 1970s that linked saccharin to bladder cancer in laboratory rats, later was shown that the carcinogenic effect of saccharin is species specific.

In 2006 the Cesare Maltoni Cancer Research Center of the European Ramazzini Foundation conducted a long-term bioassay on aspartame (APM), a widely used artificial sweetener & results of this mega-experiment indicated that APM is a multipotential carcinogenic agent, even at a daily dose of 20 mg/kg body weight, much less than the current acceptable daily intake (8).

A case-control study of 480 men and 152 women in Canada found a positive association between the use of artificial sweeteners, particularly saccharin, and risk of bladder cancer. The risk ratio for ever versus never used is 1·6 for males and a significant dose-response relationship was obtained for both duration and frequency of use. This fuelled the controversy and led to ban of saccharin in Canada (9). Andreatta MM *et al* (10) in a case-control study found that regular use of AS for 10 years or more was positively associated with Urinary Tract Tumors.

Although there are some animal studies and few epidemiologic studies also found some associations between artificial sweeteners and cancer risk in humans, but most human studies fail to support this association.

Weihrauch and Diehl in their review divided artificial sweeteners in 'first generation' sweeteners such as saccharin, cyclamate and aspartame, and found there is no evidence to suggest their carcinogenic risk but for

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Table1. List of FDA approved Artificial Sweeteners

	Acesulfame Potassium	Aspartame	Cyclamate	Neotame	Saccharin	Sucralose
omposition	A combination of an organic Acid and potassium	Two amino acids: aspartic acid and phenylalanine.	Cyclamic acid, sodium or calcium salt	Derivative of aspartame.	Sodium or calcium saccharin	Derived from sugar
ceptable Daily take ADI	0-15 mg/kg	0-40 mg/kg	0-7 mg/kg	0-2 mg/kg	0-5 mg/kg	0-15 mg/kg
weetening Power ompared Table Sugar	Up to 200 times	Up to 200 times	Up to 50 times sweeter	Up to 8000	Up to 500	Up to 600
ear Discovered	1967	1969	1937	Early 1990s	1879	1976
aloric Value	Calorie free	4 kcal/g	Calorie free	Calorie free	Calorie free	Calorie free
ses	in drinks, foods, tabletop sweeteners, oral-care and pharmaceutical products	over 6000 food and drink products due to its good sensory properties Limited use in baked products	Used as a tabletop sweetener in drinks, chewing gums, salad dressings and jams	soft drinks, juices, puddings, frozen desserts, chewing gums and jams	Used as a tabletop sweetener in drinks, desserts, confectionery and also in pharmaceutical products	Used in baked goods, desserts, ice-cream and dairy products, breakfast cereals and confectionery

'new generation' sweeteners such as acesulfame-K, sucralose and neotame it is too early to establish any epidemiological evidence about possible carcinogenic risks. However, according to the current literature, the possible risk of artificial sweeteners to induce cancer seems to be negligible (11). Gallus *et al* 2007 (12) reviewed several case-control studies and found a lack of association between saccharine, aspartame, and other sweeteners and several common neoplasms. Magnuson BA review aspartame safety based on current use levels, regulations, and toxicological and epidemiological studies and found no evidence to support an association between aspartame and cancer in any tissue (13). Bosetti *et al* (14) added further evidence on the absence of an adverse effect of low-calorie sweetener (including aspartame) consumption on the risk of Gastric, Pancreatic, and Endometrial Cancers (14).

Weight reduction

Although artificial sweeteners became popular for they can help reduce weight but epidemiologic data suggest an association between artificial sweetener use and weight gain. A prospective cohort study on drinkers of artificially sweetened beverages consistently had higher BMIs at the follow-up, with dose dependence on the amount of consumption. Average BMI gain was +1.01 kg/m^2 for control and 1.78 kg/m^2 for people in the third quartile for artificially sweetened beverage consumption (15). Similar observations have been reported in children, wherein a two-year diet soda consumption was associated with higher BMI Z-scores indicating weight gain (16).Intervention studies suggest that artificial sweeteners do not help reduce weight when used alone. Their addition to diets poses no benefit for weight loss or reduced weight gain without energy restriction and exercise (4,17). There are concerns that inclusion of artificial sweeteners in the diet causes overcompensation for the expected caloric reduction there by promotes energy intake and contributes to obesity.

Nettleton JA *et al* (18) determined associations between diet soda consumption and risk of incident metabolic syndrome, its components, and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis and found consumption of diet soda at least daily was associated with significantly greater risks of select incident metabolic syndrome components and type 2 diabetes (18).

While de Koning L *et al* (19) in their cohort study found the association between artificially sweetened beverages and type 2 diabetes.

Preload experiments generally have found that sweet taste, whether delivered by sugar or artificial sweeteners, enhanced human appetite and therby subsequent increase energy intake (20).

Migranie

In other published reports, Blumenthal (1997) reported three case studies wherein experienced migraines while chewing a popular gum with aspartame additive. In all cases, the migraines were relieved after cessation of product use. The headaches were reproducible by reintroducing the gum (21). Bigal & Krymchantowski (2006) also reported migraine to get triggered by sucralose (22).

Preterm Delivery

A prospective cohort analyses of 59,334 women from the Danish National Birth Cohort (1996-2002) concluded that daily intake of artificially sweetened soft drinks may increase the risk of preterm delivery (23).

Hepatoxicity

A case study of the hepatotoxicity of saccharin was published in 1994. A patient presented with elevated serum concentrations of liver enzymes after the oral administration of three different drugs, of which saccharin was the only common constituent (24).

Thrombocytopenia

Additionally, a case report in 2007 revealed four individuals with thrombocytopenia attributed to products containing aspartame (25).

Conclusion

Although artificial sweeteners have gained attention as dietary tools to help curtail the obesity epidemic, enhancing flavour while reducing calories, and assist in weight-loss. But key question is their safety; especially in susceptible populations for the potential deleterious effects of artificial sweeteners include diabetics, children, pregnant women, breastfeeding mothers, individuals with low seizure thresholds, and individuals at risk for migraines. More studies are required for these susceptible populations. Because of their presence in more than 6,000 products, including foods, medications, and cosmetics, it is impossible to completely eradicate them from daily encounters. Replication studies and long-term assays are required to decrease fear resulting from the limited research that currently exists.

References

1. American Heart Association and American Diabetes Association Supports Low-Calorie Sweeteners as Useful Substitutes for Sugar . The Calorie Control Council.mht. (Last accessed on Dec 2011) Available at: http://www.caloriecontrol.org/
2. The Truth about Artificial Sweeteners or Sugar Substitutes(Last accessed on Dec 2011) Available at: http://www.adaevidencelibrary.com/files/Docs/NNSResourceDraft3.pdf
3. Bellisle F, Drewnowski A. Intense sweeteners, energy intake and the control of body weight. *Eur J Clin Nutr* 2007; 61: 691-700.
4. Mattes RD, Popkin BM. Nonnutritive sweetener consumption in humans: effects on appétite and food intake and their putative mechanisms. *Am J Clin Nutr* 2009;89: 1-14.
5. American Diabetes Association. Nutrition principles and recommendations in diabetes. *Diabetes Care* 2004; 27: S36-46.
6. Mann JI, De Leeuw I, Hermansen K *et al*. Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus. *Nutr Metab Cardiovasc Dis* 2004; 14(6):373-94.
7. Mackie IC. Children's dental health and medicines that contain sugar. *BMJ* 1995;15:141-42.
8. Soffritti M, Belpoggi F, Degli Esposti D *et al*. First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. *Environ Health Perspect* 2006;114:379-85.
9. Howe GR, Burch JD, Miller AB, *et al*. Artificial sweeteners and human bladder cancer. *Lancet* 1977;2:578-81.
10. Andreatta MM, Munoz SE, Lantieri MJ, Eynard AR, Navarro A. Artificial sweetener consumption and urinary tract tumors in Cordoba, Argentina. *Prev Med* 2008;47:136-69.
11. Weihrauch MR, Diehl V. Artificial sweeteners: Do they bear a carcinogenic risk? *Ann Oncol* 2004;15:1460-65.
12. Gallus S, Scotti L, Negri E, *et al*. Artificial sweeteners and cancer risk in a network of case-control studies. *Ann Oncol* 2007;18:40-44.
13. Magnuson BA, Burdock GA, Doull J, *et al*. Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. *Crit Rev Toxicol* 2007;37:629-727.
14. Bosetti C, Gallus S, Talamini R, *et al*. Artificial Sweeteners and the Risk of Gastric, Pancreatic, and Endometrial Cancers in Italy. *Cancer Epidemiol Biomarkers Prev* 2009;18(8):2235-38
15. Fowler SP, Williams K, Resendez RG, Hunt KJ, Hazuda HP, Stern MP. Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. *Obesity (Silver Spring, Md.)* 2008;16:1894-900.
16. Blum JW, Jacobsen DJ, Donnelly JE. Beverage consumption patterns in elementary school aged children across a two-year period. J Am Coll Nutr. 2005;24:93-98.
17. Brown RJ, de Banate MA, Rother KI. Artificial Sweeteners: A systematic review of metabolic effects in youth. *Int J Pediatr Obes* 2010;5(4):305-12.
18. Nettleton JA, Lutsey PL, Wang Y, *et al*. Diet Soda Intake and Risk of Incident Metabolic Syndrome and Type 2 Diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care* 2009;32;688-94.
19. de Koning L, Malik VS, Rimm EB, Willett WC, Hu FB. Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men. *Am J Clin Nutr* 2011;93:1321-27.
20. Qing Yang, Gain weight by "going diet?" Artificial sweeteners and the neurobiology of sugar cravings.*Yale J Biol Med* 2010; 83(2): 101-08.
21. Blumenthal HJ, Vance DA. Chewing gum headaches. *Headache* 1997;37(10):665-66.
22. Bigal ME, Krymchantowski AV. Migraine triggered by sucralose--a case report. *Headache* 2006;46(3):515-17.
23. Halldorsson TI, Strøm M, Petersen SB, Olsen SF. Intake of artificially sweetened soft drinks and risk of preterm delivery: a prospective cohort study in 59,334 Danish pregnant women. *Am J Clin Nutr* 2010;92(3):626-33.
24. Negro F, Mondardini A, Palmas F. Hepatotoxicity of saccharin. *NEJM* 1994;331(2): 134-35.
25. Roberts HJ. Aspartame-induced thrombocytopenia. *Southern Medical Journal* 2007; 100(5): 543.