

## The Role of Low-calorie Sweeteners in Diabetes

Craig A Johnston, PhD,<sup>1,2</sup> Brian Stevens, BSc<sup>2</sup> and John P Foreyt, PhD<sup>1</sup>

1. Department of Medicine, Baylor College of Medicine, Houston, TX; 2. United States Department of Agriculture/Agricultural Research Service (USDA/ARS) Children's Nutrition Research Center, Department of Pediatrics-Nutrition, Baylor College of Medicine, Houston, TX

### Abstract

As the incidence and prevalence of type 2 diabetes continue to rise, the identification of components that contribute to or are associated with this disease has become a priority. One of the main factors that has been linked to type 2 diabetes is excessive weight gain, and reduction in weight has been recommended for both diabetes prevention and management. Low-calorie sweeteners (LCS) provide an alternative to added sugars and may facilitate weight loss or maintenance by limiting caloric intake. Considerable attention has been given to the role of LCS and their relationship to type 2 diabetes. Research suggests that LCS can serve an important role in diabetes prevention and management. Substituting sugars with LCS provides patients with type 2 diabetes considerable flexibility in their health goals and personal dietary preferences.

### Keywords

Type 2 diabetes, low-calorie sweeteners

**Disclosure:** The authors have no conflicts of interest to declare.

**Received:** April 8, 2013 **Accepted:** May 5, 2013 **Citation:** *US Endocrinology*, 2013;9(1):13–5 DOI: 10.17925/USE.2013.09.01.13

**Correspondence:** Craig A Johnston, Assistant Professor, USDA/ARS Children's Nutrition Research Center, Department of Pediatrics-Nutrition and Department of Medicine, Baylor College of Medicine, Houston, TX, US. E: caj@bcm.edu

**Support:** The publication of this article was supported by The Coca-Cola Company. The views and opinions expressed are those of the authors and not necessarily those of The Coca-Cola Company.

A dramatic global increase in the number of adults suffering from type 2 diabetes has been observed in the last 30 years.<sup>1</sup> Between 1980 and 2008, the prevalence of type 2 diabetes more than doubled, and it is estimated that the prevalence will be more than 500 million by 2030.<sup>1–3</sup> Additionally, type 2 diabetes has considerable healthcare cost and significantly impacts quality of life.<sup>4,5</sup> All of these factors have led to an increased focus on diabetes prevention and management.

The rise in diabetes is multifactorial.<sup>4,6,7</sup> Proposed variables that have led to an increase in prevalence include an aging population, dietary changes, and increasing levels of urbanization and sedentary lifestyles.<sup>1,3,8–10</sup> Additionally, genetics has been suggested to play a large role. For example, a high concordance rate of diabetes between monozygotic twins and an increased likelihood of first-degree relatives developing the disease support evidence for a genetic component.<sup>11–14</sup> However, one of the most salient associations of type 2 diabetes is excessive weight gain.<sup>15–17</sup> As a result, considerable attention has been given to weight management through the promotion of healthy lifestyles.<sup>18</sup>

Based on this association of weight gain and diabetes, one of the primary ways to prevent or delay the onset of type 2 diabetes is to prevent excessive weight gain.<sup>18,19</sup> For individuals who have type 2 diabetes, weight loss is also highly recommended.<sup>18</sup> For example, a remission in type 2 diabetes has been observed in patients who have lost weight and maintained these changes.<sup>19</sup> Added sugars have received considerable

attention due to their association with weight gain. For this reason, strategies to reduce added sugars have been developed. Noncaloric or low-calorie sweeteners (LCS) have been used to help prevent and control weight gain.<sup>8,20</sup> LCS are used as an alternative to sugar because they contain less calories.<sup>21,22</sup> Several LCS are available on the market today. Aspartame is possibly the most well known of these. Other LCS are tagalose, neotame, sucralose, saccharin, Luo Han Guo extract, stevia, and acesulfame K.<sup>23,24</sup>

### Reasons for Use Reduction in Caloric Intake

LCS offer a practical method for promoting a reduction in caloric intake.<sup>8,20</sup> They also offer a preventative measure to combat excessive weight gain in at-risk individuals. Foods and beverages that contain LCS offer a better alternative for individuals trying to both prevent and lose excessive weight by making a relatively simple dietary change.<sup>8,20</sup> Small changes such as this have been hypothesized to impact the high prevalence of obesity.<sup>25–27</sup> For example, changes as small as 100 calories a day have been suggested to reverse the trends in the obesity epidemic.<sup>26</sup> The replacement of added sugars with LCS is consistent with this approach.

### Treatment of Diabetes

Because added sugars are a source of increased carbohydrate intake, safe and easy ways to decrease their consumption is central to treatment. The use of LCS offers a practical approach to support the reduction

of carbohydrate intake for patients with type 2 diabetes. By replacing added sugars with LCS, individuals with diabetes and prediabetes may better be able to manage their blood glucose levels and reduce their bodyweight. The Academy of Nutrition and Dietetics, the American Heart Association, and the American Diabetes Association consider US Food and Drug Administration (FDA)-approved LCS to be safe for consumption for individuals with diabetes.<sup>24,28,29</sup> In addition, the Academy refers to LCS as 'free foods' because they do not raise blood glucose levels and offer a safe alternative to natural sugars.<sup>28</sup>

## Other Benefits

The use of LCS may also help manage reactive hyperglycemia in individuals who do not have type 2 diabetes.<sup>30</sup> For these patients, excessive sugar intake leads to increased insulin secretion, which may lead to more serious health complications. LCS offer a viable way for these individuals to help prevent this response. Excessive intake of sugar and other fermentable carbohydrates also has a detrimental effect on oral and dental hygiene and can lead to cavities, plaque buildup, and gum disease.<sup>31,32</sup> Other factors associated with the formation of dental caries include length of exposure to the teeth while in the mouth, stickiness of the food, strength of the tooth enamel, frequency of consumption, oral hygiene, and microbiology in the mouth. If ignored, gum diseases like gingivitis may lead to far more serious health complications.<sup>33,34</sup> LCS can help to improve oral hygiene and dental care.

## Low-calorie-sweetener-associated Concerns Increased Appetite

While there are multiple health benefits associated with LCS, some concerns about their use have also been raised. One of the most notable concerns is that the consumption of LCS increases appetite.<sup>35-38</sup> It has been theorized that individuals overcompensate for the calories that have been saved. The reason for this overcompensation may be the knowledge that fewer calories are consumed, which leads to increased caloric intake.<sup>35</sup> Others have theorized that a more physiologic response occurs.<sup>39,40</sup> For example, it has been suggested that LCS differ from sucrose in terms of satiety or feelings of fullness.<sup>41</sup>

Multiple studies have been conducted to examine these speculations.<sup>35,41-47</sup> No differences in hunger have been shown between LCS and meals sweetened with sucrose in humans.<sup>45-47</sup> LCS have not been shown to increase appetite.<sup>34,42,44,45</sup> Similarly, LCS have not been shown to increase caloric intake through overcompensation.<sup>46</sup> For example, a randomized trial was conducted that provided participants with either a caloric sweetener or aspartame preload condition.<sup>48</sup> Participants were given either sucrose or a low-calorie sweetener in a pill form before a meal. Those who consumed aspartame preloads did not compensate by eating more than the caloric sweetener group. Additionally, both conditions reported similar levels of satiety following meals. No differences were observed between conditions.<sup>48</sup>

## Weight Gain

Similar to the matter of increased appetite, it has also been reported that LCS may cause weight gain.<sup>49</sup> Rodent studies have shown that low-calorie sweetener consumption can promote excessive weight gain in male rats.<sup>49</sup> A positive correlation between low-calorie sweetener consumption and bodyweight has also been shown.<sup>50</sup> Based on this epidemiologic

evidence, it has been suggested that low-calorie sweetener consumption increases the likelihood of being obese.<sup>51</sup>

Epidemiologic studies are conducted only in order to develop hypotheses and not to establish causality.<sup>52</sup> Randomized controlled trials are required to test the generated hypotheses.<sup>52</sup> Based on randomized trials in humans, no evidence supports the claim that LCS cause higher bodyweights in adults.<sup>53,54</sup> In fact, randomized controlled trials suggest that the use of LCS may increase adherence to low-calorie diets and improve bodyweight and weight loss maintenance over time.<sup>20,55</sup>

## Insulin and Hormonal Response

The sweet taste of LCS can be on average several hundred times sweeter than natural sugars, which some have suggested may lead to oversensitivity to sweetness. This oversensitivity has been hypothesized to induce increased hormonal secretion.<sup>56</sup> Specifically, rodent studies have suggested that LCS may have an effect on glucoregulatory hormones.<sup>57,58</sup> These studies reported that LCS may be nutritionally active and signal a functional taste reception system, which in turn increases sugar absorption during meals. Discovering mechanisms that cause an increase in sugar absorption could have significant implications for the treatment of diabetes and obesity.<sup>57</sup>

However, human studies have not supported these findings and have found no effect of LCS on gut hormone secretion.<sup>59,60</sup> Furthermore, a recent review by the Academy of Nutrition and Dietetics reported that LCS have not been found to affect the glycemic responses in people with type 2 diabetes.<sup>28</sup>

## Other Concerns

As with most additives, there have been reports that the ingestion of LCS may result in allergic reactions or increased sensitivity that may lead to more serious health concerns.<sup>61</sup> While anecdotal experiences of low-calorie sweetener sensitivity and allergic reactions have been reported, these findings have not been confirmed by carefully controlled scientific studies.<sup>62,63</sup>

## Summary

Several concerns have been raised regarding the use of LCS based on data from rodent and correlational studies. Although studies of this nature provide direction for hypotheses, they are not sufficient to draw conclusions about causality in humans.<sup>52</sup> Current findings have documented that LCS are safe for consumption in a normal diet. These conclusions are consistent with recommendations from both the American Diabetes Association and the Academy for Nutrition and Dietetics.<sup>24, 29</sup>

## Low-calorie Sweeteners and Diabetes— Future Research

While the use of LCS for the prevention and treatment of diabetes and weight loss is promising, there is a paucity of high-quality clinical research in this important area. Much of the data regarding LCS and their role in diabetes is from observational studies, which have significant research limitations. There is a clear need for randomized controlled trials to further advance the understanding of the role that LCS plays in diabetes prevention and management. For example, additional studies on the metabolic effects of LCS in the body, especially in patients with

type 2 diabetes, could prove useful. Additional effectiveness research in the treatment of type 2 diabetes using LCS would also be beneficial to improve the flexibility and quality of treatment options.

## Conclusion

Engaging in a healthy lifestyle is central to the prevention and management of type 2 diabetes.<sup>64</sup> Steps to improve one's diet, increase levels of physical activity, and maintain a healthy weight are consistent with these

efforts. The use of LCS can assist individuals in reducing caloric intake and thereby promote a healthier weight. However, LCS are not appetite suppressants. Their ultimate effects will depend on their integration as part of a healthy lifestyle.<sup>24,64</sup>

LCS can serve an important role in diabetes prevention and management. Substituting sugars with LCS provides patients with type 2 diabetes considerable flexibility in their health goals and personal dietary choices. ■

- Danaei G, Finucane MM, Lu Y, et al., National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants, *Lancet*, 2011;378(9785):31–40.
- International Diabetes Federation, IDF Diabetes Atlas, Brussels: International Diabetes Federation; 2012. Available at: <http://www.idf.org/diabetesatlas/5e/the-global-burden>
- Vaz JA, Patnaik A. Diabetes mellitus: Exploring the challenges in the drug development process, *Perspect Clin Res*, 2012;3(3):109–12.
- Brown DW, Balluz LS, Giles WH, et al., Diabetes mellitus and health related quality of life among older adults. Findings from Behavioural Risk Factor Surveillance System (BRFSS), *Diabetes Res Clin Pract*, 2004; 65:105–15.
- Zhang P, Zhang X, Brown J, et al., Global healthcare expenditure on diabetes for 2010 and 2030, *Diabetes Res Clin Pract*, 2010;87(3):293–301.
- Berends LM, Ozanne SE, Early determinants of type-2 diabetes, *Best Pract Res Clin Endocrinol Metab*, 2012;26(5):569–80.
- Imam K, Clinical features, diagnostic criteria and pathogenesis of diabetes mellitus, *Adv Exp Med Biol*, 2012;771:340–55.
- Anderson GH, Foreyt J, Sigman-Grant M, Allison DB, The use of low-calorie sweeteners by adults: impact on weight management, *J Nutr*, 2012;142:11635–95.
- Koivula RW, Tornberg AB, Franks PW, Exercise and diabetes-related cardiovascular disease: systematic review of published evidence from observational studies and clinical trials, *Curr Diab Rep*, 2013;13(3):372–80.
- Ramachandran A, Mary S, Yamuna A, et al., High prevalence of diabetes and cardiovascular risk factors associated with urbanization in India, *Diabetes Care*, 2008;31(5):893–8.
- Kaprio J, Tuomilehto J, Koskenvuo M, et al., Concordance for type 1 (insulin-dependent) and type 2 (non-insulin-dependent) diabetes mellitus in a population-based cohort of twins in Finland, *Diabetologia*, 1992;35(11):1060–67.
- Newman B, Selby JV, King MC, et al., Concordance for type 2 (non-insulin-dependent) diabetes mellitus in male twins, *Diabetologia*, 1987;30(10):763–8.
- Kobberling JTH, *Empirical risk figures of first degree relatives of non-insulin dependent diabetes*, London: Academic Press, 1982.
- Sanghera DK, Blackett PR, Type 2 diabetes genetics: beyond GWAS, *J Diabetes Metab*, 2012;3(198):6948.
- Gray DS, Diagnosis and prevalence of obesity, *Med Clin North Am*, 1989;73:1–13.
- Inadera H, Developmental origins of obesity and type 2 diabetes: molecular aspects and role of chemicals, *Environ Health Prev Med*, 2013;18(3):185–97.
- Nasser KA, Gruber A, Thomson GA, The emerging pandemic of obesity and diabetes: are we doing enough to prevent a disaster?, *Int J Clin Pract*, 2006;60(9):1093–97.
- Maggio CA, Pi-Sunyer FX, The prevention and treatment of obesity. Application to type 2 diabetes, *Diabetes Care*, 1997;20(11):1744–66.
- Gregg EW, Chen H, Wagenknecht LE, et al., Association of an intensive lifestyle intervention with remission of type 2 diabetes, *JAMA*, 2012;308(23):2489–96.
- de la Hunty A, Gibson S, Ashwell M. A review of the effectiveness of aspartame in helping with weight control, *Nutr Bull*, 2006;31:115–28.
- Tandel KR, Sugar substitutes: Health controversy over perceived benefits, *J Pharmacol Pharmacother*, 2011;2:236–43.
- Artificial sweeteners: no calories...sweet!, *FDA Consum*, 2006;40(4):27–8.
- Gardana C, Scallianti M, Simonetti P, Evaluation of steviol and its glycosides in Stevia rebaudiana leaves and commercial sweetener by ultra-high-performance liquid chromatography-mass spectrometry, *J Chromatogr A*, 2010;1217(9):1463–70.
- Fitch C, Keim KS, Academy of Nutrition and Dietetics. Position of the Academy of Nutrition and Dietetics: use of nutritive and nonnutritive sweeteners, *J Acad Nutr Diet*, 2012;112(5):739–58.
- Hall KD, Sacks G, Chandramohan D, et al., Quantification of the effect of energy imbalance on bodyweight, *Lancet*, 2011;378:826–37.
- Hill JO, Can a small-changes approach help address the obesity epidemic? A report of the joint task force of the American Society for Nutrition, Institute of Food Technologies, and International Food Information Council, *Am J Clin Nutr*, 2009;89:1723–8.
- Hill JO, Wyatt HR, Reed JC, Peters JC, Obesity and environment: where do we go from here?, *Science*, 2003;299:853–5.
- Franz MJ, Powers MA, Leontos C, et al., The evidence for medical nutrition therapy for type 1 and type 2 diabetes in adults, *J Am Diet Assoc*, 2010;110:1852–89.
- Gardner C, Wylie-Rosett J, Gidding SS, et al., Nonnutritive sweeteners: current use and health perspectives: a scientific statement from the American Heart Association and the American Diabetes Association, *Circulation*, 2012;126:509–19.
- Espinosa I, Fogelfeld L. Tagatose: from a sweetener to a new diabetic medication?, *Expert Opin Investig Drugs*, 2010;19(2):285–94.
- Honkala E, Tala H, Total sugar consumption and dental caries in Europe—an overview, *Int Dent J*, 1987;37(3):185–91.
- Gordon Y, Reddy J, Prevalence of dental caries, patterns of sugar consumption and oral hygiene practices in infancy in S. Africa, *Community Dent Oral Epidemiol*, 1985;13(6):310–14.
- Cronin A, Periodontal disease is a risk marker for coronary heart disease?, *Evid Based Dent*, 2009;10(1):22.
- Trevisan M, Dorn J, The relationship between periodontal disease (pd) and cardiovascular disease (cvd), *Mediterr J Hematol Infect Dis*, 2010;2(3):e2010030.
- Mattes RD, Popkin BM, Nonnutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms, *Am J Clin Nutr*, 2009;89:1–14.
- Bantle JP, Dietary fructose and metabolic syndrome and diabetes, *J Nutr*, 2009;139(6):1263S–1268S.
- Hu FB, Malik VS, Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence, *Physiol Behav*, 2010;100:47–54.
- Malik VS, Hu FB, Sweeteners and risk of obesity and type 2 diabetes: the role of sugar-sweetened beverages, *Curr Diab Rep*, 2012;12(2):195–203.
- Davidson TL, Swithers SE, A pavlovian approach to the problem of obesity, *Int J Obes Relat Metab Disord*, 2004;28(7):933–5.
- Stegink LD, Filer LJ, *Aspartame: Physiology and Biochemistry. 1st ed*, New York, NY: Marcel Dekker, 1984.
- Bellisle F, Drewnowski A, Anderson GH, et al., Sweetness, satiation, and satiety, *J Nutr*, 2012;142:1149S–54S.
- Benton D, Can artificial sweeteners help control body weight and prevent obesity?, *Nutr Res Rev*, 2005;18:63–76.
- Blundell JE, Green SM, Effect of sucrose and sweeteners on appetite and energy intake, *Int J Obes Relat Metab Disord*, 1996;20(Suppl. 2):S12–17.
- Drewnowski A, Intense sweeteners and the control of appetite, *Nutr Rev*, 1995;53:1–7.
- Drewnowski A, Massien C, Louis-Sylvestre J, et al., Comparing the effects of aspartame and sucrose on motivational ratings, taste preferences, and energy intake in humans, *Am J Clin Nutr*, 1994;59:338–45.
- Rolls BJ, Laster LJ, Summerfelt A, Hunger and food intake following consumption of low-calorie foods, *Appetite*, 1989;13(2):115–27.
- Van Wymelbeke V, Beridot-Therond ME, de La Gueronniere V, et al., Influence of repeated consumption of beverages containing sucrose or intense sweeteners on food intake, *Eur J Clin Nutr*, 2004;58:154–61.
- Anton SD, Martin CK, Han H, et al., Effects of stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels, *Appetite*, 2010;55:37–43.
- Swithers SE, Sample CH, Davidson TL, Adverse effects of high-intensity sweeteners on energy intake and weight control in male and obesity-prone female rats, *Behav Neurosci*, 2013;127(2):262–74.
- Stellman SD, Garfinkel L, Artificial sweetener use and one-year weight change among women, *Prev Med*, 1986;15(2):195–202.
- Fowler SP, Williams K, Resendez RG, et al., Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain, *Obesity*, 2008;16(8):1894–900.
- Hill AB, The environment and disease: association or causation?, *Proc R Soc Med*, 1965;58(5):295–300.
- Bellisle F, Drewnowski A, Intense sweeteners, energy intake and the control of body weight, *Eur J Clin Nutr*, 2007;61(6):691–700.
- Serra-Majem L, Ribas C, Inglés C, et al., Cyclamate consumption in Catalonia, Spain (1992): relationship with the body mass index, *Food Addit Contam*, 1996;13(6):695–703.
- Phelan S, Lang W, Jordan D, Wing RR, Use of artificial sweeteners and fat-modified foods in weight loss maintainers and always-normal weight individuals, *Int J Obes (Lond)*, 2009;33(10):1183–90.
- Okuno G, Kawakami F, Tako H, et al., Glucose tolerance, blood lipid, insulin and glucagon concentration after single or continuous administration of aspartame in diabetics, *Diabetes Res Clin Pract*, 1986;2(1):23–7.
- Mace OJ, Affleck J, Patel N, et al., Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2, *J Physiol*, 2007;582:379–92.
- Renwick AG, Molinary SV, Sweet-taste receptors, low-energy sweeteners, glucose absorption and insulin release, *Br J Nutr*, 2010;104(10):1415–20.
- Steinert RE, Frey F, Topfer A, et al., Effects of carbohydrate sugars and artificial sweeteners on appetite and the secretion of gastrointestinal satiety peptides, *Br J Nutr*, 2011;105:1320–8.
- Sylvetsky A, Rother KI, Brown R, Artificial sweetener use among children: epidemiology, recommendations, metabolic outcomes, and future directions, *Pediatr Clin North Am*, 2011;58:1467–80.
- Garriga MM, Metcalfe DD, Aspartame intolerance, *Ann Allergy*, 1988;61(6 Pt 2):63–9.
- Garriga MM, Berkebile C, Metcalfe DD, A combined single-blind, double-blind, placebo-controlled study to determine the reproducibility of hypersensitivity reactions to aspartame, *J Allergy Clin Immunol*, 1991;87(4):821–7.
- Schiffman SS, Buckley CE, 3rd, Sampson HA, et al., Aspartame and susceptibility to headache, *N Engl J Med*, 1987;317:1181–5.
- American Diabetes Association, National Institute of Diabetes, Digestive and Kidney Diseases, The prevention or delay of type 2 diabetes, *Diabetes Care*, 2002;25(4):742–7.