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What we know—and don't—about non-nutritive sweeteners

Here's what's known about the safety of these sweeteners and their effect on weight, appetite, and the risk for type 2 diabetes.

PRACTICE RECOMMENDATIONS

› Advise patients who are trying to lose weight that non-nutritive sweeteners (NNSs) are not beneficial for weight loss. **A**

› Reassure patients that NNSs do not appear to cause, or increase the risk of, developing type 2 diabetes mellitus. **A**

Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

An estimated 93.3 million Americans (roughly 40% of the US population) were obese in 2015-2016, and most of them had at least 1 chronic disease.¹ As a result, patient education focused on lifestyle modification, including healthy nutrition and physical activity, has become an integral part of our everyday practice.

At the same time, the most recent dietary guidelines recommend that added sugar make up < 10% of daily calories.² In the United States, low-calorie food and beverages containing non-nutritive sweeteners (NNSs; TABLE³⁻⁸) have become a popular means of keeping the sweetness in our diet without the health ramifications associated with sugar. These NNSs (aka, artificial sweeteners, high-intensity sweeteners, and non-caloric sweeteners) are ubiquitous in soft drinks, processed grains (including breads, cereals, and granola bars), and dairy products (including yogurts, flavored milk, and ice cream). As examples, NNSs are present in 42% of flavored waters, 33% of yogurts, and all diet beverages.^{9,10} They can even be found in medications, multivitamins, toothpaste, and mouthwash.

Business is booming

Global NNS consumption has been growing more than 5% per year, meaning that by 2020, NNSs are expected to be a \$2.2 billion industry.¹¹ One study using data from the National Health and Nutrition Examination Survey (NHANES) found that the use of NNSs in the United States increased from 21.1% in 2003 to 24.9% in 2009-2010 among adults and increased from 7.8% to 18.9% over the same time period among children.¹²

The main increase in the consumption of NNSs across all age groups has been via the consumption of beverages. Approximately 11% of healthy weight, 19% of overweight, and 22% of obese adults consume diet beverages.^{13,14} Consumption of diet beverages or NNSs increases with age¹² and is especially common among women with higher levels of education and income.¹⁵

TABLE

Available non-nutritive sweeteners³⁻⁸

Chemical name	Brand name	Sweetness vs sucrose	Metabolism	Comments
Acesulfame-K	Sunett, Sweet One	200x sweeter	Not metabolized or stored; absorbed and excreted unchanged ⁶	Primarily excreted in urine
Advantame	Not sold separately	20,000x sweeter	Converted to metabolite (ANS9801-acid) rapidly in gastrointestinal tract and absorbed rapidly ⁸	A derivative of aspartame, but much sweeter; thus, a very small amount is used
Aspartame	NutraSweet, Equal, Sugar Twin	200x sweeter	Broken down into amino acids (aspartic acid and phenylalanine) and methanol ⁴	Patients with phenylketonuria should avoid
Neotame	Not sold separately	7000–13,000x sweeter	Metabolized quickly and completely eliminated from the body ⁷	Derived from aspartic acid and phenylalanine; a very small amount is often used, thus exposure to phenylalanine is insignificant (no FDA warning for patients with phenylketonuria)
Saccharin	Sweet'N Low, Necta Sweet, Sweet Twin, Sugar Twin	200–700x sweeter	Not metabolized and excreted unchanged ⁵	Longest history of use of all the NNSs
Steviol glycoside or Rebaudioside A	Stevia, PureVia, Truvia, SweetLeaf, SunCrystals	200–400x sweeter	Not metabolized ⁷	Highly purified extract from <i>Stevia rebaudiana</i> plant
Sucralose	Splenda, Nevella	600x sweeter	Poorly absorbed and excreted unchanged ⁵	Largely excreted in feces

FDA, Food and Drug Administration; NNSs, non-nutritive sweeteners.

However, concerns remain about the safety of these agents and their effect on weight, appetite, and the body's glycemic response. This article reviews the available research and current recommendations regarding the use of NNSs.

WHAT EFFECT DO NNSs HAVE ON WEIGHT?

The data on NNSs and weight are inconsistent. One randomized controlled trial (RCT) compared weight loss over the course of 1 year (12-week weight loss phase; 9-month weight maintenance phase) when 303 participants consumed either water or drinks sweetened with NNSs.¹⁶ Weight loss was significantly greater in the NNS drink group when compared with the water group.¹⁶

Observational studies have revealed similar findings.^{17,18} Data from NHANES revealed that US adults (n = 14,098) during 2 noncon-

secutive 24-hour dietary recall periods demonstrated lower total energy (calorie) intake if they consumed NNSs vs no NNSs.¹⁹ Another study using 2011-2016 NHANES data on adolescents (n = 7026) found no difference in energy intake between those who consumed beverages containing NNSs vs those who consumed beverages containing sugar.²⁰

Other lines of investigation, including animal studies, have shown that long-term use of NNSs is associated with numerous metabolic derangements including weight gain.²¹ The negative effects of NNSs appear to be the greatest in males and those who are obese and have high-calorie diets.²¹

A 2017 meta-analysis concluded that evidence from RCTs does not support a benefit of NNSs on weight management, and that routine consumption of NNSs may be associated with increased body mass index (BMI) and cardiometabolic risk.²² Another

systematic review and meta-analysis found that there was a higher pooled risk for obesity among those who drank beverages containing NNSs vs those who drank sugar-containing beverages.²³

Based on the most current literature, we conclude that NNSs are not beneficial for weight loss. While there is concern about weight gain through psychological effects (stimulation of sweetness receptors without satiety), further well-designed research is needed to explore whether this concern has merit.

WHAT IS THE EFFECT OF NNSs ON APPETITE?

There appears to be no effect. While original studies seemed to indicate there was an effect, later studies leaned to the contrary.

The notion that NNSs might enhance appetite and food intake was advanced in the 1980s by John Blundell and his research team.²⁴ The hypothesis was that since NNSs uncouple sweet taste and calories, they do not exert the normal post-ingestive inhibitory influence that real sugar does. This, in turn, disrupts appetite control mechanisms.²⁵⁻²⁷

However, subsequent research studies found no relationship between the use of NNSs and appetite.²⁸⁻³⁰ Mattes and colleagues hypothesized that such a difference in findings could result from the fact that earlier studies focused on isolating NNSs from other energy-yielding products, which emphasized an association with heightened hunger.²⁹ Subsequent studies showed that when NNSs were incorporated into energy-yielding products, there was no association between NNSs and increased hunger or appetite.

DO NNSs INCREASE THE RISK FOR TYPE 2 DIABETES MELLITUS?

The data are mixed. One study of women participating in the Nurses' Health Study II showed that those who consumed caffeinated, artificially-sweetened beverages had a 35% higher risk of developing type 2 diabetes mellitus (T2DM); however, this risk was no longer significant after adjusting for BMI and energy intake.³¹

The Health Professionals Follow-Up Trial studied more than 40,000 men for more

than 20 years and found that NNS consumption increased the risk of developing T2DM by 40%.³² However, this finding lost statistical significance after adjusting for BMI.³²

These results make it difficult to determine whether there is any association between NNSs and T2DM; rather NNS-containing beverages are likely consumed more often by those who have higher BMIs and by those trying to lose weight.

A 2017 randomized crossover study involving 10 healthy men looked at the effects of a variety of caloric and non-caloric sweeteners on 24-hour glucose profiles and found no differences.³³ Another study, a randomized, double-blind, crossover trial involving 60 non-obese adults without diabetes who did not consume NNSs, randomized the participants one-to-one to drink either 2 cans per day of either a beverage containing aspartame and acesulfame K or an unsweetened, no-calorie beverage for 12 weeks.³⁴

After a 4-week washout period, the participants then switched to the opposite beverage for 12 weeks. The study concluded that consumption of 2 cans of a beverage containing aspartame and acesulfame K over 12 weeks had no significant effect on insulin sensitivity or secretion in nondiabetic adults.³⁴

Similar results were obtained from a study involving 100 non-obese adults.³⁵ The researchers found that aspartame ingested at 2 different doses (350 or 1050 mg/d) in beverages over 12 weeks had no effect on a 240-minute oral glucose tolerance test, blood pressure, appetite, or body weight.³⁵

A 2016 systematic review critically evaluated the effect of NNSs on both glucose absorption and appetite.³⁶ The review included 14 observational prospective trials, 28 RCTs, and 2 meta-analyses. The sweeteners studied included aspartame, sucralose, saccharin, acesulfame K, and stevia.³⁶ The studies were focused largely on single-exposure outcomes (20 trials), but a minority of the studies (8 trials) looked at longer exposures from 1 to 18 weeks. Only some of the studies controlled for critical variables, such as BMI. In the end, there was no consistent pattern of increased or decreased risk for insulin resistance or diabetes.³⁶



>
Consumption of diet beverages or non-nutritive sweeteners increases with age and is especially common among women with higher levels of education and income.

Two meta-analyses tried to determine if an association exists between consumption of beverages containing NNSs and the development of T2DM.^{37,38} The first meta-analysis with 4 studies showed a slight, but significant, relative risk (RR) of 1.13 (95% confidence interval [CI], 1.02-1.25) for those who consumed beverages containing NNSs.³⁷ In the second meta-analysis (10 studies), NNS consumption had an RR of 1.48 (95% CI, 1.35-1.62), but the risk was lower (and no longer significant) after adjusting for BMI.³⁸ A study of 98 Hispanic adolescents who were overweight or obese found that chronic users (n = 9) of NNSs had higher HbA1c levels 1 year later than did controls (n = 75) and people who initiated use of NNSs between the baseline and 1-year visit (n = 14).³⁹

■ **The American Diabetes Association (ADA)** and American Heart Association joint position statement on NNSs, first published in 2012, says that NNSs can be utilized to reduce caloric and carbohydrate consumption for overall diabetes control and to obtain a healthy body weight.⁴⁰ These principles were reaffirmed in the ADA Standards of Care in 2019.⁴¹

The 2015 US Scientific Reports on Dietary Guidelines provided a consensus statement saying, “Future experimental studies should examine the relationship between artificially sweetened soft drinks and biomarkers of insulin resistance and other diabetes markers.”⁴²

DO NNSs HAVE ANY ADVERSE HEALTH EFFECTS?

Maybe. Many individuals avoid NNSs due to fear of developing cancer. While rat studies have previously shown a dose-dependent increased risk of developing cancer, epidemiologic studies in humans have not confirmed an association.⁴³ The National Cancer Institute reports that carcinogenicity studies of NNSs have not shown an association with cancer in humans.⁴⁴

A prospective study—the Nurses’ Health Study, which followed over 88,000 women for 24 years—found that consumption of > 2 diet sodas per day was associated with an increased risk for coronary heart disease (CHD) and chronic kidney disease (CKD)

compared with consumption of < 1 diet soda per month.⁴⁵ However, other prospective studies have shown that these specific negative health effects may not be present when controlling for weight.^{45,46}

While the prospective studies found some associations between medical conditions (eg, CHD and CKD) and NNS consumption, the literature is limited to intake from beverages and does not include NNS-containing foods. More studies are needed to determine the relationship between NNSs and potential adverse health events, since the current literature is observational and cannot predict causation.

A 2019 study explored the associations between long-term consumption of sugar-sweetened beverages and artificially sweetened beverages (ASBs) and the risk of mortality in the United States.⁴⁷ This study included 37,716 men from the Health Professionals Follow-up Study and 80,647 women from the Nurses’ Health Study. Subjects who had the highest consumption of ASBs had higher risks for total and cardiovascular disease mortality.⁴⁷ Cohort-specific analyses showed that an association between ASB consumption and mortality was observed in the participants from the Nurses’ Health Study but not in those from the Health Professionals Follow-up Study, warranting further investigation.⁴⁷ Cancer mortality and ASB consumption were not shown to have an association in this study.

WHY ARE THE DATA INCONCLUSIVE?

Nutritional studies are hard to complete accurately outside of the laboratory setting. Also, the science of NNSs is new and evolving.

With regard to obesity and NNSs, it is possible that findings have been due to reverse causation. People who are overweight or obese are more likely to consume low-calorie foods and beverages; they are also at greater risk for developing diseases, such as T2DM.^{48,49}

HOW SAFE ARE NNSs?

They appear to be safe, but more data are needed. Each of the 7 FDA-approved NNSs has passed extensive laboratory, animal, and



Patients at risk for, or who have been diagnosed with, type 2 diabetes mellitus can include non-nutritive sweeteners in their diet without fear of disturbing their glycemic levels.

human testing, and appears to cause no harm in the human body when consumed.⁴⁹ But clearly the data are incomplete. As we continue to gain a greater understanding of the metabolism of NNSs, we may need to revisit the issue of safety.

ARE THERE ANY NNSs THAT SOME PEOPLE SHOULD AVOID?

Yes. People with phenylketonuria, who have difficulty metabolizing phenylalanine (a component of aspartame), should avoid consumption of aspartame.⁵⁰

In addition, NNSs have been found to be present in breast milk.⁵¹ While the significance of this finding is yet to be determined, we warn against the use of NNSs by women who are breastfeeding.⁵¹

WHAT EFFECT—IF ANY—DO NNSs HAVE ON GUT MICROBIOTA?

We don't know. Disruptions in the gut microbiome have been linked to numerous metabolic abnormalities, including obesity, insulin resistance, and diabetes, as well as cardiovascular disorders.^{52,53} Diet is a main determinant of balance in the gut microbiota.⁵⁴ The gut microbiota are centrally involved in energy harvest, and studies have suggested that low gut bacterial diversity is associated with increased adiposity, insulin resistance, and low-grade inflammation.⁵⁵⁻⁶⁰ Whether NNSs have a relationship with abnormal changes in gut microbiota requires further study. **JFP**

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➤ Reverse causation may be at work with obesity and non-nutritive sweeteners. That is, people who are overweight or obese are more likely to consume low-calorie foods and beverages.

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