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## Impact of Sugar Substitutes on Glucose Control in Diabetic Patients

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**Do Sugar Substitutes Have any Impact on Glycemic Control in Patients with Diabetes?**

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## **ABSTRACT**

*OBJECTIVE:* To evaluate the impact of nonnutritive sugar substitutes on glycemic control in patients with diabetes.

*DATA SOURCES:* A comprehensive review of the literature was conducted in PubMed (1966 - March 2012) and Scopus. A combination of MeSH terms and keywords were used including: acesulfame, aspartame, diabetes, neotame, rebiana, saccharin, stevia, and sucralose.

*STUDY SELECTION AND DATA EXTRACTION:* Clinical studies evaluating the impact of nonnutritive sweeteners on measures of diabetic control, including but not limited to, blood glucose levels, postprandial blood glucose, and hemoglobin A1C were selected for review.

Searches were limited to only nonnutritive sweeteners available in the United States.

*DATA SYNTHESIS:* Nine clinical trials were found that evaluated nonnutritive sweeteners in a total of 490 patients with diabetes. Doses of sweeteners varied in the studies from doses below acceptable daily intake levels for 3 consecutive days to daily dosing for up to 18 weeks and up to 3.5 times the acceptable daily intake levels. No significant differences in overall effects on glycemic control and insulin response were found.

*CONCLUSIONS:* Nonnutritive sweeteners do not appear to affect glycemic control in patients with diabetes. Patients should be counseled to maintain an appropriate energy balance in their diet, with or without the use of nonnutritive sweeteners.

## **BACKGROUND**

More than 25 million people in the U.S. are affected by diabetes. The number of Americans diagnosed with diabetes has more than tripled in the last 30 years. In 2010, more than 1 in 4 U.S. residents over the age of 65 had a diagnosis of diabetes.<sup>1</sup> Diabetic complications result in significant morbidity, mortality, and costs to the healthcare system. Avoiding increased caloric intake is important, and many individuals elect to use sugar substitutes in food and beverages as a way to enhance taste without added calories and carbohydrates.

Nonnutritive sweeteners are agents that have little to no calories, and thus provide negligible energy. These agents are alternatives to nutritive sweeteners such as refined sugar, high fructose corn syrup, fructose, and dextrose, among others. Nonnutritive sugar substitutes are at least 100 times sweeter than regular sugar which is why such a small amount is needed for flavor.<sup>2</sup> Close to 200 million people in the U.S. consume these sweeteners with half that many consuming them daily.<sup>3</sup>

It has been hypothesized that by adding nonnutritive sweeteners in place of calorie producing sweeteners in foods, consumers would end up consuming more overall by eating or drinking additional food and drink to replace the calories that were avoided initially.<sup>4</sup> The potential benefit to using nonnutritive sweeteners in patients with diabetes is the advantage of still being able to consume sweet foods and beverages, but not increasing calories. This would, however, be disadvantageous to use these products if patients were replacing them with increased carbohydrate content to make up for missed calories.

Seven sugar substitutes are recognized as food additives Generally Recognized As Safe (GRAS) by Food and Drug Administration (FDA): acesulfame-K (Sunett®, Sweet One®), aspartame (NutraSweet®, Equal®), Luo Han Guo extract (monk fruit extract), saccharin (Sweet 'N Low®, Sugar Twin®), sucralose (Splenda®), Stevia (also known as Truvia®, Rebaudioside A, Reb-A, or rebiana), and neotame.<sup>5-7</sup> Additionally, the American Diabetes Association (ADA) and the American Dietetic Association (ADietA) have supported use of these agents when consumed within acceptable daily intake levels as defined by the FDA (Grade A recommendation).<sup>2,8,9</sup>

Treatment strategies to prevent diabetic complications are aimed at controlling blood glucose (BG), blood pressure (BP) and lipids in conjunction with other preventative care. Sugar substitutes are often used by patients as a means to avoid excess calories and carbohydrates; however the potential impact on measures of glucose control is important. The objective of this article is to review the literature to evaluate the effects of nonnutritive sugar substitutes on measures of glucose control in patients with diabetes.

## **LITERATURE REVIEW**

Pubmed (1966 – May 2012) and Scopus (1949 – May 2012) were searched using the each of the search terms acesulfame, aspartame, Luo Han Guo, monk fruit, neotame, rebiana, saccharin, stevia, and sucralose with the search term diabetes. All English language clinical studies that evaluated the impact of any of these nonnutritive sweeteners available in the U.S. on measures of diabetic control, including but not limited to, blood glucose levels, postprandial blood glucose and hemoglobin A1C were selected for review. References of the identified studies as well as position statements on nonnutritive sweeteners from the Academy of Nutrition and Dietetics, American Diabetes Association and the American Dietetic Association were

reviewed for additional studies.<sup>2, 5, 7-9</sup> Studies evaluating effects of a single dose of nonnutritive sweeteners were excluded. A total of nine clinical trials were identified and evaluated (5-aspartame, 2-stevia, 1-saccharin, and 1-sucralose). No studies were found that met the criteria with acesulfame, luohan guo extract or neotame.

### ***Aspartame***

The majority of studies assessing effects of nonnutritive sweeteners on glycemic control have utilized aspartame. Five studies were found including three that compared aspartame intake to a control. Altogether they evaluated effects of 48 to 1800 mg of aspartame in a total of 169 patients with diabetes and 6 healthy subjects with daily use for three days to eighteen weeks.<sup>10-14</sup>

Okuno and colleagues investigated the effects of 125 mg aspartame consumed daily for 2 weeks on blood glucose, insulin, and glucagon secretion compared to the week before and after the aspartame diet weeks. Nine participants with diabetes received a “jellycake” with 125 mg aspartame daily for 2 weeks. Following administration, there were no significant differences in the 50 gram glucose tolerance test or postprandial blood glucose. Additionally, no significant differences were found with fasting blood cholesterol, HDL-cholesterol, or triglycerides.<sup>10</sup>

Stern et al. evaluated the effects of 1800 mg of aspartame or placebo given daily in capsules to patients with type 2 diabetes (n=69) for 90 days in a randomized, controlled trial. At the end of the treatment period, there were no significant differences in fasting glucose levels or in serum phenylalanine, tyrosine, or weight after aspartame administration. The most common adverse effect reported was mild gastrointestinal complaints in both treatment groups.<sup>11</sup>

Colagiuri and colleagues evaluated the effects of adding 4500 mg sucrose or 162 mg aspartame daily to the usual diet of well-controlled group of patients with type 2 diabetes (n=9) for 6 weeks before crossing over to the other group for another 6 weeks. Patients added

unlabeled packets of the assigned sweetener to their food or beverages. At the end of each 6 week treatment period, there were no significant changes in fasting and post-meal glucose concentrations, overall glucose control, body weight, total cholesterol, HDL cholesterol, or triglycerides between sucrose and aspartame.<sup>12</sup>

Kullessa et al. evaluated the effects of aspartame 30 mg capsules or placebo on glycemic effects in patients diagnosed with either type 1 or type 2 diabetes (n=62). Patients were randomized to receive aspartame or placebo and were instructed to take 3 capsules with each meal, for a total of 9 capsules daily, for 18 weeks with follow-up visits approximately every 3 weeks. At the conclusion of the study, there were no significant changes in plasma glucose or A1C levels in either group. The patients also experienced similar adverse reactions, including constipation, itching, gastroenteritis, and diarrhea, in both the placebo and aspartame group.<sup>13</sup>

Shigeta et al. evaluated the effects on fasting plasma glucose of diets sweetened with 24 to 48 mg of aspartame for three days in 20 patients with type 2 diabetes and in 6 healthy patients. No significant differences were found in plasma glucose levels in either group when compared to baseline.<sup>14</sup>

### ***Saccharin***

One randomized, controlled, cross-over trial has been conducted evaluating the effects of saccharin on glucose and insulin levels in a total of seventeen patients with type 2 diabetes.<sup>15</sup> Cooper and colleagues compared supplementation of a regular diet with either 28 g sucrose or 30 g of starch and saccharin (equivalent in sweetness and energy, respectively to 28 g sucrose) daily for 6 weeks. No information was provided about what type of starch was used or any more specifics of the saccharin dose used in the study. No statistically significant effects were found



with the saccharin on plasma glucose levels, insulin and glucagon levels at any time point after ingestion.<sup>15</sup>

### ***Stevia***

Stevia leaves are composed of multiple steviol glycosides: stevioside, rebaudiosides A through F, steviolbioside, and dulcoside A. All of the glycosides produce a sweet taste; however, stevioside and rebaudioside A are the most sweet and most abundant.<sup>16</sup> Two randomized, controlled trials have been reported evaluating the effects of steviol glycosides on blood glucose in 152 patients with type 1 and type 2 diabetes.<sup>17-18</sup> Barriocanal et al. evaluated the effects of steviol glycosides on blood glucose and blood pressure in a parallel study in 16 patients with type 1 diabetes, 30 with type 2 diabetes, and 30 healthy patients. Patients were randomized to receive either placebo or steviol glycosides 250 mg capsules three times daily for 3 months. No statistically significant differences were found between baseline and post treatment assessments in fasting blood glucose, A1C, systolic blood pressure, or diastolic blood pressure in the type 2 diabetes group and the healthy patient group. There were statistically significant differences reported in the type 1 diabetes placebo group for changes in mean systolic blood pressure (SBP) and fasting blood glucose. Mean SBP levels were 108.3 mmHg at baseline versus 105.7 mmHg at the end of the study ( $p<0.05$ ). Mean glucose levels in the placebo group changed from baseline to end of the study from 219 to 298 mg/dl in patients with type 1 diabetes, from 131 to 119 mg/dl ( $p<0.05$ ) in patients with type 2 diabetes and from 83 to 84 mg/dl in patients without diabetes. A1C levels changed from 8.2% to 8.3% in type 1, from 6.8% to 6.7% in type 2 and from 5.3% to 5.4% in patients without diabetes.<sup>17</sup>

Maki et al. conducted a multi-center, randomized, double-blind, placebo controlled, 16-week trial investigating the effects of rebaudioside A on glycemic and hemodynamic effects in 122 patients with type 2 diabetes. Patients were randomized to receive either placebo or rebaudioside A in four 250 mg capsules daily (1,000 mg daily). No statistically significant differences were found with the primary outcome of the study, change in A1C from baseline to week 16. A1c was 6.71% and 6.70% in the rebaudioside A and placebo groups respectively at baseline and increased by 0.11% and 0.09% respectively ( $p = 0.355$ ) at week 16. No statistically significant differences were reported for fasting levels of glucose, insulin, C-peptide, intakes of total energy, or percentages of energy from carbohydrates from baseline to end of the study. No differences in hypoglycemic events were reported between the groups.<sup>18</sup>

### ***Sucralose***

One randomized, double-blind, placebo-controlled trial evaluated the effects of either sucralose 667 mg ( $n = 67$ ) or placebo ( $n = 69$ ) daily on glycemic control in patients with type 2 diabetes.<sup>19</sup> Patients participated in a 4-week placebo run in phase and then were randomized to either placebo or sucralose provided in capsules to be taken with meals for 13 weeks. Participants were asked to follow a diet of 14% protein, 30-36% fat and 48-55% carbohydrate and to measure capillary blood glucose at least three times daily. No statistically significant difference was found between the treatment groups in A1C over time. A1C levels were reported to have decreased significantly after 2 weeks of treatment in the sucralose group; however, A1C at this time point would not have been specific to the sucralose beginning only 2 weeks prior. No statistically significant differences were reported in fasting plasma glucose concentrations between the groups (between treatment difference from baseline  $-1.13$  mg/dL,  $p = 0.89$ ) or in

fasting C-peptide (between treatment difference 150 ng/mL,  $p = 0.29$ ). No adverse events were documented related to sucralose.<sup>19</sup>

## **DISCUSSION**

Nine clinical trials were found that evaluated nonnutritive sweeteners in a total of 490 patients with diabetes.<sup>10-15,17,18</sup> Doses of nonnutritive sweeteners varied in the studies, but all were below the acceptable daily intake levels in studies of aspartame and saccharin. The studies evaluating sucralose and stevia utilized doses up to 3.5 times the acceptable daily intake levels for a 70 kg adult (table 1).<sup>2,17-19</sup> The studies evaluated effects of daily intake over a period of 3 days to 18 weeks. The study by Kullessa et al. evaluated the highest dose of a nonnutritive sweetener (2.7 g/day of aspartame) for the longest time period (18 weeks).<sup>13</sup> No significant differences in overall effects on glycemic control and insulin response were found in any of the multiple dose studies.

Many of the studies evaluated were randomized, cross-over studies assessing a nonnutritive sweetener against a control. In most cases the control used was cellulose which has been shown to have no significant impact on glycemic control.<sup>11-13,17,18,20</sup> The study by Cooper and colleagues added starch to the saccharin dose to be an equal amount of energy to the sucrose in the other trial arm. The addition of the calories with the starch to equal that of sucrose would decrease the beneficial effects that were being investigated with replacing sucrose with a nonnutritive sweetener. It is not surprising that no changes in glucose levels were identified in this trial. Doses of nonnutritive sweeteners in amounts similar or greater than what is usually consumed in a packet of the nonnutritive sweetener were used. Most of the studies however, evaluated a small number of patients and did not measure long term glycemic control and safety.

It is understandable that doses of nonnutritive sweeteners in the study were often consumed via capsules; however, ideally, consumption of the nonnutritive sweeteners would have been via food products as this would be more true to normal consumption. Most studies used A1C as the primary measure of glycemic control, which would be an inadequate marker in the studies that were conducted over fewer than 120 days. There is a possibility that patients in the studies consumed a healthier diet than what they would normally consume because they knew they were enrolled in a study and would be monitored.

Mattes and Popkin reviewed the literature evaluating the effects of nonnutritive sweeteners on appetite and food intake in humans and reported that only observational studies have evaluated long-term use of nonnutritive sweeteners in the diet. The studies they found produced conflicting evidence, but principally found no overall effects on the primary variable measured, body mass index (BMI).<sup>21</sup> Larger, randomized trials assessing chronic effects on post-prandial blood glucose levels and A1C, dietary compliance and body weight control may be beneficial to confirm results found in shorter term studies.

## **SUMMARY**

Overall, it appears that nonnutritive sweeteners may be used by patients with diabetes without affecting glycemic control. These agents have been generally recognized as safe when consumed in amounts below the acceptable daily intake levels. Patients should be counseled to maintain an appropriate energy balance in their diet, with or without the use of nonnutritive sweeteners.

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**Table 1. Acceptable Daily Intake for Nonnutritive Sweeteners**

<b>Sweetener</b>	<b>Acceptable Daily Intake (ADI) (mg/kg/day)<sup>2,7</sup></b>	<b>Dose ranges in studies in patients with diabetes<sup>9-15, 17, 18</sup></b>
Acesulfame K	15	
Aspartame	50	48 - 1800 mg
Luo han guo extract	Not determined	
Neotame	18	
Saccharin	5	135 mg – (equivalent of 28 g of sucrose)
Stevia	4 (steviol glycosides) 12 (rebaudioside A)	750 - 1000 mg
Sucralose	5	667 – 1000 mg