The prevalence, consumption, and overall health effects of nonnutritive sweeteners

T Flora

Introduction

Artificial sweeteners remain a controversial topic despite their prevalence in our foods. Artificial sweeteners are used as sugar substitutes or sugar alternatives in foods, beverages and/or sweetener packets. There are several types of artificial sweeteners including sugar alcohols, nutritive sweeteners, nonnutritive sweeteners and dietary supplements. The most commonly discussed and controversial type of sweetener is the nonnutritive sweetener (NNS). NNSs are also known as high-intensity sweeteners or low-calorie sweeteners, because they are many times sweeter than sugar and therefore contribute little to no calories. Replacing sugar with a NNS makes a food or beverage become less energy dense which is why many health professionals have encouraged the use of NNSs for patients on weight-loss or weight-maintenance programs. The theory is that consuming food sweetened with NNS instead of sugar will result in a lower daily energy intake and help patients or clients adhere to their diet plans.[1]

The prevalence of NNS in food products has risen steadily in past decades for economic reasons and in response to diet trends.[2] Manufacturers can save money by using NNS in their products since only a small amount is needed compared to sugar for the same sweet taste. Diet trends are steering away from added sugars and rely on NNS or other sweeteners to maintain the sweet taste needed for certain foods. Recent legislation will require several changes to the Nutrition Facts Label. As of January 1, 2020, Nutrition Facts Labels will be required to include the amount of added sugar in the food.[3] This will be another motivating factor for manufacturers to replace sugar with NNS or other sugar alternatives. According to one study, over 6,000 new foods and beverages containing NNS were introduced to the United States between the years 1999 and 2004.[2]

As the prevalence and consumption of NNS increases, the public concern of possible adverse effects seems to rise as well. Until recently, NNS were regarded as a useful tool in decreasing energy and sugar intake and supporting a goal of weight management, weight loss, and/or glycemic blood control.[4] However, recent studies have shown that there is not a significant correlation between NNS use and weight loss.[5,6] Several observational studies have shown that NNS consumption is associated with increased BMI and weight gain.[5-8] This review of literature aims to examine the prevalence, consumption and overall effects of nonnutritive sweeteners on human health.

Consumption of Nonnutritive Sweeteners

Consumption of nonnutritive sweeteners has been increasing for decades according to the National Health and Nutrition Examination Survey (NHANES). One meta-analysis determined that 30% of Americans reported daily use of NNS in 2008.[5] The 2001-2002 NHANES study reported that the national average consumption of NNS was 24%. The 2007-2008 NHANES study reported that the national average NNS consumption increased to 28%.[8] Dietary data is collected for the NHANES surveys using two 24-hour diet recalls. The first diet recall is obtained through an in-person interview and the second diet recall is recorded over the phone 3-10 days after the in-person interview.[8] It is important to note that consumption rates also vary across regions of the United States. A study that focused on the NNS consumption by rural Virginian residents showed that 33% of the participants consumed NNS which is higher than the estimated national average.[7] Rural Virginia was an important research area because rural populations are more health-disparate, have a higher prevalence of obesity and related health complications.[7] There was no determined significance of the correlation of higher rates of

obesity, health disparity, and higher consumption of NNS, but this information may be helpful in future studies.

Another recent study analyzing data from two cycles of the cross-sectional NHANES studies was conducted with a total sample size of 16,986 participants. Consumption rates differed among sociodemographic populations. Previous studies have shown that NNS consumption rates increase with income status, weight status, and age. Females also have a higher consumption rate of NNS. Sylvetsky and colleagues sought to determine difference in NNS consumption depending on circumstance of an individual and their environment. The researchers also wanted to categorize the source of NNS consumption. Results revealed that 70% of NNS were consumed in the participant's home. In addition, 41.4% of adults consumed NNS at least one of the two days of food recall, and 25.1% of children consumed NNS on at least one day of the food recall. The researchers also categorized the intake by source and found that 30.8% of adult intake came from beverages, 10.3% from foods, and 14.1% from sweetener packets. The collected data also showed that 64% of adults and 62% of children consumed NNS as part of a meal. When compared to overall food intake, the proportion of NNS-containing foods was relatively low. For example, only 1-2.5% of all desserts consumed in NHANES 2009-2012 contained NNS. However, the proportion of NNS-containing yogurt was more significant with 25% of yogurt consumed by adults containing NNS.[6] Understanding which subgroups of the population have higher use of NNS, and the etiology of higher use, will help shape future studies and planned interventions regarding the possible health effects.[8]

Approved Nonnutritive Sweeteners

In the United States, the Food and Drug Administration (FDA) regulates and approves all added food ingredients.[3] NNS is regulated as a food additive and therefore must undergo

premarket review and receive FDA approval before it can be used in foods. An exception to this approval process occurs if a NNS is only to be used as a sweetener and not as a food ingredient. Instead of needing to go through the FDA approval process, it can be deemed generally recognized as safe (GRAS). A GRAS substance is not required to get premarket approval. A company can determine a food GRAS without notifying the FDA if a qualified expert with scientific training has concluded that the substance is safe. Scientists and experts are involved in both FDA and GRAS approval processes. The FDA approval or determined GRAS means there is a "reasonable certainty that a substance is not harmful under the intended conditions of use."[3]

There are currently six NNS approved for use in the United States. These include acesulfame potassium (Ace-K), advantame, aspartame, neotame, saccharin, and sucralose. Each NNS has a different Acceptable Daily Intake (ADI) because they have different chemical compositions and are metabolized differently in the human body.[9] The metabolic processes, research, and general use of each NNS will be discussed further in the next section.

How Nonnutritive Sweeteners are Metabolized and their Acceptable Daily Intake

Rolfes and colleagues state, "[c]onsidering that all substances are toxic at some dose, it is little surprise that large doses of artificial sweeteners (or their components or metabolic by-products) may have adverse effects."[1] The important question to ask is whether NNSs are safe for human ingestion in the amounts that they are likely to consume. The way the human body responds to the chemical composition of artificial sweeteners is also important to understanding the possible effects on human health. Nonnutritive sweeteners provide very little energy because the body does not digest or absorb the sweetener or sweetener components.[1]

- Acesulfame potassium (Ace-K): Ace-K is composed of potassium salt and is not digested or absorbed by the human body. It is 200 times sweeter than sucrose (sugar) and

contributes 0 kcal/g.[1] Ace-K is often mixed with other sweeteners and is heat stable making it perfect for use in baked goods. There are more than 90 studies that support the safety of Ace-K consumption.[3] The current Acceptable Daily Intake (ADI) is 15mg/kg body weight, or 30 cans of diet soda.[1]

- Advantame: Advantame is the most recent non-nutritive sweetener to be approved in 2014. It is about 20,000 times sweeter than sucrose and is approved for use as a general-purpose sweetener under certain conditions. Advantame is heat stable and thus makes a good sugar substitute in baked goods. The FDA determined that advantame was safe to consume after reviewing data from 37 animal and human studies.[3] The Academy of Nutrition and Dietetics (AND) has not yet issued a conclusion statement on this sweetener.[9]
- Aspartame: Aspartame is composed of a methyl group and the amino acids phenylamine and aspartic acid. It is digested and absorbed by the human body and is 200 times sweeter than sucrose. Aspartame can be categorized as a nonnutritive or nutritive sweetener.[1,3] Alone it provides 0 kcal/g, however in powdered form it is typically mixed with lactose and thus provides 4 kcal/g.[1] The FDA first approved aspartame for use in 1981 under certain conditions and eventually expanded the approval to "general purpose sweetener" in 1996.[3] Aspartame is the most extensively studied sweetener used in the human food supply, with over 100 studies declaring that it is safe for human consumption. Although it has been determined that the general population can consume aspartame without significant health effects, people with the rare hereditary disease phenylketonuria (PKU) cannot consume aspartame safely. Those who are diagnosed with phenylketonuria cannot efficiently metabolize the amino acid phenylalanine, which is a component of aspartame.

Consumption of aspartame can therefore lead to a toxic buildup of phenylalanine in individuals with PKU. The FDA requires foods and beverages containing aspartame to include a warning labels for consumers with PKU.[3] The current ADI for the healthy population is 50mg/kg body weight, or 18 cans of diet soda.[1]

- Neotame: Neotame is aspartame with an additional side group attached. It is also not digested or absorbed by the human body. The additional side group makes this NNS about 8,000 times sweeter than sucrose. The ADI is 18mg/day. No warning label is needed for PKU consumers. Due to the intense sweetness of neotame, there is a negligible amount of phenylalanine broken down in the body.[1] Neotame was first approved by the FDA in 2002 as a general-purpose sweetener and flavor enhancer in all foods, except in meat and poultry. The FDA reviewed 113 animal and human studies to evaluate possible toxic effects of neotame before approval.[3]
- Saccharin: Saccharin is composed of benzoic sulfimide which is rapidly absorbed and excreted by the human body. It is 450 times sweeter than sucrose and the ADI is 5mg/kg body weight, or about 10 packets of the sweetener. Saccharin was first discovered in 1879 and has been used in food and beverage products since that time. However, in the 1970s several research studies linked dietary saccharin intake with the development of bladder cancer in laboratory rats. Congress mandated that products containing saccharin have a warning label until the year 2000. The National Institute of Health concluded that saccharin was safe for human consumption and removed the sweetener from the potential carcinogen list because the metabolic pathway that linked saccharin to bladder cancer in rats is completely different in humans. This is a great example of why animal studies are

not a gold standard of research by any means. The same adverse effects of saccharin have not been replicated in humans to date.[3]

- Sucralose: Sucralose is sucrose with chlorine (Cl) atoms in place of hydroxyl groups (OH). Most of sucralose is not digested or absorbed by the human body (85%) and is excreted unchanged in the urine.[7] Sucralose provides 0 kcal/g. It is approved for use in both the United States and Canada and sold under the brand name Splenda. Sucralose is approximately 600 times sweeter than sucrose. The ADI is 5 mg/kg body weight, or about 6 cans of diet soda.[1] Sucralose was approved for use as a general-purpose sweetener in 1999 and is commonly found in beverages, chewing gum, and frozen dairy desserts. It is heat stable making it suitable for baking and used regularly in baked goods. The FDA reviewed over 110 studies before determining the safety of sucralose use in food.[3] AND, in its review of related research, also determined the safety of sucralose consumption. However, every conclusion statement made by the Evidence-based Analysis Library (EAL) has been given a Grade III (Limited) due to limited evidence.[9]

Nonnutritive Sweeteners and Potential Health Effects

The researchers of one study aimed to determine whether continuous consumption of NNS by adults and adolescents were associated with long-term adverse cardiometabolic effects. Azad and his colleagues noted that a previous meta-analysis reported conflicting evidence between randomized control trials (RCTs) and observational studies. Various RCTs analyzed whether NNS consumption had weight loss effects and determined a positive association between NNS intake and weight loss. However, observational studies have reported a slight increase in body mass index (BMI) after long-term consumption of NNS.[5]

Azad and his colleagues looked at both RCT and prospective cohort studies to determine the long-term effects of NNS on health. Various health outcomes aside from body composition were used. To be included in the meta-analysis, the studies had to have a minimum study duration of 6 months, and the participants had to be at least 12 years old. A total of 7 RCTs and 30 cohort studies met the criteria, resulting in a total of 406,910 study participants.[5]

The primary outcome observed in this study was change in BMI, and the secondary outcomes included change in body weight, adiposity, glucose metabolism, and diagnosis of metabolic syndrome. The cohort studies found an association between the routine intake of NNS and an increased risk of obesity, hypertension, metabolic syndrome, and stroke. However, it is important to note that results of cohort studies cannot always be replicated in clinical trials and are therefore not considered evidence-based.[5]

Metabolic Effects of Nonnutritive Sweeteners

Other researchers studied the potential mechanisms that may make NNSs metabolically active and potentially lead to adverse metabolic effects.[6] Miller and Perez conducted a systematic literature review in which they examined what the evidence was regarding the effect of NNS on three metabolic mechanisms. These mechanisms included learned responses by the human body that contributed to glucose homeostasis, the effect NNS had on gut microbacteria, and the interaction of NNS on sweet-taste receptors with insulin secretin triggers. Until recently there was a general understanding that NNS was a healthy alternative to sugar and was metabolically inactive. NNS was also believed to provide a sweet taste without the glycemic effects and added calories of sugar. However, recent studies have associated NNS consumption with adverse metabolic effects and weight gain.[6]

Miller and Perez discussed two hypotheses for the recent association between NNS intake and metabolic effects. First, those results could be due to reverse causation. Overweight and obese individuals have a higher consumption rate of NNS, but the cause and effect is not certain. It is possible that overweight individuals who are more likely to have metabolic disorders without NNS consumption have a higher intake because they are trying to use NNS to manage their weight. The second hypothesis is that contrary to popular belief, NNS are metabolically active and affect biological processes involved with energy and glucose regulation.[6]

Studies conducted on animal subjects have shown that consuming NNS results in heavier mice with reduced thermic responses to food. However, these results cannot be compared to humans due to the differences in digestion mechanisms. Humans, unlike mice, have learned responses that influence glucose and energy homeostasis. Therefore, future studies need to examine learned responses in humans to obtain more accurate data results.[6]

One definitive benefit of NNS intake is the reduction in dental cavities compared to regular sugar intake. NNS are resistant to fermentation and can stop bacteria from reproducing. While this is beneficial to the health of the human mouth, it may be detrimental to the gut. Gut microbacteria is essential to human health, and NNS may reduce the body's "good" bacteria that fights off the "bad" bacteria.[6]

Overall, human studies on the potential metabolic effects of NNS are limited. Only two of the mechanisms of Pepino's study have been researched in humans.[4] One considered mechanism was whether NNS triggers glucose intolerance by changing gut microbacteria. The study of effects on the human body's gut microbiome is limited to saccharin, which is only one of six NNS currently approved as a food additive. The second mechanism studied in humans is whether the recently found sweet taste receptors located in the gut and pancreas can influence

insulin secretion. There are too many inconsistencies in the data results in sweet taste receptors studies to adequately determine any effects.[4] Further studies must be done on human subjects to determine and understand the metabolic mechanisms and potential effects of NNS consumption on human health.[6]

NNS as a Useful Dietary Tool

A meta-analysis conducted by Miller and Perez aimed to evaluate the association between NNS, body weight and composition. The reason that these researchers decided to focus on body weight and composition is because of the obesity prevalence. They wished to determine the safety of NNS consumption as a dietary tool to help people maintain or lose excess weight. The authors systematically reviewed and quantitatively evaluated 15 RCTs and 9 prospective cohorts. There was a total of 1,951 participants across all examined studies. The minimum study duration for RCTs was 2 weeks, and the minimum for the cohort studies was 6 months. They found a small association between increased BMI and NNS consumption in the prospective cohort studies, but no association with increased body weight. The RCTs indicated that substituting NNS for sugar reduced body weight, BMI, fat mass and waist circumference. The two types of studies contradicted each other on the BMI outcomes of participants, but RCTs are the gold standard in research design. Therefore, Miller and Perez concluded that NNS could be a safe, useful tool in managing body weight.[6]

Limitations of NNS Research

A limitation in all artificial sweetener consumption studies is the difficulty of quantifying the amount of artificial sweetener in a product. With the exception of saccharin, manufacturers are not required to disclose the quantity of added artificial sweeteners on product labels. Another limitation to the cross-sectional studies are the reliance on diet recalls which provide subjective

data and may not be accurate. Therefore, the amount of artificial sweetener intake is an unreliable estimation.[8]

The Position of the Academy of Nutrition and Dietetics on Nonnutritive Sweetener Use

The AND routinely reviews and analyzes research to determine their safety and to create guidelines for human consumption of artificial sweeteners. A systematic review utilizing data collected from the EAL is used in determining the guidelines. It is the position of AND that consumers can safely ingest the artificial sweeteners that have been approved by the FDA as long as the consumption follows the ADI guidelines. Currently there are 6 nonnutritive sweeteners approved by the FDA, each with a different ADI. Artificial sweeteners are shown to be effective in weight loss management by reducing energy intake. They are approved for use in those who have diabetes since they are a safe alternative to sugar. There is also evidence to suggest that artificial sweeteners can reduce dental cavities by inhibiting bacteria growth. For these reasons, the AND approves the use of artificial sweeteners.[9]

Limitations of the EAL

The limitations to the method used for the EAL include the amount of artificial sweetener studies that meet criteria. Once a conclusion has been reached about a research question, the conclusion statement is graded based upon the strength of the supporting evidence and analysis. It is important to note that many of the EAL conclusions made by the Nutritive and Non-Nutritive Sweeteners (NNNS) workgroup are graded as a III, which means there is "Limited" evidence to support them. Also, many of the conclusions have not been updated since 2006, and the use of artificial sweeteners has increased since then. Another important aspect to note is the funding sources of the NNNS workgroup include the Coca-Cola Company. This may be a

potential conflict considering the profits that Coca-Cola earns from selling diet sodas sweetened with artificial sweeteners.[9]

Conclusion

Although NNSs have been used in foods for decades now, controversy remains on the overall effects of these substances on human health. NNS have generally been used as a calorie-free replacement for sugar, which can make food items less energy dense. Healthcare professionals have supported the consumption of foods sweetened with NNS as part of a weight loss or weight maintenance program. However, recent studies have not supported the previous claim that consumption of NNS can help with significant weight loss. Past RCTs have found an association of NNS consumption and reduced body weight, reduced fat mass, and reduced BMI. On the contrary, epidemiological studies have associated NNS consumption with an increase in BMI.[5]

The limitations of past research studies that focused on NNS prevalence and consumption should be addressed. One of the biggest limitations in most dietary studies is the error of self-reported diets.[8] The accuracy of dietary studies of NNS consumption is hindered even further because food manufacturers do not have to include the amount of NNS in their product.[3,8] Researchers, professionals and consumers should advocate for policy reform on this issue so that the public can be better informed and researchers can work with a more reliable database.

The goal of this paper was to evaluate the prevalence, consumption and overall effects of NNSs. Most research on NNSs has focused on body weight and composition as the outcome of the study. Other outcomes have included risk of obesity and other metabolic effects such as hypertension, metabolic syndrome and stroke. Research consistently shows conflicting evidence

between RCTs and epidemiological observational studies on the metabolic outcomes of NNS consumers.

The prevalence and consumption of NNS has been on the rise, but the research has not kept pace. RCTs are the gold standard of research studies, and most of these studies have not shown significant results in any short-term metabolic effects. However, there have been no RCTs conducted to study the long-term effects of NNS. Although the prevalence of NNS consumption has increased, the amount of research studies done about NNS effects have not. It is difficult to find studies conducted within the past 10 years. In fact, the most referenced RCT by peer-reviewed journal articles was published in 1997.[10] More research needs to be done to investigate potential long-term effects of NNS and to evaluate whether the possible weight loss benefits of NNS is maintainable long-term.

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