SUGAR & ARTIFICIAL SWEETENERS

Sugar, ahh sweet sugar. Sugar has been with us since at least 8,000 BC where New Guinea locals domesticated sugarcane and would chew on the reeds for the sweetness (History). While sugar took a long time to reach Europe, it has been cultivated in India since at least 800 B.C. (UCLA)

From India, sugar spread to China and Persia. The Crusaders brought sugar with them to Europe in the 11th century and it became available (to the wealthy) of other countries by way of the Venetians. It wasn't until the 16th century that sugar entered cooking, as described by Nostradamus (UCLA).

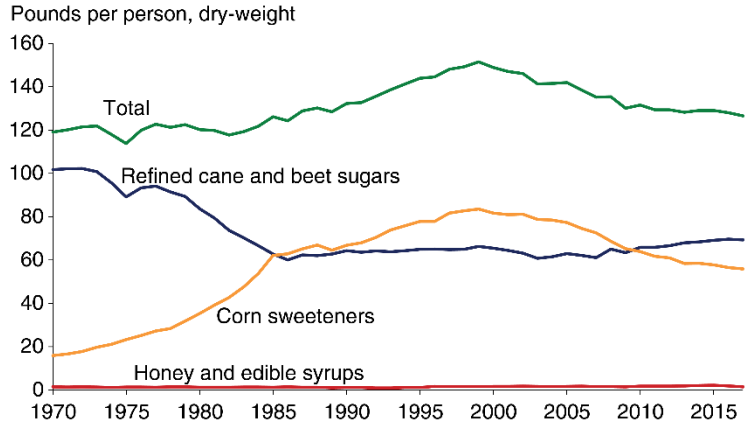
By 350 A.D, India learned to crystalize sugar in a portable form and with this "sweet spice", India began its profitable trade with other countries, including China and Persia. China learned from India how to cultivate sugar around 640 A.D. and by 800 A.D. sugar cane was grown extensively in Southern Europe following the Persian conquest of the region.

Sugar continued to spread throughout the Eastern Mediterranean and African regions. Crusaders brought sugar, "sweet salt," to Europe from the Holy Land around 1096 A.D. (Association).

The large-scale refinement of sugar began around 1455 A.D. in Madeira. Sugar then made it to the New World in 1480 A.D. when the Portuguese brought sugar to Brazil after which it spread to the Caribbean and the rest of South America. By the late 1700s sugar represented 20% of European imports with the West Indies producing 80% of it (Association).

The German chemist Andreas Marggraf identified sugar in beetroots in 1747 A.D. The first U.S. sugar beet factory was built in Northhampton, Massachusetts in 1838 A.D. and by 1870 California had the first successful, commercial sugar beet production in the U.S. (Association).

U.S. per capita caloric sweetener availability, 1970-2017



Notes: Corn sweeteners include high-fructose corn syrup (HFCS), glucose syrup, and dextrose. Edible syrups include sorgo (sweet sorghum), maple and sugarcane syrup, edible molasses, and edible refiners' syrup.
Source: USDA, Economic Research Service, Food Availability Data.

As sugar production spread around the world, its consumption also increased (Renter, 2013).

- In 1700 the average consumption was 4 pounds per year.
- In 1800 the average person consumed around 18 pounds of sugar per year.
- By 1900 this increased to 90 pounds per year.
- In 2009, 50% of Americans consumed ½ pound of sugar per day. A whopping 180 pounds per year.

According to the US Census total ***ADDED* sugar** consumption was around 130.7 pounds per person, per year in 2009 (Census, 2012) with 50% of Americans consuming 180 pounds annually (Renter, 2013)! Thankfully, total sugar consumption has been decreasing and in 2018 the total caloric sweetener consumption was 124.4 pounds per person, annually (USDA, 2019).

This much sugar (124 pounds), is too much. The World Health Association (WHO, 2015) recommends that consumers should limit their sugar intake to no more than 10% of total calories and a further reduction to below 5% would provide ***additional health benefits.*** That comes out to around 25 grams per day (6 level-teaspoons/day or 20 pounds per year) for an adult male consuming a 2000 calorie diet.

SPOILER ALERT! ONE 12-oz can of Coke™ has 39 grams of sugar.

If we take the US position that Americans should consume 10% or fewer calories from added sugar (USDA, Dietary Guidelines For Americans 2015 - 2020, 2015), that would be roughly 40 pounds per year for a 2000 calorie diet.

During the years 1994-1996, a survey of Americans showed that added sweeteners (sugar, fructose, glucose) accounted for 16% of total calories (Guthrie JK, 2000). However, 71.4% of adults consume 10% or more and 10% of adults consume 25% of their calories from added sugars (Quanhe Yang, 2014).

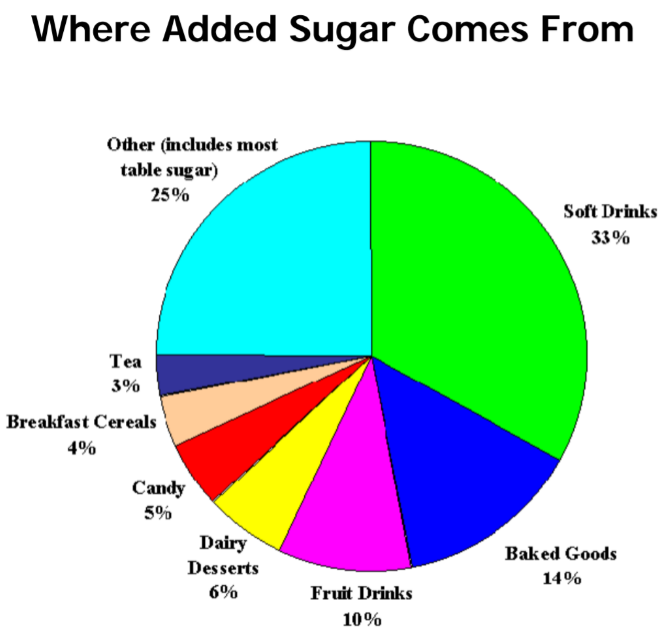
> *Consuming over 10% of calories from added sugar increases risk of heart disease by 30%. Consuming over 25% of calories from sugar increases that risk by 275%*

Looking at *just heart disease*, those who consumed between 10% to 24.9% of their calories were 30% more likely to die from heart disease compared to those consuming *under* 10%. More striking, those consuming *over* 25% of their calories from sugar were ***275% more likely*** to die.

One of the most difficult things for consumers to recognize is the many names for sugar. When you read the label, you can easily be misled by the names. Here are some of the many names for "sugar" you will find on product labels:

- Sugar
- Glucose
- Honey
- Sorghum syrup
- Lactose
- Fruit juice concentrate
- Dextrose
- Fructose
- Corn syrup
- Sorbitol
- Molasses
- High-fructose corn syrup
- Maltose
- Corn sweetener
- Sucrose
- Brown sugar
- Syrup

And finally, here is where we are getting all the extra added sugars in our diet.



Sources of added sugars

- Sugary drinks: Sodas, energy drinks, and sports drinks, coffee and tea, juice & fruit drinks.
- Sweetened breakfasts: energy bars, granola & muesli, hot & cold cereals, yogurts, smoothies.
- Syrups and sweets: syrups, honey & molasses, jelly, jam & spreads, drink mixes, candy.
- Sweet baked goods: cakes, cookies, and brownies, pies and cobblers, donuts & pastries, sweet rolls.
- Frozen snacks: dairy desserts like ice cream & gelato, frozen yogurt, popsicles, sherbet & sorbet.

Adverse Effects of Sugar

The adverse effects of sugar have been recognized since at least the end of the nineteenth century. In his book, *Graded Lessons,* Dr. William Krohn wrote,

> "Excessive amounts of sugar cause the liver to be overworked and a bilious attack results."

Glucose is the body's fuel and is the building block of carbohydrates. Fructose is "fruit-sugar". It's a simple carbohydrate like glucose. We naturally find fructose in fruit, honey, agave, and most root vegetables. It can also be added to processed foods as high-fructose corn syrup.

While glucose raises your insulin levels almost immediately and is transported into cells to be used as energy, fructose must be converted by the liver before it can be used as fuel. As a result, it does not raise or effect insulin as much as glucose. However, it still raises triglyceride levels and leads to fatty liver disease (JM, 2006) (AJ, 2002).

Table sugar, sucrose, is made up of one molecule of glucose and one molecule of fructose. The small intestine splits sucrose into glucose and fructose, after which they are both absorbed into the bloodstream and metabolized as described above.

Because sugar is broken down into both glucose and fructose, the glucose raises insulin in the body which also affects the fructose. More fructose is used to make fat compared to when just fructose is

Fructose-sweetened (not glucose-sweetened) beverages increase belly fat and lipids. Fructose makes you feel less full after eating.

consumed. One 10-week study compared fructose-sweetened beverages to glucose-sweetened beverages and found the fructose led to an 8.6% increase in belly fat, compared to a 4.8% increase for glucose beverages (Kimber L. Stanhope, 2009). Fructose can also increase the hunger hormone **ghrelin** and make you less full after eating.

Excess sugar has been associated with several adverse health effects. Some researchers believe sugar will increase your risk of obesity, coronary heart disease, diabetes, metabolic syndrome, and non-alcoholic fatty liver disease.

Here are some of the known and suspected risks of too much sugar (sweeteners and ingredients in food):

- Weight gain (Lisa Te Morenga, 2012)
- High blood pressure (Ian Brown, 2011)
- Heart disease (from obesity, high blood pressure, and inflammation) (Malik VS, 2010)
- Type 2 diabetes (from obesity and insulin resistance) (Malik VS, 2010)
- Dyslipidemias (lower HDL, increased triglycerides and LDL) (Ms. Jean A. Welsh, 2010)
- Risk of cancer (esophageal, small intestine, pleural, and ovarian) (Natasa Tasevska, 2012); colon cancer (Marcus D. Gonclalves, 2019)
- Depression (Anika Knuppel, 2017)
- Skin aging (from advanced glycation end products) (Shoubing Zhang, 2018)
- Increase cellular aging (shortening of telomeres which increases cellular aging) (Cindy W. Leung, 2018)
- Fatigue (spike in blood sugar followed by a crash; inactivity in diabetes) (Kalra, 2018) (Martine M. Goedendorp, 2014)
- Fatty Liver (fructose overloads the liver and is stored as fat in the liver). This (*NOT ALCOHOL*) is the leading cause of **liver failure** and **liver transplantation** *worldwide* (JM, 2006) (AJ, 2002)
- Kidney disease risk (primarily from the fructose) (Rafieian-Kopaei, 2015) (James J. DiNicolantonio, 2016)
- Dental health (cavities) (Moynihan, 2016)
- Gout (sugars raise uric acid from fructose metabolism by the liver) (Richard J Johnson, 2013) (Cristiana Caliceti, 2017)
- Dementia (high-sugar can lead to impaired memory) (Paul K. Crane, 2014) (Heike Wersching, 2018)

It is primarily the fructose in sugar that drives insulin resistance, obesity, liver disease, heart disease, kidney disease, and other illnesses. Fructose is half of what makes up table sugar, the other half is glucose.

Artificial Sweeteners

Most of my patients are proud to tell me that they only drink “diet” soda or consume foods made with artificial sweeteners. While I applaud their effort, they are still reluctant to abandon old ways for newer healthier ways. But, in all fairness, if this can get us away from added sugars and promote health it is worth looking at.

Here is a study from 2010 looking at obesity and artificial sweetener use from 1961 – 2006 (Yang, 2010). This chart is pretty impressive in demonstrating a spike in obesity corresponding to the use of artificial sweeteners. This certainly does not prove that sweeteners caused the increase, but it is interesting.

Also of note is the increase in the percentage of the population with a BMI over 30, starting just before 1980. This corresponds to the increase in processed carbohydrates such as flour and cereal products.

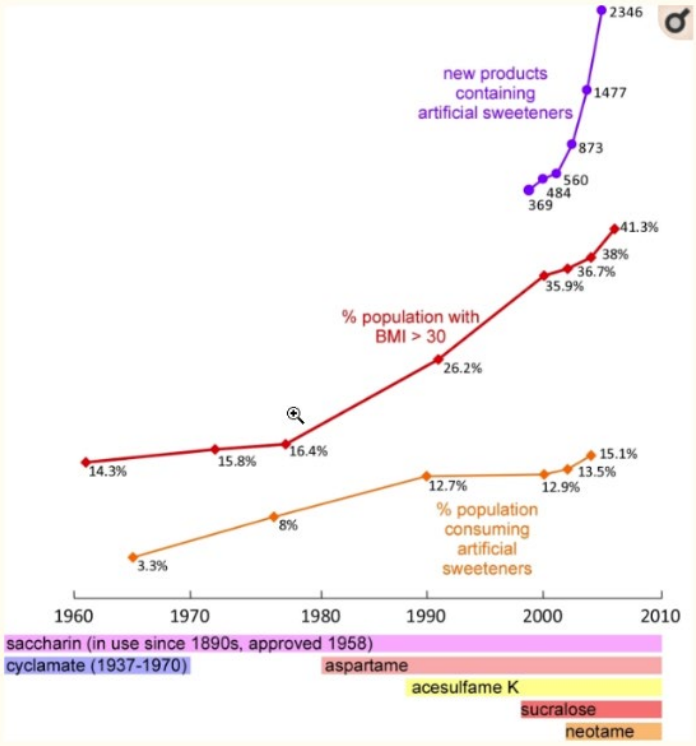


Figure 1

Time line of artificial sweetener use and obesity trends in the United States. Blue line: changes in the percentage of the population who are obese (BMI >30) from 1961 to 2006. Source: National Health and Nutrition Examination Survey [57]. Orange line: changes in the percentage of the population who are regular artificial sweetener users from 1965 to 2004. Source: National Household Survey [2]. Purple line: changes in the number of new artificial sweetener containing food products introduced to the American market from 1999 to 2004. Source: Mintel Market Analysis [14]. Bars below the time axis indicates the type and availability of artificial sweeteners in the United States over time. Source: Kroger et al [9].

Saccharin was accidentally discovered in 1879 and for decades was on stores’ shelves as a diabetic treatment. In 1937 **cyclamate** was discovered and later blended with saccharin to improve its taste.

The cancer scares came about, and the FDA banned cyclamate in 1969. In 1977 the FDA was also going to ban saccharin when laboratory rats developed bladder cancer. It was eventually determined that the cancer was due to unique rodent physiology and the saccharin warning labels were removed in 2000.

Sweetener use by the general population was limited until newer products were developed.

Aspartame was discovered in 1965. This newer sweetener was unique because it was made from two amino acids and could be metabolized by the human body. The earlier sweeteners were excreted by the body unchanged. This great new sweetener became **NutraSweet**™ in 1984.

The most potent sweetener on the market, **neotame**, was approved in 2002. Neotame is 7,000 times sweeter than sucrose. As more and more sweeteners came to market the number of new products containing them exploded and between 1999 and 2004, more than 6,000 new products were released.

As of 2014, the FDA has approved six “high-intensity sweeteners” for use in food:

- Saccharin – Sweet'N Low, Sweet Twin, and Necta Sweet.
- Aspartame – Equal and NutraSweet.
- Acesulfame potassium (Ace-K) - Sunett, Sweet One.
- Sucralose – Splenda.
- Neotame – Neotame.
- Advantame – no brand names.

Are Sweeteners Safe?

I have been telling my patients for years to avoid artificial sweeteners. The entire reasoning for the use of artificial sweeteners is to lose weight and help treat diabetes by avoiding the added calories of sugar. Unfortunately, data from several studies have shown that artificial sweeteners, mainly in diet sodas, are associated with obesity, metabolic syndrome, and type 2 diabetes (M Pearlman, 2017) (Iryna Liauchonak, 2019).

How can this be you say? How can something with NO CALORIES promote weight gain and diabetes? That is what we are going to find out.

1. The first hypothesis is that people that are likely to develop diabetes or gain weight choose to use sweeteners as a strategy to lose weight. Instead of changing a bad habit, they look for ways to make it a little "less bad."
2. The second hypothesis is that sweeteners are not just a simple chemical that gives us sweetness without affecting the body.

It is the second hypothesis that we are going to explore. You already know if you fit into the first category.

Learned Responses

Our evolution has resulted in our looking for sweet taste as a good source of energy and survival. Bitter tastes are associated with potentially harmful foods. These are part of our five tastes – sweet, salty, sour, bitter, and Umami.

According to this hypothesis, chronic use of sweeteners weakens our ability to predict the amount of energy we derive from sweet foods (sweet predicts calories).

Consistent with this theory, rats fed glucose compared to rats given sweeteners are different (Swithers SE, 2008). Rats fed sweeteners apparently lose the ability to predict the number of calories consumed related to sweets and overeat and are fatter than rats fed glucose (Swithers SE M. A., 2010) (Davidson TL, 2011).

In addition, the rats fed sweeteners had a lower metabolic response to their normal chow and their blood sugar levels were higher than the glucose-fed rats.

While this effect is present in test animals, it is not clear that learned responses or conditioning plays a role in humans (Sanne Griffioen-Roose, 2013) (MR, 2012).

Gut Microbiota Leading To Glucose Intolerance

More than 1000 species of microorganisms have been identified with about 160 species present in the gut of any one individual (Rajilic-Stojanovic M, 2014). There is a lot of evidence that the bacteria in our gut plays a major role in obesity and diabetes (Guinane CM, 2013). Mounting evidence is proving that diet, both habitual and long-term/shorter-term dietary changes are the most significant factor influencing the overall composition of the gut microorganisms.

One of the great things about artificial sweeteners is that they do reduce cavities, not by elimination of the sugar, but by killing the bacteria in the mouth (Fitch C, 2012). Studies in vitro, animal models and human suggest that the bacteriostatic effects of these sweeteners, *including stevia*, occurs in the gut (Suez J, 2014).

Suez showed that 11 weeks of exposure to saccharin, sucralose, or aspartame caused a greater increase in blood glucose in animals when exposed to a sugar load compared to animals that were not exposed to sweeteners. They also showed that the sugar resistance was transferrable to other animals by transferring the bacteria from the animals exposed to sweeteners. They also found this effect in humans who were regular users of saccharin.

Another very interesting result from Suez was the effect of saccharin on a high-fat diet. Mice fed a high-fat diet with saccharin, developed glucose intolerance; compared to a control group fed the high-fat diet with *sugar* as the sweetener. In regard to humans, non-caloric artificial sweetener (NAS) consumption is associated with increased central obesity, higher fasting glucose (diabetes), A1C (diabetes), and ALT (liver enzyme).

Other investigators also showed that doses of aspartame, equivalent to 2-3 diet soft drinks per day, (Palmnas MS, 2014) changed the bacteria in the gut and resulted in higher blood sugar levels and interfered with the effects of insulin.

Interaction With Sweet-Taste Receptors

One of the exciting discoveries of this century is that taste receptors are not just in the mouth. Researchers have found receptors that identify sugar in the gut and small intestines (Mace OJ, 2007). When these receptors are exposed to sugar, they release hormones that tell the pancreas to release insulin (Margolskee RF, 2007).

Since the 1960's we have known about the "incretin effect" which is, sugar in the mouth will result in higher insulin levels than the same amount of sugar intravenously (McIntyre N, 1964). The sweet-taste signaling in the gut also affects sugar absorption from the intestine into the body (Gorboulev V, 2012).

Artificial sweeteners activate this sweet-taste receptor in the intestine resulting in increased secretion of insulin (Malaisse WJ, 1998). Sweeteners in the diet increases body fat and insulin resistance in mice with diet-induced obesity (Mitsutomi K, 2014).

These same effects have been found in humans. Studies show sucralose promotes insulin resistance and insulin levels are about 20% higher when obese people consume sucralose before consuming sugar (Pepino MY, 2013)

Stem & Fat Cells

A study presented at a conference for the endocrine society (Gingery, 2018) showed that human stem cells (a cell with the ability to develop into other cells such as fat, muscle, brain, blood or bone cells, etc. to replace damaged or lost cells) accumulate *extra fat* when exposed to sweeteners. They also looked at fat cells from obese individuals that consume sweeteners. There were similar results in those cells.

The author believes the effect is worse in obese and diabetic individuals due to more insulin resistance. As little as 4 cans of diet soda per day showed fat production and inflammation. Normal weight, healthy persons did not show as marked a response as obese persons.

Sucralose, one of the tested sweeteners, promoted oxygen radicals which interfered with cell activity and slowed metabolism, promoting fat accumulation in the cells.

Soft Drinks and Mortality

A 2019 study of 451,743 individuals in 10 European countries found a higher risk of mortality due to the consumption of total, sugar-sweetened, and artificially sweetened soft drinks. Artificially sweetened soft drinks were associated with deaths from cardiovascular disease and sugar-sweetened soft drinks were associated with deaths by digestive disease (Amy Mullee, 2019).

Overall, those who consumed 2 or more glasses per day vs those consuming less than 1 glass per month of *all* soft drinks had a 17% higher rate of deaths. When this was separated into sugar vs artificial sweeteners, sugar-sweetened soft drinks had an 8% increased mortality while artificially sweetened soft drinks had a 26% increased mortality.

Sugar sweetened soft drinks had an 8% increased mortality. Artificially sweetened soft drinks had a 26% increased mortality.

If we just look at cardiovascular deaths, artificially sweetened soft drinks were 52% higher. Sugar-sweetened drinkers had a 59% higher risk of deaths from digestive disease.

STEVIA

Stevia is not an artificial sweetener but rather a natural plant from South America. There is a difference between the product on the supermarket shelves and what you can actually grow at home. Stevia products do not contain the whole leaf, it is a highly refined stevia leaf extract called *rebaudioside A* (Reb-A). Stevia products have very little stevia.

Sweeteners made with Reb-A are usually blended with different sweeteners, such as erythritol and dextrose. Truvia is a blend of Reb-A and erythritol. Stevia in The Raw is a blend of Reb-A and dextrose or maltodextrin.

Stevia is subject to an import alert which was updated in 2019 (FDA, 2019). Currently, Stevia leaves and its crude extract are *not approved as a food additive* and is not Generally Recognized as Safe (GRAS) due to inadequate toxicological information. Regarding dietary supplements, Stevia is not subject to regulations, i.e. it is not regulated.

Steviol glycosides (Reb-A and others) are considered to be different from the leaves as they are purified extracts obtained from the leaves. These products are not subject to the ban and can be imported. These products are used in a variety of foods in many countries.

Metabolism Of Steviol Glycosides

A major review of stevia was presented at the 2017 annual meeting of the American Society of Nutrition (Priscilla Samuel, 2018). Steviol glycosides are not digested in the stomach or upper gastrointestinal tract. When it comes into contact with bacteria of the colon is it degraded by removing the sugar moieties after which the Steviol backbone is absorbed and metabolized by the liver and excreted in the urine in humans. The sugar moieties are not absorbed and are probably used as fuel for the bacteria.

Priscilla further reviews safety studies upon which the FDA and other countries determined that Stevia is generally safe for human consumption.

A 2017 study on Stevia showed that it increased blood pressure in subjects when compared to sugar consumption (Emad A.S. Al-Dujaili, 2017). The study was only one week in duration yet there were increases in the stress hormone cortisol and elevated blood pressure using Stevia vs sugar. Yet other studies show no effect on blood pressure (Onakpoya IJ, 2015) or blood lipids.

In contrast to the above study, other studies show beneficial effects of Stevia (Ashwell, 2015). Stevia also appears to be neutral in regard to fasting blood glucose, insulin, and A1c when used to replace sugar in the diet.

Some studies (Jeppesen PB, 2000) show that Stevia can increase the release of insulin in the presence of blood glucose with more insulin being released the higher the blood glucose level is. In other words, if you are prediabetic or diabetic with elevated blood sugar, and insulin resistance, stevia can increase the amount of insulin released by your body. This is similar to other studies showing no effect of stevia in healthy individuals but an increase in insulin levels in diabetics. Some studies suggest (Chen TH, 2005) that stevia not only enhances insulin secretion but also slows the production of glucose by the liver.

Some studies show Stevia appears to increase insulin sensitivity (Nordentoft I, 2008) and can delay insulin resistance in diabetes (Chang J-C, 2005). One last study also shows no effect of Stevia on sugar or insulin in obese individuals (PARINYA SAMAKKARNTHAI, 2018).

Although the purified Stevia is allowed as a food additive, one must question the reasoning behind the distinction. I have searched for articles that prove long-term safety or harm for Stevia, but it is unfortunately too new for long-term studies.

Knowing that the body responds to sweetness via behavior, hormonal, and bacterial changes, there is no reason to believe that the body should respond any different to Stevia simply because it is plant-derived. And, with the 2017 study by Emad (Emad A.S. Al-Dujaili, 2017), knowing that blood pressure and stress hormones are elevated with Stevia, I would be cautious using any sweetener.

Two studies (S L Tey, 2017) (Stephen D. Anton, 2010) examined the effects of stevia on hunger and found that stevia did not cause individuals to overcompensate (eat more) and the insulin resistance was improved when compared to sugar or Aspartame. However, Anton reported that there was increased *calorie consumption* when using stevia or other sweeteners while sugar led to large spikes in blood glucose and insulin responses.

Just as other sweeteners (acesulfame K, saccharin, aspartame, and sucralose) affect the bacteria in our gut, so does Stevia (Gardana C, 2003). When several studies are examined, it appears as if the effect of stevia on gut bacteria, while present, is minimal (Priscilla Samuel, 2018), although, as discussed above, the bacteria does *metabolize* stevia.

PJ Rogers reviewed 90 animal studies and 12 cohort studies in humans (PJ Rogers, 2016). A review of 68 animal studies showed that 59 of the studies showed **no significant weight change**. PJ Rogers also reviewed 12 human studies with 14 comparisons of sweeteners to either sugar or water. These showed *inconsistent results* in regard to weight gain and loss with six comparisons showing weight loss with sweeteners and eight studies showing no weight loss.

PJ Rogers felt that the weight of evidence indicates that LES does not increase caloric intake and probably lowers body weight.

One last consideration is panel bias (Erik Paul Millstone, 2019). This is a great review paper about the regulatory process of approving aspartame in Europe. Instead of reviewing the numerous available studies about aspartame, this looked at potential bias by the European Food Safety Authority's (EFSA) Panel. This panel was charged with determining the *safety and/or toxicity* of aspartame. The EFSA panel looked at 154 empirical studies and then decided whether the study was reliable or not. 81 of these studies stated that aspartame was safe and the panel decided that 62 of these studies were reliable while 19 were not.

73 studies determined that aspartame *was not safe* and the EFSA panel determined that *ALL* 73 studies were **not reliable**. The authors of this review determined that the official government panel charged with determining safety was biased.

Even though the USA has determined stevia as being generally safe, one should still be cautious.

Avoid all artificial sweeteners. Stevia is not an artificial sweetener; however, it does affect the gut bacteria and insulin production. Until long-term studies are available, use Stevia, but with caution.

DRINK WATER

BOTTOM LINE

- Avoid non-caloric artificial sweeteners (NAS).
- If you *must* have a sweetener, use Stevia until long-term safety studies are available.
- NAS glucose intolerance is via bacteria in gut and stevia interacts with the bacteria.

References

AJ, M. (2002). Update on nonalcoholic fatty liver disease. *J Clin Gastroenterol, 34*, 255-262.

Amy Mullee, D. R.-S. (2019, September 3). *Association Between Soft Drink Consumption and Mortality in 10 European Countries.* Retrieved from JAMA Network: https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2749350

Anika Knuppel, M. J. (2017). Sugar intake from sweet food and beverages, common mental disorder and depression: prospective findings from the Whitehall II study. *Sci Rep, 7*(6287), 1-10. doi:10.1038/s41598-017-05649-7

Ashwell, M. (2015). Stevia, Nature's Zero-Calorie Sustainable Sweetener. *Nutrition Today, 50*(3), 129-134.

Association, S. (n.d.). *History of Sugar*. Retrieved Oct 27, 2019, from The Sugar Association: https://www.sugar.org/sugar/history/

Census, U. (2012). *Health and Nutrition.* Retrieved Oct 26, 2019, from United States Census Bureau: https://www.census.gov/library/publications/2011/compendia/statab/131ed/health-nutrition.html

Chang J-C, W. M.-M.-T. (2005). Increase of insulin sensitivity by stevioside in fructose-rich chow-fed rats. *Horm Metab, 37*, 610-6.

Chen TH, C. S. (2005). Mechanism of the hypoglycemic effect of stevioside, a glycoside of Stevia rebaudiana. *Planta Med, 71*, 108-13.

Cindy W. Leung, e. a. (2018). Diet Quality Indices and Leukocyte Telomere Length Among Healthy US Adults: Data From the National Health and Nutrition Examination Survey, 1999–2002. *Am J Epidemiol, 187*(10), 2192-2201.

Cristiana Caliceti, D. C. (2017). Fructose Intake, Serum Uric Acid, and Cardiometabolic Disorders: A Critical Review. *Nutrients, 9*(4), 395.

Davidson TL, M. A. (2011). Intake of high-intensity sweeteners alters the ability of sweet taste to signal caloric consequences: implications for the lerned control of energy and body weight regulation. *Quarterly journal of eperimental psychology., 64*(7), 1430-41.

Emad A.S. Al-Dujaili, H. T. (2017). Effect of Stevia Consumption on Blood Pressure, Stress Hormone Levels and Anthropometrical Parameters in Healthy Persons. *American Journal of Pharmacology and Toxicology, 12*(1), 7-17.

Erik Paul Millstone, E. D. (2019). EFSA's toxicological assessment of aspartame: was it even-handedly trying to identify possible unreliable positives and unreliable negatives? *Archives of Public Health, 77*(34), 1-22.

FDA. (2019, August 16). *Import Alert 45-06*. Retrieved October 18, 2019, from U.S. Food & Drug: https://www.accessdata.fda.gov/cms_ia/importalert_119.html

Fitch C, K. K. (2012). Position of the Academy of Nutrition and Dietetics: use of nutritive and nonnutritive sweeteners. *Journal of the Academy of Nutrition and Dietetics, 112*(5), 739-58.

Gardana C, S. P. (2003). Metabolism of stevioside and rebaudioside A from Stevia rebaudiana extracts by human microflora. J. *J Agric Food Chem, 51*, 6618-22.

Gingery, J. G. (2018). Consuming low-calorie sweeteners may predispose overweight individuals to diabetes. *Endocrine Society* (pp. 1-3). Chicago: Endocrine Society. Retrieved Oct 19, 2019, from https://www.endocrine.org/news-room/2018/consuming-low-calorie-sweeteners-may-predispose-overweight-individuals-to-diabetes

Gorboulev V, S. A. (2012). Na(+)-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. *Diabetes, 61*(1), 187-96.

Guinane CM, C. P. (2013). Role of the gut microbiota in health and chronic gastrointestinal disease: understanding a hidden metabolic organ. *Therap Adv Gastroenterol, 6*, 295-308.

Guthrie JK, M. J. (2000). Food sources of added sweeteners in the diets of Americans. *J Am Diet Assoc, 100*(1), 43-51.

Heike Wersching, e. a. (2018). Sugar- and artificially-sweetened beverages in relation to stroke and dementia - Are soft drinks hard on the brain? *Stroke, 48*(5), 1129-1131.

History, S. (n.d.). *History of Sugar*. Retrieved Oct 27, 2019, from Sugar History: http://www.sugarhistory.net/who-made-sugar/history-of-sugar/

Ian Brown, J. S. (2011). SUGAR-SWEETENED BEVERAGE, SUGAR INTAKE OF INDIVIDUALS AND THEIR BLOOD PRESSURE: INTERMAP STUDY. *Hypertension, 57*(4), 695-701.

Iryna Liauchonak, e. a. (2019). Non-Nutritive Sweeteners and Their Implications on the Development of Metabolic Syndrome. *Nutrients, 11*(3), 644.

James J. DiNicolantonio, J. B. (2016). Added sugars drive chronic kidney disease and its consequences: A comprehensive review. *Journal of Insulin Resistance, 1*(1), 6 pages.

Jeppesen PB, G. S. (2000). Stevioside acts directly on pancreatic β cells to secrete insulin: actions independent of cyclic adenosine monophosphate and adenosine triphosphate— sensitive K+-channel activity. *Metabolism, 49*, 208-14.

JM, C. (2006). The epidemiology of nonalcoholic fatty liver disease in adults. *J Clin Gastroenterol, 40*(Suppl 1)), 255-262.

Kalra, S. (2018). Diabetes Fatigue Syndrome. *Diabetes Ther, 9*, 1421-1429.

Kimber L. Stanhope, e. a. (2009). Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest, 119*(5), 1322-1334.

Lisa Te Morenga, e. a. (2012). Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ, 345*, e7492. doi:10.1136/bmj.e7492

M Pearlman, J. O. (2017). he Association Between Artificial Sweeteners and Obesity. *Curr Gastroenterol Rep, 19*(12), 64.

Mace OJ, A. J. (2007). Sweet taste receptors in rat small intestine stimulate glucose absorption through apical GLUT2. *J Physiol, 582*(Pt 1), 379-92.

Malaisse WJ, V. A.-L. (1998). Effects of artificial sweeteners on insulin release and cationic fluxes in rat pancreatic islets. *Cellular signalling, 10*(10), 727-33.

Malik VS, P. B. (2010). Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation, 33*(11), 2477-2483.

Marcus D. Gonclalves, e. a. (2019). High-fructose corn syrup enhances intestinal tumor growth in mice. *Science, 363*(6433), 1345-1349.

Margolskee RF, D. J.-B. (2007). T1R3 and gustducin in gut sense sugars to regulate expression of Na+-glucose cotransporter 1. *Proc Natl Acad Sci U S A., 104*(38), 15075-80.

Martine M. Goedendorp, e. a. (2014). Chronic Fatigue in Type 1 Diabetes: Highly Prevalent but Not Explained by Hyperglycemia or Glucose Variability. *Diabetes Care, 37*(1), 73-80.

McIntyre N, H. C. (1964). New Interpretation of Oral Glucose Tolerance. *Lancet, 2*(7349), 20-1.

Mitsutomi K, M. T. (2014). Effects of a nonnutritive sweetener on body adiposity and energy metabolism in mice with diet-induced obesity. *Metabolism, 63*(1), 69-78.

Moynihan, P. (2016). Sugars and Dental Caries: Evidence for Setting a Recommended Threshold for Intake. *Adv Nultr, 7*(1), 149-156.

MR, Y. (2012). Flavour–nutrient learning in humans: An elusive phenomenon? *Physiology and Behavior, 106*, 345-355.

Ms. Jean A. Welsh, M. R. (2010). Caloric Sweetener Consumption and Dyslipidemia Among US Adults. *JAMA, 303*(15), 1490-1497.

Natasa Tasevska, L. J. (2012). Sugars in diet and risk of cancer in the NIH-AARP Diet and Health Study. *Int J Cancer, 130*(1), 159-169.

Nordentoft I, J. P. (2008). Isosteviol increases insulin sensitivity and changes gene expression of key insulin regulatory genes and transcription factors in islets of the diabetic KKAy mouse. *Diabetes Obes Metab, 10*, 939-49.

Onakpoya IJ, H. C. (2015). Effect of the natural sweetener, steviol glycoside, on cardiovascular risk factors: a systematic review and meta-analysis of randomised clinical trials. *Eur J Prev Cardiol, 22*, 1575-87.

Palmnas MS, C. T. (2014). Lowdose aspartame consumption differentially affects gut microbiota-host metabolic interactions in the diet-induced obese rat. *PloS one, 9*(10), e109841.

PARINYA SAMAKKARNTHAI, M. P. (2018). Effect of Stevia on Glycemic and Insulin Responses in Obese Patients—A Randomized, Double-Blind, Placebo-Controlled Crossover Study. *Diabetes, 67*(Supplement 1), 1.

Paul K. Crane, R. W. (2014). Glucose Levels and Risk of Dementia. *NEJM, 369*(6), 540-548.

Pepino MY, T. C. (2013). Sucralose Affects Glycemic and Hormonal Responses to an Oral Glucose Load. *Diabetes Care, 36*(9), 2530-5.

PJ Rogers, P. H. (2016). Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including metaanalyses, of the evidence from human and animal studies. *International Journal of Obesity, 40*, 381-394.

Priscilla Samuel, K. T.-R. (2018, July 06). Stevia Leaf to Stevia Sweetener: Exploring Its Science, Benefits, and Future Potential. *The Journal of Nutrition, 148*(7), 1186S - 1205S. Retrieved from https://doi.org/10.1093/jn/nxy102

Quanhe Yang, e. a. (2014, April). Added Sugar Intake and Cardiovascular Diseases Mortality. *JAMA, 174*(4), 516-24.

Rafieian-Kopaei, H. N. (2015). Diabetes mellitus and renal failure: Prevention and management. *J Res Med Sci, 20*(11), 1112-1120.

Rajilic-Stojanovic M, d. V. (2014). The first 1000 cultured species of the human gastrointestinal microbiota. *FEMS Microbiol Rev, 38*, 996-1047.

Renter, E. (2013, Jan 16). *Average Person Consumes 300% more Sugar Daily than 'Recommended'*. Retrieved Oct 27, 2019, from Natural Society: https://naturalsociety.com/sugar-the-toxicity-question-and-what-to-do-about-it/

Richard J Johnson, T. N. (2013). Sugar, Uric Acid, and the Etiology of Diabetes and Obesity. *Diabetes, 62*(10), 3307-3315.

S L Tey, N. B. (2017). Effects of aspartame-, monk fruit-, Stevia-, and sucrose-sweetened beverages on postprandial glucose, insulin and energy intake. *International Journal of Obesity, 41*(3), 450-7.

Sanne Griffioen-Roose, P. A. (2013). Effect of Replacing Sugar with Non-Caloric Sweeteners in Beverages on the Reward Value after Repeated Exposure. *PLOS ONE, 8*(11), e81924.

Shoubing Zhang, E. D. (2018). Fighting against Skin Aging: The Way. *Cell Transplantation, 27*(5), 729-738.

Stephen D. Anton, P. C. (2010). Effects of stevia, aspartame, and sucrose on food intake, satiety, and postprandial glucose and insulin levels. *Appetite, 55*(1), 37-43.

Suez J, K. T.-S. (2014). Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature, 514*(7521), 181-6.

Swithers SE, D. T. (2008). A role for seet taste:calorie predictive relations in energy regulation by rats. *Behavioral neuroscience., 122*(1), 161-73.

Swithers SE, M. A. (2010). High-intensity sweeteners and energy balance. *Physiology & behavior, 100*(1), 55-62.

UCLA. (n.d.). *Spices*. Retrieved Oct 27, 2019, from UCLA History & Special Collections: https://unitproj.library.ucla.edu/biomed/spice/index.cfm?displayID=23

US Department of Agriculture, E. R. (2013). Calories: average daily per capita calories from the US food supply, adjusted for spoilage and other waste. LossAdjusted Food Availability Data .

USDA. (2015, Dec). *Dietary Guidelines For Americans 2015 - 2020*. Retrieved Oct 27, 2019, from health.gov: https://health.gov/dietaryguidelines/2015/resources/2015-2020_dietary_guidelines.pdf

USDA. (2019, July 18). *Sugar and Sweeteners Yearbook Tables.* Retrieved Oct 26, 2019, from USDA Economic Research Service: https://www.ers.usda.gov/data-products/sugar-and-sweeteners-yearbook-tables/sugar-and-sweeteners-yearbook-tables/#U.S.%20Sugar%20Supply%20and%20Use

WHO. (2015, March 4). *WHO calls on countries to reduce sugars intake among adults and children*. Retrieved Oct 25, 2019, from World Health Organization: https://www.who.int/mediacentre/news/releases/2015/sugar-guideline/en/

Yang, Q. (2010). Gain weight by “goingdiet?” Artificial sweeteners and the neurobiology of sugar cravings. *Yale Journal of Biology and Medicine, 83*, 101-108.